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Introduction: Beyond the core linguistic deficits, individuals with aphasia exhibit concomitant deficits in executive functions, in particular working memory (WM) (e.g., Caplan, Michaud, & Hufford, 2013; Murray, 2012), which is responsible for active mental manipulation. Syntactic processing in sentence comprehension requires such a storage and computational system, and deficits in WM have been shown to predict sentence comprehension in post-stroke aphasia (Pettigrew & Hillis, 2014; Varkanitsa & Caplan, 2018). Little research has been done in primary progressive aphasia (PPA) despite the existence of sentence comprehension deficits in all variants. In this study, we asked whether performance on a prevalent WM task (Digit Span backward; DSB) predicts performance on sentence comprehension (SOAP Test) (Love & Oster, 2002) and which brain areas mediate such effects, particularly the left middle frontal gyrus (MFG), an important area for WM or the left inferior frontal gyrus (IFG), a typical language area.

Methods: Thirty-six participants with PPA (mean age 67.05 ± 5.86 years) underwent comprehensive baseline cognitive-linguistic evaluations followed by an MRI, specifically a pseudo-continuous arterial spin labeling (pCASL) sequence. All MRI scans were performed on a 3T MRI scanner with 8-channel head coil (Philips Healthcare, Best, Netherlands). pCASL sequence scan parameters were: field of view = 205 × 205 mm2, matrix = 64 × 64, 39 axial slices, thickness = 3.2 mm, TR/TE = 5817/9.3 msec, labeling duration = 1.8 seconds, post-labeling delay = 1.8 seconds, 6 pairs of label and control images, 3D gradient-and-spin-echo with background suppression, duration 5 minutes 14 seconds. Cerebral blood flow (CBF) maps were generated from the pCASL MRI images using JHU's cloud-based ASL analysis software, ASL-MRICloud (https://braingps.mricloud.org/asl) (Li et al., 2019). Relative CBF (i.e., perfusion) was calculated by dividing CBF within a brain region by total CBF over the entire brain. Simple linear regression showed predictive values for behavioral measures (DSB and SOAP scores) and perfusion, and multiple linear regression revealed mediation effects (Shrout & Bolger, 2002).

Results: Performance on DSB significantly predicted performance on sentence comprehension, SOAP scores (see Table 1). DSB was also significantly associated with perfusion of the left MFG and left IFG opercularis (IFGoperc). Importantly, DSB was not associated with perfusion of the IFG triangularis (IFGtri). When DSB and the left MFG were used in a multiple linear regression for SOAP, DSB had less predictive power of SOAP scores than the simple linear regression of DSB on SOAP, indicating a partial mediation effect of the left MFG. Similarly, when DSB and the left IFGoperc were used in a multiple linear regression for SOAP, DSB again had less predictive power of SOAP scores than its corresponding simple linear regression, indicating another partial mediation effect of the left IFGoperc.

Conclusions: The present study indicates that the left MFG and left IFGoperc partially mediate WM associations with sentence comprehension as previously shown in Turken & Dronkers, 2011 and Zaccarella & Friederici, 2015. These findings highlight that performance on a basic WM test may predict sentence comprehension, mostly to the extent that MFG and IFG operc (but not IFGtri) are involved. We present a simple mediation model that future studies could investigate unique contributions of other brain areas or differences between variants as mediators of correlations between cognitive functions to language.

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Table 1: Simple and Multiple Linear Regression Results of Behavioral Scores & CBF of Brain Areas

Regression Description (df = 34)	DSB Coefficient	DSB Adjusted R^2	DSB t-statistic	p-value
DSB on SOAP	3.18	42%	5.14	0.00001
DSB on CBF of left MFG	0.09	37%	4.63	0.00005
DSB on CBF of left IFGoperc	0.04	21%	1.80	0.08
DSB on CBF of left IFGtri	0.02	-0.1%	0.97	0.34
DSB + left MFG on SOAP	2.40	45%	3.12	0.003
DSB + left IFGoperc on SOAP	2.81	47%	4.54	0.00007