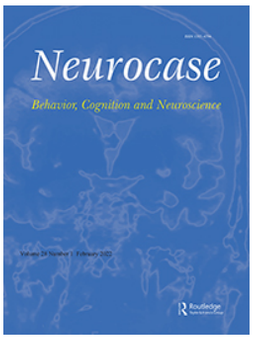

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Electrophysiological abnormalities as indicators of early-stage pathology in Primary Progressive Aphasia (PPA): A case study in semantic variant PPA

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ABSTRACT

Language induced and spontaneous oscillatory activity was measured using MEG in a patient with the semantic variant of Primary Progressive Aphasia (svPPA) and 15 healthy controls.The patient showed oscillatory slowing in the left anterior temporal lobe (ATL) that extended into non-atrophied brain tissue in left and right frontal areas. The white matter connections were reduced to the left and right ATL and left frontal regions, exhibiting electrophysiological abnormalities. Altered diffusion metrics in all four language tracts, indicted compromised white matter integrity. Task-related and spontaneous oscillatory abnormalities can indicate early neurodegeneration in svPPA, providing promising targets for intervention.

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KEYWORDS
Semantic PPA; MEG; sentence comprehension; resting state oscillations; slowing

Introduction

The semantic variant of Primary Progressive Aphasia (svPPA) is the most clearly distinguishable of the three PPA subtypes, with TDP-43-based neurodegeneration in the ventral and lateral portions of the anterior temporal lobes (Mesulam et al., 2003; M. Mesulam et al., 2009; Wicklund et al., 2014). Evidence from neuroimaging studies confirms the role of the anterior temporal lobes in semantic deficits found in individuals diagnosed with svPPA. Most of these studies have examined language processing at the single word level in patients with svPPA (Giaquinto & Ranghi, 2009; Hurley et al., 2009). The focus on language processing at the sentence-level is limited to only a few task-related neuroimaging and electrophysiological studies in svPPA (Kielar et al., 2018, 2019). In the current study, we present a case of a 61 year old female with svPPA who completed a sentence comprehension task while electrophysiological responses were recorded using magnetoencephalo graphy (MEG).

Our aim was to assess changes in oscillatory responses in our patient with svPPA during a task requiring processing of linguistic components at a sentence-level, compared to elderly healthy controls. In addition to task MEG data, we also analyzed resting-state MEG data to study changes in spontaneous oscillatory activity. To capture different aspects of the disease in the patient we examined the relationship between gray matter atrophy and integrity of white matter connections to cortical regions that showed altered oscillatory responses. Using this multimodal approach, we sought to identify structural and oscillatory markers that can serve as potential indicators of dementia progression in the patient.

In our prior MEG work, which included other variants of PPA (7 nonfluent PPA, 6 logopenic PPA), we demonstrated altered language-related oscillatory responses during sentence comprehension, primarily involving the left inferior parietal regions. Interestingly, these areas fell outside the area most severely affected by structural atrophy that we measured by quantifying gray matter volume loss (Kielar et al., 2018). Compared to age-matched healthy controls, patients with PPA showed event-related synchronization of oscillatory activity in the alpha and beta frequency bands (8–30 Hz ERS), indicating decreased activity, whereas event-related desynchronization (ERD) of 8–30 Hz power (indicating increased neural activation to language) was found in controls during the sentence comprehension task. Additionally, abnormal task-induced oscillatory responses in PPA were characterized by delayed peak latencies of 8–30 Hz ERD, and the extent of the delay was associated with more impaired performance on the sentence comprehension task and lower performance on off-line tests of language and other cognitive functions, beyond what could be accounted for by the structural atrophy alone (Kielar et al., 2019). These results suggest that the sentence comprehension deficits in PPA may be related to slowed information processing in relatively intact tissue, i.e. regions that are not yet exhibiting disease-related neuronal loss.

We also examined spontaneous oscillatory changes in PPA in our prior work by measuring resting-state electrophysiological activity with MEG (Kielar et al., 2016a; Shah-Basak et al., 2019). Spontaneous signals in PPA indicated slowing, characterized by increased spectral (relative) power in delta (1–4 Hz) and theta (4–7 Hz) frequency bands but decreased power in the alpha (8–12 Hz) and beta bands (15–30 Hz). This shift toward

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lower frequency is in contrast with observed patterns over healthy aging, which is characterized by decreased delta/theta and increased alpha/beta power (Kielar, et al., 2016a2016b, 2019). Slowing of spontaneous activity in PPA was found to be correlated with impairments of memory and executive function. Our follow-up analyses indicated that these relationships could not be explained by gray matter atrophy alone (Kielar et al., 2019; Shah-Basak et al., 2019). Finally, comparing our spontaneous data to language task data, we showed that the spontaneous shift to lower frequencies was associated with reduced amplitude and peak latency of language task-evoked responses (Kielar et al., 2019).

Our previous findings show that oscillatory power changes and their relationship with impaired performance in PPA are independent of the disease-induced neuronal atrophy (quantified by the loss of gray matter volume) and were largely localized to non-atrophied brain tissue (Kielar et al., 2019; Shah-Basak et al., 2019). This suggests that oscillatory abnormalities may signal earlier stages of the disease progression that affect neuronal microcircuits or neurotransmitter systems prior to the appearance of frank atrophy. In the present study, we examined oscillatory responses in our patient with svPPA, and evaluated the distribution of oscillatory abnormalities relative to the structural atrophy (gray and white matter).

Previous studies in healthy controls and animals suggest that electrophysiological slowing in specific frequency bands in PPA may reflect ongoing structural and biochemical changes in brain tissue resulting from disease (Babiloni et al., 2018; Osipova et al., 2003; Riekkinen et al., 1990; Villa et al., 2000). Transient administration of scopolamine in healthy adults has been found to induce increases in spontaneous delta/theta power accompanied by reduction of alpha/beta power, similar to that found in Alzheimer's Disease (Osipova et al., 2003; Sloan et al., 1992). Neuropathological and imaging studies indicate loss of basal forebrain cholinergic neurons and decreased cortical cholinergic activity in PPA, which is greater in the language dominant left hemisphere (Mesulam et al., 2019; Teipel, Raiser et al., 2016; Lizio et al., 2011). However, the pathophysiological mechanisms that modulate alpha and beta power in PPA are not well understood.

In addition to altered neurotransmitter activity, axonal pathology, deafferentation of neuronal connections, and functional and structural disconnection can modulate oscillatory power. In particular, disconnection of white matter pathways can lead to the loss of input and neuronal dysfunction that manifests as a shift of spectral power to lower frequencies and reduction of activity at higher frequencies (Bells et al., 2017; Hawasli et al., 2016; Jeong, 2004; Teipel, Grothe et al., 2016). Neurodegenerative changes in PPA are thought to spread along major white matter pathways (Mandelli et al., 2016) and compromised white matter integrity and connectivity is correlated with cognitive decline (Filley & Fields, 2016; S. Wang et al., 2021). Disruption of white matter connections and microstructural integrity has been associated with increased slow wave activity (Sanchez et al., 2019) and decreases in alpha, beta and gamma power (Hawasli et al., 2016). This suggests that white matter affects cognitive functions by coordinating timing of impulse transmission between cortical regions and maintaining oscillatory synchronization/desynchronization patterns between and within critical regions. Disruption of white matter connectivity and integrity to the cortical regions in our patient with svPPA may contribute to the oscillatory slowing and impaired task performance.

Modulations in theta, alpha and beta frequency power have been previously linked to various cognitive functions in healthy individuals, including language, working memory, encoding in short term-memory, and storage and retrieval from long-term and episodic memory (Jensen & Tesche, 2002; Klimesch, 1999; Klimesch et al., 2001; Röhm et al., 2001; Sauseng et al., 2010; Stella & Treves, 2011). Alpha and beta power (8–30 Hz) are often modulated during active processing of linguistic and sensory information (Hanslmayr et al., 2012; Kielar et al., 2015; Meltzer et al., 2017). In particular, beta and alpha power changes are associated with semantic processing, verbal working memory and active maintenance of current cognitive state (Jensen et al., 2002; Piai et al., 2015a; Piai et al., 2015bb; L. Wang et al., 2012; Weiss & Mueller, 2012).

In this study, we examined modulation of oscillatory activity during sentence comprehension and at rest in an individual with the diagnosis of svPPA (P08), presenting with a semantic deficit. We expected altered oscillatory activity in the form of increased 8–30 Hz ERS during the sentence comprehension task. We expected altered electrophysiological activity in the anterior temporal lobes and surrounding areas that are not fully atrophied but might be dysfunctional due to ongoing disease-related processes. For resting-state data, we expected slowing, as measured by spectral power changes in the delta/theta and alpha/beta bands, localized to non-atrophied neural tissue, indicating early neuronal dysfunction. As noted earlier, because axonal pathology and structural disconnection can modulate spectral power, we also examined the integrity of white matter tracts that project to the anterior temporal cortex and adjacent regions. We hypothesized that atrophy of the white matter tracts could result in the disconnection of cortical areas anchored to these tracts from the rest of the language network, contributing to the language symptoms and abnormalities in oscillatory activity.

Materials and methods

Case Presentation. We present data from a 61-year-old native English speaking, right-handed female (P08), who was seen at the Baycrest Health Sciences memory clinic in Spring 2015. P08 was diagnosed with semantic variant PPA (svPPA) by the referring neurologist and speech-language pathologist (RJ) after presenting with a progressive deficit in word comprehension. The patient had 17 years of education, and was actively employed before diagnosis. Medical history was free of injuries and hospitalizations and P08 did not take any prescription medications.

At the time of this study, the participant presented with a 4–5-year history of decline in comprehension and retrieval of single words. Her husband, who accompanied her to all assessments, noticed about 4 years ago that she could not understand some simple words (e.g., *cube*). Nonverbal pragmatic skills (e.g., body language, physical proximity, eye

contact) were relatively intact. On a neurocognitive assessment, P08 displayed impairments in verbal memory and visuo-spatial function, but language was most impaired.

Verbal expression

Spontaneous speech was fluent, clearly articulated, with good prosody and grammar but very vague. There were prominent circumlocutions and semantic paraphasias and notable absence of nouns resulting from a significant word finding difficulty. P08 often used the word *"country"* as a substitute for nouns that were inferred from the context as "*company", province", "place*", and *"location"*. Oral description of the "Cookie Theft" was characterized by good fluency but lacked specific vocabulary. She frequently substituted word "nice" for potential adjectives that she could not retrieve (e.g., *nice shoe for wet shoe*).

Oral repetition of words and nonwords was relatively spared (Psycholinguistic Assessments of Language Processing in Aphasia (PALPA 8, Kay et al., 1992), Children Nonword Repetition Test (CNRT, Gathercole et al., 1991), respectively), while repetition of sentences was in the impaired range for the longer low predictability sentences (Boston Diagnostic Aphasia Examination (BDAE, Goodglass et al., 2001). Naming to confrontation (Boston Naming Test (BNT, Kaplan et al., 2001) was profoundly impaired. P08 was able to name 2/60 pictures spontaneously. Errors consisted of circumlocutions (e.g., *bed: "you sleep on it")* and semantic substitutions (e.g., *rake for comb, blow for whistle, wood for saw*).

Auditory comprehension

Auditory comprehension of single words was severely impaired (Peabody Picture Vocabulary Test, PPVT-4, Dunn & Dunn, 2007). Comprehension of verbal commands (3/15 correct) was slightly better than comprehension of single words, but also impaired (BDAE). Comprehension of grammatical structures of varying degrees of complexity was tested via a sentence-picture matching task and was impaired on complex noncanonical constructions (NAVS-Sentence comprehension test, passive sentence and object relative sentences (Cho-Reyes & Thompson, 2012; Thompson, 2011). Comprehension of active sentences and subject relative sentences was spared. Comprehension of aurally presented paragraphs was severely impaired (BDAE). The patient had difficulty understanding individual components of questions, (e.g., *"What's a cork?"*).

Reading and writing

Oral reading of regularly spelled words was preserved but reading of irregular words was impaired (33% correct on PALPA 35, Kay et al., 1992), indicting surface dyslexia (e.g., *Island read as /eezland/ or yacht as /yachet/)*. P08's spelling of single words to dictation was relatively intact for regular but severely impaired for irregular words (10% correct on PALPA 44, Kay et al., 1992), consistent with surface dysgraphia (e.g., *elephant-elafant, squirrel-squrl*). Reading of paragraph length material (My Grandfather) was marked by numerous sound substitutions resulting in nonwords (e.g., *beard – /beerd/, minus-/meenus/*).

Cognitive Skills: P08 was oriented to time, place and person. Her encoding, storage and retrieval of information was severely impaired on both immediate and delayed recall (Arizona Battery for Communication Disorders (ABCD) Story retell, Bayles & Tomoeda, 1991). Verbal fluency was impaired for both phonemic (FAS words) and semantic (animal names) tests (Delis et al., 2001).

Semantic knowledge

Word knowledge was profoundly impaired (PPVT-4). Interestingly, she was able to comprehend nouns that were derivatives of verbs or contained aspects of motion or action, such as kicking, painting, throwing, and dressing, but could not understand even the simplest of nouns, such as cookie or lamp. Access to semantic store from pictures was also severely impaired.

Motor peripheral examination

Examination of oro-facial structures revealed normal anatomy and mechanics (Motor Speech Exam, Dabul, 2000; Wertz et al., 1984). Testing for speech praxis did not reveal any abnormality.

The language profile fulfilled all core and supporting criteria for the semantic variant of primary progressive aphasia (Gorno-Tempini et al., 2011). The available scores on language measures are shown in Table 1. In addition to linguistic assessment, general cognitive status was measured using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005).

To compare language performance and imaging results from P08, linguistic test scores and MR data were obtained in a group of 15 healthy older controls (right-handed native speakers of English; 4 females and 11 males; age: Mean = 68, SE = 1.77, education: Mean = 17.86, SE = 0.69). All controls participated in a larger study (described earlier) examining MEG responses in a group of patients diagnosed with nonfluent and logopenic PPA (Kielar et al., 2018).

The tests that are designed to assess aphasia severity were not administered to controls. These included Western Aphasia Battery Revised (WAB, Bedside Record Form), (Kertesz, 2007), BDAE and ABCD. These clinical language batteries are commonly used to classify symptoms of aphasia. They were administered only to P08 but not in controls because other norming studies have established that most controls perform at ceiling on these tests (Borod et al., 1980; Fromm et al., 2017; McCullough et al., 2019; Wilson et al., 2018). Other linguistic and cognitive tests have a more variable range of performance among controls, and thus were administered to our control participants. Control participants tested within normal limits on all tests.

All participants were recruited from the greater Toronto area by Research Ethics Board (REB) approved advertisements and from the Baycrest Health Sciences research subject pool. All participants reported normal hearing and normal or corrected-to-normal vision. Older healthy volunteers had no history of neurological, psychiatric, speech, language, or learning

Table 1. Language and cognitive test scores for P08 and older control (OC) group means.

	P08	Controls	
	Test Score (z-score)	**Mean**	**SE**
Age(years)	61	68	1.77
Education(years)	17	17.46	0.69
Time post Onset(years)	4 years	N/A	
Test Scores			
Cognitive state-MOCA (out of 30)	6(−3.57)	27	0.44
Naming-BNT (out of 60)	2(−3.69)	57	0.60
Letter fluency D-KEFS	10(−2.32)	49.85	3.41
Category fluency D-KEFS	0(−2.99)	44.13	2.24
Repetition-CNRT%	90(0)	90	3.18
Sentence Comprehension-NAVS_SCTcan %	100 (0)	100	0.0
Sentence Comprehension-NAVS_SCT noncan%	47(−3.75)	100	0.0
Receptive Vocabulary-PPVT (scaled)	63(−2.9)	119	3.06
Semantics-Camel and Cactus%	0(−3.69)	90	1.10
Repetition-PALPA 8%	97(−0.28)	97.5	0.73
Reading–PALPA 35-regular words%	90(−3.25)	99	0.35
Reading–PALPA 35-irregular words%	33(−3.72)	99	0.54
Spelling-PALPA 44-regular words%	90(−1.98)	98	0.83
Spelling-PALPA 44-irregular words%	10(−3.68)	96	1.14
WAB-Fluency(out of 10)	8	N/A	
WAB-Repetition (out of 10)	6	N/A	
WAB-Comprehension (out of 10)	7	N/A	
WAB-Commands (out of 10)	1	N/A	
WAB-Naming (out of 10)	3	N/A	
WAB BAS (out of 100)	52	N/A	
WAB BLS (out of 100)	50	N/A	
BDAE-sentence repetition (out of 10)	7	N/A	
BDAE-reading comprehension (out of 10)	0	N/A	
BDAE-verbal commands (out of 15)	3	N/A	
BDAE-comprehension of paragraphs (out of 8)	0	N/A	
BDAE-Yes/No questions (out of 4)	1	N/A	
ABCD-delayed recall (out of 17)	0	N/A	
ABCD-immediate recall (out of 17)	1	N/A	

disorders and none were taking neuroleptic or mood-altering medications at the time of the study. They participated in all neuroimaging assessments completed by P08. This study was approved by the Research Ethics Board at Baycrest Health Sciences, University of Toronto. All volunteers gave their written informed consent prior to the study and were compensated for their participation.

Sentence comprehension task

All participants completed a visual sentence-judgment task during MEG acquisition. A detailed description of the procedure can be found in the Supplementary Materials and in our previous papers (Kielar et al., 2015, 2016b). In this paper, we focus on the responses associated with processing of semantic anomalies, and on spontaneous oscillatory activity in P08. The correct condition (COR) consisted of grammatically and semantically correct English sentences, ranging from 6 to 12 words in length (e.g., *She will go to the bakery for a loaf of bread*). The sentences with semantic anomalies (SEM) were created by replacing the final words of the sentences with unexpected completions *(e.g., She will go to the bakery for a loaf of books)*. A constraint was that the final word should be the same part of speech as the original word. For analyses of semantic anomalies, the anomalous final word was compared directly with correct final words.

MEG recording and analysis

We applied Synthetic Aperture Magnetometry (SAM) to the MEG data in order to localize oscillatory brain responses to semantic anomalies in P08 and controls. The time windows, frequency bands, and conditions to compare were guided by our previous results using the same paradigm in healthy controls (Kielar et al., 2015) and patients with post-stroke aphasia and PPA (Kielar et al., 2018, 2019; Kielar et al., 2016b). A detailed description of MEG signal acquisition and analysis can be found in the Supplementary Materials and in our previous papers (Kielar et al., 2018; Shah-Basak et al., 2019).

Spontaneous brain activity was recorded for 5 minutes while participants viewed a white fixation cross presented in the center of the screen on a black background.

Diffusion weighted imaging (DWI) acquisition and analysis

Because neurodegeneration can affect white matter tracts in addition to causing cortical gray matter atrophy, we collected and analyzed diffusion weighted imaging data. Our diffusion weighted imaging (DWI) scans (30-directions, axial acquisition, TR = 7900 msec, TE = 84 msec, flip angle 90, FOV = 242 mm, 68 contiguous slices, voxel size: 2.0 × 2.0 × 2.0 mm isotropic, three B0 images) were processed using a GPU-enabled High-Performance Computing cluster with a BIDS Singularity container (https://bitbucket.org/dpat/bipbids/src/master/) to ensure replicable results. The processing pipeline used FSL 5 to perform eddy current correction, local diffusion parameter modeling, diffusion tensor fitting, and probabilistic tractography (Behrens et al., 2003, Behrens et al., 2007; Hernandez-Fernandez et al., 2019) with connectivity-based parcellation (Behrens et al., 2003; Johansen-Berg et al., 2005).

For each tract, we examined scalar white matter measures (parallel diffusivity [PD], radial diffusivity [RD], mean diffusivity [MD], fractional anisotropy [FA], and mode [MO]) and parcellation of associated seed regions. Parcellation defines cortical regions by their connectivity (Anwander et al., 2007; Behrens et al., 2003; Johansen-Berg et al., 2005). To characterize cortical regions accurately at both ends of the tract, we applied parcellation iteratively and bidirectionally: iterative parcellation shrank each seed region until a stable set of gray matter voxels was identified (subsequently referred to as the "final endpoints"). Patterson et al. (2014) demonstrated that this bidirectional iterative parcellation (BIP) is a sensitive technique for characterizing connectivity, and following Behrens and Johansen-Berg et al. (2005) we hypothesize that such parcellations represent the extent to which the tract fibers penetrate the seed regions. Following Patterson et al. (2014), tracts and parcellations were thresholded and warped into standard space for comparison across subjects.

Each scalar measure (PD, RD, MD, FA, and MO) reflects characteristics of white matter integrity. PD (parallel diffusivity) measures diffusivity parallel to the primary axis of the tract. Reduction in PD is thought to identify axonal damage (Song et al., 2003). RD (radial diffusivity) measures diffusivity perpendicular to the primary axis of the tract. An increase in RD is thought to identify myelin damage (Galantucci et al.,

2011; Mukherjee et al., 2008; Song et al., 2002). Mean diffusivity (MD) averages parallel and radial diffusivities. Mean diffusivity values reflect isotropic diffusion and increase when structure degenerates. Fractional anisotropy (FA) is calculated from diffusion tensor eigenvalues (Basser et al., 1994; Beaulieu, 2002), and describes the shape of diffusion ranging from sphere-like (0) to ellipsoid (1). FA provides a standardized measure of anisotropy. MO (mode), a continuous measure ranging from −1 (sphere-like) to +1 (linear), further characterizes the shape of anisotropy and is mathematically orthogonal to FA (Douaud et al., 2011; Ennis & Kindlmann, 2006; Yoncheva et al., 2016). Mode can distinguish differences in diffusion shape that FA conflates (e.g., An FA value of 0.7 may correspond to a variety of shapes, ranging from disk-like (MO = −1) to tubular (MO = +1). Together MO and FA more fully characterize the shape of diffusion than either measure alone. For each participant and tract, we compared PD, RD, MD, FA, and MO between P08 and controls using one-way ANOVAs following a method for comparing a single case against control group means (Crawford & Garthwaite, 2012; Mycroft et al., 2002).

Selected tracts projected to the BA47, posterior inferior frontal gyrus (pIFG), anterior temporal lobe (ATL), and/or temporo-parietal (TP) and inferior parietal regions (IPL), all of which showed altered oscillatory responses in P08 and are thought to be involved in the language network. These tracts include the arcuate fasciculus [ARC], extreme capsule [EmC], middle longitudinal fasciculus [MdLF] and uncinate fasciculus [UNC]). We examined these tracts in both the left and right hemisphere, hypothesizing that language-specific degeneration would be focused in the left hemisphere. The seed regions for each tract were identified and verified in 97 adults (Patterson et al., 2014) and are available as an FSL-compatible atlas (https://osf.io/cbk3u/). The detailed characterization of each tract is available in the (https://osf.io/cbk3u/). The detailed characterization of each tract is available in the Supplementary materials.

Results

Behavioral performance on the MEG task

On the sentence comprehension task, P08 scored 96% correct on the correct sentences (COR), but comprehension performance was significantly impaired on sentences with semantic (SEM) anomalies (d′ = −0.303), indicating a general bias to accept sentences as correct. For P08, reaction times were 795 msec on COR and 878 msec on SEM. For older control participants mean reaction times were faster (688.61 msec (SE = 51.56) on COR; 643.27 msec (SE = 51.80) on SEM). The mean percent accuracy for controls (standard error, SE) was 93.24 (SE: 1.24) for COR: and 96.8 (SE = .70), for SEM, a d′ value of 3.50 (SE = .15), indicating good discrimination between the two sentence types.

Grey matter volumes

Voxel-based morphometry (VBM) implemented in SPM12 software (Wellcome Department of Cognitive Neurology, London, UK), was used to derive segmented, smoothed and normalized gray matter maps for P08 and older control participants. The gray matter volumes in P08 relative to the older control group are shown in Figure 1A. The statistical maps were corrected at a voxel-wise threshold of $p < .001$, and corrected for multiple comparisons by controlling the family-wise error (FWE) at the cluster level $p < .05$. The pattern of atrophy was consistent with the diagnosis of svPPA. The regions with the most marked gray matter volume loss were the anterior temporal lobes (ATL) and temporal pole (BA 38). In the left hemisphere the atrophy extended from the anterior temporal pole (ATP), posteriorly into the left middle and inferior temporal gyri. In the right hemisphere cortical damage was less extensive and included the ATP and the ventral portion of ATL.

White matter volumes

The results of VBM analysis of the white matter maps are shown in the Figure 1B. The analysis revealed decreased white mater volume in the left and right ATL and inferior, middle and superior temporal cortices. The statistical maps were corrected at a voxel-wise threshold of $p < .001$, and corrected for multiple comparisons by controlling the FWE at the cluster level $p < .05$.

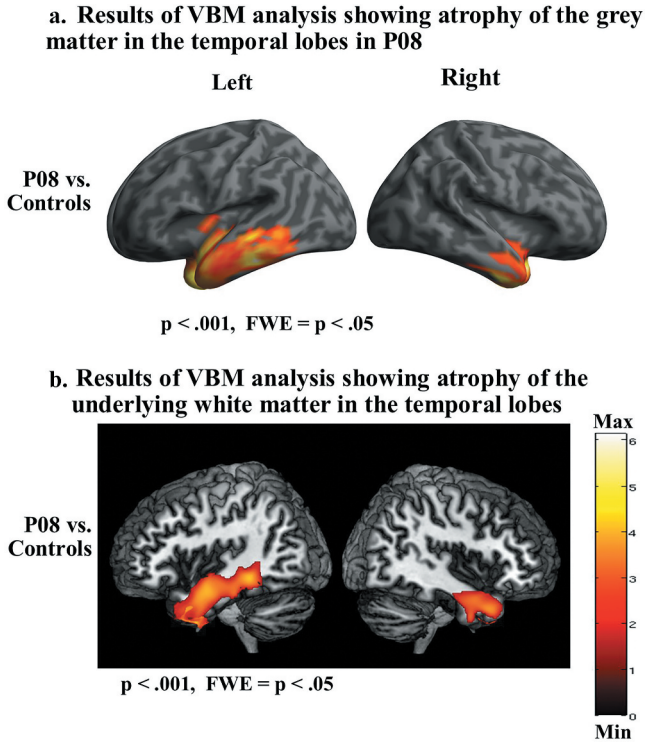

Figure 1. The gray matter volumes in the patient P08 relative to the older control group (OC) obtained using Voxel Based Morphometry (VBM). (A) The gray matter volume in the temporal lobes in the P08. Yellow-red color scale indicates atrophy of the gray matter in the left temporal lobe and the right anterior temporal lobe. (B) The white matter atrophy in the temporal lobes in P08. Brighter colors indicate greater volume loss.

SAM localization of oscillatory responses during the MEG task

Whole-brain maps of oscillatory activity were generated using SAM beamforming. Neural "activation" is indicated by *power decrease*, or event-related desynchronization (ERD), in the alpha/beta frequency range (8–30 Hz) from 400 to 1000 msec, which was chosen as our main analysis window. In Figure 2, power decreases (reflecting *increased neuronal activity*) are mapped in a blue color scale on the surface of a standard reference brain in MNI space, while 8–30 Hz power increases (associated with *reduced neural activity*) are mapped in a yellow-red color scale. The statistical maps were corrected for multiple comparisons at a cluster-wise level of $p < .05$ and thresholded to a minimum cluster size of 86 voxels (a voxel-wise threshold of $p < .001$). The maps for P08 were thresholded at the 38% of the maximum amplitude. This value was chosen because it corresponded to the threshold value at $p = 0.01$ in the control group after correction for multiple comparisons. Singleton t-tests were conducted in AFNI to compare whole-brain oscillatory response maps in the time-frequency window of 8–30 Hz, 400–1000 msec (relative to critical word onset) between P08 and the 15 older controls. The statistical threshold was set to $p < 0.01$ and corrected for multiple comparisons.

Semantic responses (SEM-COR): 8–30 Hz

Figure 2A shows activation maps for semantic anomalies minus control words in P08 in the main analysis window (8–30 Hz and 400–1000 ms). The most prominent finding for P08 was the 8–30 Hz *ERS* in the left ATL with a maximum in the left temporal pole (BA38). This region also showed the most severe gray matter loss in the VBM analysis (see, Figure 1A). Interestingly, ERS extended to areas outside of the region of primary atrophy in the left ATL. The 8–30 Hz ERS (reduced neural activation, in contrast to ERD seen in controls) was found in the pars orbitalis (BA47) and pars opercularis (BA44) of the left inferior frontal gyrus (IFG), insula (BA13), precentral gyrus (BA6), dorsolateral frontal (BA9), and postcentral regions extending to the inferior parietal lobule (BA40). In the right hemisphere, 8–30 Hz ERS was also found along the precentral and postcentral gyri, including the anterior (BA40) and superior parietal lobules (BA7). The 8–30 Hz ERS was present in the right posterior middle and inferior temporal gyrus, fusiform gyrus, and cerebellum. These regions of reduced task-related activation did not show significant gray matter atrophy. P08 showed 8–30 Hz ERD in the right dorsolateral frontal cortex (BA46), which was structurally preserved based on the VBM analysis.

P08 vs. older controls. semantic responses (SEM-COR): 8–30 Hz

For comparisons with P08, the results for older controls are shown in Figure 2B, which have been described in detail in our previous study (Kielar et al., 2018). Figure 2C displays results of a singleton t-test comparing oscillatory responses for P08 against 15 older controls. Because ERD represents a negative quantity (suppression of oscillations), positive values in the subtraction map (P08 vs. controls) reflect decreased neural activity in P08. This analysis revealed reduced activation (8–30 Hz ERS) for P08 in the left anterior temporal lobe (ATL), extending into the left BA47 and posterior IFG. In the right hemisphere, P08 showed 8–30 Hz ERS in the posterior superior and middle temporal and parietal regions (BAs 7, 40, 39), and also in postcentral and posterior middle frontal areas. In comparison to controls, P08 showed increased 8–30 Hz ERD (more activation) in the right dorsolateral frontal cortex (BA46).

Time-course and latency of oscillatory responses

The time-course of oscillatory responses to semantic anomalies and correct words was examined by averaging across frequencies within the 8–30 Hz frequency bands and plotting the two conditions across time. We examined the latency and amplitude of oscillatory responses in regions-of-interest (ROI) analyses between P08 and healthy controls. Specifically, we plotted the average power time-courses in the 8–30 Hz band for semantic violations and correct words based on virtual signals in three representative ROIs: the anterior temporal lobe (ATL), pars orbitalis (BA 47) of the IFG, and middle frontal (MFG) gyrus (See, Figure 2D). These ROIs were examined in the left and right hemispheres. These regions were examined because they showed gray matter atrophy and/or altered oscillatory responses. In P08, the left ATL was affected by gray matter atrophy and showed electrophysiological abnormalities. Left BA47 and MFG ROIs were not significantly atrophied, but displayed abnormal oscillatory responses.

Examination of ROI time-course plots revealed that, compared to the older controls, language-related oscillatory responses for P08 were absent or attenuated and had later onsets. For controls, we observed strong oscillatory responses for semantic anomalies compared to the corresponding correct words (Figure 2B), reflected in power decrease (ERD) in the 8–30 Hz range, with an onset around 400 msec and extending in time to about 1000 msec (Figure 2D, time course plots). In contrast, 8–30 Hz ERD responses for semantic anomalies in P08 were observed with an onset around 1000 msec and lasting until about 2000 msec.

To formally investigate changes in neural response latency in P08, we computed peak latencies of 8–30 Hz ERD from time-courses of virtual channels from 0.1 to 2.5 sec post-stimulus onset. The latency of responses at specific channels was measured using a peak finding algorithm (see Supplementary information). The box plots in Figure 2E illustrate peak latency values for P08 and older controls in the three representative ROIs. In comparison controls, P08 showed increased peak latencies that were especially delayed for the semantically anomalous words. The values for each ROI are presented in Supplementary Table S1. For P08, the peak latencies were significantly longer for semantic anomalies in left and right BA47 (left: $F(1,14) = 25.01$, $p < .001$, svPPA = 1.32 sec, OC = 0.59 sec; right: $F(1, 14) = 33.61$, $p < .001$, svPPA = 1.32 sec, OC = 0.57 sec), and right ATL ROIs ($F(1,14) = 42.85$, $p < .001$, svPPA = 1.26 sec, OC = 0.60 sec). Left and right BA47 were not significantly atrophied but showed abnormal responses (8–30 Hz ERS) to language stimuli and delayed peak latencies. These results indicate that for P08, the abnormal electrophysiological responses extended to the frontal regions beyond the significant and quantifiable gray and white matter atrophy in ATL.

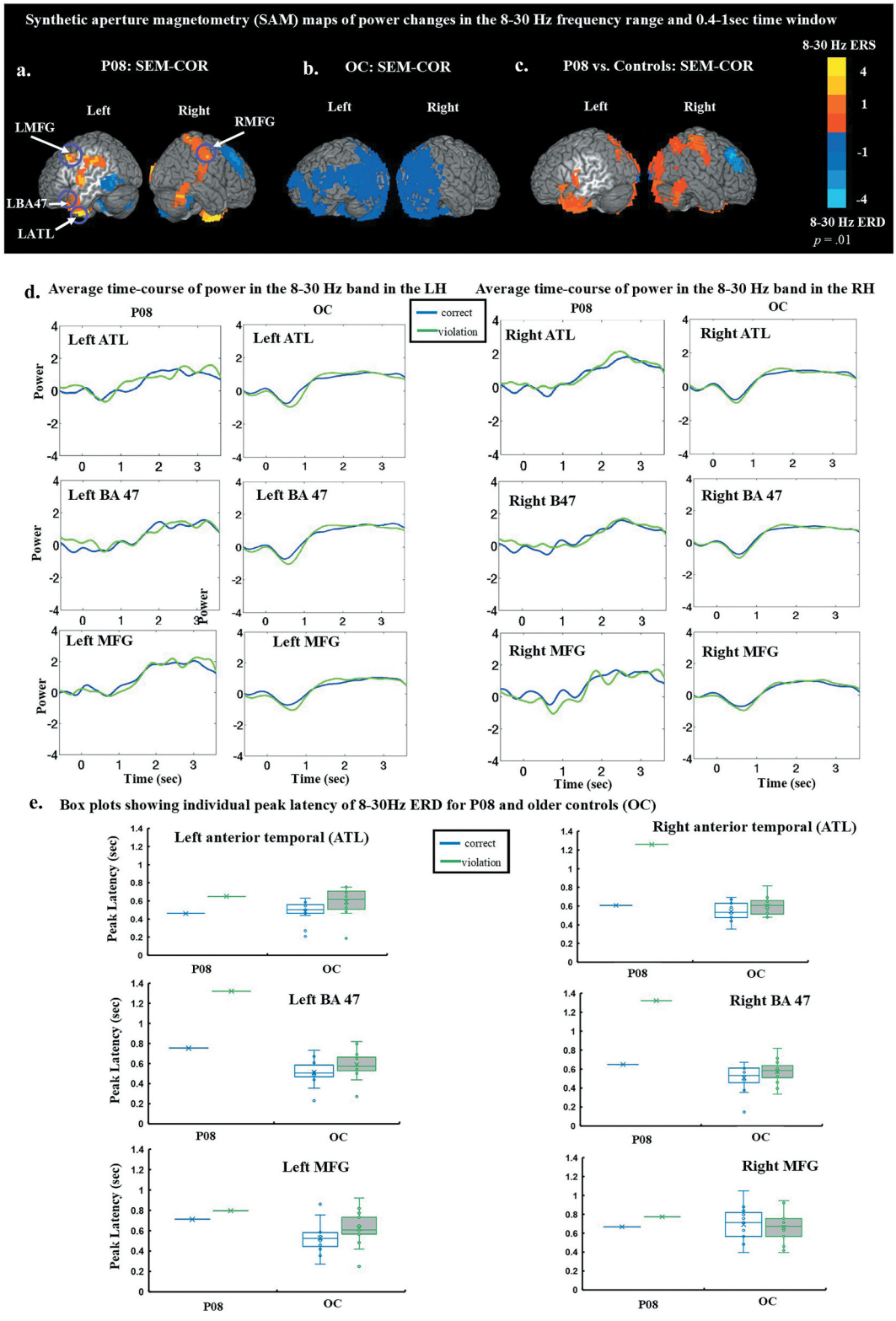

Figure 2. Synthetic aperture magnetometry (SAM) maps of power changes in the 8–30 Hz frequency range and 0.4–1 sec time window after critical word onset for P08 and healthy older controls (OC). For controls the statistical maps were thresholded at a minimum cluster-size criterion of 86 voxels and $p < .01$. (A) Power changes for semantic anomalies vs. correct words for P08. (B) Power changes for semantic anomalies vs. correct words for controls. (C) Results of singleton t-test comparing 8–30 Hz oscillatory activity for P08 vs. controls. The yellow-red color scale shows areas that displayed more 8–30 Hz ERS in P08. (D) Average time course of power in the 8–30 Hz band, for semantic anomalies and correct words in P08 and controls. (E) The box plots showing peak latency values (sec) for P08 and individual older controls in the left and right anterior temporal (ATL), BA47, and middle frontal (MFG) ROIs.

Spectral measures of MEG Resting data

To evaluate oscillatory responses related to spontaneous activity in P08, we plotted the average power spectra for the ATL, BA47 and MFG ROIs. Power spectra plots (Figure 3) revealed a decrease in alpha and beta spectral power (from about 10–30 Hz) in P08 relative to older controls for all three ROIs. In contrast to our previous findings with logopenic and nonfluent PPA, there was no widespread increase in delta and theta power in P08 relative to the control group. Delta power (1–4 Hz) increased in the frontal ROI, but not in the ATL or BA47 ROIs. The spectral plots indicate attenuation of resting-state oscillatory activity that was most pronounced in the alpha and beta bands, from 10 to 30 Hz.

White matter connectivity

Tract diffusion measures for older controls and patient P08

Tract volumes and diffusion metrics are summarized in Supplementary **Table S2**. Altered diffusion metrics were found in all four tracts in both hemispheres for P08. PD was reduced in P08 relative to older controls in the right ARC and UNC, and bilateral EmC and MdLF. RD and MD values were significantly increased in P08 relative to controls in ARC, EmC, MdLF, and UNC in both left and right hemispheres. There were no significant differences in FA between P08 and controls. MO was reduced in P08 in the left UNC, suggesting a less linear and more disk-like mode of diffusion. The increased mean and radial diffusivities indicate that white matter integrity had been compromised by myelin loss in P08. Although for P08 FA was comparable to the control group, there is some indication that MO captured an important difference in left UNC.

Indicators of Tract Connectivity to the Cortical Regions

Parcellation reflects the extent to which tract fibers penetrate seed regions. However, differences in the initial volume of gray matter in each seed region, especially differences between P08 and controls, might incorrectly inflate parcellation differences. To address this issue, we segmented the seed regions for each participant to include only that individual's gray matter, and then converted that volume back to standard space for

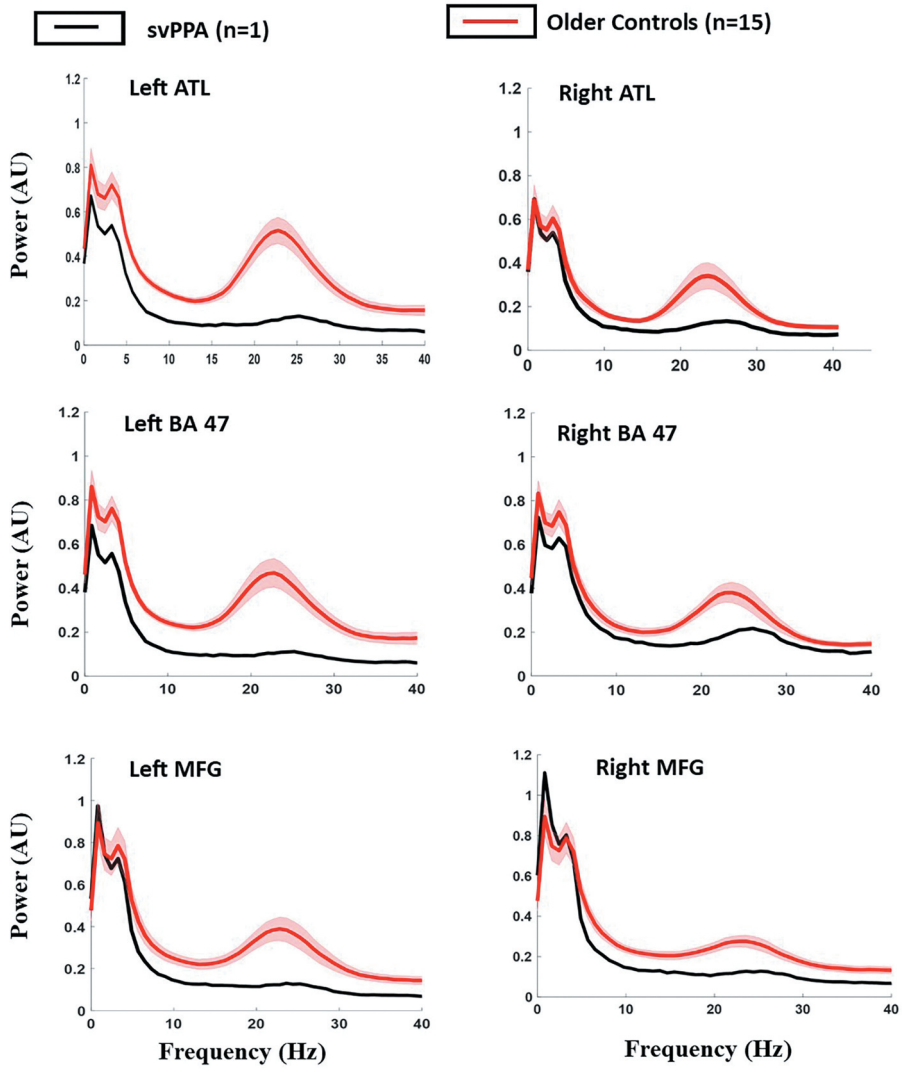

Figure 3. Resting-state power spectra plots for P08 and Older Controls (OC) in the three representative ROIs: the left and right anterior temporal (ATL), BA47, and middle frontal gyrus (MFG). The spectral plots indicate attenuation of resting-state oscillatory activity for P08 that was most pronounced in the alpha and beta bands, from 10 to 30 Hz.

comparison to other participants. We call these initial endpoints. After iterative parcellation, the final endpoints are reduced in size. The initial and final endpoint volumes are presented in the Supplementary Table S3.

For P08 and older controls the location of ARC, EmC, MdLF, and UNC and the volumes of the final endpoints (box plots) are shown for left and right hemispheres (Figure 4). Unsurprisingly, the initial volumes of the left and right ATL were significantly smaller for P08 (**Table S3**; MdLF_left, UNC_left, $F(1,14) = 175.32$, $p < .001$; MdLF_right, UNC_right, $F(1,14) = 35.13$, $p < .001$). In addition, the initial volume of the left IPL was smaller for P08 (ARC_left, EmC_left, $F(1, 14) = 8.351$, $p = 0.012$). After bidirectional iterative parcellation, differences in the final endpoints emerged based on the connecting tracts. The final volumes of the left and right ATL remained significantly smaller in P08 compared to controls (MdLF_left, $F(1,14) = 24.20$, $p < .001$; UNC_left, $F(1,14) = 10.84$, $p = .006$; UNC_right, $F(1,14) = 6.03$, $p < .029$). In addition, the final volume of left BA47 was smaller in P08 (UNC_left, $F(1, 14) = 7.204$, $p = 0.019$). These results are consistent with the atrophy of the gray matter and disconnection of white matter tracts in the left and right ATL in P08. Although left BA 47 was not significantly atrophied, the connectivity to the white mater tracts was reduced in P08, compared to controls.

Discussion

In the present study, we examined oscillatory dynamics in a patient presenting with semantic variant PPA. Consistent with the diagnosis of svPPA, gray matter atrophy was most pronounced in the anterior temporal lobes, with larger involvement in the left hemisphere. Neurodegeneration of the anterior temporal lobes manifested as a deficit in object naming and impaired language comprehension, with preserved speech production and fluency. On the sentence comprehension task, P08 achieved 100% on the correct sentences but she was impaired on detecting sentences with semantic anomalies. Consistent with a dissociation between impaired semantic processing and spared motor speech and phonological function, P08 relied on phonological strategies to compensate for the semantic deficit. On the reading task, she attempted to read irregular words using phonological strategy (e.g., Island read as */eezland/* or yacht as */yachet/*), indicating that she lost knowledge of irregular spelling. These results are consistent with the critical role of the anterior temporal lobes in computing conceptual representations and word comprehension (Lambon Ralph et al., 2010; Mesulam et al., 2015).

Consistent with speech-language evaluation and performance on the language assessments, MEG data indicated that P08 showed attenuated amplitude and delayed peak latencies of oscillatory responses to semantic anomalies. The abnormal oscillatory responses during the language task (8–30 Hz ERS) extended from the left ATL and into the BA47, and left and right inferior and posterior middle frontal areas that were not yet significantly atrophied. In the same areas we found slowing of resting-state oscillatory activity, manifested as decreased power in the alpha and beta frequency bands (8–30 Hz).

The pattern of results in the current study is consistent with our previous findings with nonfluent and logopenic PPA, indicating that neuropathological changes in P08 resulted in slowed neuronal dynamics both during a language task and at rest. Electrophysiological changes were prominent in the anterior temporal lobes that were undergoing atrophy. Interestingly, these electrophysiological abnormalities extended into the frontal regions that did not show detectable structural atrophy. In contrast to our previous studies with nonfluent and logopenic PPA, we did not find widespread delta or theta power increases in P08. Compared to controls, spontaneous delta/theta power was increased only in the right frontal region, whereas alpha/beta oscillatory activity was consistently reduced in P08. Increases in spontaneous delta/theta activity and decreases in alpha/beta have been associated with depletion of cholinergic inputs from the basal forebrain to the cortex (Kikuchi et al., 2000; Sloan et al., 1992). However, role of cholinergic activity in P08 is unclear because decreases have been found mainly in logopenic variant of PPA, but less so in the semantic PPA subtype (Mesulam et al., 2019; Schaeverbeke et al., 2016).

The analysis of white matter tracts involved in language processing indicated reduced connectivity of the ventral tracts (MdLF, UNC) to ATL and BA47 regions in P08. Volumes of left and right ATL connected to the left MdLF and left and right UNC were significantly reduced in P08. This is consistent with gray matter atrophy patterns and suggests disconnection of this anterior temporal region from the connecting white matter pathways. Although left BA47 was not significantly atrophied, there was also reduction of connectivity from this region to the left UNC. This indicates that white matter disconnection may have contributed to slowing of electrophysiological activity in the brain regions that are still structurally preserved. White matter disconnection and microstructural damage have been found to disrupt propagation of cortical oscillatory activity, which in turn leads to cognitive decline (Filley & Fields, 2016; Hinault et al., 2020; Wang et al., 2021). Previous studies of brain connectivity suggest that brain atrophy in PPA spreads between language-related cortical regions along the white matter pathways that connect them (Mandelli et al., 2016; Teipel, Grothe et al., 2016). Thus, the relationship between gray matter atrophy and integrity of white matter connections to cortical regions can function as a potential indicator of dementia progression.

In addition, we found altered diffusion metrics in all tracts suggesting microstructural changes in white matter integrity in P08. While most studies focus on decreases in FA or increases in MD, we simultaneously assessed a whole range of scalar diffusion markers including FA and MD but also axial (PD), radial (RD) diffusivities and MO. We found that for P08, changes in MD, PD and RD were more sensitive markers of white matter changes than FA. Reduction in PD is thought to reflect myelin degeneration, whereas increased RD signals direct axonal damage. MD reflects isotropic diffusion and increase indicates degeneration of white matter fibers in P08. MO was reduced in the left UNC indicating a less linear and more disk-like shape of diffusion. MO is sensitive in capturing subtle differences in the white matter fibers, in particular in crossing fiber regions

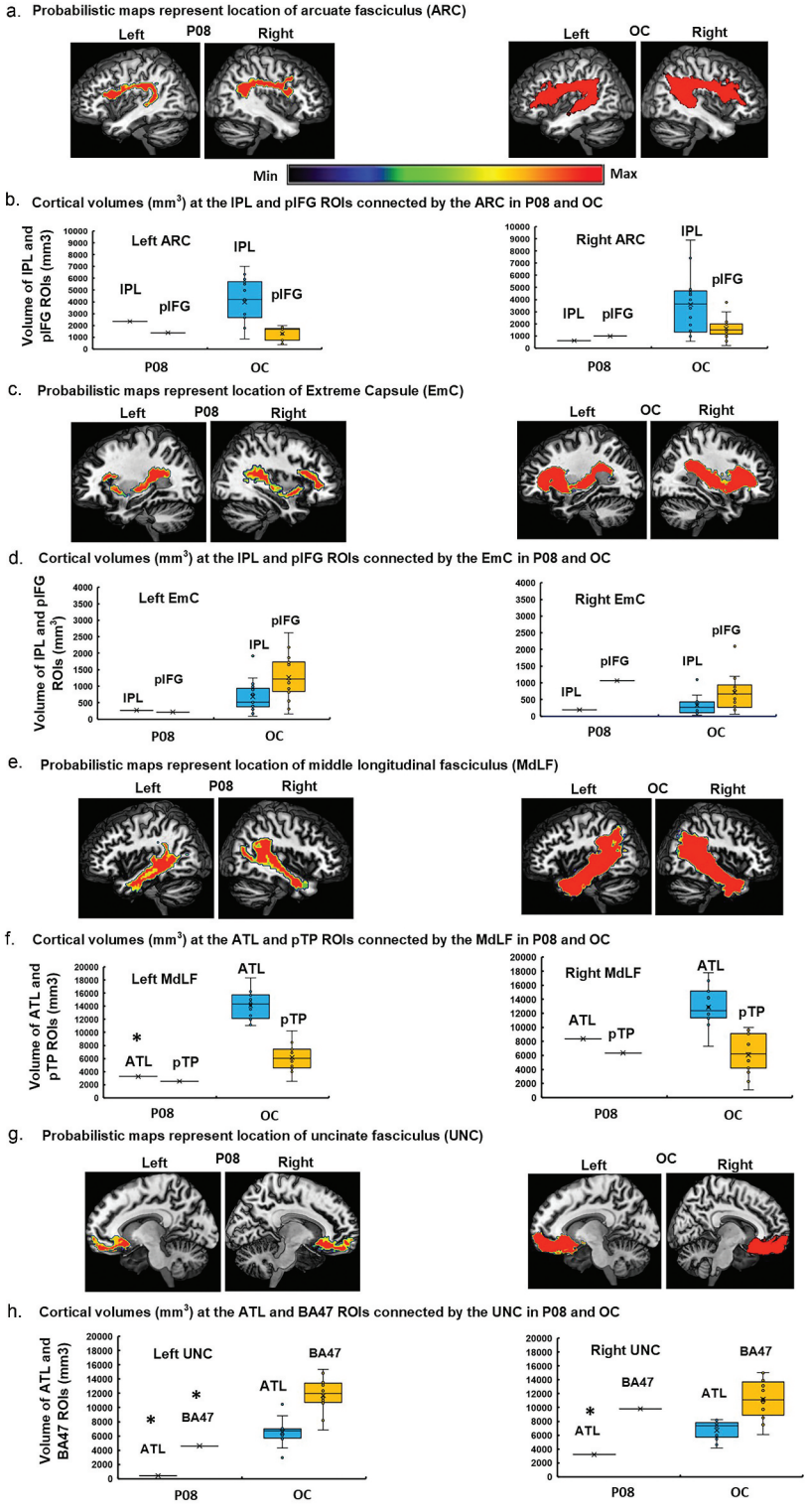

Figure 4. Results of Bidirectional Iterative Parcellation (BIP) analysis of the DWI data. (A) Probabilistic maps showing location of the arcuate fasciculus (ARC) white matter pathway reconstructed by the BIP procedure in the right and left hemispheres. (B) The box plots show the final cortical volumes connected by the ARC tracts for individual participants in the left and right hemisphere. (C) Probabilistic maps showing location of the extreme capsule (EmC). (D) The box plots show the final cortical volumes connected by the EmC for individual participants. (E) Probabilistic maps showing location of the middle longitudinal fasciculus (MdLF). (F) The box plots show the final cortical volumes connected by the MdLF for individual participants. (G) Probabilistic maps showing location of the uncinate fasciculus (UNC). (H) The box plots show the final cortical volumes connected by the UNC for individual participants.

(Douaud et al., 2013). Increased MO in P08 most likely reflects structural degeneration of the UNC. Alterations in diffusion metrics are of clinical significance because they signal microstructural damage to the white matter fibers and may predict spread of neurodegeneration at the early stages. Early intervention may offer an opportunity for a potential treatment

to be more effective in slowing down progression of PPA.

Our results indicate that slowing of language related and spontaneous oscillatory responses in P08 may reflect neuronal dysfunction before detectable gray matter atrophy takes place. The results suggest that the disconnection of cortical regions from the underlaying white matter pathways and altered diffusivity in P08 can contribute to the functional abnormalities, especially in the ventral pathways that connect anterior temporal lobes with ventral frontal regions and mediate semantic processing. Identification of early signatures of the disease in structurally intact tissue offers the possibility of targeting treatments to arrest or reverse such abnormalities.

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Abbreviations

MOCA: Montreal Cognitive Assessment (Nasreddine et al., 2005). Measured out of 30 points; Values from 30 to 26 points indicate normal performance.

BNT = Boston Naming Test (Kaplan et al., 2001); PPVT = Peabody Picture Vocabulary Test (Dunn and Dunn, 2007); Camel and Cactus (Adlam et al., 2010); Letter and Category fluency from D-KEFS: (Delis et al., 2001); CNRT = Children's Test of Nonword Repetition (Gathercole et al., 1991); NAVS SCT = Northwestern Assessment of Verbs and Sentences-Sentence Comprehension Test (Cho-Reyes & Thompson, 2012; Thompson, 2011), can = canonical sentences percent correct, noncan = noncanonical sentences percent correct; PALPA = Psycholinguistic Assessments of Language Processing in Aphasia (Kay et al., 1992).

WAB = Western Aphasia Battery **(scores out of 10)**: Bedside version, Flu = Spontaneous Speech Fluency, Rep = Repetition, Comp = Auditory Verbal Comprehension, Com = Sequential Commands, Naming = Object naming, BAS: Bedside Aphasia Score; BLS: Bedside Language Score; NT: Test scores not available; Control participants did not complete WAB.

Bedside Language Score (WAB_BLS) was determined by summing the Speech Content, Fluency, Auditory Verbal Comprehension, Sequential Commands, Repetition, Object Naming, Reading, and Writing scores, dividing the sum by 8 and multiplying the result by 10.

Bedside Aphasia Score (WAB_ BAS) was determined by summing the Speech Content, Fluency, Auditory Verbal Comprehension, Sequential Commands, Repetition, and Object Naming scores, dividing the sum by 6 and then multiplying result by 10.

BDAE = Boston Diagnostic Aphasia Examination (Goodglass et al., 2001), Controls did not complete this test.

ABCD = Arizona Battery for Communication Disorders (Bayles & Tomoeda, 1991), Controls did not complete this test.

N/A indicates that the test was not performed. We did not administer WAB, BDAE, and ABCD to controls because these are clinical test batteries developed to assess language deficits in aphasia.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, AK, upon reasonable request.

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