CORTEX 171 (2024) 165–177

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Behavioural Neurology

Assessing processing speed and its neural correlates in the three variants of primary progressive aphasia with a non-verbal tablet-based task

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ARTICLE INFO

Article history:
Received 26 May 2023
Reviewed 31 July 2023
Revised 29 September 2023
Accepted 18 October 2023
Action editor Brad Dickerson
Published online 2 November 2023

Keywords:
Digital assessment
Primary progressive aphasia

ABSTRACT

Prior research has revealed distinctive patterns of impaired language abilities across the three variants of Primary Progressive Aphasia (PPA): nonfluent/agrammatic (nfvPPA), logopenic (lvPPA) and semantic (svPPA). However, little is known about whether, and to what extent, non-verbal cognitive abilities, such as processing speed, are impacted in PPA patients. This is because neuropsychological tests typically contain linguistic stimuli and require spoken output, being therefore sensitive to verbal deficits in aphasic patients. The aim of this study is to investigate potential differences in processing speed between PPA patients and healthy controls, and among the three PPA variants, using a brief non-verbal tablet-based task (Match) modeled after the WAIS-III digit symbol coding test, and to determine its neural correlates. Here, we compared performance on the Match task between PPA patients (n = 61) and healthy controls (n = 59) and across the three PPA variants.

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https://doi.org/10.1016/j.cortex.2023.10.011

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Processing speed
Fronto-parietal regions

We correlated performance on Match with voxelwise gray and white matter volumes. We found that lvPPA and nfvPPA patients performed significantly worse on Match than healthy controls and svPPA patients. Worse performance on Match across PPA patients was associated with reduced gray matter volume in specific parts of the left middle frontal gyrus, superior parietal lobule, and precuneus, and reduced white matter volume in the left parietal lobe. To conclude, our behavioral findings reveal that processing speed is differentially impacted across the three PPA variants and provide support for the potential clinical utility of a tabled-based task (Match) to assess non-verbal cognition. In addition, our neuroimaging findings confirm the importance of a set of fronto-parietal regions that previous research has associated with processing speed and executive control. Finally, our behavioral and neuroimaging findings combined indicate that differences in processing speed are largely explained by the unequal distribution of atrophy in these fronto-parietal regions across the three PPA variants.

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1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative syndrome clinically characterized by a progressive and relatively isolated speech-language impairment. Three main clinical variants, namely the nonfluent/agrammatic variant (nfvPPA), the semantic variant (svPPA), and the logopenic variant (lvPPA), have been previously described and associated with distinctive clinical features driven by neurodegeneration in specific regions of the speech-language network (Gorno-Tempini et al., 2011). While speech-language deficits represent the core of each PPA syndrome, deficits in other cognitive domains have also been reported during the clinical assessment of these patients, such as those involving memory, visuospatial abilities, behavioral and affective changes, and general as well as social cognition (Watson et al., 2018; Fittipaldi et al., 2019; Eikelboom et al., 2018; Foxe et al., 2022; O'Connor et al., 2016; Ulugut et al., 2022; Van Langenhove et al., 2016; Matias-Guiu et al., 2019; Ramanan et al., 2020; 2022). Nevertheless, there is still a need for better characterization of potential differences in non-linguistic cognitive skills across the three PPA variants, as the diagnosis of PPA can remain challenging in some cases (Tippett, 2020).

Particularly, a few studies in PPA patients have focused on investigating cognitive domains other than language such as executive functioning (Basaglia-Pappas et al., 2023; Coemans et al., 2022; Foxe et al., 2021; Macoir et al., 2017; Ramanan et al., 2020) or visuospatial processing (Ramanan et al., 2020; Tee et al., 2022; Watson et al., 2018). For example, prior literature has suggested that the assessment of executive functions (EF) might be useful in discriminating the PPA variants, with lvPPA patients generally showing worst performance, svPPA patients exhibiting overall the mildest EF impairments, and nfvPPA patients sitting somewhat in between (Basaglia-Pappas et al., 2023; Butts et al., 2015; Eikelboom et al., 2018; Watson et al., 2018; Kamath et al., 2020; Macoir et al., 2017). Similarly, a recently published meta-analysis of studies looking at executive functioning in PPA, found that PPA patients suffer from an important decline compared to healthy age-matched controls, with significant differences across variants (Coemans et al., 2022). While shifting, updating and inhibiting aspects of executive functions were covered in this systematic review, speed of processing has rarely been the focus of research in PPA, therefore remaining a largely unexplored topic. It is noteworthy, however, that some previous studies included commonly used paper-pencil processing speed proxies in the neuropsychological assessment of these patients such as the Trail Making Test Part A (Basaglia-Pappas et al., 2023; Butts et al., 2015; Matias-Guiu et al., 2019).

Processing speed is a theoretical construct that is typically operationalized in terms of how fast individuals perform cognitive tasks (Salthouse, 1993, 1996). It is also considered an important factor in how well basic cognitive mechanisms can be recruited in the service of goal-oriented actions. Processing speed has been proposed to be a key cognitive resource, alongside with attention, working memory and inhibition, underlying performance in a wide range of cognitive domains (Kail & Salthouse, 1994). There are many reasons why investigating speed of processing in PPA is critical. First, processing speed is considered one of the strongest predictors of performance across a range of cognitive tasks in older healthy adults (Rast, 2011; Salthouse, 2000; Salthouse & Ferrer-Caja, 2003; Finkel et al., 2007). Second, impaired processing speed appears to be related to cognitive dysfunction in a wide range of neurodegenerative conditions such as Alzheimer's disease (AD), behavioral variant of frontotemporal dementia, vascular dementia, and mild cognitive impairment (MCI; Heyanka et al., 2010; Reul et al., 2017). Third, a significant slowing in processing speed has been associated with overall cognitive decline and consequently with assistance in daily living activities (Ticha et al., 2023). Finally, impairments in processing speed have also been shown to impact other cognitive functions such as semantic memory and language abilities in patients with neurodegenerative diseases (e.g., Alzheimer's disease; Jokel et al., 2019; van Boxtel & Lawyer, 2021) and psychiatric populations (Boyle et al., 2008).

Similarly, a growing body of evidence in the post-stroke aphasia literature shows that non-linguistic cognitive deficits commonly co-occur with aphasia and may contribute to

language profiles and outcomes (Murray, 2012; Villard & Kiran, 2017). Furthermore, recent reports have consistently shown that deficits in language (aphasic symptoms) and non-language cognitive domains frequently co-exist in lvPPA and svPPA patients, including visuospatial processing and executive functioning deficits in lvPPA patients (Owens et al., 2018; Ramanan et al., 2020, 2022), and visual perception and face recognition deficits in svPPA patients (Binney et al., 2016; Ding et al., 2020; Kumfor et al., 2015), even in early cases. Despite this evidence, to date, there are no studies that have, for example, investigated the role of processing speed in non-linguistic as well as linguistic deficits in the three variants of PPA. This is mainly because many of the neuropsychological tests designed to measure non-verbal cognitive domains such as processing speed and executive functioning contain linguistic stimuli and require verbal output, being therefore inadequately designed for, and usually not administered in, aphasic patients. While not administering these tests in aphasic patients seems understandable, it is also a missed opportunity to characterize some of the specific difficulties that PPA patients face with respect to other cognitive domains (Schumacher et al., 2022). Non-verbal tests, on the other hand, have only rarely been used to assess executive functioning and processing speed in PPA patients (Macoir et al., 2017).

In this context, a better characterization of the neural correlates of processing speed in PPA is also required, if we are to understand from a brain-behavior mapping perspective why processing speed may or may not be differentially affected across PPA variants. Specifically, previous neuroimaging studies in healthy young adults and aging adults have been instrumental in showing that performance on tasks that tap into processing speed depends on coordinated activity in distributed brain networks and that age-related decline in performance on processing speed tasks can be attributed to disrupted brain connectivity (Schulz et al., 2022). For instance, in a functional magnetic resonance imaging (fMRI) study of young participants, Usui et al. (2009) reported increased activation in a set of fronto-parietal cortical regions, including the bilateral inferior frontal sulci, left middle frontal gyrus and left posterior parietal cortex when subjects performed a modified version of the WAIS-III digit symbol coding test compared to a baseline condition. Moreover, Turken et al. (2008) found that performance on a virtually identical task was positively correlated with white matter microstructural changes in the parietal and temporal lobes bilaterally, as well as in the left middle frontal gyrus. Fiber tractography indicated that these regions are consistent with the trajectories of the superior and inferior longitudinal fasciculi. While it is widely acknowledged that damage to specific left-lateralized brain regions drives differential patterns of performance across language tasks, little is known about where brain damage might impair processing speed in patients diagnosed with PPA. Likewise, it remains to be established if these potential effects differ across the three PPA variants. Here, we hypothesized that the brain regions supporting processing speed would be differentially affected across patients with PPA due to the distinctive patterns of atrophy associated with each PPA variant (Gorno-Tempini et al., 2004).

In the current study, we examined how well 61 PPA patients performed a novel, non-verbal tablet-based task, that primarily measures processing speed. This task, named "Match", has been shown to have high sensitivity and specificity to detect mild cognitive impairment (MCI) and, most importantly, cognitive decline in preclinical and prodromal stages of the neurodegenerative process in both typical and atypical dementia syndromes (Possin et al., 2018; Rodríguez-Salgado et al., 2021; Tsoy et al., 2020). Match is modeled after the WAIS-III digit symbol coding test (Wechsler, 1997), which is one of the psychometric tools in neuropsychology research and practice most commonly used to assess processing speed, albeit executive functioning, visuospatial processing, focused attention, response selection, and motor execution are also taxed to some extent by this test (Jaeger, 2018; Lezak et al., 2012; Wechsler, 1997). Importantly, none of the three variants of PPA have previously been characterized in terms of performance on the Match task. Therefore, this study has three main aims: (i) to determine differences in non-verbal cognition (processing speed specifically) between PPA patients and healthy controls, and among the three PPA variants; (ii) to investigate whether scores from our digital task (Match) are associated with other paper-pencil tasks that tap into linguistic and non-linguistic cognitive functions; and, finally, (iii) to reveal the patterns of brain tissue loss associated with poor performance on Match by relating task scores to voxel-wise indices of gray and white matter volumes in PPA patients.

2. Methods

2.1. Participants

Healthy volunteers and patients with a diagnosis of PPA according to current clinical consensus criteria (Gorno-Tempini et al., 2011) were recruited at the Memory and Aging Center of the University of California, San Francisco (UCSF). Healthy participants were classified as cognitively normal based on neurological examination, neuropsychological evaluation, Clinical Dementia Rating (CDR), and absence of subjective cognitive concerns, and included in the current study if they achieved above cut-off scores (>25) on the Mini-Mental State Examination (MMSE; Folstein et al., 1975), and completed the Match task. A total of 59 healthy volunteers met our inclusion criteria. PPA patients were included in the study if they had: (i) a high-resolution T1-weighted magnetic resonance imaging (MRI) scan of sufficient quality for analysis; (ii) a MMSE total score higher than 10 and (iii) completed our digital task of interest (Match). A total of 61 PPA patients met our inclusion criteria, 20 were diagnosed with lvPPA, 18 with nfvPPA, and 23 with svPPA. The study was performed in accordance with the revised Declaration of Helsinki, and after obtaining approval from the local ethics committee. All patients provided their written consent to participate.

2.2. Cognitive testing

Match is a task modeled after the WAIS-III digit symbol coding test (Possin et al., 2018; Tsoy et al., 2020, 2021), and is a part of the Brain Health Assessment, which is a 10-min tablet-based cognitive battery programmed in the UCSF TabCAT software platform (https://memory.ucsf.edu/research-trials/professi-

onal/tabcat). The TabCAT software platform is currently free of charge, however, license fees will be implemented in the near future. The mandatory requirements to use TabCAT and most of their tasks, that target other cognitive domains, is to complete an account request form and agree to a user agreement.

All participants performed the task on a 9.7-in. iPad guided by a trained examiner in a private testing room. During the Match task, participants are shown a fixed legend of numbers 1 through 7 with corresponding simple, abstract pictures that appear just below each number, as well as in a different order and spatial arrangement along the bottom of the screen (see Fig. 1). The participants are instructed that each time a number appears in the middle of the screen, they should tap the corresponding picture at the bottom of the screen as quickly as possible. After each response, a new number appears. Performance is measured as a sum of all accurate responses within 2 min.

In addition, all participants (PPA patients and healthy controls) underwent a comprehensive neuropsychological assessment, as previously described (Gorno-Tempini et al., 2004; Kramer et al., 2003). More precisely, the assessment includes paper-pencil tasks designed to measure executive functioning, visuospatial processing, verbal memory, and language functions. Only PPA patients underwent comprehensive language testing. Please see Table 1 for more details.

2.3. Statistical analyses of behavioral data

A one-way analysis of covariance (ANCOVA) was conducted to evaluate the statistically significance of group differences (controls, lvPPA, nfvPPA and svPPA) in Match scores while controlling for demographic and clinical variables of no interest, including (i) age at testing, (ii) sex, (iii) MMSE scores (as a proxy of disease severity), (iv) a clinical severity rating for motor difficulties; and (v) scores from the VOSP (Visual Object and Space Perception Battery) number location task (as a proxy of visuospatial difficulties). Holm–Bonferroni post-hoc tests were carried out when examining specific between-group differences in Match performance.

To evaluate how performance on other language and non-language tasks may be associated with Match scores in PPA patients, we carried out a series of partial correlation analyses (Holm-Bonferroni-corrected for multiple comparisons) on the raw scores from a set of paper-pencil tasks that were part of our language and neuropsychological assessments of patients, while at the same time covarying out the influence of age at testing, sex and disease severity using CDR Sum of Boxes scores (CDR-SB).

The statistical analyses were conducted in JASP version 0.17.2.1 and R version 4.3.3.0 (R Project for Statistical Computing).

2.4. Structural MRI image acquisition and pre-processing

T1-weighted MRI scans from 61 PPA patients were acquired on either of two Siemens MAGNETOM scanners: one patient underwent imaging in a 3T Trio scanner and 60 in a 3T Prisma scanner. In all cases, a T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was deployed to collect the whole-brain images. For the 3T Trio scanner, the imaging parameters were: 160 sagittal slices; voxel size = 1.0 × 1.0 × 1.0 mm^3; FoV = 256 × 256 mm^2; matrix size = 256 × 256; TR = 2300 msec; TE = 2.98 msec; flip angle = 9°. For the 3T Prisma scanner, these were: 160 sagittal slices; voxel size = 1.0 × 1.0 × 1.0 mm^3; FoV = 256 × 256 mm^2; matrix size = 256 × 256; TR = 2300 msec; TE = 2.90 msec; flip angle = 9°.

All T1-weighted whole-brain images were quality checked by means of visual inspection to rule out the presence of artifacts and/or excessive motion. Next, these T1-weighted images were pre-processed with the Computational Anatomy Toolbox (CAT12; Gaser et al., 2022) using default parameters, in the Statistical Parametric Mapping (SPM12) running under Matlab 2020b (The MathWorks, Inc., Natick, MA, USA). Modulated gray matter (GM) and white matter (WM) images from CAT12 were spatially smoothed with an 8 mm full width at half-maximum isotropic Gaussian kernel to compensate for residual anatomical variability and to permit application of random field theory for statistical inference in SPM (Flandin & Friston, 2017). Finally, to estimate the frequency with which each voxel in the brain was atrophic across patients, voxelwise W-maps of the GM and WM images were created as previously described (Ossenkoppele et al., 2015).

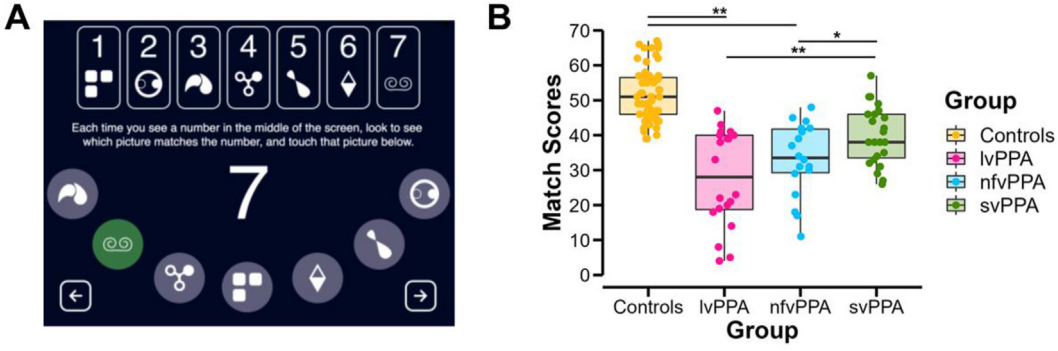

Fig. 1 – Example of stimuli from the Match task (A) and boxplots showing significant differences in performance on the Match task between PPA patients and controls and among the three PPA variants (B). Significant differences at **$p < .001$ and *$p < .05$.

Table 1 – Demographic, speech-language and neuropsychological data for the healthy controls and PPA patients.

	Participants				F-test
	HC	lvPPA	nfvPPA	svPPA	
Demographics					
Sample size (n)	59	20	18	23	
Age (mean/SD)	68.7 (6.5)	67.5 (9.1)	68.6 (6.6)	67.8 (6.1)	ns
Education (mean/SD)	17.3 (2.0)	17.3 (1.5)	16.3 (1.7)	16.0 (2.6)	ns
Gender (male/female)	22/37	12/8	8/10	12/11	ns
Handedness, (right/left)	52/7	20/0	16/2	21/2	ns
MMSE (mean/SD)	29.7 (.6)	21.2 (4.4)	25.6 (4.1)	24.4 (3.7)	***
CDR sum of boxes (mean/SD)	0 (0)	3.2 (1.4)	1.8 (1.8)	4.5 (2.5)	***
Executive functions					
Match (correct responses)	51.7 (7.6)	27.8 (13.8) [c]	33.1 (10.5) [c]	39.9 (8.4)	***
Match (incorrect responses)	.51 (1.12)	1.15 (1.27)	.78 (.73)	.44 (.95)	ns
Stroop color naming ±	92.1 (15.3)	36.6 (18.6) [c]	41.6 (14.9) [c]	67.1 (21.3)	***
Stroop total correct ±	52.6 (13.1)0	18.3 (11.6) [b,c]	27.2 (9.4) [c]	41.4 (17.8)	***
Digit span backwards ±	5.3 (1.2)	3.3 (1.0) [c]	3.7 (1.7) [c]	5.0 (1.0)	***
Digit span forwards	7.0 (1.2)	4.5 (.9) [c]	4.7 (1.6) [c]	5.7 (1.1)	***
Modified trials (in seconds) ±	24.3 (9.8)	75.6 (37.4) [c]	62.2 (42.4)	49.3 (26.5)	***
Modified trials (# of correct lines) ±	13.3 (2.9)	11.2 (4.6)	10.7 (5.4)	12.8 (3.9)	*
Phonemic (D-letter) fluency ±	16.2 (5.0)	7.1 (3.0)	5.8 (4.2)	9.2 (4.2)	***
Semantic (animals) fluency ±	23.4 (4.4)	8.8 (4.0)	12.7 (6.4)	11.6 (6.6)	***
Design fluency: number of correct ±	11.9 (3.2)	5.7 (3.0)	6.3 (2.5)	7.5 (2.9)	***
Visuospatial function/memory					
VOSP number location (10)	9.3 (.8)	8.1 (2.1)	8.6 (2.1)	8.8 (2.5)	*
Benson figure copy (17) ±	15.5 (.8)	12.8 (3.8) [b,c]	14.6 (1.7)	15.0 (1.7)	***
Benson delayed recall (17)	12.1 (2.4)	6.9 (4.2) [b]	9.9 (3.2) [c]	6.3 (5.3)	***
CVLT trials 1–4 (40)	–	13.5 (4.6) [b]	25.0 (6.8) [c]	18.8 (7.7)	***
Language production					
Boston naming test (15)	14.6 (.8)	9.0 (3.1) [b]	12.7 (2.5)	6.3 (5.3) [a,b]	***
Sentence repetition (%)	–	76.2 (8.7) [c]	84.1 (19.6)	92.0 (7.0)	*
Arizona reading regular words (18)	–	17.1 (1.3)	16.5 (3.6)	16.7 (3.9)	ns
Arizona spelling pseudowords (10)	–	5.6 (2.5)	5.6 (3.8)	6.7 (2.3)	ns
Language comprehension					
Peabody picture vocabulary test (16)	–	14.1 (1.5)	14.2 (1.8)	10.2 (3.7) [a,b]	***
WAB auditory word recognition (60)	–	58.8 (1.7)	59.2 (1.6)	56.3 (5.2) [a,b]	*
WAB sequential command (80)	–	62.7 (14.6) [b]	73.8 (10.6)	71.8 (11.7)	*
Sentence comprehension (%) ±	–	91.1 (7.9)	90.1 (10.2)	95.5 (5.6)	*

Values shown are mean (SD). Asterisks denote significantly impaired relative to healthy controls at *$p < .05$; **$p < .01$; ***$p < .001$. Superscript letters denote significantly impaired compared to the [a]non-fluent variant, [b]logopenic variant and [c]semantic variant at $p < .05$. Group differences ($p < .05$; one-way Analysis of Variance (ANOVA) and Holm–Bonferroni Test). **Abbreviations**: VOSP = Visual Object and Space Perception Battery, CVLT = California Verbal learning Test, HC = healthy controls, F-test = main effect of group in ANOVA, ns = non-significant; % = percentage of correct responses (maximum score of 100); ± = tests that survived Holm–Bonferroni correction (see Results and Fig. 2).

2.5. *Atrophy maps estimation and thresholding*

W-maps quantify the degree to which voxelwise brain tissue volumes in each patient deviate from those in healthy controls considering the influence of a specific number of covariates. In particular, the effect of age, sex, total intracranial volume (TIV) and scanner on brain tissue volume was covaried out by fitting a multiple regression model to the pre-processed imaging data from an independent sample of 124 healthy controls (mean age ± SD = 68.9 ± 6.57 years, range = 52–79 years; 78 females) that were not included in further analyses. The model coefficients from the regression in healthy controls were then applied to the pre-processed imaging data from each patient (i.e., GM and WM images) to derive covariate-adjusted brain tissue volumes (i.e., W-scores) with the following formula: (observed brain tissue volume – expected brain tissue volume)/standard deviation of the residuals for that voxel in healthy controls. Since the distribution of W-scores is analogous to that of Z-scores, the W-map for each patient was binarized using an uncorrected voxel-level threshold of $p < .05$ one-tailed (i.e., W-score < -1.64) and a cluster extent threshold of at least 100 contiguous voxels, generating a binary map of the presence or absence of atrophy at each voxel across the brain.

2.6. *VBM analysis of processing speed*

Statistical analysis of brain–behavior relationships was performed using the general linear model for voxel-based morphometry (VBM; Ashburner & Friston, 2000) in SPM12. We carried out two voxel-based multiple regression analyses: one based on unthresholded W-maps for GM, and one based on unthresholded W-maps for WM. In both of these analyses the following three nuisance covariates were entered: (i) scores from the VOSP number location task (to account for visuospatial processing), (ii) a clinical severity rating for motor

difficulties, and (iii) total amount of GM (or WM) atrophy (to account for global effects of atrophy).

Each VBM analysis consisted of one regressor of interest: the scores from Match. Based on this regressor, we investigated the GM or WM regions where greater tissue loss is associated with poorer Match scores. A total of 61 patients contributed data to the VBM analyses. The search volume was defined by an explicit mask of the GM (or WM) tissue probability map provided with SPM12, after being thresholded at a voxelwise value equal to, or greater than, .2. For each computed T-contrast, the corresponding statistical map was evaluated at a voxel-level threshold of $p < .001$ uncorrected and a cluster-level threshold of $p < .05$ family-wise-error-corrected.

3. Results

3.1. lvPPA and nfvPPA patients perform worse on Match compared to svPPA patients and healthy controls

Demographic and clinical characteristics for each participant group are presented in Table 1. Control participants (n = 59) were matched by age ($p = .552$), sex ($p = .095$), education ($p = .065$), and handedness ($p = .314$) to PPA patients. The three PPA groups did not differ on demographic variables or disease severity (MMSE and CDR-SB scores) (Table 1).

Overall, we found that the 61 PPA patients performed worse on Match compared to the 59 healthy controls ($p < .001$, Fig. 1). Furthermore, a one-way ANCOVA showed that there was a significant main effect of group on the Match scores ($F(3,111) = 8.827$, $p < .001$) after controlling for demographic, neuropsychological, and clinical variables including age at testing, sex, visuospatial skills (VOSP number location score), general motor abilities (clinical severity rating), and disease severity (MMSE score).

Post-hoc pairwise comparisons using a Holm–Bonferroni correction (adjusted alpha cut-off of $p = .0125$) indicated that lvPPA and nfvPPA patients performed worse on the Match task than svPPA patients ($p = .027$ and $p = .006$, respectively) and healthy controls ($p = .006$ and $p < .001$, respectively). In contrast, there were no statistically significant differences in Match scores between svPPA patients and healthy controls ($p = .380$) or between lvPPA and nfvPPA patients ($p = .563$).

When demographic variables (age and sex) were excluded (i.e., controlling only for visuospatial skills, general motor abilities and disease severity), the same pattern of results was obtained ($F(3,113) = 8.303$, $p < .001$).

Match scores are significantly related to paper-pencil tasks that tap into language ability, processing speed, executive functioning, and visuospatial processing.

A series of partial correlation analyses showed that 10 out of the 21 paper-pencil measures examined (see Table 1 for details) were significantly correlated (after Holm–Bonferroni correction: adjusted cut-off of $p = .002$) with Match scores in PPA patients: sentence comprehension ($r = .468$, $p = .001$), digit span backwards ($r = .654$, $p < .001$), the modified version of the Trail Making Test (MTTtime: $r = -.759$, $p < .001$ and MTTCorr: $r = .576$, $p < .001$), the Stroop color naming and interference test (StrpCN: $r = .730$, $p < .001$ and StrpCorr: $r = .716$, $p < .001$); the phonemic, semantic and design fluency tasks ($r = .488$, $r = .487$, $r = .441$, $p < .001$; respectively) and the Benson figure copy ($r = .515$; $p < .001$). See Fig. 2 for details.

3.2. Poor performance on Match correlates with atrophy in left fronto-parietal regions

The W-maps of atrophy for the three groups of PPA patients (nfvPPA, lvPPA, and svPPA) are illustrated in Supplementary Fig. 1. Importantly, these maps were created covarying out the influence of a specific number of clinical and demographic variables (i.e., age, sex, TIV and scanner; see Methods). These nuisance covariates were not included in the VBM analyses,

VBM regression analyses performed across all 61 PPA patients showed that worse performance on the Match task was significantly associated with greater tissue loss (after controlling for visuospatial skills, a clinical severity rating for motor difficulties, and total amount of atrophy) in four distinct clusters (three GM and one WM) that became our regions of interest for all subsequent analyses. They were located in specific parts of the left superior parietal lobule GM at peak coordinates −24, −59, +48 (Z-score = 4.84), the left middle frontal gyrus GM at peak coordinates −44, +30, +23 (Z-score = 3.93), the left precuneus GM at peak coordinates −2, −63, +44 (Z-score = 3.89), and the left parietal lobe WM at peak coordinates −29, −36, +45 (Z-score = 4.62). Interestingly, all four regions fell in the vicinity of the first and second branches of the left superior longitudinal fasciculus (SLFI and SLFII) as shown in Fig. 3A.

A post-hoc analysis showed that these VBM effects were primarily driven by (i) the nfvPPA and lvPPA patients for the left middle frontal gyrus (LMFG) GM region ($r = .504$, $p = .039$ and $r = .557$, $p = .011$, respectively), (ii) the lvPPA patients for the left superior parietal lobule (LSPL) and left precuneus (LPrec) GM regions ($r = .705$, $p < .001$ and $r = .706$, $p < .001$, respectively), and (iii) the nfvPPA patients for the left parietal lobe (LpWM) WM region ($r = .556$, $p = .016$). The svPPA patients did not significantly contribute to any of the identified VBM effects; see Fig. 3C for details. One-way ANOVAs confirmed that there were statistically significant differences in the degree of atrophy across the identified regions (LMFG ($F = 6.192$, $p = .040$), LSPL ($F = 9.500$ $p < .001$), LPrec ($F = 10.176$, $p < .001$), and LpWM ($F = 4.353$ $p = .017$)), with Holm–Bonferroni corrected post-hoc tests showing greater atrophy in: (i) LMFG for lvPPA than svPPA ($p = .004$) and nfvPPA than svPPA ($p = .045$); (ii) LSPL for lvPPA than nfvPPA ($p = .008$) and lvPPA than svPPA ($p < .001$); (iii) LPrec for lvPPA than nfvPPA ($p < .001$) and lvPPA than svPPA ($p = .001$); (iv) LpWM for lvPPA than svPPA ($p = .033$) and nfvPPA than svPPA ($p = .041$), see Fig. 3B for details.

4. Discussion

The main aim of the current study was to investigate potential differences in processing speed between PPA patients and healthy controls, and among the three PPA variants by using Match – a non-verbal tablet-based task that primarily taps into processing speed. Non-linguistic cognitive functions, such as processing speed, are not commonly assessed in

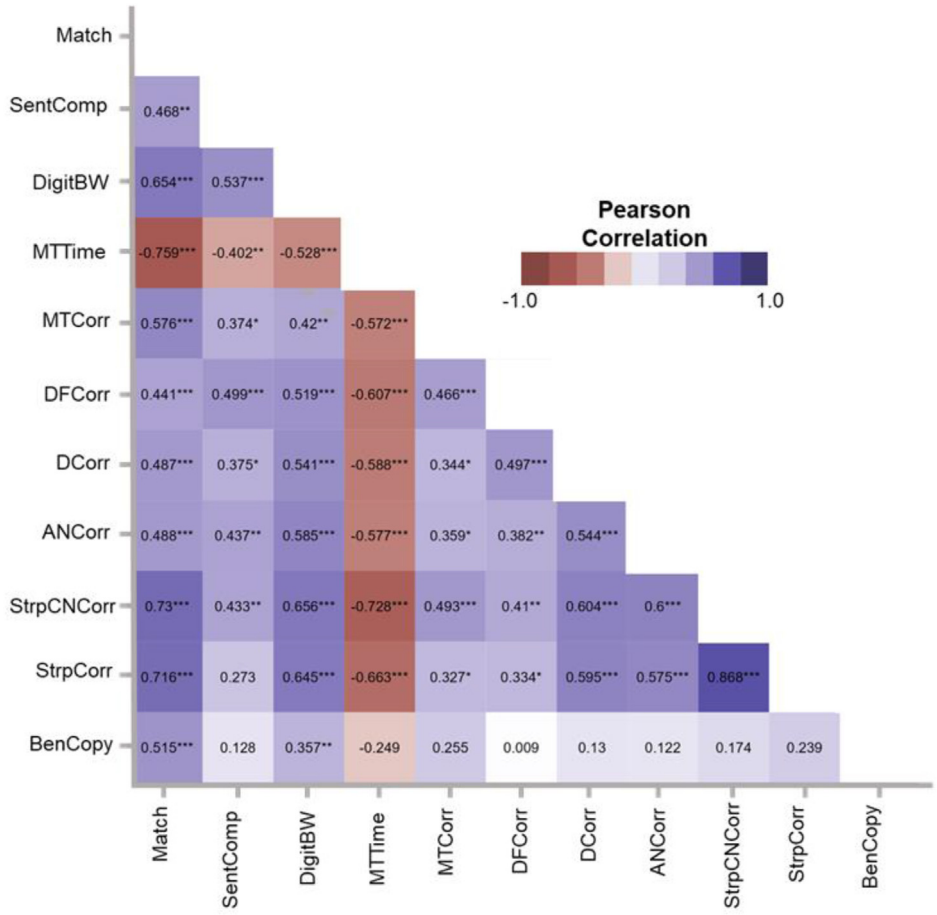

Fig. 2 – Partial correlation matrix heatmap of the neuropsychological paper-pencil tasks and Match scores in PPA patients. ***$p < .001$, all p-values were Holm–Bonferroni corrected for multiple comparisons (adjusted alpha cut-off of $p = .002$). A series of partial correlations were performed between paper-pencil tasks that are part of the neuropsychological assessment of patients and scores from Match controlling for confounding factors such as age at testing, disease severity and sex. Abbreviations: SentComp = sentence comprehension; DigitBW = digit span backwards; MTTime = Modified trials (time in seconds); MTCorr = Modified trials (number of correct); DFCorr = design fluency (number of correct); DCorr = phonemic (D-letter) fluency; ANCorr = semantic (animal) fluency; StrpCNCorr = Stroop color naming; StrpCorr = Stroop total correct; BenCopy = Benson figure copy.

aphasic patients due to the verbal nature of many neuropsychological tests. This is problematic because it is not known whether and to what extent processing speed impairments may co-occur with, or even influence, language impairments in PPA patients. The second aim was to investigate associations between performance on the Match task and performance on other tasks that tax linguistic and non-linguistic cognitive functions. The third aim was to delineate the neural correlates of Match in PPA patients to determine the brain regions where tissue loss is likely to drive any observed behavioral differences. In brief, we found that performance on the Match task discriminated between PPA patients and healthy controls, and more importantly among the three PPA variants. As expected, scores from the Match task were significantly associated with traditional paper-pencil tasks that measure processing speed, but also with other tasks that measure sentence processing, executive functioning and visuospatial processing. In addition, the voxel-based multiple regression analyses of GM and WM identified distinct neural correlates of processing speed deficits in PPA patients. Taken together, these findings complement prior literature by furthering our understanding of the degree to which nonverbal cognitive skills differ across the three PPA variants and revealing the neural substrates of such differences. They also illustrate how digital assessments with minimal or no verbal content could be potentially used in future research and in clinical settings for helping with (i) the identification of cognitive changes besides language impairments in early or more advances stages, (ii) refining the existing diagnostic criteria in PPA and other dementias and (iii) as well as for therapeutic purposes by selecting, for example, processing speed as target for cognitive interventions.

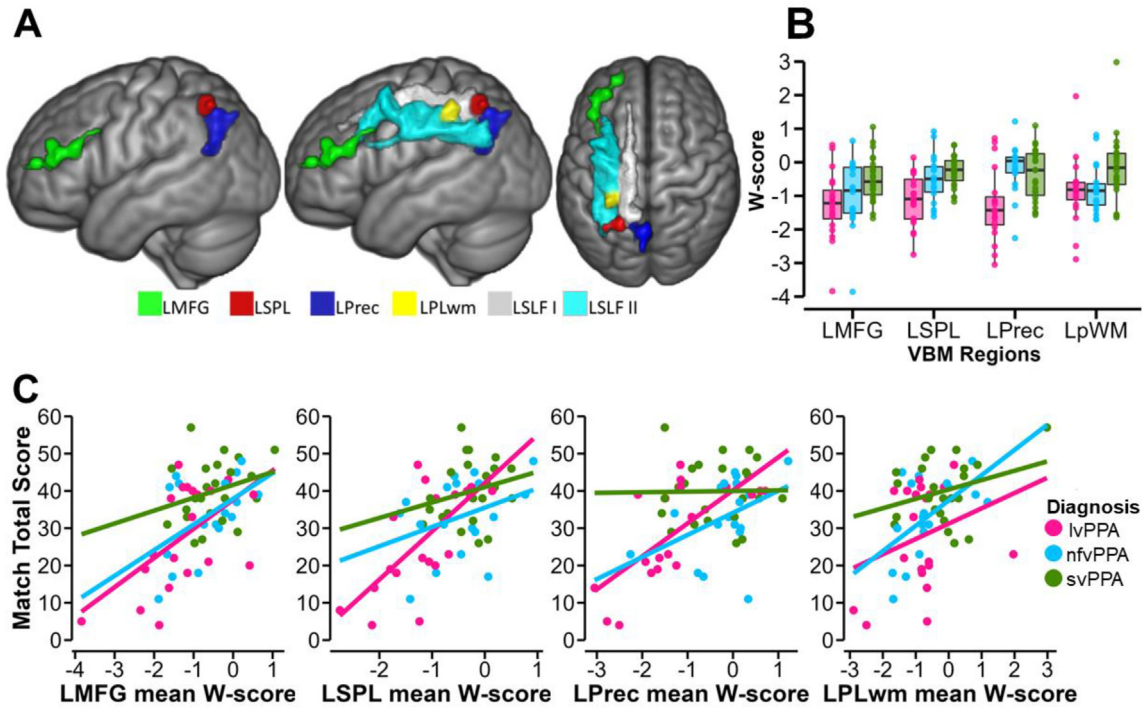

Fig. 3 – Brain-behavior relationships and post-hoc analyses in PPA patients. (A) Gray matter (LMFG, LSPL, and LPrec) and white matter (LPLwm) regions identified in our voxel-based multiple regression analyses, and the first and second branches of the superior longitudinal fasciculus (SLFI and SLFII, tract reconstructions are from Rojkova et al., 2016), are rendered in a template from healthy controls. (B) Grouped boxplot showing mean W-score (see Methods) within each region for each patient. (C) Scatterplots illustrating post-hoc analyses where regional W-scores were correlated with Match scores in each PPA variant separately. Abbreviations: LMFG = left middle frontal gyrus; LSPL = left superior parietal lobule; LPrec = left precuneus; LPLwm = left parietal lobe white matter; LSLFI = left superior longitudinal fasciculus, first branch; LSFLII = left superior longitudinal fasciculus, second branch.

4.1. *lvPPA and nfvPPA patients performed worse on Match compared to svPPA patients and healthy controls*

Match was modeled after the digit symbol coding task from the WAIS-III (Wechsler, 1997) – a widely used measure that has been shown to be sensitive for the detection of cognitive deficits in neurodegenerative diseases (Galvin et al., 2020; Tsatali et al., 2021). Prior literature has found that performance on this task is influenced to varying degrees by several cognitive components such as processing speed, executive functioning, associative learning/memory, visuospatial processing, and graphomotor skills; with the first two cognitive processes (processing speed and executive functioning) explaining a substantial proportion of the variance in task performance, and the remaining three playing a subsidiary role only (Joy et al., 2003). Therefore, in the current study we focused on the key cognitive aspect of Match: that is, processing speed.

Findings of our study showed that this non-verbal tablet-based task was a sensitive measure to differentiate PPA patients from healthy controls, and, more importantly, among the three PPA variants, with lvPPA and nfvPPA patients performing significantly worse compared to svPPA patients. A few previous studies examining language and other cognitive domains have reported that neuropsychological profiles differ among the three PPA variants. For instance, lvPPA patients have shown poorer performance on executive and visuospatial tasks compared to nfvPPA and svPPA patients (Basaglia-Pappas et al., 2023; Butts et al., 2015; Watson et al., 2018; Foxe et al., 2021; Kamath et al., 2020; Ramanan et al., 2022; Tee et al., 2022).

In our study, we found that lvPPA and nfvPPA patients performed significantly worse on the Match task (which measures primarily processing speed) compared to svPPA patients and healthy subjects after controlling for demographic factors and other variables that may have influenced task performance including disease severity, motor as well as visuospatial abilities. Our findings are in line with previous studies that, for example, have reported similar levels of performance in lvPPA and nfvPPA patients on (i) a visuospatial/executive composite measure that combined scores from backward spatial span, a modified version of the Trail Making Test, and design fluency (Watson et al., 2018), (ii) working memory tests (Harris et al., 2019), (iii) verbal short-term memory (Foxe et al., 2021), and (iii) processing speed as indexed by the paper-pencil version of the Trail Making Test Part A (Basaglia-Pappas et al., 2023). Moreover, as in our study, Watson et al. (2018) also found that healthy controls and svPPA patients performed significantly better than nfvPPA

and lvPPA patients. Future research should investigate whether the same patterns of behavioral performance on Match (and other digital tasks that are part of the TabCAT Brain Health Assessment) are observed as disease progresses by following PPA patients longitudinally.

4.2. *Processing speed deficits are associated with other cognitive and language deficits in PPA*

Our results show that Match scores are significantly correlated with a paper-pencil sentence comprehension task, which may be particularly affected in nfvPPA patients. Indeed, prior research has shown that nfvPPA patients may present with agrammatic sentence production and comprehension (Wilson, et al., 2010). Importantly, accumulated evidence from behavioral studies in healthy participants as well as lesion and neuroimaging studies suggests that processing speed and executive functioning may contribute to sentence processing in healthy controls (Caplan & Waters, 1999; Rogalsky et al., 2008) and patients with neurological conditions (Grossman et al., 2002; Peelle et al., 2008; Colman et al., 2011; Gajardo-Vidal et al., 2018). For example, Grossman and colleagues posited that sentence comprehension difficulties in patients with Parkinson's disease may in part be related to impaired processing speed, thus assigning it a crucial role in grammatical processing (Grossman et al., 2002). Similarly, it has been suggested that the difficulties of nfvPPA patients in comprehending grammatically complex sentences may be in part explained by deficits in non-linguistic cognitive processes such as executive functioning and processing speed (Macoir et al., 2017; Peelle et al., 2008). Taken together, this body of work motivates future research to investigate whether processing speed could potentially be selected as a target for cognitive interventions in PPA, and whether any identified treatment effects generalize to other cognitive domains (including language).

In addition, and as expected, Match was also significantly correlated with other paper-and-pencil tasks that tap into processing speed, executive functioning and visuospatial processing in PPA patients including our in-house modified and abbreviated version of the Trail Making Test, design fluency, verbal fluency, the Stroop test and digit span backwards (Fig. 2). This supports the validity and utility of our tablet-based task to examine non-verbal cognition in this neurodegenerative syndrome in which language impairments are the central and most prominent feature. Only a few studies have utilized these technologies with PPA patients, either in assessment or intervention (Lavoie et al., 2020; Plonka et al., 2021). The use of tablet-based clinical tools provides advantages including the possibility to record accuracy as well as response times automatically. Furthermore, they have the potential to be more ecological and reproducible and have proven to be an efficient method for remote administration, repeated testing and monitoring of patients (Staffaroni et al., 2020).

4.3. *Diminished performance on Match was associated with tissue loss in fronto-parietal regions*

Our first voxel-based multiple regression analysis in PPA patients indicated that diminished performance on Match was associated with reduced GM volume in three regions located within the left middle frontal gyrus (LMFG), LSPL and left precuneus (LPrec; Fig. 3). Critically, our post-hoc analyses revealed that the left middle frontal gyrus effect was primarily driven by the lvPPA and nfvPPA patient groups, while the left superior parietal lobule and left precuneus effects were mainly driven by the lvPPA patient group. Furthermore, our findings are in line with previous functional imaging studies of healthy controls indicating that these three gray matter (GM) regions (LMFG, LSPL, and LPrec) play an important role in the execution of the digit symbol coding test (Kerchner et al., 2012; Usui et al., 2009). Likewise, a recent study in patients with dementia and mild cognitive impairment found that Match correlated positively with GM volumes predominantly in right and left lateral frontal, parietal, and subcortical regions (Possin et al., 2018). Therefore, based on prior literature, we can postulate that these regions may contribute to distinct aspects of our task of interest. For instance, the LMFG is likely to support the speeded aspect of Match, while the LPrec – a region that has been involved in a wide range of cognitive skills including visuo-spatial imagery and episodic memory retrieval (Cavana & Trimble, 2006) – may have contributed to the visual choice component of the task. Similarly, due to its multiple connections with the prefrontal and occipital cortices, the LSPL has been shown to have a critical role in both executive functioning and visuospatial processing in healthy controls, for example, by responding to tasks that rely on selective attention to visual stimuli (Sylvester et al., 2003).

Several previous studies have investigated the relationship between white matter (WM) integrity and performance on tasks that place high demands on processing speed (Turken et al., 2008; Kerchner et al., 2012). By showing that worse performance on Match was correlated with reduced tissue volume in a WM region lying medially to the junction of the postcentral sulcus and the intraparietal sulcus, our findings support prior literature that implicated the left parietal WM in processing speed. As shown in Fig. 3, the anatomical location of this WM region is consistent with the trajectory of the superior longitudinal fasciculus (branches I and II; SLFI and SLFII). The SLF is a WM tract that has previously been (i) involved in the interplay between more dorsally located left frontal and parietal areas and (ii) associated with processing speed in healthy younger and older adults (Kerchner et al., 2012). While SLFI has been found to be critical for maintaining a task set that ensures fluid execution of the sequence of operations involved in the digit symbol coding task (Turken et al., 2008), SLFII has been associated with speed of visuospatial processing (Thiebaut de Schotten et al., 2011). Furthermore, lesion-symptom mapping studies of neurological patients have indicated that lesions of the left parietal lobe and underlying WM are associated with poorer performance on the digit symbol coding task than lesions elsewhere (Turken et al., 2008). Importantly, our post-hoc analysis showed that the effect in the left parietal WM was primarily driven by the nfvPPA patients. This finding is in line with previous research that used tractography to demonstrate that different branches of the SLF contribute to speech-language functions and are commonly affected in nfvPPA (Galantucci et al., 2011; Grossman et al., 2013; Mandelli et al., 2014).

In addition, studies of functional connectivity have shown that the broad neural networks that support both linguistic and non-linguistic functions are affected in PPA syndromes (Reyes et al., 2019). This is relevant because previous research on the digit symbol coding task highlights that, while processing speed is one of the main task components, associative memory and visuospatial processing may also play a (albeit less important) role in task performance (Joy et al., 2003). Therefore, performance on the Match task cannot be considered as a unitary construct, but rather a reflection of the interaction of multiple cognitive processes that results from the coordinated activity of different brain regions. In fact, findings from previous functional imaging studies in healthy controls (Marek & Dosenbach, 2018) add to the results of our VBM analysis in PPA patients by revealing that two of the identified GM regions may be part of a fronto-parietal network, which is functionally distinct from and spatially adjacent to the canonical language network (Braga et al., 2020). This fronto-parietal network has been involved in a wide variety of tasks including working memory, attention, shifting, and reasoning (Martínez et al., 2013; Niendam et al., 2012). The left precuneus has, on the other hand, been considered a key node of the default-mode network, which is closely linked with the medial prefrontal cortex (Damoiseaux et al., 2006). Therefore, depending on the PPA variant and underlying atrophy patterns, some functional networks and associated cognitive functions are more likely to be affected than others. Indeed, we found that the left fronto-parietal regions subserving critical components of our task of interest (Match), such as processing speed, were differentially impacted in the three PPA variants, giving rise to a non-verbal cognitive profile that may help to distinguish lvPPA and nfvPPA patients from svPPA patients.

5. Conclusions

Our findings show the utility of Match, a non-verbal tablet-based task that places high demands on processing speed, to capture distinguishable patterns of non-linguistic cognitive performance in the three PPA variants. The most impaired groups on this task were lvPPA and nfvPPA, thus stressing the importance of evaluating non-verbal cognition as an aid in the differential diagnosis of these clinical syndromes. Critically, the left fronto-parietal regions that were associated with Match performance align well with the anatomy of the three PPA variants, ultimately explaining the observed behavioral effects. Future work will benefit from incorporating other non-verbal digital tasks, such as those that are part of the Brain Health Assessment, to better characterize the cognitive trajectories of PPA patients.

Funding

This work was supported by the National Institutes of Health (M.L.G-T., NINDS R01 NS050915, NIDCD K24 DC015544; NIA U01 AG052943). A.G-V. and D.L.L-P. were each supported by a postdoctoral fellowship from the Chilean National Agency for Research and Development (ANID BECAS-CHILE 74200065 and ANID BECAS-CHILE 74200073, respectively). D.L.L-P. is supported with funding from the Chilean National Agency for Research and Development (ANID SUBVENCIÓN A LA INSTALACIÓN EN LA ACADEMIA 85220006).

CRediT roles

Gajardo-Vidal Andrea: Conceptualization, Formal Analysis, Writing – Original Draft. **Montembeault Maxime:** Conceptualization, Writing – Original Draft. **Lorca-Puls Diego:** Formal Analysis, Writing – Review & Editing. **Licata Abigail**: Data Curation, Formal Analysis. **Bogley Rian**: Data Curation, Formal Analysis. **Erlhoff Sabrina**: Resources, Data Curation. **Ratnasiri Buddhika**: Data Curation. **Ezzes Zoe**: Data Curation. **Battistella Giovanni**: Formal Analysis. **Tsoy Elena**: Writing – Review & Editing. **Pereira Christa**: Writing – Review & Editing. **DeLeon, Jessica:** Writing – Review & Editing. **Tee Boon Lead**: Writing – Review & Editing. **Henry Maya:** Writing – Review & Editing. **Miller Zachary**: Writing – Review & Editing. **Rankin Katherine:** Writing – Review & Editing. **Maria Luisa Mandelli:** Formal analysis, Writing – Review & Editing. **Possin Kate**: Conceptualization, Writing – Review & Editing. **Gorno-Tempini Maria Luisa:** Supervision, Writing – Review & Editing, Funding Acquisition.

Data availability

The conditions of our ethics approval do not permit public archiving of anonymized study data. Data requests can be submitted here: https://memory.ucsf.edu/research-trials/professional/open-science. Following a UCSF-regulated procedure, access will be granted to designated individuals in line with ethical guidelines on the reuse of sensitive data. This would require submission of a Material Transfer Agreement. Commercial use will not be approved. No specific code was created for the statistical analyses, which were computed using the Graphical User Interface (GUI) of two free and open-source software packages: JASP (https://jasp-stats.org/download/) and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/download/).

Declaration of competing interest

None.

Acknowledgments

We would like to thank all participants and their families for their generous support to our research.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.10.011.

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