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Slowing is slowing: Delayed neural responses to words are linked to abnormally slow resting state activity in primary progressive aphasia

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ABSTRACT

Neurodegenerative disorders are often characterized by neuronal "slowing," which may be assessed in different ways. In the present study, we examined the latency of neural responses to linguistic stimuli in participants diagnosed with primary progressive aphasia (PPA), as well as changes in the power spectra of resting state activity, both measured with MEG. Compared to both age-matched and younger controls, patients with PPA showed a delayed latency of 8–30 Hz event-related desynchronization (ERD) in response to semantic anomalies. In addition, resting-state MEG revealed increased power in the lower frequency delta and theta bands, but decreased activity in the higher alpha and beta bands. The task-induced and spontaneous measures of neural dynamics were related, such that increased peak latencies in response to words were correlated with a shift of spontaneous oscillatory dynamics towards lower frequencies. In contrast, older controls showed similar task related ERD latencies as younger controls, but also "speeding" of spontaneous activity, i.e. a shift towards faster frequencies. In PPA patients both increased peak latencies on task and increased slow oscillations at rest were associated with less accurate performance on the language task and poorer performance on offline cognitive measures, beyond variance accounted for by structural atrophy. A mediation analysis indicated that increased theta power accounted for the relationship between delayed electrophysiological responses and reduced accuracy in PPA patients. These results indicate that the neuropathological changes in PPA result in slowing of both task-related and spontaneous neuronal activity, linked to functional decline, whereas the speeding of spontaneous activity in healthy aging seems to have a protective or compensatory effect.

1. Introduction

Primary Progressive Aphasia (PPA) is a neurodegenerative disorder characterized by a gradual deterioration of language functions (Mesulam, 2003; Mesulam et al., 2009; Wilson et al., 2012). Depending on the distribution of neurodegeneration, individuals with PPA experience varying degrees of impairments in production, comprehension, syntactic processing, or repetition (Gorno-Tempini et al., 2004, 2011; Mesulam et al., 2009, 2014). Neuropsychological studies indicate that patients with PPA process language differently from neurotypical controls and show altered neural responses to language stimuli (Grossman and Moore, 2005; Peele et al., 2007). Results of word monitoring studies during sentence comprehension indicate that sentence comprehension difficulty in PPA may be due to slowed information processing speed (Grossman et al., 2005). Delayed processing of phonological information during naming has been also observed in both logopenic and agrammatic PPA (Mack et al., 2013).

The high temporal resolution of electrophysiological techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) allows one to directly investigate the latency of neural responses in PPA. Electrophysiological studies indicate that event-related potential (ERP) responses elicited by linguistic stimuli are altered in patients with PPA. For example, Giaquinto and Ranghi (2009) recorded ERPs while participants with PPA performed a word recognition task. They found that the N400 potential, associated with word recognition, was delayed and reduced in amplitude in these patients, and progressively deteriorated until it was no longer present. Similarly, PPA patients showed abnormal N400 effects to unrelated mismatch words in an

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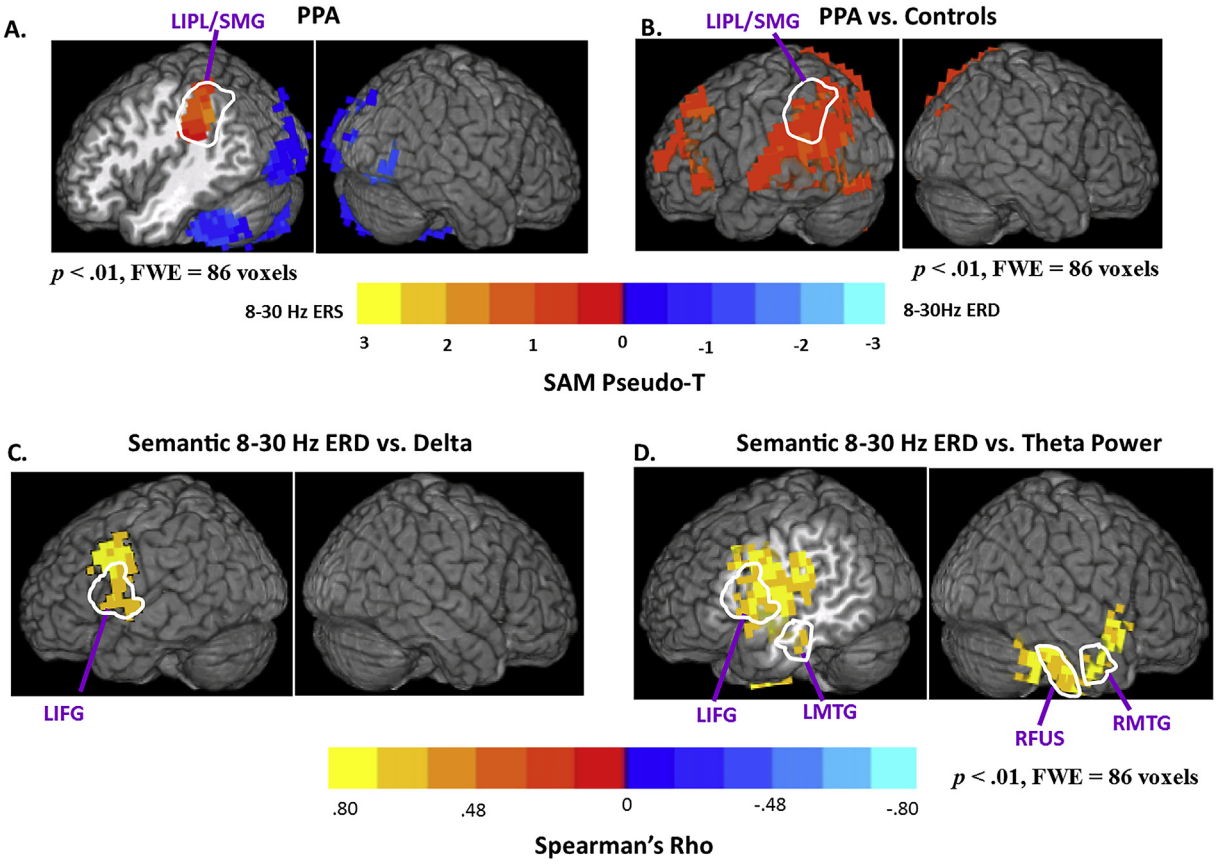

Fig. 1. Synthetic aperture magnetometry (SAM) maps of power changes in the 8–30 Hz frequency range and 0.4-1s time window after critical word onset for healthy age-matched controls and participants with PPA. Statistical maps were thresholded at a minimum cluster-size criterion of 86 voxels and $p < 0.01$. (A) Power changes for semantic anomalies vs. correct words for patients with PPA. (B) **Between-group voxel-wise contrast maps of power changes in the 8–30 Hz frequency range and 0.4–1 s time window after critical word onset.** As ERD is a negative quantity, the activation decreases in patients are reflected by positive values in the subtraction map. Subtraction map for PPA patients minus age-matched controls (AM) on semantic anomalies (semantic anomalies – correct sentences). Statistical maps were thresholded at a minimum cluster-size criterion of 86 voxels and $p < 0.01$. (C) Whole brain correlations (Spearman's Rho) between 8 and 30 Hz ERD for semantic anomalies and relative delta power in patients with PPA. (D) Whole brain correlations (Spearman's Rho) between 8 and 30 Hz ERD for semantic anomalies and relative theta power in PPA. Statistical maps were thresholded at a minimum cluster-size criterion of 86 voxels and $p < 0.01$.

object-word matching ERP task (Hurley et al., 2009).

In a recent MEG study, we examined oscillatory activity during sentence comprehension in patients with PPA and age matched controls (Kielar et al., 2018). The results revealed abnormal language-related oscillatory responses in PPA. The responses were especially altered in left inferior parietal regions outside of the areas most severely affected by structural atrophy. In this region, control subjects exhibited event-related desynchronization (ERD) of 8–30 Hz power while performing a sentence comprehension task (indicating increased neural activation to language), whereas patients with PPA showed instead an event-related synchronization of oscillatory activity (8–30 Hz ERS, indicating decreased activity). The abnormal responses to language stimuli in several regions were characterized by delayed latencies and attenuated amplitude. These results suggest that the sentence comprehension deficits in PPA may be linked to slowed information processing in relatively intact tissue, beyond the regions exhibiting frank atrophy due to neuronal loss.

In addition to language task-induced oscillatory responses, spontaneous patterns of oscillatory cortical activity have also been studied during the resting state. Neural oscillations are frequently divided into named bands including delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (15–30 Hz), and gamma (> 40 Hz). Shifts in the relative power in different bands have been associated with various neurological disorders (Fernández et al., 2013; López et al., 2014). In particular, the presence of increased slow-wave activity is a marker of cortical dysfunction. Shifts to lower frequencies have been observed in Alzheimer's Disease (Park et al., 2007; Poza et al., 2007), MCI (Park et al., 2007), and in stroke (Chu et al., 2015; Kielar et al., 2016a,b). In a recent MEG study, Ranasinghe et al. (2017) examined resting state coherence and spectral power of alpha, beta and delta-theta frequency bands in PPA patients. In comparison to the control group, patients showed hypo-synchrony and reduced power of alpha and beta frequency bands. In contrast, they displayed synchrony and increased power in the delta-theta frequency range. Similarly, we recently examined resting state oscillatory activity in PPA and its relationship with gray matter (GM) volume and cognitive status in multiple domains, including language, memory, and executive function (Shah-Basak et al., 2018). PPA patients exhibited both oscillatory slowing and gray matter reductions. However, oscillatory slowing in PPA predicted cognitive dysfunction beyond that accounted for by GM volumetric reductions. These results indicate that abnormal slowing of resting-state brain oscillations in PPA may reflect incipient neuronal dysfunction in brain tissue that is affected by the disease but has not yet undergone structural degeneration. However, these previous studies did not look directly at the relationship between altered spontaneous oscillatory patterns and induced oscillations associated with language task-related responses.

The primary goal of the present study is to extend our previous finding of abnormal task-related responses in PPA patients and to investigate its relationship with resting-state oscillatory activity and off-line task performance. We hypothesized that abnormal slow-wave activity, present in the cortex of PPA patients at rest, would be associated with the slowing of task-related responses, and could be linked to their

language deficits.

In contrast to the slowing commonly seen in neurodegenerative conditions, neurologically healthy aging is often linked to the opposite pattern, i.e., a shift to higher frequency bands or "speeding" with advanced age in neurologically healthy participants (Hong and Rebec, 2012; Kielar et al., 2016a,b), although activity may again slow down beyond the age of 70 years, indicating a U-shaped trajectory (Gómez et al., 2013; Hashemi et al., 2016). A secondary goal of this study is to examine the relationship between the latency of task-induced oscillatory responses and "speeded" resting-state activity in older controls, and possible links to behavioral variability within healthy older adults. It is uncertain whether age-related speeding represents a pathological process, or instead a compensatory or protective one. Based on our prior findings in the whole-brain analysis, the focus in the current study was on the left frontal, temporal and parietal areas that exhibited abnormal responses to semantically anomalous words in PPA (see Fig. 1A). Specifically, we investigated the peak latencies and oscillatory responses in the left inferior and superior parietal regions, and in the left inferior frontal and middle temporal areas, all of which showed decreased 8–30 Hz ERD (less activity during language task) in PPA compared to controls (see Fig. 1B).

Previous studies report that these areas show a high degree of vulnerability to neurodegenerative changes. In particular, parietal regions experience elevated levels of amyloid deposition, molecular changes and decreased resting state metabolism across major neurodegenerative dementias (Buckner et al., 2009; Greicius et al., 2004; Pievani et al., 2011). The altered electrophysiological signals in the parietal regions may therefore signal early neurodegenerative changes in PPA.

2. Methods

2.1. Participants

Language and resting state data were acquired using MEG from 13 patients with PPA and 15 age-matched healthy controls, along with 11 young controls. This study was approved by the Research Ethics Board at Baycrest Health Sciences, affiliated with the University of Toronto. All volunteers gave their written informed consent prior to the study and were compensated for their participation. Individual patient demographic and clinical characteristics are presented in Table 1.

Participants with PPA were recruited from several sources in Toronto, Ontario and surrounding areas. These included the Memory Clinic at Baycrest Health Sciences, the Aphasia Institute (www.aphasia.ca), and the March of Dimes Aphasia and Communication Disabilities Program (http://www.marchofdimes.ca/EN/programs/acdp/Pages/AphasiaAndCommunicationDisabilitiesProgram.aspx). Patients (7 females) ranged in age from 58 to 83 years (Mean = 69.62, SE = 2.08), and had 12–20 years of education (Mean = 14.38, SE = 0.85). All participants were right handed as measured by the Edinburgh Handedness Inventory (Oldfield, 1971; Williams, 2010). They were all native speakers of English, and had normal hearing and normal or corrected to normal vision. All patients retained sufficient capacity of language comprehension to consent for the study and follow task instructions. Exclusion criteria were earlier neurological diseases, childhood language disorders, head traumas or brain surgery, epilepsy, severe psychiatric disorders, and unstable or poor health. Participants were diagnosed with PPA prior to the study by a speech language pathologist and/or board certified neurologist. PPA diagnosis was based on the convergence of the clinical presentation, narrative speech samples, and the results of standardized tests. A diagnosis of PPA required progressive deterioration of language functions, with the deficit largely restricted to language at the onset and throughout the early stage of the disease (first 2–3 years). All patients in this study were diagnosed with nonfluent/agrammatic or logopenic variants based on recent guidelines (Gorno-Tempini et al., 2011). Seven individuals with effortful, halting speech and/or agrammatic language were classified as nonfluent (nfvPPA), and six patients with impaired word retrieval and phrase/sentence repetition were classified as logopenic (lvPPA). None of the PPA participants were taking cholinesterase inhibitors at the time of the study. One participant was taking memantine.

Participants with PPA were matched with a group of healthy older controls (OC) for age, $F < 1$. All healthy volunteers were recruited from the greater Toronto area by REB approved advertisements from the University of Toronto community and from the Baycrest Health Sciences subject pool. All of the heathy volunteers (age-matched: 4 females, age: Mean = 69, SE = 1.77, education: Mean = 17.46, SE = 0.69; young controls (YC): 4 females, age: Mean 23.18, SE = 0.74, education: Mean = 16.36, SE = 0.61) were right handed native speakers of English, and reported normal hearing and normal or corrected-to-normal vision. Participants had no history of neurological, psychiatric, speech, language, or learning disorders and none were taking neuroleptic or mood altering medications at the time of the study. Age-matched controls participated in all behavioral and neuroimaging assessments completed by the PPA patients, while younger controls did not undergo neuropsychological testing beyond the MEG experiment. All older control participants tested within normal limits on all cognitive and linguistic tests. The language test scores for PPA patients and age matched controls are shown in Table 2.

Table 1
Demographic and clinical characteristics for individual PPA patients, age-matched control (OC) and young control (YC) means.

	PPA Type	Gender	Age (years)	Education (years)	time post onset (years)	MoCA
PPA1	nfv	male	74	12	3	25
PPA2	nfv	male	58	17	3	19
PPA3	nfv	female	75	20	3	14
PPA4	lv	male	60	20	3	14
PPA5	nfv	female	75	12	4	22
PPA6	lv	female	83	16	2	12
PPA7	nfv	male	71	12	1	21
PPA8	lv	female	61	12	2	26
PPA9	nfv	male	69	15	2	23
PPA10	lv	female	68	15	3	25
PPA11	lv	female	63	12	2	26
PPA12	nfv	male	70	12	3	23
PPA13	lv	female	78	12	2	7
PPA	Mean(*SE*)		69.62(*2.08*)	14.38(*0.85*)	2.54(*0.22*)	19.77(*1.69*)
OC	Mean(*SE*)		69(*1.77*)	17.46(*0.69*)	N/A	27(*0.45*)
YC	Mean(*SE*)		23.18(0.74)	16.36(0.61)	N/A	NT

MoCA: Montreal Cognitive Assessment (Nasreddine et al., 2005). Measured out of 30 points; Values from 30 to 26 points indicate normal performance; nfv = nonfluent variant PPA; lv = logopenic variant PPA; NT: Test scores not available.

Table 2
Language test scores for individual patients with PPA and control group (OC) means.

	subtype	BNT	Letter fluency	SPPT	SCT	PPVT	APB word	APB sent	WAB Flu	WAB Rep	WAB Comp	WAB BAS
Max score		*60*	*Scaled scores*	*100%*	*100%*	*Scaled scores*	*100%*	*100*	*10*	*10*	*10*	*100%*
PPA1	nfv	57	5	87	100	103	98	100	NT	NT	NT	NT
PPA2	nfv	23	5	NT	50	78	NT	NT	NT	NT	NT	NT
PPA3	nfv	53	4	NT	87	105	45	67	NT	NT	NT	NT
PPA4	lv	27	2	23	80	96	29	33	5	7	9	58
PPA5	nfv	49	5	83	100	95	91	83	9	9	10	95
PPA6	lv	8	6	97	63	84	95	83	9	9	9	73
PPA7	nfv	54	2	100	100	108	95	83	9	10	10	91
PPA8	lv	40	4	90	100	79	97	100	9	9	10	94
PPA9	nfv	46	6	NT	60	87	66	NT	4	4	9	68
PPA10	lv	51	3	90	100	96	83	50	9	9	9	85
PPA11	lv	40	8	97	100	89	95	83	9	9	10	93
PPA12	nfv	39	1	73	83	92	84	67	4	9	10	77
PPA13	lv	31	3	33	70	90	82	50	6	7	9	73
PPA Mean		40	4	77	84	92	80	73	7	8	8	81
SE		*3.8*	*0.5*	*7.5*	*5.0*	*2.6*	*6.2*	*5.94*	*0.6*	*0.5*	*0.7*	*3.6*
NF PPA (n = 7)												
Mean		46	4	86	83	95	80	67	7	8	10	83
SE		*4.4*	*0.7*	*4.1*	*7.7*	*4.1*	*7.9*	*13.2*	*1.1*	*0.9*	*0.2*	*4.8*
logo PPA (n = 6)												
Mean		33	4	72	86	89	80	67	8	8	9	79
SE		*6.02*	*0.91*	*13.8*	*6.8*	*2.7*	*10.6*	*10.5*	*0.7*	*0.5*	*0.2*	*5.7*
OC Mean		57	14	99.56	100	119	99	100	N/A	N/A	N/A	N/A
SE		*0.6*	*0.9*	*0.3*	*0*	*3.1*	*0.3*	*0*	*N/A*	*N/A*	*N/A*	*N/A*

Explanation of Abbreviations: nfv = nonfluent variant PPA; lv = logopenic variant PPA; BNT = Boston Naming Test (score out of 60); Letter fluency: FAS (D-KEFS, scaled scores); SPPT = Northwestern Assessment of Verbs and Sentences Sentence Production Priming Test. NAVS_SCT = Northwestern Assessment of Verbs and Sentences-Sentence Comprehension Test, total: overall score on all sentence types; PPVT = Peabody Picture Vocabulary Test; APB word: Aphasia Bank repetition words; APB sent: Aphasia Bank repetition sentences; WAB = Western Aphasia Battery: Bedside version, Flu = Spontaneous Speech Fluency, Comp = Auditory Verbal Comprehension, Rep = Repetition; BAS: Bedside Aphasia Score; BLS: Bedside Language Score; NT: Test scores not available.
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.

2.2. Cognitive and language assessment

Prior to participation in the MEG experiment, patients and age-matched controls completed a thorough neuropsychological battery assessing various domains of cognition, including language, memory, executive function (EF), and visuospatial abilities. General cognitive status was measured using the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) and the scores for patients and controls are presented in Table 1. Tests of language function included the Western Aphasia Battery Revised (WAB, Bedside Record Form, Kertesz, 1982; 2007). WAB is a test that targets language deficits in aphasic disorders. It was administered only to patients with PPA because extensive norming studies have established that controls perform at ceiling on this test. The other tests have a more variable range of performance and were also administered to age-matched controls. We decided to add the WAB to the study to further characterize aphasic deficits in PPA compared to stroke after the first three patients had already been studied; as such, not all patients have scores on this. The lvPPA and nfvPPA subtypes did not differ significantly on the measures of repetition (WAB repetition, Aphasia Bank repetition of words (APB words) and sentences (APB sentences), *Fs* < 1). However, both PPA subtypes scored significantly lower than age-matched controls (APB words: nfvPPA vs. OC, $F(1, 19) = 13.14$, $p = 0.002$; lvPPA vs. OC: $F(1, 19) = 8.27$, $p = 0.01$; APB sentences: nfvPPA vs. OC, $F(1, 19) = 14.81$, $p = 0.001$; lvPPA vs. OC: $F(1, 19) = 27.14$, $p = 0.00005$). Mean scores and standard errors for patients and controls on selected measures are presented in Table 2. The test battery has been described in detail in Kielar et al. (2018).

2.3. Sentence comprehension task

All participants completed a visual sentence-judgement task during MEG acquisition. Detailed description of the sentence materials and procedure can be found in our previous papers reporting results from young healthy controls and patients with post-stroke aphasia (Kielar et al., 2015, 2016b). In this paper, we focus on the latency results related to processing semantically anomalous words.

2.4. MRI scans acquisition and processing

MRI data were always acquired after the MEG session, either the same day or up to two weeks after. Structural MRI scans were acquired on a 3-T scanner (Siemens TIM Trio) with an MPRAGE sequence (1 mm isotropic voxels, TR = 2000 ms, TE = 2.63 ms, FOV = 256 × 256mm, 160 axial slices, scan time = 6 min, 26s). The structural image was used to construct a head model for MEG source modeling. MR-visible markers were placed at the fiducial points for accurate coregistration of MEG and MRI data, aided by digital photographs from the MEG session. T1 images were skull stripped in AFNI software (Cox, 1996).

2.4.1. Voxel-based morphometry

Voxel-based Morphometry (VBM) implemented in SPM12 (Wellcome Department of Cognitive Neurology, London, UK), was used to derive segmented, spatially normalized, bias corrected, and smoothed GM maps for participants in all groups (Ashburner and Friston, 2005). Before processing, T1 images were evaluated for quality and manually repositioned to set the anterior commissure as the origin to ensure consistent starting estimates for the unified segmentation routine. To increase the accuracy of inter-participant alignment, non-linear deformation toolbox (Ashburner, 2007). For each participant, flow fields were calculated during template creation that contained the nonlinear deformation information on the native image transformation to the template. These flow fields were applied to each participant's

image. Next, the final template was registered to MNI space using an affine transform and this transformation was incorporated into the warping process, so that the individual spatially normalized scans could be brought into the common MNI space. During this final normalization step, the gray and white matter probability maps were scaled by their Jacobian determinants and smoothed using a 10 mm FWHM isotopic Gaussian kernel. The GM volumes were downsampled to match the resolution of the MEG power maps for the ROI analyses with latency and resting state oscillations. To increase the accuracy of inter-participant alignment, nonlinear deformation parameters were calculated with the high dimensional diffeomorphic anatomical registration through exponentiated lie (DARTEL) algorithm and the predefined templates within the SPM DARTEL. To identify cortical atrophy at the group level, the images for the PPA patients were compared with age matched controls using an independent sample *t*-test, with age, sex, and total intracranial volume included as covariates.

2.5. Task-related MEG analysis

2.5.1. Behavioral results: sentence comprehension performance

The accuracy and reaction times for patients and controls are presented in Table 3. The behavioral results and within and between groups statistical tests are discussed in detail in Kielar et al. (2018). Because the overall error rate on the sentence comprehension task could be influenced by participants' response bias, we calculated d'-prime, to estimate individual participants' ability to discriminate targets (anomalous sentences) from non-targets (correct sentences). We used d'-prime values for behavioral analyses, and to examine correlations between task performance, 8–30 Hz ERD, and resting state measures.

2.5.2. Time-frequency analysis on virtual channels

For initial characterization of the time-frequency dynamics induced by the paradigm in the three participant groups, we analyzed activity in 90 virtual channels placed in *a priori* locations throughout the brain, as reported in Kielar et al. (2015). Using the macroanatomical brain parcellation of Tzourio-Mazoyer et al. (2002), consisting of 90 cortical and subcortical regions (e.g., left supramarginal gyrus, left putamen, etc.), we took the centre of each region and warped it into the coordinate space of each subject's MEG data.

We conducted time-frequency analysis on these virtual channels in source space, computing virtual signals as a product of beamforming weights and the sensor data. The beamforming weights for virtual channels were computed with Synthetic Aperture Magnetometry (SAM), using the MRI-derived head model and the data covariance matrix in a broad time-frequency window (bandwidth 0–100 Hz, time −1 to +4 s) for the final word for semantic anomalies and the corresponding control condition. This allowed us to identify time periods and frequency ranges that were maximally responsive to the contrasts of interest.

Table 3
Mean percent accuracy (standard error of the mean) and reaction time in milliseconds (standard error of the mean) on the sentence comprehension task for young controls (YC, n = 11) age-matched control group (OC, n = 15), and PPA patients (n = 13, logopenic and nonfluent variants combined).

Group	Condition	Accuracy%(SE)	RT(SE)	*d'*
YC	COR	93.45(1.5)	477.03(33.31)	
	SEM	96.36(0.92)	467.54(33.56)	3.50(0.13)
OC	COR	93.24(1.24)	688.61(51.56)	
	SEM	96.80(0.70)	643.27(51.80)	3.50(0.15)
PPA	COR	77.35(3.23)	979.86(80.62)	
	SEM	81.75(6.24)	933.22(67.01)	1.98(0.29)

d' statistic: accuracy corrected for response bias. Higher value indicates better sensitivity to discriminate violations from correct sentences.
COR: correct sentences; SEM: semantic anomalies.

We performed time-frequency analysis on the virtual channel signals using EEGLAB software (version 9.0.4.5) running in the Matlab 2010 (v 7.6) environment. Single-trial epochs were analyzed using a moving window short-time Fourier transform with 200 overlapping time windows per trial. The length of the time window in the spectrogram analysis was 0.512 s (320 samples at a sampling rate of 625 Hz). Values at each time-frequency point were averaged over trials of each specific condition. The average log-power in the baseline period for both word conditions was used as a common baseline, subtracted from log-power at each time-frequency point, yielding the measure conventionally known as "event-related spectral perturbation," or ERSP (Makeig, 1993). This procedure ensured that the same baseline power values were used across all conditions; thus, any differences between conditions could not be attributable to differences in the baseline. Analysis of source space virtual channels is an alternative to analyzing the raw sensor data, with the additional advantage of artifact reduction. The initial stage of virtual channel analysis served to identify the time and frequency windows in which oscillatory reactivity occurred for patients and control groups (see results).

2.6. Resting MEG data acquisition and analysis

Spontaneous brain activity was recorded while participants looked at a white fixation cross presented in the centre of the screen on a black background. During the recording participants were asked to relax and to minimize head and body movements. Resting-state MEG data were collected for 5 min. The resting state MEG recording was divided into arbitrary 2.5-s epochs for analysis and averaging.

For the resting-state analysis, we computed beamforming weights on a whole-brain grid of locations spaced 10 mm apart. These weights were then multiplied with the original sensor time series data to yield a new, spatially filtered, time series signal at each voxel ($10\,mm^3$). Normalized weights were used to render virtual signals in dimensionless units of signal-to-noise ratio, with noise power estimated as the lowest singular value of the sensor covariance matrix (Vrba and Robinson, 2001). Signals were filtered at 0–100 Hz prior to beamforming. Raw MEG sensor signals were screened for artifacts, and epochs containing obvious signal disruptions were rejected ($< 1\%$ of all epochs). Power spectral densities of the voxel-wise virtual signals were computed using the multitaper method in MATLAB (Thomson, 1982).

To evaluate quantitative parameters related to slowing of spontaneous activity, we computed measures of relative power from the resulting power spectra. Relative power of the delta (1–4 Hz), theta (5–7 Hz), alpha (8–12 Hz) and beta (15–30 Hz) frequency bands were calculated as the ratio of the power of each specific frequency band divided by the total power across 0–80 Hz. Computing relative power over the frequency spectrum avoids potential confounds introduced by the normalized beamformer weights (Luckhoo et al., 2014) and effectively bases the analysis on spectral shape rather than levels of absolute power.

2.7. Derivation of latency and spectral power in regions of interests

To investigate the relationship between peak latency values and resting state measures quantitatively, we computed peak latencies of 8–30 Hz ERD from time-courses of virtual channels from 0.1 to 2.5 s post-stimulus onset. The latency of responses at specific channels was measured using the publicly available PeakFinder Toolbox in Matlab (https://terpconnect.umd.edu/~toh/spectrum/PeakFindingandMeasurement.htm). The relative power in delta, theta, alpha, and beta frequency ranges were extracted from ROIs centred around the virtual channels, with a 5 mm radius and averages were computed across voxels within each ROI. The peak latencies and resting-state values were extracted in the same way for each participant, separately for correct words and semantic anomalies. GM volumes were also extracted from each ROI in the same way. The ROIs were the

left inferior parietal cortex, including left inferior parietal lobule (LIPL, x = −43, y = −51, z = 50), left supramarginal gyrus (LSMG, x = −56, y = −39, z = 34), and left precuneus (x = −7, y = −61, z = 52), the left middle temporal (LMTG, x = −53, y = −25, z = −11) and the left inferior frontal gyri (LIFG, x = −45, y = 24, z = 18). The LIPL and LSMG showed the strongest event-related synchronization of oscillatory activity (8–30 Hz ERS, indicating abnormal responses) to semantic anomalies vs. control sentences within PPA (Fig. 1A). There areas also showed the strongest difference from age-matched controls (Fig. 1B). In addition, we investigated responses in the right middle temporal gyrus (RMTG, x = 60, y = −6, z = −20) and right fusiform gyrus (RFUS, x = 34 y = −44, z = −16), as these regions showed significant correlations between ERD responses and resting state power in the whole-brain voxel-wise correlation analysis (Fig. 1 D).

2.8. Statistical analysis

To examine the relationship between MEG activation to semantic anomalies (reflected by amplitude of 8–30 Hz ERD) and resting state oscillatory measures, we performed whole-brain voxelwise rank-order correlations (Spearman's Rho) for PPA patients and controls. To correct for multiple comparisons across the whole brain, resulting statistical maps were subjected to voxel-wise thresholding and a minimum cluster-size criterion of 86 voxels, resulting in a cluster-wise corrected family-wise error (FEW) rate of $p < 0.05$. The cluster size criterion was determined by Monte Carlo simulations conducted in the AFNI program 3dClustSim, with a voxel-wise threshold of $p < 0.01$. The group differences in peak latencies and resting state delta, theta, alpha and beta relative power for PPA patients, age-matched and younger controls were investigated using one-way ANOVAs applied to data extracted from ROIs. The relationship between peak latencies of 8–30 Hz responses and resting-state MEG measures for PPA and controls were investigated using Spearman's rank-order correlations. In addition, we investigated the 3-way relationships between peak latencies, resting-state measures and task performance. In the cases where there was a significant relationship between task performance and both peak latencies and relative power we employed step wise regression to investigate the contributions of each measure to behavioral performance. To account for effects of atrophy, gray matter (GM) volume was included in the model. The dependent variable was task accuracy and the independent variables were relative resting state oscillatory power, latency and GM volume. For the cases in which task performance was significantly predicted by both peak latencies (task-related responses) and relative power (resting state oscillations), we employed mediation analyses to evaluate which electrophysiological measure was more directly related to the observed variability in task performance.

3. Results

3.1. Gray matter volumes in PPA patients in comparison to healthy controls

The statistical maps comparing GM volumes in PPA patients versus the age-matched control group are shown in Kielar et al. (2018) Fig. 3G. The maps were corrected for multiple comparisons by controlling the FWE at the cluster level $p < 0.05$ and voxelwise level $p < 0.001$ (Hayasaka and Nichols, 2004; Woo et al., 2014). Patients showed areas of reduced gray matter within the left hemisphere perisylvian language network, affecting inferior frontal gyrus (BA 45/44) and middle frontal areas (BA 46, 8 and 6). The areas of reduced GM volume extended into the left middle and superior temporal gyri (BA 21 and 22) and posterior inferior temporal gyrus (BA 20), including fusiform gyrus (BA 37).

3.2. Whole-brain voxelwise correlations between 8 and 30 Hz ERD language responses and resting state oscillatory activity

The correlation maps showing a significant relationship between 8 and 30 Hz ERD for semantic anomalies and resting state oscillations are presented in Fig. 1 C and D. For PPA patients, the analysis revealed significant correlations between 8 and 30 Hz ERD and delta power in the left precentral and inferior frontal gyrus (LIFG, BA 44/45), indicating that reduced ERD is associated with increased delta power (because ERD is a negative quantity, a reduced ERD linked to increased delta power comes out as a positive correlation). There were also significant correlations between 8 and 30 Hz ERD and theta power in the left precentral gyrus, left inferior frontal gyrus (LIFG, BA 44/45) and left middle temporal gyrus (LMTG, BA 21/22). In the right hemisphere, significant correlations between 8 and 30 Hz ERD and theta power were found in the middle temporal gyrus (RMTG) and extended into the fusiform gyrus (RFUS). For all of these correlations, reduced ERD was associated with greater spontaneous power in slow frequency bands. There were no significant correlations between 8 and 30 Hz ERD and alpha or beta power.

3.3. Time-frequency results

The inspection of time-frequency results revealed that compared to age-matched controls, responses for PPA patients were attenuated and had a later onset (Fig. 2 A). For age-matched and younger controls, we observed strong oscillatory responses for semantic anomalies compared to their corresponding correct words (Fig. 2 B and C), reflected in power decrease (ERD) in the 8–30 Hz range, with an onset around 0.4 s and extending in time past 1 s. In contrast, ERD responses for semantic anomalies in the PPA group were observed from about 8 to 30 Hz with an onset around 1 s and lasting until about 3 s.

3.4. Group differences in peak latencies of 8–30 Hz responses

Fig. 2 D-G illustrate the differences in 8–30 Hz ERD peak latencies between patients with PPA and age-matched controls in the left inferior parietal lobule (LIPL) and supramarginal gyrus (LSMG), LMTG and LIFG (BA45). The results by the PPA subtype (nonfluent and logopenic) are shown in Supplementary materials (Fig. S1). No significant differences between the two subtypes were observed.

The analysis revealed that compared to age-matched controls, patients showed significantly delayed peak latencies of 8–30 Hz ERD responses in the LIPL (sentences with semantic anomalies, $F(1, 26) = 23.301$, $p = 0.000053$; correct sentences, $F(1, 26) = 9.497$, $p = 0.005$) and LSMG, (sentences with semantic anomalies, $F(1, 26) = 11.33$, $p = 0.002$; correct sentences, $F(1, 26) = 8.317$, $p = 0.008$). In the left precuneus latencies were significantly delayed for correct sentences ($F(1, 26) = 5.22$, $p = 0.031$), but not for semantic anomalies ($F(1,26) = 3.47$, $p = 0.074$). In addition, patients with PPA showed significantly delayed peak latencies of 8–30 Hz ERD responses in the LMTG (sentences with semantic anomalies, $F(1, 26) = 5.58$, $p = 0.026$; correct sentences, $F(1, 26) = 6.17$, $p = 0.02$), and LIFG BA45 (sentences with semantic anomalies, $F(1, 26) = 14.26$, $p = 0.003$; correct sentences, $F(1, 26) = 11.26$, $p = 0.002$). In the RMTG latencies were significantly delayed for semantic anomalies, $F(1, 26) = 4.85$, $p = 0.037$, but not for correct sentences, $F(1, 26) = 2.173$, $p = 0.151$). There were no significant latency differences between patients and controls in the RFUS (semantic anomalies, $F(1, 26) = 1.79$, $p = 0.193$; correct sentences, $F > 1$).

The 8–30 Hz ERD latencies were also significantly slower in PPA compared to the young controls in LIPL (semantic anomaly, $F(1, 22) = 19.479$, $p = 0.00022$; correct, $F(1, 23) = 11.377$, $p = 0.003$), LSMG (semantic anomaly, $F(1, 26) = 14.30$, $p = 0.001$; correct, $F(1, 26) = 5.926$, $p = 0.023$), LMTG (semantic anomaly, $F(1, 26) = 6.189$, $p = 0.021$; correct, $F(1, 26) = 9.65$, $p = 0.005$), and LIFG (semantic

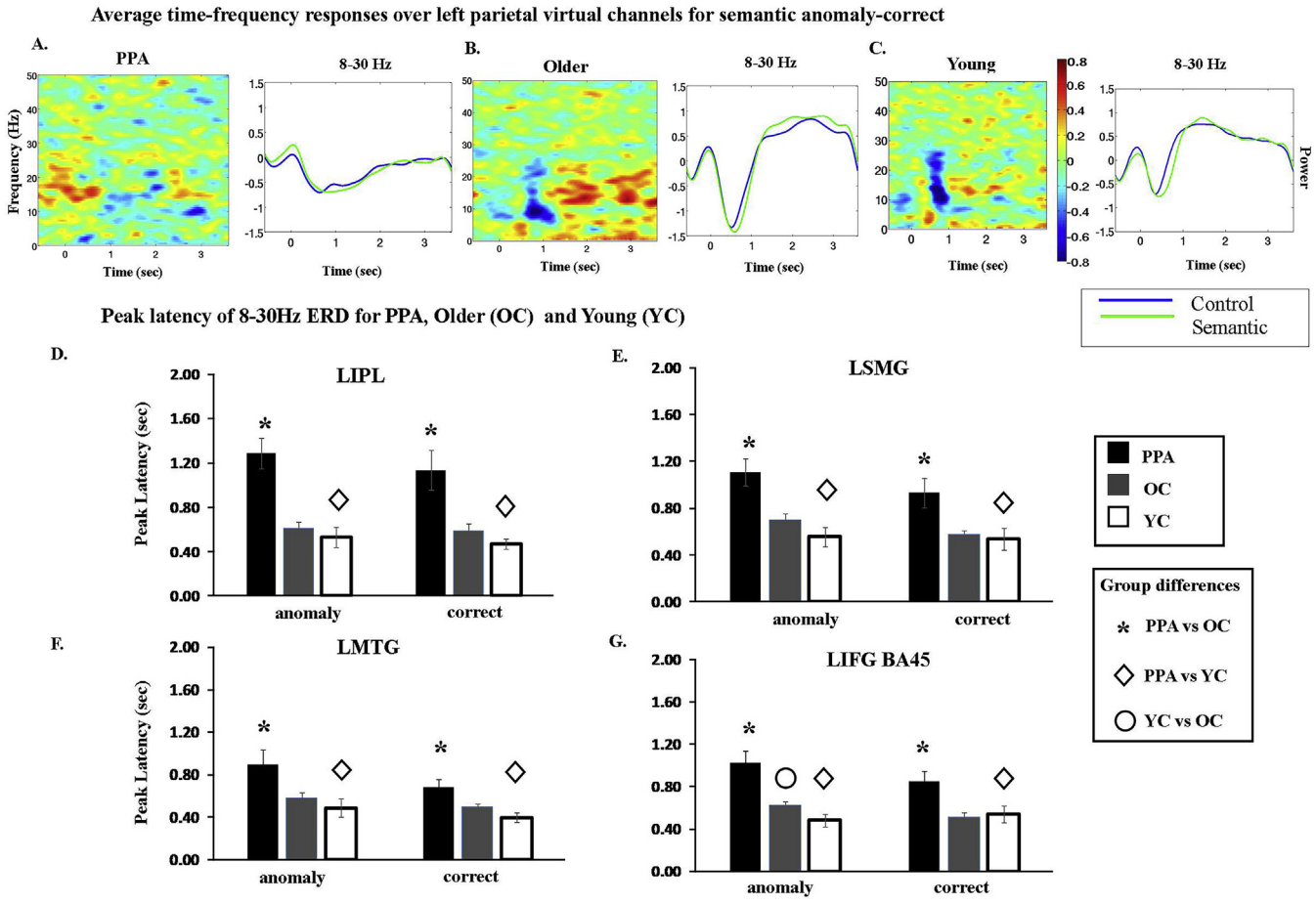

Fig. 2. Time-frequency dynamics of SAM virtual signals averaged across left hemisphere parietal cortical channels. (A) patients with PPA (B) Older Age Matched controls and (C) young controls. Time-frequency plots showing subtraction of semantic violation – correct words and average time course of power in the 8–30 Hz band, for semantic violation and correct conditions. (D) Bar graph showing peak latencies of 8–30 Hz ERD responses to semantic anomalies and correct sentences at the left inferior parietal channel (LIPL) for patients with PPA, age-matched older controls (OC), and young controls (YC). (E) Bar graph showing peak latencies of 8–30 Hz ERD responses to semantic anomalies and correct sentences at the left supramarginal (LSMG) channel for PPA patients, age-matched older controls (OC), and young controls (YC). (F) Bar graph showing peak latencies of 8–30 Hz ERD responses to semantic anomalies and correct sentences at the left middle temporal channel (LMTG) for PPA patients, age-matched older controls (OC), and young controls (YC). (G) Bar graph showing peak latencies of 8–30 Hz ERD responses to semantic anomalies and correct sentences at the left inferior frontal channel (LIFG) for patients with PPA, age-matched older controls (OC), and young controls (YC). Symbols indicate statistically significant between group differences.

anomaly, $F(1, 26) = 18.05$, $p = 0.0003$; correct sentences, $F(1, 26) = 6.10$, $p = 0.002$). There were no significant differences in the left precuneus (semantic anomaly, $F(1, 26) = 1.962$, $p = 0.175$; correct, $F < 1$), or in the RMTG, RFUS, all $Fs > 1$.

For age-matched controls compared to young controls, we found significantly longer peak latencies on semantic anomalies in the LIFG BA45 ($F(1, 26) = 5.256$, $p = 0.031$), but not correct sentences, $F < 1$. There was no significant difference in the latency of 8–30 Hz responses between older and younger controls in other regions (LIPL: semantic anomaly, $F < 1$; correct, $F(1, 24) = 1.932$, $p = 0.177$; LSMG: semantic anomaly, $F(1, 24) = 2.21$, $p = 0.150$; correct, $F < 1$; left precuneus: semantic anomaly, $F < 1$, correct, $F(1,26) = 2.14$, $p = 0.156$; LMTG: semantic anomaly, $F(1, 26) = 1.097$, $p = 0.305$; correct, $F(1, 26) = 4.131$, $p = 0.053$; RMTG: correct, anomaly $F < 1$; RFUS: correct, anomaly, $F < 1$).

3.5. Group differences in resting measures

Fig. 3 shows differences in the resting state measures for patients and controls. The results for the PPA subtypes (nonfluent and logopenic) are shown in Supplementary materials (Fig. S2). No significant differences between the two subtypes were observed.

The analysis revealed that compared to the age-matched controls, PPA patients showed significantly increased resting-state delta power in the LIPL, $F(1, 26) = 9.48$, $p = 0.005$, LSMG, $F(1, 26) = 10.57$, $p = 0.003$, left precuneus, $F(1, 26) = 9.17$, $p = 0.005$; LMTG, $F(1, 26) = 11.22$, $p = 0.002$, LIFG, $F(1, 26) = 7.77$, $p = 0.01$, RMTG, $F(1, 26) = 15.48$, $p = 0.001$, and RFUS, $F(1, 26) = 17.37$, $p = 0.0003$. Theta power was significantly increased for individuals with PPA in the LIPL, $F(1, 26) = 5.51$, $p = 0.027$, LSMG, $F(1, 26) = 7.49$, $p = 0.011$, left precuneus, $F(1, 26) = 5.04$, p = 0.033; LMTG, $F(1, 26) = 4.57$, $p = 0.042$, $p = 0.027$, and LIFG, $F(1, 26) = 4.38$, $p = 0.046$.

Alpha power was significantly decreased in PPA relative to the age-matched controls in the LIPL, $F(1, 26) = 8.247$, $p = 0.008$, LSMG, $F(1, 26) = 13.17$, $p = 0.001$, left precuneus, $F(1, 26) = 5.707$, $p = 0.024$, LMTG, $F(1, 26) = 29.19$, $p = 0.000$, LIFG (BA45), $F(1, 26) = 5.09$, $p = 0.033$, RMTG, $F(1, 26) = 11.81$, $p = 0.002$, and RFUS, $F(1, 26) = 5,52$, $p = 0.027$. In addition, patients showed significantly decreased beta power in the LIFG, $F(1, 26) = 8.94$, $p = 0.006$. There were no significant differences in the resting relative power between PPA patients and younger controls (all $ps > .20$).

Differences between older and younger controls tended to go in the opposite direction from the differences between patients and age-matched controls (i.e. younger controls were more similar to PPA patients).

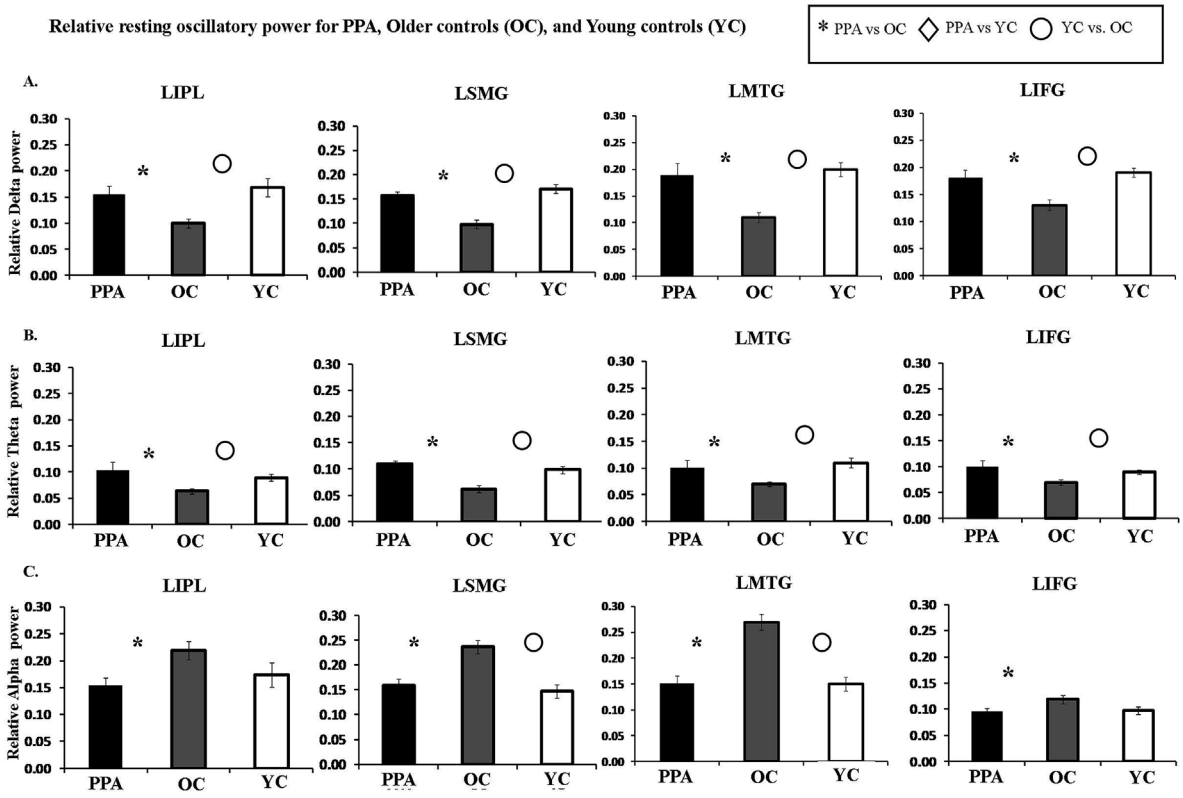

Fig. 3. Relative spontaneous oscillatory power for PPA, Older controls (OC), and Young controls (YC) at LIPL, LSMG, LMTG, and LIFG channels. (A) Bar graphs show group differences in the relative delta power. (B) Bar graphs show group differences in the relative theta power. (C) Bar graphs show group differences in relative alpha power.

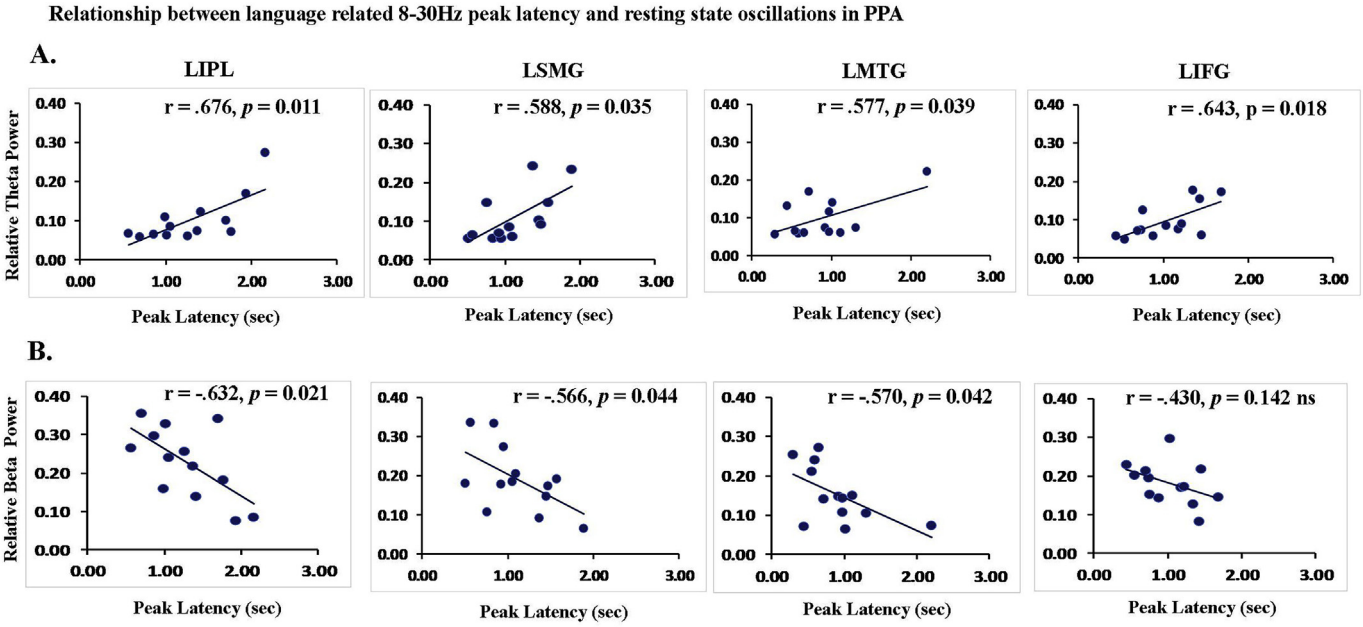

Fig. 4. (A) Scatter plots showing relationship between the latency of 8–30 Hz ERD responses to the language task and resting state relative theta power in PPA patients in LIPL, LSMG, LMTG, and LIFG. (B) Scatter plots showing relationship between the latency of 8–30 Hz ERD responses to language task and resting state relative beta power in PPA patients in LIPL, LSMG, LMTG, and LIFG.

In comparison to the younger group, older controls showed *decreased* delta power in the LIPL, $F(1, 24) = 15.10$, $p = 0.001$, LSMG $F(1, 24) = 23.586$, $p < 0.00006$, left precuneus, $F(1, 26) = 8.835$, $p = 0.007$, LMTG, $F(1, 24) = 31.21$, $p = 0.00001$, LIFG, $F(1, 24) = 17.72$, $p = 0.0003$, RMTG, $F(1, 24) = 26.796$, $p = 0.00003$; and RFUS, $F(1, 24) = 33.642$, $p = 0.000006$. The older controls also exhibited *decreased* theta power (LIPL, $F(1, 24) = 10.93$, $p = 0.003$, LSMG, $F(1, 24) = 26.72$, $p < 0.00003$, left precuneus, $F(1, 26) = 4.15$, $p = 0.05$, LMTG, $F(1, 24) = 20.59$, $p < 0.0001$, LIFG, $F(1, 24) = 11.025$, $p = 0.003$; RMTG, $F(1, 24) = 21.978$, $p < 0.00009$;

RFUS, $F(1, 24) = 10.55$, $p < 0.003$). In contrast to young adults, older adults showed i*ncreased* alpha and beta power (alpha power: LSMG, $F(1, 24) = 18.31$, $p = 0.0002$, LMTG, $F(1, 24) = 35.03$, $p < 0.0000004$, RMTG, $F(1, 24) = 17.25$, $p < 0.0004$, RFUS, $F(1, 24) = 5.984$, $p < 0.022$; beta power, LIPL, $F(1, 24) = 6.10$, $p = 0.021$, LSMG, $F(1, 24) = 4.306$, $p = 0.049$). The differences were not significant for alpha in LIFG, $F(1, 26) = 3.54$, $p = 0.072$, left precuneus, $F(1, 26) = 1.089$, $p = 0.307$, and LIPL, $F(1, 26) = 2.55$, $p = 0.124$, and for beta in LIFG, $F(1,26) = 3.35$, $p = 0.08$, left precuneus, $F(1, 26) = 2.557$, $p = 0.123$, and LMTG, $F(1,26) = 1.15$, $p = 0.294$. There were no significant differences between older and younger adults for beta power in RMTG, $F < 1$ or RFUS, $F < 1$.

In summary, patients with PPA exhibited widespread slowing of spontaneous activity compared to older (age-matched) controls, with a shift towards delta and theta power and away from alpha and beta power. But compared to younger controls, PPA patients exhibited largely similar resting state power, because they failed to exhibit the normal "speeding" of spontaneous power present in healthy aging, i.e. a shift away from delta and theta towards alpha and beta, present in the healthy older control group. This pattern underscores the necessity of considering the normal course of aging when comparing PPA patients to either older or younger healthy controls.

3.6. Relationship between peak latency of 8–30 Hz responses and resting measures for PPA and controls

Fig. 4 shows the relationship between latency of 8–30 Hz responses for semantic anomalies and resting state measures for PPA patients in the LIPL, LMTG, and LIFG regions. The correlation coefficients and *p*-values are shown in Table 4 A. There was a positive relationship between theta power and peak latencies for semantic anomalies in the LIPL, $r_s(13) = 0.676$, $p = 0.011$ and LSMG, $r_s(13) = 0.588$, $p = 0.035$, the LMTG, $r_s(13) = 0.577$, $p = 0.039$ and LIFG (BA45), $r_s(13) = 0.643$, $p = 0.018$ (Fig. 4 A). There was a significant negative relationship between beta power and peak latencies for semantic anomalies, in the LIPL $r_s(13) = -0.632$, $p = 0.021$, LSMG, $r_s(13) = -0.566$, $p = 0.044$, and LMTG, $r_s(13) = -0.570$, $p = 0.042$ (Fig. 4B). These results indicate that increased theta power and decreased beta power (both aspects of slowed spontaneous activity) are associated with longer latencies for 8–30 Hz ERD responses. No significant correlation was found between beta power and latencies in the LIFG and the left precuneus (*ps* > .05). In the RMTG a significant positive relationship was found between delta power and peak latencies $r_s(13) = 0.764$, $p = 0.002$, theta power and peak latencies, $r_s(13) = 0.687$, $p = 0.009$, and a negative relationship between beta power and peak latencies, $r_s(13) = -0.802$, $p = 0.001$. There were no significant correlations in the RFUS ROI (all *ps* > .05).

Similarly, for correct sentences, increased latencies were positively correlated with theta power in LIPL $r_s(13) = 0.795$, $p = 0.001$ and left precuneus $r_s(13) = 0.600$, $p = 0.03$. There was also a significant negative correlation between latency and beta power, in LIPL, $r_s(13) = -0.558$, $p = 0.047$ and left precuneus $r_s(13) = -0.669$, $p = 0.012$. There were no significant correlations for correct sentences with other frequency bands and regions (all *ps* > .05). Table 4 also shows relationships between gray matter (GM) volume and resting measures. For PPA patients, there was a significant negative relationship between decreased GM volume and increased delta and theta power in the LSMG, indicating that reduced gray matter volume is associated with more oscillatory slowing. On the other hand, there was a positive relationship between resting beta power and GM volume in LSMG and left precuneus, again suggesting that faster spontaneous oscillations are linked to better brain preservation. There were no significant relationships between GM volume and peak latencies. The correlation coefficients and p values for these comparisons are shown in the supplementary results Table S1.

The same analysis was conducted for age-matched controls and young controls. The correlation coefficients and *p*-values are shown in Table 4 B. Older controls showed a *negative relationship* between beta power and latencies in RMTG, $r_s(15) = -0.744$, $p = 0.001$ (Fig. 5A), RFUS, $r_s(15) = -0.754$, $p = 0.001$ (Fig. 5B), and LIFG (BA 45) $r_s(15) = -0.600$, $p = 0.018$ (Fig. 5C), indicating that increased resting beta power is associated with shorter task-related latencies. In contrast to what we observed in patients, longer latencies of 8–30 Hz responses to semantic anomalies in the age matched controls were associated with *increased* alpha power in the LMTG, $r_s(15) = 0.631$, $p = 0.012$ (Fig. 5D), left precuneus $r_s(15) = 0.528$, $p = 0.043$, LIFG (BA45), $r_s(15) = 0.548$, $p = 0.034$ (Fig. 5E), RMTG, $r_s(15) = 0.545$, $p = 0.036$, and RFUS, $r_s(15) = 0.720$, $p = 0.002$. Older adults also showed a significant negative correlation between 8 and 30 Hz ERD latencies to semantic anomalies and delta power in LMTG, $r_s(15) = -0.548$, $p = 0.035$, indicating that longer latencies were associated with less delta power (Fig. 5F). Unlike patients, the correlations with theta power were not significant in age-matched controls (all *ps* > .16).

The analysis for correct sentences in the age-matched controls revealed *a negative* relationship between 8 and 30 Hz ERD peak latencies and beta power in LMTG, $r_s(15) = -0.567$, $p = 0.027$, RMTG, $r_s(15) = -0.555$, $p = 0.032$ and RFUS, $r_s(15) = -0.571$, $p = 0.026$. In the right FUS there was *a negative* relationship between relative delta power and peak latencies, $r_s(15) = -0.597$, $p = 0.019$. There was also a positive *relationship* between alpha power and latencies in the left precuneus, $r_s(15) = 0.548$, $p = 0.03$, and RMTG, $r_s(15) = 0.591$, $p = 0.02$. There were no significant correlations for correct sentences with other frequency bands and regions (all *ps* > .20). There were no significant relationships between GM volume and resting state power in older controls (Table 4B). There was a significant negative correlation between peak latency for control sentences and GM volume in only one region, the LIFG, $r_s(15) = -0.668$, p = 0.006 (Supplementary Table S1).

For young controls, increased peak latencies for correct sentences were associated with larger theta power in LSMG, $r_s(11) = 0.633$, $p = 0.036$, and increased delta power in the RMTG, $r_s(11) = 0.635$, $p = 0.036$. There were no significant correlations for correct sentences or semantic anomalies with any other frequency bands in any region (all *ps* > .18). The overall pattern of results in older controls was different from PPA. Older controls showed an increase in faster frequencies and a decrease in slower frequencies. However as in PPA, increased resting beta power was associated with shorter task-related latencies for older controls.

3.7. Relationships of peak latencies and resting measures to task performance

To investigate whether increased latencies were associated with sentence comprehension performance we performed Spearman's rank order correlations between 8 and 30 Hz peak latency values and accuracy (d'-prime) on semantic anomalies. For PPA patients there was a negative relationship in the LIPL between d'-prime values and 8–30 Hz ERD peak latency values for semantic anomalies, $r_s(13) = -0.560$, $p = 0.046$, and correct sentences, $r_s(13) = -713$, $p = 0.006$. There were no significant correlations in other regions (semantic: LSMG $r_s(13) = -0.357$, $p = 0.231$; left precuneus, $(13) = -0.131$, $p = 0.671$; LMTG $r_s(13) = -0.022$, $p = 0.943$; LIFG $r_s(13) = -0.495$, $p = 0.08$; RMTG $r_s(13) = -0.176$, $p = 0.566$; RFUS $r_s(13) = 0.412$, $p = 0.162$; correct: LSMG: semantic, $r_s(13) = -0.198$, $p = 0.516$, left precuneus, $(13) = -0.257$, $p = 0.397$; LMTG $r_s(13) = -0.452$, $p = 0.121$, LIFG $r_s(13) = -0.470$, $p = 0.105$, RMTG $r_s(13) = 0.008$, $p = 0.979$; RFUS $r_s(13) = 0.175$, $p = 0.569$). The correlations were not significant for age-matched controls, or young adults at any of the regions of interest either for semantic anomalies or correct sentences (all *ps* > .05).

We also investigated whether resting state measures are associated with sentence comprehension accuracy on semantic anomalies (d'-values). For patients with PPA, increased theta power was associated with lower accuracy in the LIPL ($r(13) = -0.842$, $p = 0.00031$), LSMG, (r_s

Table 4
Relationship between task-related 8–30 Hz peak latency, GM volume, resting delta, theta, alpha and beta power (Spearman's rank-order correlations and p-values) for patients with PPA (n = 13) and age-matched controls (OC, n = 15).

		delta		theta		alpha		beta	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
A. PPA									
LIPL	latency control	0.338	0.258	**0.795****	**0.001**	0.336	0.262	**−0.558***	**0.047**
	latency anomaly	0.33	0.271	**0.676***	**0.011**	0.352	0.239	**−0.632***	**0.021**
	GM	−0.301	0.342	**−0.650***	**0.022**	−0.154	0.633	0.329	0.297
LSMG	latency control	0.129	0.673	0.424	0.149	0.361	0.226	−0.317	0.292
	latency anomaly	0.258	0.394	**0.588***	**0.035**	0.396	0.181	**−0.566***	**0.040**
	GM	**−0.712****	**0.009**	**−0.592***	**0.033**	0.220	0.492	**0.755****	**0.005**
LMTG	latency control	0.179	0.558	0.504	0.079	0.116	0.707	−496	0.085
	latency anomaly	0.322	0.284	**0.577***	**0.039**	−0.102	0.741	**−0.57***	**0.040**
	GM	0.085	0.795	−0.329	0.297	−0.168	0.602	0.105	0.746
LIFG	latency control	0.286	0.343	*0.525*	*0.065*	0.314	0.297	−0.248	0.415
	latency anomaly	0.412	0.162	**0.643***	**0.018**	0.093	0.762	−0.43	0.142
	GM	−0.350	0.266	0.112	0.729	−0.189	0.557	0.105	0.746
Lprec	latency control	0.239	0.431	**0.600***	**0.03**	0.047	0.879	**−0.669***	**0.012**
	latency anomaly	0.292	0.334	0.215	0.481	0.006	0.986	−0.264	0.383
	GM	−0.462	0.131	−0.448	0.145	−0.126	0.697	**.594***	**0.042**
RMTG	latency control	−0.091	0.767	0.091	0.767	0.465	0.11	−0.207	0.496
	latency anomaly	**0.764****	**0.002**	**0.687****	**0.009**	−0.176	0.566	**−0.802****	**0.001**
	GM	−0.217	0.499	−0.545	0.067	−0.203	0.527	**0.615***	**0.033**
RFUS	latency control	0.042	0.893	−0.075	0.808	0.346	0.246	−0.058	0.850
	latency anomaly	−0.047	0.879	−0.072	0.815	0.479	0.098	0.042	0.893
	GM	−0.336	0.286	0.007	0.983	−0.091	0.779	0.042	0.897
B. OC									
LIPL	latency control	−0.417	0.122	−0.347	0.206	0.375	0.168	−0.096	0.734
	latency anomaly	−0.186	0.508	−0.168	0.550	0.268	0.334	−0.296	0.283
	GM	−0.200	0.475	0.121	0.666	0.225	0.420	0.193	0.491
LSMG	latency control	0.300	0.278	0.233	0.403	0.163	0.561	−0.400	0.140
	latency anomaly	0.271	0.329	0.111	0.693	0.108	0.703	−0.463	0.082
	GM	.421	.118	−0.021	.940	-.343	.211	.182	.516
LMTG	latency control	−0.152	0.589	−0.069	0.808	0.372	0.172	**−0.567***	**0.027**
	latency anomaly	**−0.548***	**0.035**	−0.36	0.187	**0.631***	**0.012**	−0.263	0.343
	GM	−0.207	0.459	0.157	0.576	0.043	0.879	−0.046	0.869
LIFG	latency control	−0.057	0.840	0.002	0.995	−0.155	0.580	−0.318	0.248
	latency anomaly	0.222	0.426	0.038	0.894	**0.548***	**0.034**	**−0.600***	**0.018**
	GM	0.018	0.950	0.032	0.909	0.171	0.541	0.246	0.376
Lprec	latency control	−0.423	0.116	−0.108	0.703	**0.548***	**0.034**	−0.133	0.638
	latency anomaly	−0.349	0.203	−0.135	0.632	**0.528***	**0.043**	−0.343	0.210
	GM	0.057	.840	0.446	0.095	−0.157	0.576	0.182	0.516
RMTG	latency control	−0.482	0.069	−0.327	0.234	**0.591***	**0.020**	**−0.555***	**0.032**
	latency anomaly	0.038	0.894	0.050	0.859	**0.545***	**0.036**	**−0.744****	**0.001**
	GM	0.214	0.443	0.082	00.771	0.200	0.475	−0.064	0.820
RFUS	latency control	**−0.597***	**0.019**	0.129	0.646	0.314	0.254	**−0.571***	**0.026**
	latency anomaly	−0.276	0.318	0.047	0.869	**0.720****	**0.002**	**−0.754****	**0.001**
	GM	0.286	0.302	0.464	0.081	−0.032	0.909	0.068	0.810

*correlation significant at $p < 0.05$.
**correlations significant at $p < 0.01$.
LIPL: left inferior parietal lobule; LSMG: left supramarginal gyrus, LMTG: left middle temporal gyrus; LIFG: left inferior frontal gyrs, Lprec: left precuneus, RMTG: right middle temporal gyrus, RFUS: right precuneus.

(13) = −0.599, $p = 0.031$), RMTG (r_s (13) = −0.852, $p = 0.0002$), RFUS (r_s (13) = −0.818, $p = 0.001$), left precuneus (r_s (13) = −0.845, $p = 0.0002$), and in LIFG, (r_s (13) = −0.747, $p = 0.003$). More accurate task performance was associated with increased beta power in the LIPL r_s (13) = 0.609, $p = 0.027$ and RMTG, r_s (13) = 0.562, $p = 0.045$. In addition, for age-matched controls better task accuracy was associated with increased beta power in the LIPL, r_s (15) = 0.563, $p = 0.029$ and left precuneus, r_s (15) = 0.515, $p = 0.049$. The correlations were not significant for age-matched controls at any of the other regions of interest (all *ps* > .05). There were no significant correlations between accuracy and resting state measures for young controls (all *ps* > .05).

Together, these results suggest that in the PPA patients, longer peak latencies of 8–30 Hz ERD responses and increased theta power in LIPL are associated with impaired performance on the sentence comprehension task. For age-matched controls, better task accuracy was associated with increased resting beta power.

3.8. Multiway relationships of delayed latencies, task-related oscillatory slowing, gray matter atrophy, and task accuracy

The pairwise correlations presented above indicated that resting-state oscillatory slowing (more theta, less beta power) was associated with prolonged latencies of task-related electrophysiological responses in PPA patients, and that both of these measures were related to some extent to task accuracy. Furthermore, resting state oscillatory activity was related to gray matter atrophy in some regions. To clarify the relative contributions of these various aspects of disease-related pathology, we performed a series of step-wise regressions. To test whether the observed electrophysiological abnormalities could explain more variance than that accounted for by cortical atrophy alone, we included the GM volume of each ROI in the models.

In the first set of analyses, the dependent variable in the regression model was peak latency and the independent variables were resting state relative power (theta, beta), and GM volumes. After accounting for

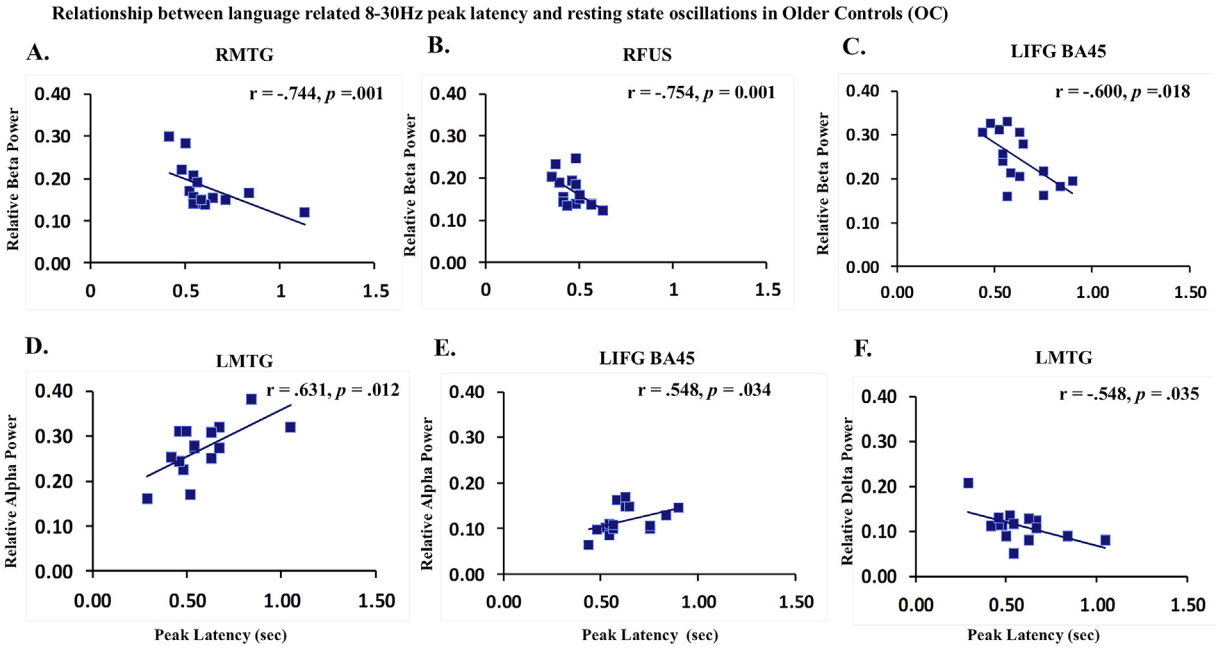

Fig. 5. (A) Scatter plots showing relationship between the latency of 8–30 Hz ERD responses to the language task and resting state relative beta power in older controls in the RMTG, (B) RFUS, and (C) LIFG. (D) Scatter plots showing relationship between the latency of 8–30 Hz ERD responses to language task and resting state relative alpha power in older controls in the LMTG and (E) LIFG. (F) Scatter plots showing relationship between the latency of 8–30 Hz ERD responses to language task and resting state relative delta power in older controls in the LMTG.

GM volume, the theta power predicted ERD peak latency in the LIPL (b = 6.39, $p = 0.001$), LSMG (b = 4.150, $p = 0.021$), LMTG (b = 5.658, $p = 0.039$), and LIFG (b = 5.538, $p = 0.018$). Beta power was a significant predictor of ERD peak latencies only in the RMTG (b = −4.89, $p = 0.002$). GM volumes did not improve model fit in any of the ROIs. These results suggest that resting state theta and beta power predicted task-related latencies in PPA, beyond the contribution of GM atrophy alone.

In the next stage, we investigated the contribution of peak latencies, and oscillatory slowing to task accuracy in PPA. The dependent variable in the regression model was task accuracy (d'-prime), and the independent variables were peak latency and resting state relative power (theta, beta). The gray matter (GM) volume was included as a covariate in the analyses to account for possible contributions of cortical atrophy to impaired sentence comprehension. The *beta* and *p* values for dependent and independent variables are shown in Supplementary Table S2.

After accounting for GM volume, theta power predicted task accuracy in the LIPL (b = −14.305, $p = 0.001$), indicating that increased resting theta power is related to lower accuracy on the sentence comprehension task. In the LSMG both theta (b = −20.91, $p = 0.00002$), and beta (b = 8.388, $p = 0.013$) predicted task performance, indicating that increased theta predicts worse performance and increased beta predicts more accurate task performance. Resting theta power was a significant predictor of task accuracy in the LMTG (b = −14.829, $p = 0.005$), LIFG (b = −16.198, $p = 0.007$), left precuneus (b = −19.347, $p = 0.001$), RMTG (b = −16.405, $p = 0.0003$), and RFUS (b = −18.410, $p = 0.001$). Neither beta power nor GM volume contributed to task performance in these regions.

3.9. Mediating effect of resting state oscillations

Together, these results suggest that for the PPA patients, longer peak latencies of 8–30 Hz ERD responses and increased theta power in LIPL are associated with impaired performance on the sentence comprehension task. To understand the directionality of this relationship, we performed mediation analysis to investigate whether spontaneous oscillatory "slowing" (reflected by increased theta power) mediates impaired task performance by delaying processing during the task (reflected by 8–30 Hz ERD latencies). Regression analysis was used to investigate the hypothesis that theta mediates the effect of latency on accuracy. The model is summarized in Fig. 6. The results indicated that 8–30 Hz ERD latencies were by themselves a significant predictor of theta power, $b = 0.901$, $SE = 0.025$, $p = 0.005$. This establishes link between the independent variable and the mediator and indicates that increased resting-state theta power is linked to delayed neural responses during the task. Theta power was also a significant predictor of task accuracy, $b = -14.748$, $SE = 4.32$, $p = 0.007$, establishing link between increased resting theta oscillations and decreased task performance. In isolation, increased ERD latencies also predicted lower task accuracy, $b = -1.302$, $SE = 0.51$, $p = 0.03$. However, 8–30 Hz ERD latencies no longer predicted task accuracy after controlling for theta power, $b = 0.027$, $SE = 0.53$, $p = 0.960$. These results indicate that increases in resting theta power contribute to both increased ERD latencies and lower task accuracy. On its own latency is associated with accuracy, however the increase in theta power seems to be mediating this relationship. For completeness we also investigated an alternative model with latency as a mediator. Again, theta power was a significant predictor of latency and accuracy but there was no evidence that latency mediated this relationship. The details are in the supplementary results and the model is presented in Fig. S3.

3.10. Relationship between peak latencies and resting measures to offline cognitive performance

Our results indicate that increased resting state theta power and decreased beta power were associated with delayed task-related latencies in PPA and less accurate task performance. To investigate the clinical significance of the variability in peak latencies and resting state oscillations, we computed correlations between the MoCA score, selected language measures, task-related latency, beta and theta power at each ROI. The relationship with gray matter volume was also evaluated. The results for PPA patients are shown in Table 5A. In several ROIs, the MoCA scores were negatively correlated with both peak latencies and

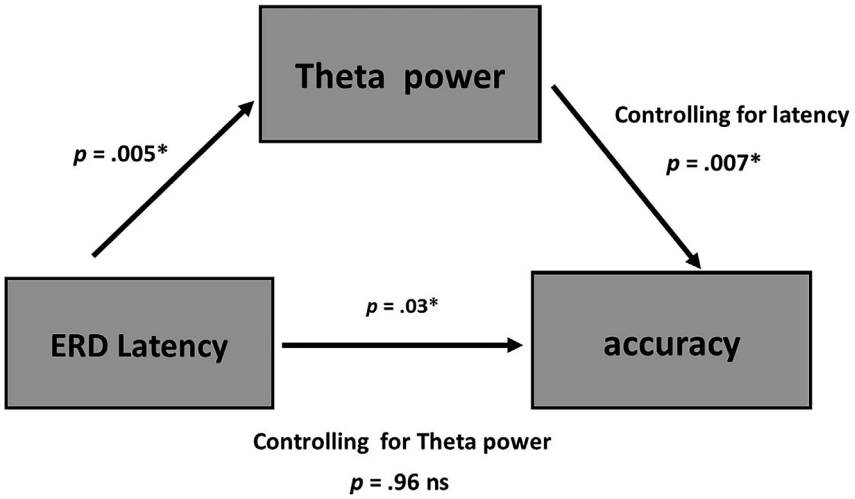

Fig. 6. A schematic depiction of the relationship among elements in the mediation model with ERD latency as a predictor, task accuracy (d-prime) as outcome and theta power as a mediator. Resting theta power mediated the relationship between ERD latency and task accuracy.

theta power. Similar negative correlations were found for language measures with these two electrophysiological measures. These results indicate that increased latencies and resting theta power are linked to worse language scores and worse overall cognitive performance in PPA. In contrast, there was a significant positive relationship of resting-state beta power with language measures and MoCA scores, suggesting that beta power is linked to better performance. In addition, there was a significant positive relationship between GM volume and MoCA scores in LIPL, LSMG, and left precuneus, indicting (as expected) that gray matter atrophy in PPA is related to worse cognitive status.

The pattern of results in our older control group was different from PPA patients. We found speeding of electrophysiological activity in older adults. However, similar to PPA we found that in our older group increased resting beta power was associated with shorter task-related peak latencies and more accurate task performance. We computed correlations to investigate the relationships of task-related peak latencies and theta and beta power to cognitive performance (see Table 5B). Correlations with language measures were not informative because controls scored at ceiling on these tests. For control participants, we found a significant negative relationship for MoCA scores with latencies and theta power, and a positive relationship between MoCA scores and beta power. Together, these results indicate that in both PPA and healthy older adults, increased resting beta power is associated with higher cognitive status. For older controls there was no significant relationship between GM volume and MoCA scores.

4. Discussion

In primary progressive aphasia, neurodegeneration of the left hemisphere language regions manifests as a progressive impairment in language comprehension and production. Major neurodegenerative disorders are often associated with altered amplitude and latency of electrophysiological responses during cognitive tasks. In addition, neuropathological changes are frequently accompanied by altered spectral composition of spontaneous electrophysiological signals, e.g. slowing of resting brain oscillations. This spectral slowing is characterized by enhanced power in low-frequency bands including the delta and theta frequency bands, with a decrease in the higher-frequency alpha and beta bands (López et al., 2014; Stoffers et al., 2007; Stomrud et al., 2010). In patients with dementia, this abnormally elevated low-frequency activity predicts the degree of cognitive impairment (Shah-Basak et al., 2018) and indexes transition from mild to severe stages of the disease (Fernández et al., 2013). An important question that arises is the nature of the relationship between task-related electrophysiological responses and resting oscillatory activity in patients with neurodegenerative disease. Do delayed latency responses and increased “slow waves” reflect a common mechanism of slowed neuronal activity? Another question is the degree to which abnormal task-related responses and resting state oscillations contribute to language performance. In this context, it is also important to characterize task related and resting state oscillatory patterns in healthy aging and their relationship to behavioral performance, to better understand the specific impact of pathological processes in dementia.

In the present study, we investigated the temporal dynamics of oscillatory activity both during a language task and at rest using MEG in patients with PPA and healthy controls (both older and younger controls). MEG is an electrophysiological technique that can directly measure altered task-related temporal dynamics and resting-state oscillations in specific areas. We therefore examined MEG data to characterize the relationship between task related and spontaneous oscillatory patterns in PPA, and compared it with relationships present in healthy aging. We also investigated the consequences of altered oscillatory activity during task and rest for performance on a sentence comprehension task.

Compared to both young and older controls, PPA patients exhibited significantly delayed peak latencies of 8–30 Hz language related responses. In addition, patients with PPA showed significantly increased resting delta and theta power, accompanied by decreases in alpha and beta power. Critically, delayed peak latencies of language related responses (8–30 Hz ERD) in PPA were associated with slowing of spontaneous neural oscillations (increased theta power and attenuated beta power). Together with the previous findings of altered task-related responses (Kielar et al., 2018), the present results indicate that neuropathological changes in PPA patients result in slowed neuronal dynamics both at rest and during a language task. This effect was in the opposite direction in faster frequency ranges, such that delayed latencies of 8–30 Hz ERD responses were associated with a decrease in relative beta power. Furthermore, spectral slowing observed at rest and delayed peak latencies during the task were associated with reduced accuracy on the sentence comprehension task. In contrast, better task accuracy was associated with enhanced beta power. In addition, increased 8–30 Hz ERD latencies and resting state oscillatory slowing were associated with more severe cognitive deficits (lower MoCA scores), impaired language performance on the WAB, and reduced repetition scores. These results suggest that variability in latencies and resting state oscillations can be of clinical significance in PPA, and possibly in other neurodegenerative conditions as well.

The results of step-wise regressions indicated that abnormally

Table 5
Relationship between 8 and 30 Hz peak latency, resting theta and beta power, gray matter volumes (GM), and MoCA scores and selected language measures (Spearman's rank-order correlations and p-values) for patients (PPA, n = 13) and older controls (OC, n = 15).

A. PPA										B. OC
ROI		MoCA (n = 13)	WAB FLU (n = 10)	WAB REP (n = 10)	WAB BAS (n = 10)	WAB BLS (n = 10)	letter fluency (n = 13)	APB sent (n = 13)	APB words (n = 13)	MoCA (n = 15)
LIPL	latency control									
	r	**−0.645***	−0.591	−0.454	**−0.760***	**−0.720***	−0.309	**−0.588***	**-.621***	−0.164
	p	**0.017**	0.072	0.188	**0.011**	**0.029**	0.305	**0.044**	**0.031**	0.558
	latency anomaly									
	r	−0.406	**−0.802***	−0.485	**−0.636***	−0.633	−0.528	**−0.705***	**-.711***	−0.129
	p	0.169	**0.005**	0.155	**0.048**	0.067	0.063	**0.010**	**0.009**	0.648
	theta									
	r	**-.641***	−0.514	−0.381	−0.733	**-.767***	−0.36	−0.351	−0.465	**−0.520***
	p	**.018***	0.128	0.277	0.016	**.016**	0.227	0.264	0.128	**0.047**
	beta									
	r	**.608***	0.185	0.071	0.467	0.500	**.722****	0.19	0.38	0.344
	p	**.028**	0.609	0.845	0.174	0.17	**0.005**	0.555	0.223	0.209
	GM									
	r	**.622***	.129	.200	.133	.310	.511	.477	.456	.255
	p	**.031**	.741	.606	.732	.456	.089	.138	.156	.359
LSMG	latency control									
	r	−0.443	−0.445	−0.293	**-.646***	**-.756***	−0.233	−0.151	0.014	−0.350
	p	0.129	0.198	0.412	**0.043**	**0.018**	0.444	0.64	0.965	0.201
	latency anomaly									
	r	−0.467	−0.165	−0.149	−0.406	−0.467	−0.163	−0.344	−0.345	−0.421
	p	0.108	0.65	0.682	0.244	0.205	0.594	0.274	0.272	0.119
	theta									
	r	**-.591***	−0.596	−0.537	**-.867****	**-.817****	−0.354	−0.54	**-.585***	−0.475
	p	**0.033**	0.069	0.11	**0.001**	**0.007**	0.235	0.070	**.046**	0.074
	beta									
	r	**.666***	0.35	0.187	0.624	**0.667***	**0.672***	0.236	0.408	**0.663****
	p	**0.013**	0.322	0.604	0.054	**0.050**	**0.012**	0.460	0.187	**0.007**
	GM									
	r	**.594***	.020	-.026	-.067	-.048	**.804****	.079	.312	.208
	p	**.042**	.960	.947	.865	.911	**.002**	.816	.350	.456
LMTG	latency control									
	r	**-.608***	−0.158	0.162	−0.182	−0.276	−0.241	−0.063	−0.078	−0.421
	p	**.027**	0.663	0.655	0.614	0.472	0.427	0.846	0.81	0.118
	latency anomaly									
	r	−0.331	−0.041	0.266	0.03	0.042	−0.443	0.208	0.152	0.115
	p	0.27	0.91	0.458	0.934	0.915	0.129	0.517	0.638	0.682
	theta									
	r	**-.638***	−0.535	−0.627	**-.818****	**-.917****	−0.351	**-.630***	**-.627***	−0.291
	p	**.019**	0.111	0.052	**0.004**	**0.001**	0.239	**0.028**	**0.029**	0.292
	beta									
	r	**.655***	0.446	0.317	**0.758***	**0.717***	**.562***	0.429	0.549	**0.590***
	p	**.015**	0.197	0.372	**.011**	**.030**	**.046**	0.164	0.064	**0.021**
	GM									
	r	.439	**.782***	**.731***	**.700***	**.905****	-.123	.323	.211	.300
	p	.153	**.013**	**.025**	**.036**	**.002**	.702	.333	.533	.278
LIFG	Latency control									
	r	**-.643***	−0.315	−0.304	**-.709***	**-.800***	**-.600***	**-.630***	−0.556	−0.482
	p	**.018**	0.375	0.393	**.022**	**.010**	**.030**	**.028**	0.06	0.069
	latency anomaly									
	r	−0.46	−0.452	−0.213	−0.576	−0.60	−0.321	−0.308	−0.317	**-.613***
	p	0.114	0.189	0.554	0.082	0.088	0.285	0.33	0.316	**0.015**
	theta									
	r	−0.494	**-.816****	**-.653***	**-.818****	**-.800***	−0.271	**-.734****	**-.690***	−0.053
	p	0.086	**.004**	**.041**	**.004**	**.010**	0.370	**.007**	**.013**	0.852
	beta									
	r	0.149	0.541	0.459	0.285	0.367	0.335	0.34	0.472	**0.573***
	p	0.627	0.106	0.182	0.425	0.332	0.264	0.28	0.121	**0.026**
	GM									
	r	.197	-.069	-.017	.133	.381	.533	.435	.519	.463
	p	.540	.859	.965	.732	.352	.075	.181	.101	.082

(*continued on next page*)

Table 5 (*continued*)

A. PPA										B. OC
ROI		MoCA (n = 13)	WAB FLU (n = 10)	WAB REP (n = 10)	WAB BAS (n = 10)	WAB BLS (n = 10)	letter fluency (n = 13)	APB sent (n = 13)	APB words (n = 13)	MoCA (n = 15)
Lprec	latency control									
	r	−0.548	−0.351	−0.006	−0.486	−0.519	−0.197	0.117	0.109	0.112
	p	0.053	0.321	0.986	0.154	0.152	0.52	0.718	0.735	0.690
	latency anomaly									
	r	−0.241	−0.076	0.201	0.34	0.151	−0.546	−0.149	−0.24	−0.265
	p	0.428	0.836	0.578	0.336	0.699	0.054	0.644	0.453	0.340
	theta									
	r	**−0.745***	−0.432	−0.42	**-.636***	**−0.727***	−0.227	−0.319	−0.416	−0.158
	p	**0.003**	0.213	0.227	**.048**	**0.026**	0.456	0.313	0.179	0.573
	beta									
	r	**0.637***	0.206	0.239	0.624	0.617	0.484	0.276	0.331	**0.681****
	p	**0.019**	0.569	0.506	0.054	0.077	0.094	0.386	0.293	**0.005**
	GM									
	r	**0.626***	−0.050	0.044	0.350	0.405	**0.621***	0.351	0.550	0.378
	p	**0.030**	0.899	0.911	0.356	0.320	**0.031**	0.290	0.079	0.165
RMTG	latency control									
	r	−0.42	−0.065	0.324	−0.055	−0.192	**-.560***	−0.179	−0.036	−0.121
	p	0.153	0.858	0.361	0.881	0.62	**.047**	0.578	0.913	0.666
	latency anomaly									
	r	−0.519	−0.103	−0.032	−0.309	−0.333	**-.708***	−0.032	−0.155	−0.359
	p	0.069	0.777	0.929	0.385	0.381	**.007**	0.921	0.631	0.189
	theta									
	r	**-.608***	**-.761***	−0.537	**-.782****	**-.850***	−0.418	**-.590***	**-.676***	−0.204
	p	**.028**	**.011**	0.11	**.008**	**.004**	0.156	**.043**	**.016**	0.465
	beta									
	r	**0.724****	0.432	0.265	**0.733***	**0.733***	**0.586***	0.351	0.437	**0.59***
	p	**0.005**	0.213	0.459	**0.016**	**0.025**	**0.035**	0.264	0.156	**0.021**
	GM									
	r	.309	.604	**.705***	**.800****	**.905****	.511	.505	.459	.479
	p	.328	.085	**.034**	**.010**	**.002**	.089	.133	.156	.071
RFUS	latency control									
	r	−0.305	0.017	0.611	0.037	−0.119	−0.452	0.079	0.139	**−0.591***
	p	0.311	0.962	0.061	0.919	0.761	0.121	0.806	0.668	**0.020**
	latency anomaly									
	r	0.208	0.121	0.566	0.232	0.101	−0.272	0.315	0.432	−0.366
	p	0.496	0.74	0.088	0.519	0.796	0.369	0.319	0.161	0.180
	theta									
	r	**-.704****	−0.617	−0.472	**-.721***	**−0.783***	−0.313	−0.455	−0.542	−0.163
	p	**.007**	0.057	0.168	**.019**	**0.013**	0.298	0.138	0.069	0.563
	beta									
	r	**0.702****	0.432	0.226	**0.685***	**0.683***	**0.606***	0.326	0.43	**0.636****
	p	**0.008**	0.213	0.53	**0.029**	**0.042**	**0.028**	0.302	0.163	**0.011**
	GM									
	r	.137	**-.772***	-.548	-.317	-.310	.282	−0.098	.064	.446
	p	.671	**.015**	.126	.406	.456	.374	.775	.851	.096

*correlation significant at $p < 0.05$.
**correlations significant at $p < 0.01$.
MoCA: Montreal Cognitive Assessment (Nasreddine et al., 2005); WAB = Western Aphasia Battery: Bedside version, Flu = Spontaneous Speech Fluency; Rep = Repetition; BAS: Bedside Aphasia Score; BLS: Bedside Language Score; Letter fluency: FAS (D-KEFS, scaled scores); APB_sent: Aphasia Bank Sentence Repetition; APB_words: Aphasia Bank word repetition.
LIPL: left inferior parietal lobule; LSMG: left supramarginal gyrus, LMTG: left middle temporal gyrus; LIFG: left inferior frontal gyrs, Lprec: left precuneus, RMTG: right middle temporal gyrus, RFUS: right precuneus.

increased spontaneous theta power in PPA impaired task performance and delayed latencies of neuronal responses during the sentence comprehension task. More importantly, this relationship between latency and slowing was observed beyond the effect of gray matter atrophy alone. These results indicate that physiological abnormalities can signal incipient neuronal dysfunction before atrophy takes place. Mediation analysis revealed that although increased latency is associated with lower sentence comprehension accuracy, it is the increased resting theta power that is mediating this relationship. Overall the results indicate that resting state abnormalities are a main contributor both to slowing of task-related electrophysiological responses and to impaired sentence comprehension performance in PPA. To our knowledge, this is the first study to investigate the relationship between altered task-related and resting state oscillatory activity in PPA, and the relationship of both to the degree of language impairment.

The association between enhanced slow wave spectral activity and cognitive impairment has been widely studied in dementia and pathological aging (Bonanni et al., 2012; Fernández et al., 2013; Stoffers et al., 2007; Stomrud et al., 2010). It has been suggested that the increase in delta and theta power accompanied by the parallel reduction

in alpha power may be indicative of neurological disorders (Klimesch, 1999; Rossini et al., 2007). Neurodegenerative changes lead to profound alterations in the structure and chemistry of brain tissue, including neuronal cell loss, disruption of synaptic transmission, and white mater disconnection (Gloor et al., 1977; Hansen et al., 1988). Previous reports suggest that the potential sources of increased delta activity are deafferentation resulting from the loss of pyramidal neurons and white matter lesions (Fanciullacci et al., 2017; John and Prichep, 2006). Another strong candidate is loss of cholinergic inputs. Changes in EEG and MEG delta power have been associated with reduced cholinergic transmission (Jeong, 2004; Osipova et al., 2003). Consistent with this, animal EEG data indicate that decreased acetylcholine concentration leads to spectral slowing of brain oscillations (Villa et al., 2000). Attenuated high frequency cortical rhythms have been associated with decreased MMSE scores in MCI and AD patients (López et al., 2014; Stam et al., 2006), and patients with Alzheimer's disease show significant relationships between increased delta power and cholinergic concentration in CSF (Riekkinen et al., 1990). Our findings are consistent with this and indicate that increased theta and attenuated beta are associated with lower cognitive status and impaired language performance. In sum, the converging evidence suggests that reduced cholinergic input alters the composition of neural oscillations reflected as slowing of the cortical rhythms. It is possible that a similar mechanism plays a role in pathological slowing in PPA, particularly in the logopenic subtype which exhibits similar neuropathology as Alzheimer's disease. However, we did not observe any significant differences in resting state activity between nonfluent and logopenic subtypes in this study, suggesting that specific cholinergic dysfunction may not be required for pathological slowing to be present.

In light of previous reports of increased delta and theta power mediated by cholinergic deficits, our findings of a link between elevated spontaneous slow frequency power and delayed task-related latencies that we found in this study likely indicates dysfunctional synaptic transmission in PPA. We posit that neurodegenerative events in PPA lead to increased latencies of neuronal responses/brain activation and reduced cognitive processing speed, underpinning the observed impaired sentence comprehension performance in our patients. Consistent with this view, our results indicate that increased theta power in PPA impairs language processing and increases latencies of neuronal responses. We observed that this relationship was the strongest in the left parietal regions. The resting state oscillatory slowing predicted abnormal task-related latency responses independently of GM atrophy, indicating that these abnormal physiological responses can occur before frank structural atrophy takes place.

Healthy controls exhibited a very different pattern of responses. There were no significant differences between older controls and young controls in the peak latency of language-related responses in the left parietal and temporal regions. However, in the LIFG, older controls exhibited slower responses than younger controls. In resting state activity, we found decreases in delta and theta power and a corresponding increase in alpha and beta power for older controls in comparison to patients with PPA and our younger group. This pattern is consistent with our previous findings involving a partially overlapping set of healthy older participants, matched to stroke patients (Kielar et al., 2016a,b). The age-related increase of resting alpha-beta electrophysiological activity has been reported in other studies (Bruce et al., 2009; Holschneider and Leuchter, 1995). Reduced theta power has been observed during a word recognition task (Cummins and Finnigan, 2007) and also during rest (Kielar et al., 2016a,b; Vlahou et al., 2014). Although the underlying mechanism is not well understood, it has been suggested that age-related speeding of the frequency spectrum may reflect compensatory activity in response to decreased nerve conduction velocities (Hong and Rebec, 2012).

Surprisingly, in older controls, we found that decreased delta power and augmented alpha power were associated with longer latencies of 8–30 Hz ERD. Beta power behaved differently, such that elevated beta power was correlated with better task accuracy and higher MoCA scores, consistent with an aging-related compensatory increase of higher frequency oscillatory activity. Consistent with this, increased resting theta power and delayed latencies were associated with worse cognitive functioning in older adults.

Recent quantitative research suggests that age-related changes in memory and cognitive speed are most likely due to decreased synaptic plasticity that results from decreases in synaptic density and changes in synaptic morphology (Morrison and Hof, 1997), white matter connectivity changes (Guttmann et al., 1998; Xiong and Mok, 2011), or decreases in NMDA receptor levels (Morrison and Hof, 1997). Thus, in contrast to PPA or Alzheimer's disease, which are characterized by a widespread loss of neurons, age-related decreases in cognitive function and variability in performance are more likely to reflect subtle structural alternations and molecular changes in specific neuronal circuits (Morrison and Hof, 1997). Therefore, the reduction of the speed of neural activity and slowing of behavioral responses observed in healthy aging may have qualitatively different neurobiological substrates, compared to the neurodegenerative pathology observed in PPA.

In fact, the age-related speeding of electrophysiological activity that we observed in the present study is consistent with fMRI research addressing compensatory neural recruitment in aging. Several studies have found increased brain activation levels in healthy older participants during variety of cognitive and motor tasks (Grady et al., 2005; Zöllig and Eschen, 2009). In these studies, older adults who showed better performance recruited different brain regions compared to young controls, or older adults who did poorly on the task. This indicates that to maintain high levels of performance, some older participants compensate by recruiting additional brain regions to accomplish the task. In this context, age-related changes in myelin may cause delays in nerve conduction velocities, which in turn result in localized slowing of neuronal communication (Hong and Rebec, 2012; Peters, 2002). In order to overcome these delays in information transmission, neurons may need to increase their firing rate. A compensatory shift to higher frequency activity may play help to overcome time lags in communication between neurons. Because of the increased metabolic demands needed to support higher firing rates, these compensatory processes may not be effectively maintained when the neurodegenerative events take place, leading to attenuation of high frequency power and overall spectral slowing, as seen in PPA or Alzheimer's disease.

The present results suggest that speeding of spontaneous activity is not simply the reverse of the pathological slowing seen in PPA patients. However, task accuracy and cognitive status were associated negatively with elevated theta power in PPA patients, and positively with increased beta power in PPA and in age-matched controls (with no significant relationship seen in young controls for task accuracy, although the other cognitive tests were not administered in that group). In general, these results suggest that a “faster” pattern of spontaneous activity is linked to better cognition in older adults, and thus the age-related speeding may indeed represent a compensatory process. Thus, if aging leads to the localized slowing of neuronal communication (Vlahou et al., 2014), healthy individuals have enough resources to compensate for this delay by upregulating neuronal activity to higher frequencies.

In contrast to our findings, some previous studies have reported that higher resting theta power in older adults is associated with better task performance and cognitive status (Finnigan and Robertson, 2011; Gómez et al., 2013). To account for these somewhat inconsistent findings in aging and dementia, it has been proposed that two types of theta power increases may exist. According to one idea, an increase in theta power accompanied by a parallel reduction in alpha and beta power is indicative of neurological disorder, whereas when alpha slowing is not present, high theta power may be a sign of healthy aging (Finnigan and Robertson, 2011; Klimesch, 1999). However, another possibility is that enhanced low frequency power may reflect subtle neuropathological changes that will eventually lead to a significant cognitive decline. Combined with reductions in brain metabolism, brain volume, and

impaired cognitive performance, such slowing is more likely to precede overt neurodegeneration such as that seen in PPA.

Further studies of spontaneous and task related electrophysiological activity in older adults are warranted, coupled with a broader sampling of cognitive variability in that population. Given that the mechanisms underlying slowing may be partially reversible in response to interventions, these electrophysiological measures may serve as useful biomarkers for the effectiveness of such interventions.

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Appendix A. Supplementary data

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