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Non-right handed primary progressive apraxia of speech

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ABSTRACT

In recent years a large and growing body of research has greatly advanced our understanding of primary progressive apraxia of speech. Handedness has emerged as one potential marker of selective vulnerability in degenerative diseases. This study evaluated the clinical and imaging findings in non-right handed compared to right handed participants in a prospective cohort diagnosed with primary progressive apraxia of speech. A total of 30 participants were included. Compared to the expected rate in the population, there was a higher prevalence of non-right handedness among those with primary progressive apraxia of speech (6/30, 20%). Small group numbers meant that these results did not reach statistical significance, although the effect sizes were moderate-to-large. There were no clinical differences between right handed and non-right handed participants. Bilateral hypometabolism was seen in primary progressive apraxia of speech compared to controls, with non-right handed participants showing more right hemispheric involvement. This is the first report of a higher rate of non-right handedness in participants with isolated apraxia of speech, which may point to an increased vulnerability for developing this disorder among non-right handed participants. This challenges prior hypotheses about a relative protective effect of non-right handedness for tau-related neurodegeneration. We discuss potential avenues for future research to investigate the relationship between handedness and motor disorders more generally.

1. Background

In recent years a large and growing body of research has greatly advanced our understanding of primary progressive aphasia (PPA) and primary progressive apraxia of speech (PPAOS) [1–3]. PPA refers to a group of degenerative disorders characterized by early involvement of language, which is accompanied by speech problems in some patients [1]. In contrast, PPAOS is characterized by early speech involvement in the form of apraxia of speech, with no evidence for aphasia [2]. As such, while the disorders are closely related and distinction may be hard with disease progression, PPAOS refers to a well characterized and distinct neurodegenerative syndrome [2,4–6].

Although several cohorts were limited to right hand dominant (RH) participants, it has been suggested that non-right handedness (nRH) may be over-represented in the semantic variant of PPA and under-represented in the agrammatic/nonfluent variant [7]. Altered hemispheric specialization, with more symmetry and less lateralization expected in nRH participants, has been proposed as the reason for these differences. By implication, it has been suggested that the difference in cerebral organization predisposes participants to TDP-43 pathology, the most common pathology observed in the semantic variant of PPA [7,8]. The lower than expected rate of nRH in the agrammatic/nonfluent variant of PPA was hypothesized to result from an increased susceptibility to tau-related neurodegeneration in participants with concurrent hemispheric control for language and their dominant hand (as is seen in most right handers) [7]. PPAOS has not been evaluated, but offers an

Abbreviations: AOS, apraxia of speech; nRH, non-right handed/non-right handedness/non-right hand dominant; PPA, primary progressive aphasia; PPAOS, primary progressive apraxia of speech; RH, right handed/right handedness/right hand dominant

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opportunity to test the above-mentioned hypothesis because the overwhelming majority of PPAOS participants have an underlying 4R-tauopathy as opposed to the mix of tau and TDP-43 seen in the agrammatic/nonfluent variant of PPA [2,5,6,9–13].

In addition to evaluating the distribution of handedness among PPA subtypes, researchers have compared participants based on handedness and found no difference in clinical or imaging measures [7]. This is somewhat surprising, given the suspected differences in hemispheric specialization in non-right handed participants [14,15] and the various disorders that have been associated with left handedness [16,17]. Consider, for example, the distribution of handedness in the population. It is estimated that approximately 90% of the population is RH, and that 90–95% of RH participants are left lateralized for language [17,18]. In contrast, ~75% of the nRH population is left lateralized for language, meaning that the most common situation among nRH individuals is a dissociation between hemispheric representation and control of the dominant hand and the hemispheric lateralization for language [18]. One could reasonably expect such differences in cerebral organization to have an effect on clinical and imaging findings in degenerative diseases targeting highly lateralized networks. While the association between handedness and cerebral organization for language is complex and not entirely understood, the implications of handedness on the motor system may be simpler. In both RH and nRH participants the system underlying the planning of skilled motor movements appears to be left lateralized [19], and in RH the left primary sensorimotor area seems dominant for speech [20]. In either case, the hand area of the sensorimotor strip is larger contralateral to the dominant hand, but in nRH this dissociation between the lateralization of planning skilled movements and the subsequent execution with the preferred hand is associated with more widespread and bilateral activation during motor planning and execution [21]. Speech has not been assessed in the same detail, but an effect of handedness in motor speech disorders, such as PPAOS, would be expected to at least a similar degree as that seen in PPA.

We set out to evaluate handedness in PPAOS to assess (a) whether nRH was over or under represented in this population (b) whether there were clinical differences between RH and nRH participants and (c) whether or not there were FDG-PET differences in RH compared to nRH participants at the group or individual level, such as more right hemispheric involvement in nRH cases.

2. Methods

2.1. Participants

Patients with a degenerative speech or language disorder were prospectively recruited and diagnosed with a PPAOS as described in detail elsewhere [3]. Briefly, participants were evaluated by a neurologist (K.A.J) and a speech pathologist (J.R.D or E.A.S), which included a full neurologic examination, screening for alternative diagnoses using standardized tools and criteria, as well as a comprehensive motor speech and language battery [2,3]. Handedness was assessed by self-report during the neurologic evaluation and neuropsychological evaluation. At a consensus meeting at a later date, operational definitions were used to categorize participants blinded to the results of the imaging studies [3]. PPAOS was diagnosed if apraxia of speech was the initial manifestation. No more than equivocal evidence for aphasia could be present, although dysarthria was allowed [3,4]. For the imaging portion of the analysis, participants were compared to cognitively normal, amyloid imaging negative controls matched for age, gender and handedness from the Mayo Clinic Study of Aging [22]. The Mayo Clinic Institutional Review Board approved this study and all participants and/or their surrogates signed appropriate informed consent.

2.2. Imaging protocol and image processing

As part of a standardized protocol, all participants had 3.0 T MR imaging which included a 3-D MPRAGE sequence, as well as FDG PET/CT imaging using a PET/CT scanner (GE Healthcare) operating in 3D mode. Details of the imaging protocols have been described previously [2,3]. Individual participant level maps of hypometabolism were generated using 3-dimensional stereotactic surface projections with CortexID (GE Healthcare, Waukesha, WI, USA). This is a fully automated analysis including realignment, spatial normalization, non-linear warping, followed by sampling of 16,000 predefined cortical locations which are then projected onto a 3D brain surface. Participant PET data is normalized to the pons and compared to a normative database, resulting in a 3D stereotactic surface projections *Z*-score image. These images were analyzed visually and quantitatively as outlined below.

2.3. Imaging analyses

Group level analyses of FDG-PET images were performed using SPM 12. MR images were normalized to the Mayo Clinic Adult Lifespan Template (MCALT) (https://www.nitrc.org/projects/mcalt/). PET images were co-registered to the MR images using 6 DOF registration. The pons was identified after propagating the automated anatomical labeling atlas to native MRI space, and all voxels in the PET images were then divided by the median uptake in the pons. The resulting FDG uptake ratio images were spatially normalized to the template using the parameters from MRI normalization. Voxel-level comparisons of FDG-PET were performed using two-sided *t*-tests. RH and nRH PPAOS patients were compared to RH and nRH controls, respectively. In addition, RH and nRH control and PPAOS groups were compared to each other. Age and sex were included in as covariates in all analyses. Results were viewed after correcting for multiple comparisons using false discovery rate (FDR) at $p < 0.05$ and uncorrected at a threshold of $p = 0.001$. In addition, for results not surviving correction, effect size and –log 10 p-value maps were created and visualized.

Analysis at the individual level was done visually and quantitatively. One author (H·B) visually reviewed all 3D stereotactic surface projections *Z*-score images from CortexID and determined whether or not it represented normal metabolism, left or right dominant hypometabolism or symmetric hypometabolism. In addition, the Z-scores from the following regions were extracted for further analysis: frontal association cortices and medial frontal lobes, anterior cingulate lobes, caudate nuclei, sensorimotor cortices, parietal association cortices and medial parietal lobes, posterior cingulate lobes, temporal association cortices, occipital association cortices and visual cortices. Hypometabolism for each of these regions was defined as a Z-score of < -1.5. The pattern determined visually, together with the mean Z-scores per region and the number of participants with hypometabolism in a given region were then compared between RH and nRH individuals.

3. Results

3.1. Handedness and clinical results

A total of 30 participants were included. Six were nRH (5 left handed, 1 ambidextrous). Based on a population estimate of nRH of 10% [7,17], the rate of nRH was double the expected rate (6/30, 20%), with medium effect size, although it did not reach statistical significance (X^2 3.33, $p = 0.068$, Cramer's V = 0.33). When compared to the rate reported for agrammatic/nonfluent PPA in a prior study (4%), the rate in PPAOS was significantly different (X^2 20.00, $p < 0.001$, Cramer's V = 0.82). Results of neurologic and speech and language evaluations are shown in Table 1. There were no significant differences

Table 1
Clinical and demographic results as well as participant level FDG-PET findings in PPAOS. Significant differences shown in bold.

	PPAOS (30)		
	RH	nRH	P (ES)[a]
No (%)	24 (80)	6 (20)	0.068 (0.33)
Age (y)	70.5 ± 9.2	69.3 ± 7.4	0.778 (0.12)
Sex (F/M)	14/10	2/4	0.272 (0.20)
Duration (y)	3.5 ± 1.9	4.5 ± 2.4	0.280 (0.42)
Education (y)	15.6 ± 2.5	16.5 ± 2.1	0.465 (0.28)
WAB AQ (/100)	97.7 ± 2.0	96.1 ± 1.3	0.0835 (0.68)
BNT (/15)	14.2 ± 1.0	14.2 ± 1.0	1.000 (0.00)
BNT Rec failure	0.1 ± 0.3	0.2 ± 0.4	0.559 (0.22)
TT (/22)	20.6 ± 1.5	19.8 ± 1.6	0.281 (0.42)
PPT (/52)	50.2 ± 1.4	50.7 ± 1.0	0.431 (0.30)
FF (/10)	9.3 ± 1.7	10.0 ± 0.0	0.324 (0.38)
ASRS (/64)	18.7 ± 7.0	20.2 ± 11.5	0.693 (0.15)
AOS severity (/4)	1.5 ± 0.8	1.8 ± 1.0	0.355 (0.36)
NVOA (/32)	26.0 ± 8.1	23.0 ± 10.1	0.440 (0.30)
IMA (/60)	55.9 ± 5.0	56.3 ± 4.2	0.853 (0.07)
MMSE (/30)	29.4 ± 0.9	29.2 ± 1.3	0.n (0.18)

Abbreviations: AOS = Apraxia of Speech; ASRS = AOS Rating Scale; BNT = Boston Naming Test; FF = Famous Faces; IMA = Ideomotor Apraxia (From WAB); MMSE = Mini-Mental State Exam; NVOA = Nonverbal Oral Apraxia; PiB = Pittsburgh B; PPT = Pyramids and Palm Trees; TT = Token Test; WAB AQ = Western Aphasia Battery Aphasia Quotient.

[a] For effect size, Cramer's V was computed for nominal data (0.10 = small effect, 0.30 = medium effect, 0.50 = large effect) and Cohen's D was computed for continuous variables (0.20 = small, 0.50 = medium, 0.80 = large).

in demographics, disease duration, neuropsychological results or speech and language findings in nRH compared to RH participants. nRH cases are reviewed in more detail on a single participant level below.

3.2. Group level imaging findings

Results of the group-level analyses for RH participants are shown in Fig. 1 and for nRH participants in Fig. 2. Compared to controls, RH PPAOS participants had focal hypometabolism centered around the precentral gyri and the SMA bilaterally, with a left sided predominance. Compared to nRH PPAOS participants, there was focal hypometabolism in the right fusiform and inferior temporal gyrus, which did not survive correction for multiple comparisons. The effect size and –log 10 p-value maps suggested that there may have been involvement of similar regions on the left, albeit to a lesser extent.

A similar pattern was seen in the nRH participants when compared to controls when viewed at an uncorrected threshold. After correction, most of the significant areas of hypometabolism were on the right, including the precentral and inferior frontal gryri. There were small areas of hypometabolism in the region of the SMAs bilaterally and a focus in the left precentral gyrus. When compared to RH PPAOS participants, there was a small focus of hypometabolism in the right SMA/superior frontal gyrus. Effect size and −log 10 p-value maps suggested more widespread right motor and premotor hypometabolism in nRH compared to RH participants.

Results for the contrasts between RH and nRH controls are shown in Supplemental Fig. 1. No areas remained after thresholding at p = 0.001. Only moderate the effect sizes were found, with a trend for RH controls to have reduced left precentral/postcentral hypometabolism and for nRH controls to have reduced right fusiform and inferior temporal hypometabolism.

3.3. Participant level imaging findings

Data from the review of *Z*-score surface projected images from CortexID are summarized in Table 2. Equivocal to normal metabolism was commonly observed in RH PPAOS. When hypometabolism was noted it was often focal posterior frontal and medial frontal, with a left sided predominance, but often did not involve enough of a given region to push the z-score below −1.5. As such, median z-scores for this group as a whole were near zero. There were 3 RH (12.5%) and 2 nRH (33.3%) PPAOS participants with right greater than left sided hypometabolism.

3.4. Non-right handed participants

Additional clinical details on nRH participants are provided in Table 3 and representative imaging findings in Fig. 3.

Four of the nRH PPAOS participants (P1–2 and P4–5) were described in detail previously [5] and did not have any atypical clinical findings. Two of these participants had more widespread hypometabolism than is typically observed in PPAOS, predominantly right sided in P2 and predominantly left sided in P5. The remaining PPAOS participants (P3 and P6) had no atypical clinical features, but P3 had more severe hypometabolism than is usually seen early in the disease course.

4. Discussion

In the current study, we evaluated the effect of handedness on the clinical and imaging features of PPAOS. Our main findings were: (1) handedness may be over represented in PPAOS compared to the rate expected in the general population; (2) handedness did not appear to significantly alter the clinical findings in PPAOS; (3) nRH PPAOS participants may have more right sided motor/premotor involvement when compared to RH participants. Before discussing handedness as a potential risk factor for PPAOS in particular, we review the use of handedness as a surrogate for cerebral specialization in the context of neurological disorders. Following this, we turn to PPAOS and motor disorders more broadly to interpret our findings and suggest further avenues of research.

4.1. Handedness and hemispheric specialization

While the exploration of handedness as a potential marker of increased vulnerability to neurodegeneration is in its infancy, it is a modern reflection of the longstanding view that non-right handedness, and specifically left handedness, is in some way a risk factor [17,23,24]. In Western society negative views regarding left handedness and high rates of required switching contributed to declining rates of left handers, which reached a nadir of 3–4% around the end of the 19th century [17]. In many parts of the world the practice of switching left handed children continues, as does the discrimination faced by left handers, with rates in the single digits reported recently in parts of Africa and Asia [24].

When handedness is studied in neurology it is generally used as a surrogate for altered structural or functional brain organization, most commonly reduced asymmetry or hemispheric specialization. For example, reduced asymmetry in the planum temporale may be used as a surrogate for reduced hemispheric specialization for language [7]. In other words, the assumption is that reduced or altered hemispheric specialization may be associated with a reduced chance of right handedness, and may predispose to some neurologic conditions. There are good reasons to believe hemispheric specialization is adaptive and may constitute a special example of cost efficient brain network organization [25,26]. As such, altered or reduced asymmetry may be associated with inefficient processing, higher metabolic costs, and increased risk of network failure [27].

However, our understanding of handedness and its potential association with brain structure or function has changed substantially in the last 2–3 decades, and it is worth considering handedness as a surrogate for hemispheric specialization in light of more recent research. Firstly, it is not uncommon in the neurologic literature for handedness to be viewed as binary (right handed vs left-handed or non-right handed) or

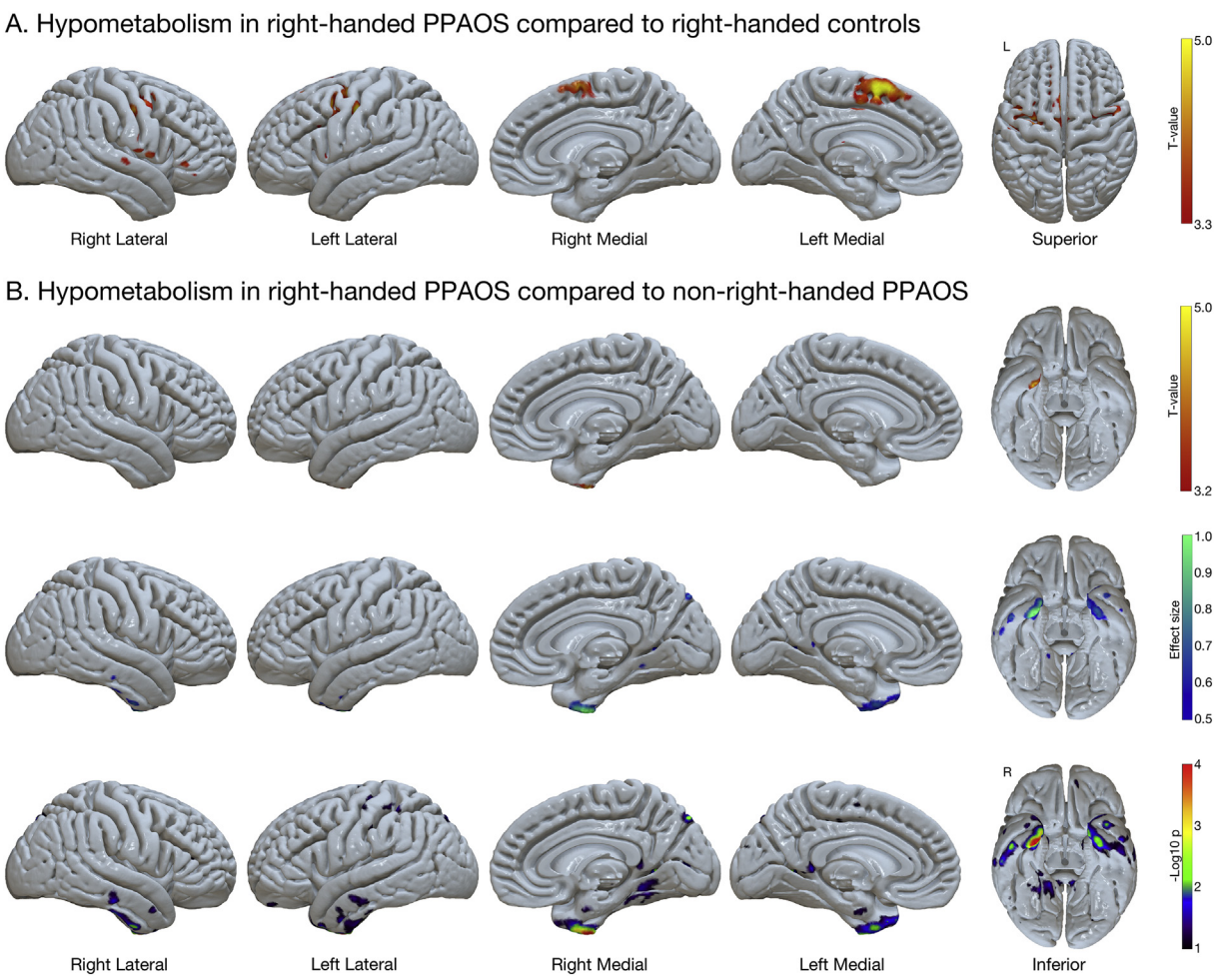

Fig. 1. Three-dimensional brain renderings showing FDG-PET hypometabolism in right-handed PPAOS.
(A) Compared to controls, RH PPAOS participants had focal hypometabolism most marked in the posterior medial frontal lobe in the area of the SMA bilaterally, as well as bilateral precentral gyri, left greater than right. Results are shown corrected for multiple comparisons using FDR at $p < 0.05$. (B) Compared to nRH PPAOS participants, RH participants had focal of hypometabolism of the right fusiform and inferior temporal gyrus (results shown uncorrected for multiple comparisons, at $p = 0.001$). Effect size (Cohen's d) and $-\log 10$ p-value maps are also shown. An effect size of 0.5–0.8 is commonly interpreted as "moderate" whereas values above 0.8 are considered "large". A –log 10 p-value of 3 corresponds to 0.001, while 2 and 4 correspond to 0.01 and 0.0001, respectively. Three dimensional displays of the MCALT atlas used here were created with Surf Ice (https://www.nitrc.org/projects/surfice/). Abbreviations: L = left, PPAOS = primary progressive apraxia of speech, R = right.

as consisting of a few distinct categories (right, left and mixed/ambidextrous), and for handedness to be assessed through self-report without the use of a standardized tool or task [7]. This is problematic since the degree of hand preference cannot be estimated, which has been shown to be important when exploring the relationship between handedness and brain structure, function or behavior [28,29]. It is also prone to bias introduced by cultural views of non-right handers and by the hand used for certain tasks. For example, self-identified left-handers may in fact use their right hand for the majority of activities on a standardized questionnaire [18] whereas some participants may self-identify as right handers because of their writing hand while using their left hand for the majority of their daily activities [24]. This is a clear limitation to the current study, and to prior investigations into handedness in PPA [7].

Secondly, in contrast to simple views of the association between handedness and cerebral laterality implied by ideas like Annett's 'right shift theory', handedness has a complex evolutionary, genetic and environmental basis [14,30]. Population level limb preference has been documented in more than half of the mammals studied, at times at a higher rate than the 90% rightward bias seen in humans, and as such an explanation that links handedness to uniquely human faculties such as complex language is questionable [31]. Handedness is also only weakly heritable and has a polygenetic basis [30]. Familial sinistrality seems to affect the degree of hand preference regardless of the side of preference [32]. In addition, it has been suggested that a family history of sinistrality modifies the relationship between handedness and lateralization for language, such that non-right handed patients without a family history are the most likely to have atypical, right-sided representation of language [33]. We do not have data on familial sinistrality in our cohort and as such cannot explore the possibility of familial sinistrality acting as a risk factor or modifier in PPAOS.

Thirdly, traditional views on the relationship between handedness and hemispheric specialization have been questioned. The purported structural differences between left and right handers have likely been overstated [34,35], as recent large studies balanced for handedness failed to demonstrate differences in cortical thickness, volume, or surface area between right and left handers [36]. The relationship between structural asymmetries and functional specialization has also been questioned, especially with regards to grey matter asymmetries [37]. This includes the size of the PT, which is left lateralized in humans and non-human species regardless of handedness, but is not associated with language lateralization [36,38]. This is further exacerbated by the fact that the direction of asymmetry depends on the measure used (for example, surface area versus cortical thickness) [39]. The majority of non-

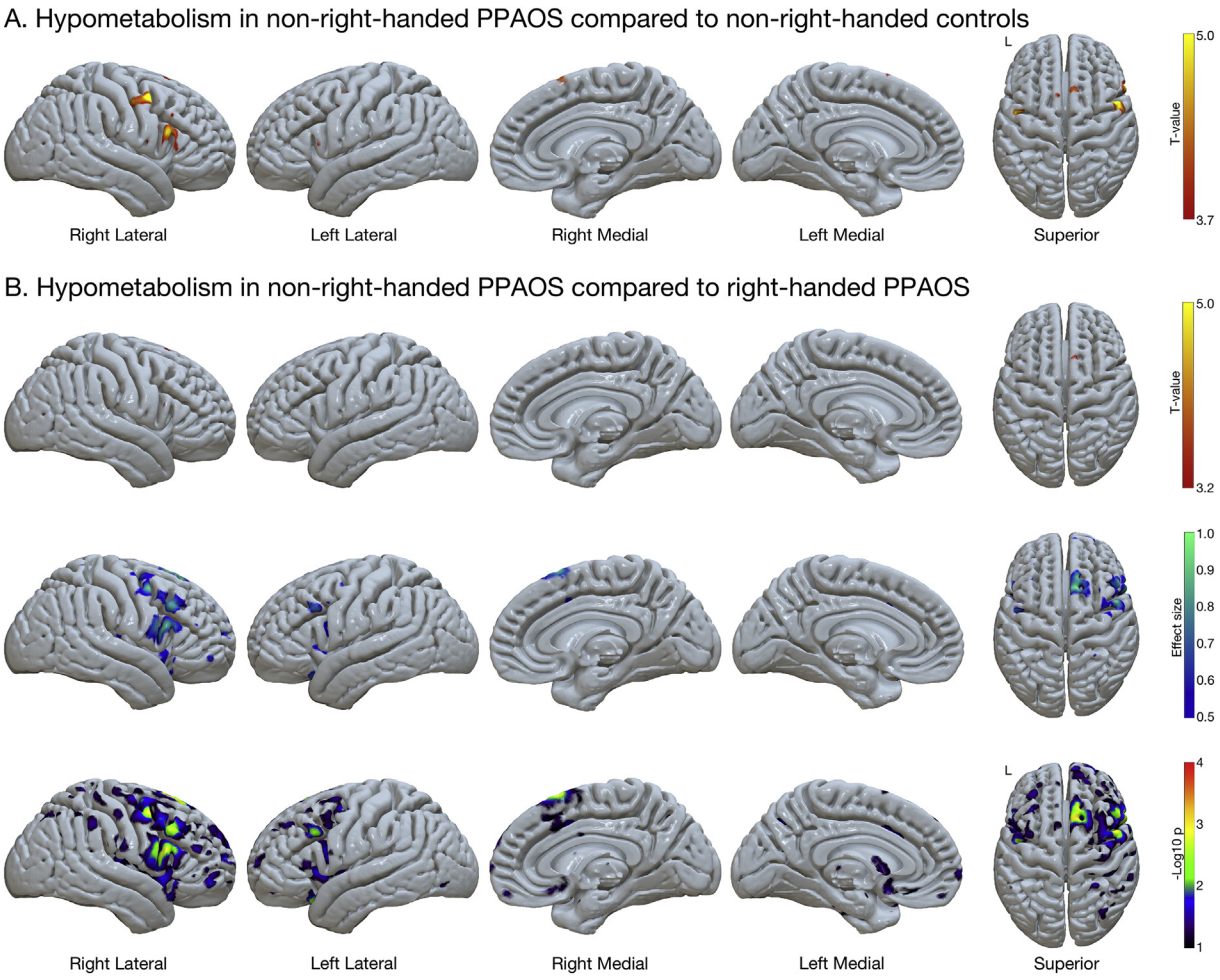

Fig. 2. Three-dimensional brain renderings showing FDG-PET hypometabolism in non-right-handed PPAOS.
(A) Compared to controls, nRH PPAOS participants had focal hypometabolism most marked in the right precentral and inferior frontal gyri, with smaller areas involving the SMA bilaterally. Results are shown corrected for multiple comparisons using FDR at $p < 0.05$. (B) Compared to RH PPAOS participants, there was a small focus in the right superior frontal gyrus that was relatively hypometabolic in nRH participants. Effect size (Cohen's d) and $-\log 10$ p-value maps are also shown. Both suggest more widespread precentral/premotor involvement that may have failed to reach significance because of the small numbers despite large effect sizes. An effect size of 0.5–0.8 is commonly interpreted as "moderate" whereas values above 0.8 are considered "large". A –log 10 p-value of 3 corresponds to 0.001, while 2 and 4 correspond to 0.01 and 0.0001, respectively. Three dimensional displays of the MCALT atlas used here were created with Surf Ice (https://www.nitrc.org/projects/surfice/). Abbreviations: L = left, PPAOS = primary progressive apraxia of speech, R = right.

right handers also have typical intra-hemispheric functional connectivity, and despite the fact that left handers are more likely to have atypical connectivity, the ~2.6% of atypical participants at a population level would be split evenly between RH and nRH [28]. It is also becoming clear that the association between right handedness and left hemispheric dominance for speech and language likely occurs by chance, as illustrated by large cohorts balanced for handedness who fail to find an association between hand preference and language lateralization [18]. Similarly, the relationship between handedness and lateralization of visuospatial functions is weak, if it exists at all [29]. Similar to the case of handedness, hemispheric specialization has been documented in non-primate species only distantly related to humans and so, once again, an explanation that links handedness or limb preference to human brain organization is not overwhelmingly supported [25].

Finally, because handedness appears to be a weak surrogate for hemispheric specialization it is not surprising that the relationship between handedness and developmental disorders has been questioned, even as the idea that altered hemispheric specialization may underlie some of these disorders has grown in prominence [16]. Manual preference direction, strength and familial sinistrality accounts for little, if any, differences in visuospatial and language performance, and this effect is dwarfed by that of education, age, sex and other socio-demographic factors [32].

4.2. Handedness in primary progressive apraxia of speech

The current study is the first to explore the effect of handedness in primary progressive apraxia of speech. Although it did not quite reach statistical significance, our finding of twice the expected number of nRH participants in PPAOS suggests an important effect of handedness in this disorder. A prior study found a lower than expected rate of nRH in patients with the agrammatic/nonfluent variant of PPA [7], which most commonly is associated with an underlying tauopathy [11–13], and hypothesized that this may be due to nRH participants being less susceptible to tau-related neurodegeneration. By extension, it was suggested that ipsilateral speech/language and hand dominance is indicative of an increased risk for developing a tauopathy, as is the case in RH participants.

Since PPAOS is almost exclusively associated with underlying 4-repeat tau, our findings do not support this hypothesis [2,6,9,10]. While our small sample limits conclusions based on the comparison between PPAOS and the expected rate in the population, it is unlikely that the rate of non-right handedness suggested in the prior study (4%) is true

Table 2
Overall PET pattern and median z-scores (Z) and number (N) of participants with a z-score > 1.5 for each region reviewed on individual z-score surface projected image (CortexID) broken down by handedness.

Overall pattern[a]	RH (n = 24)		nRH (n = 6)	
	N	%	N	%
Left dominant (%)	7	29.2	3	50
Right dominant (%)	3	12.5	2	33.3
Symmetric (%)	4	16.7	1	16.7
Normal/Equivocal (%)	10	41.7	0	0
Regional data	Z	N < −1.5 (%)	Z	N < −1.5 (%)
Parietal Association R	−0.48	3 (12.5)	−1.195	3 (50)
Parietal Association L	−0.665	6 (25)	−0.89	2 (33.3)
Temporal Association R	−0.785	2 (8.33)	−0.73	2 (33.3)
Temporal Association L	−0.895	2 (8.33)	−0.905	1 (16.6)
Frontal Association R	−0.71	3 (12.5)	−1.26	2 (33.3)
Frontal Association L	−1.02	4 (16.6)	−1.44	2 (33.3)
Occipital Association R	−0.6	1 (4.16)	−0.885	2 (33.3)
Occipital Association L	−0.595	2 (8.33)	−0.935	2 (33.3)
Posterior Cingulate R	−0.605	2 (8.33)	−0.985	1 (16.6)
Posterior Cingulate L	−0.665	3 (12.5)	−0.995	1 (16.6)
Anterior Cingulate R	−0.49	2 (8.33)	−1.11	2 (33.3)
Anterior Cingulate L	−0.58	2 (8.33)	−1.12	1 (16.6)
Medial Frontal R	−1.03	3 (12.5)	−1.45	3 (50)
Medial Frontal L	−1.165	6 (25)	−1.485	3 (50)
Medial Parietal R	−0.46	3 (12.5)	−0.74	2 (33.3)
Medial Parietal L	−0.585	3 (12.5)	−0.875	2 (33.3)
Sensorimotor R	−1.055	6 (25)	−1.24	2 (33.3)
Sensorimotor L	−1.07	8 (33.3)	−1.235	3 (50)
Visual R	−0.455	0 (0)	−0.79	1 (16.6)
Visual L	−0.355	1 (4.16)	−1.005	2 (33.3)
Caudate R	−0.995	4 (16.6)	−1.585	4 (66.6)
Caudate L	−1.1	4 (16.6)	−1.375	3 (50)

Abbreviations: L = Left, nRH = non-right handed, PPAOS = primary progressive apraxia of speech, R = Right, RH = right handed.

[a] Dominant side (if any) of hypometabolism based on review of individual z-score surface projected images for PPA subgroups and PAOS subgroups. Percentages represent the proportion of participants with a given pattern for each handedness group.

Table 3
Detailed demographic, neurologic, speech and language findings in nRH participants. AOS = Apraxia of Speech; ASRS = AOS Rating Scale; BNT = Boston Naming Test; CBS = corticobasal syndrome; DAOS = Dominant AOS (PPAOS that developed aphasia during follow up); Eq = Equivocal; FF = Famous Faces; IMA = Ideomotor Apraxia (From WAB); MMSE = Mini-Mental State Exam; N/A = not available; NVOA = Nonverbal Oral Apraxia; PiB = Pittsburgh B; PPT = Pyramids and Palm Trees; PSPS = progressive supranuclear palsy syndrome; Sym = Symmetric; TT = Token Test; WAB AQ = Western Aphasia Battery Aphasia Quotient.

	P1	P2	P3	P4	P5	P6
Age at onset (y)	71	63	58	61	62	74
Duration at evaluation (y)	4	5	1	8	3	6
Diagnosis (initial)	PPAOS	PPAOS	PPAOS	PPAOS	PPAOS	PPAOS
Sex (M/F)	M	M	F	M	M	F
Education (y)	12	16	18	18	20	15
WAB-AQ (/100)	96.3	95.2	96.2	97.6	97.4	94.1
WAB-Repetition (/10)	9.6	8.8	9.8	9.8	9.7	9.2
TT (/22)	21	21	17	21	20	19
Agrammatism (Y/N)	No	No	No	No	No	No
BNT (/15)	13	13	14	15	15	15
Failed to recognize	0	0	1	0	0	0
PPT (/52)	52	51	51	51	50	49
AOS (Y/N)	Yes	Yes	Yes	Yes	Yes	Yes
AOS Severity (/4)	1	3	1	3	1	2
ASRS (/64)	21	35	4	30	11	20
NVOA (/32)	29	4	21	24	32	28
Dysarthria (Y/N)	Eq	Yes	No	Eq	No	Yes
IMA (/60)	58	51	58	60	60	51
FF (10)	10	10	10	10	10	10
PET Pattern	Left	Right	Right	Left	Left	Sym
Diagnosis (follow-up)	PPAOS	CBS/ PSPS	N/A	PPAOS	DAOS	CBS/PSPS
Duration (last visit)	7	6	N/A	10	9	8

for PPAOS based on our findings. In terms of imaging, there was a trend for nRH PPAOS participants to have more right motor/premotor involvement at a group level. These findings were not similar to the differences between RH and nRH controls, suggesting that they are related to the disease process in PPAOS rather than a manifestation of handedness in and of itself. The data support the idea that the right hemisphere motor system may play a larger role in speech planning and execution in nRH participants.

It should be noted, however, that this is not the same as suggesting that these patients are right lateralized for language or motor planning, especially in light of the aforementioned complexities surrounding handedness and hemispheric specialization, and also does not imply that RH participants should not have a significant amount of right sided involvement. Imaging is often normal in PPAOS early on and with disease progression most patients appear to have bilateral involvement [3,5]. This coupled with the inherent heterogeneity of the disorder, where some patients have predominantly prosodic impairment and others primarily phonetic or articulatory breakdown, possibly due to the relative hemispheric involvement, makes translating group level findings to the single participant level difficulty [40]. Having said that, we found that most RH patients with an abnormal PET pattern have more left sided involvement, and most nRH participants had predominantly right sided involvement, although there were exceptions on both sides.

As alluded to previously, the current and prior investigations into handedness and degenerative disease suffer from a significant limitation in the manner handedness was assessed. Based on the current data, for example, it is not possible to estimate whether or not there were strong left-handers who may be more likely to have atypical speech and language lateralization or intra-hemispheric connectivity. But assuming the self-reported handedness is reflective of the participants' true handedness, and in light of the fact that we only had 1 ambidextrous participant, there are a few possibilities to consider.

PPAOS is best viewed as a motor disorder, as it affects speech, not language. A significant subset of these participants goes on to develop features of PSPS or CBS [5] and most remain free of aphasia for many years. As the motor speech programming system seems to be targeted, the differential distribution of motoric handedness may be more directly related to the neurobiology of the disease than in the case of PPA. Although the effect of handedness on speech planning/programming lateralization has not been assessed, recent work on handedness and limb praxis as well as advances in our understanding of speech and orofacial praxis may offer some insights. The system involved in planning complex gestures (termed the “praxis network”), including the inferior parietal/supramarginal gyrus and dorsal premotor and supplementary motor regions, is left lateralized in nearly all RH and the overwhelming majority of nRH, regardless of the hand used in the gesture [19,21]. The small minority of left handed participants who are right lateralized for language seem to also be right lateralized for praxis [19]. During gesture planning left-handed participants, however, show more right parietal, premotor and supplemental motor activity, especially when the non-dominant right hand is used in the subsequent activity [21]. During motor execution, right handers show sensorimotor, premotor and supplementary motor activation contralateral to the hand used, with some ipsilateral activation when the non-dominant left hand is used. In contrast, left-handed participants show bilateral activation regardless of the hand used, including frontoparietal regions that extended beyond the regions seen in right handers. On direct comparison right handers show more left frontal activation while left handers showed more right SMA activation. Overall these results suggest that motor planning and execution involves more bilateral and

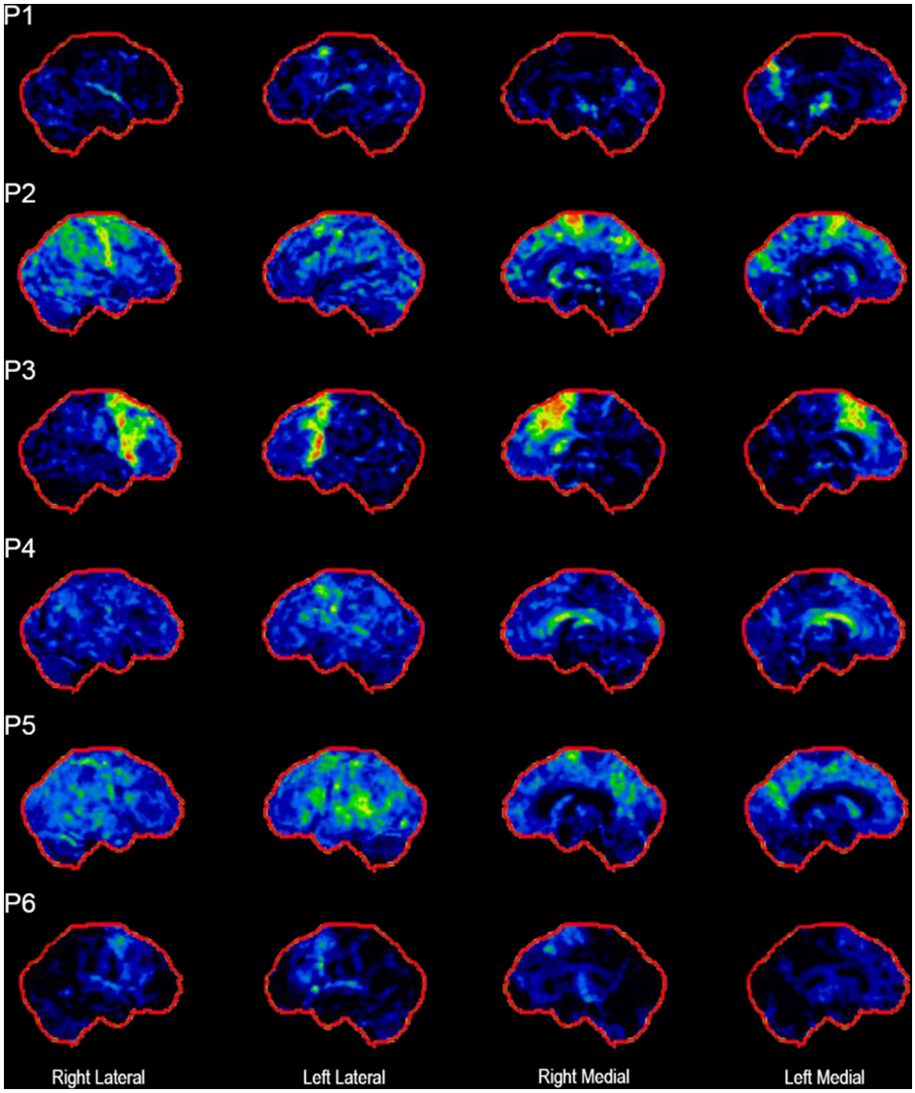

Fig. 3. FDG-PET statistical stereotactic surface projection maps of nRH participants.
See text and Table 3 for details.

distributed systems in left handers than right handers.

Recently, it has been argued that the network of regions underlying the motor aspects of segmental speech production is bilaterally distributed, involving the sensory and motor cortices in the area of the face/larynx, the premotor and inferior frontal regions, the supplementary motor area, basal ganglia structures and the cerebellum, among others [41], with the left hemisphere playing a dominant role in planning/programming aspects. Electrophysiological evidence also supports the bilateral distribution, with both hemispheres participating in sub-lexical sensory-motor transformations [42]. Some degree of bilateral representation is to be expected, given the mostly symmetric and simultaneous motor activity that underlies speech and the bilateral auditory input during monitoring. The fact that right sided strokes can result in lower facial apraxia and the fact that degenerative nonverbal oral apraxia is associated with bilateral atrophy offers further support [43,44]. During articulation, the supramarginal gyri are recruited into the abovementioned resting-state network bilaterally, but the left hemisphere remains the dominant influence with left hemispheric networks showing stronger integration [41]. This is consistent with decades of clinical experience, lesional case studies, split brain studies and intra-operative inhibition studies suggesting that speech is a specialization of the left hemisphere more so than the right (e.g [20,45,46].). Most stroke related apraxia of speech results from left sided motor/premotor damage, which further supports this lateralization [47]. Presumably, the left language network couples with the speech network during planning/programming of speech. There are multiple areas of overlap in the abovementioned “speech network” and the previously discussed “praxis network,” especially the supramarginal gyrus, premotor regions and SMA, suggesting these play a role in skilled motor movements regardless of the effector(s). The large proportion of PPAOS participants that go on to develop ideomotor apraxia supports this association. Right sided brain activity, beyond the expected involvement in the latter stages of the articulation process, where the motor strip serves as the final common pathway, may be more important for prosody and pragmatic aspects of speech [46]. Focal right sided damage can result in aprosody, supporting this distinction [48].

We hypothesize that nRH participants should show more right sided activity during speech planning and more widespread activity during articulation, as was found for limb praxis. This may, in turn, result in a suboptimal network configuration, both in terms of cost efficiency and signal-to-noise ratio. This may place the “praxis network” at higher risk in aging nRH patients. This is a testable hypothesis: the work on handedness and limb praxis can be extended to verbal and nonverbal oral praxis and the proportion of nRH in other motor disorders, such as CBS or PSP, can be evaluated, to name but two examples. What is clear from our data is that the hypothesis that a pattern of ipsilateral

language and hand dominance is indicative of an increased risk for developing a tauopathy, which by extension implies a lower risk for nRH, is inconsistent with the fact that nRH is represented at twice the expected rate in PPAOS, a disorder almost exclusively caused by an underlying tauopathy [6,7,9,10].

4.3. Limitations

Our study has several notable limitations. Handedness was assessed by asking the participant and their informant whether they identify as left handed, right handed or ambidextrous, during both the neurologic examination and neuropsychological testing. Although this is the same method used in prior studies of handedness in PPA [7], the limitations of the resulting dichotomization are plentiful. Future studies should aim to quantify handedness with the use of standardized tools like the Edinburgh Handedness Inventory, now available in short form [49]. Another limitation stems from the small numbers in this and prior studies [7]. It is worth noting that differential handedness distributions have been reported in other conditions, with larger cohorts, only to be dismissed by much larger meta-analyses [50,51]. Given the rarity of PPAOS, this is not a limitation that would be overcome easily. Finally, we did not have any pathological confirmation, cerebrospinal fluid or imaging biomarkers to assess the potential effect of handedness on underlying pathology. Asymmetric TDP-43 has been described in a left-handed PPA patient with right sided language lateralization [52], and asymmetric amyloid beta has also been described in right handed participants with PPA [53]. A prior paper from our group, which did not assess the effect of handedness, suggested that PPAOS is associated with fairly symmetric tau PET uptake [54]. Future biomarker studies in PPAOS and PPA should include handedness as a biological variable of interest.

5. Conclusions

In summary, we found that nRH is over represented in participants with PPAOS. Although caution is needed in its interpretation, the data are not consistent with prior hypotheses that differing hemispheric dominance for speech and language and dominant hand control is relatively protective against tau-related neurodegeneration. We have discussed alternative hypotheses to account for the higher rate of nRH and offered some testable hypotheses. In light of the lack of clinical differences between RH and nRH participants, we also attempted to offer a more nuanced view of handedness which may inform future studies into handedness and degenerative diseases. We did find more right motor/premotor involvement in nRH patients, and offered avenues to explore altered hemispheric specialization as a risk factor for PPAOS.

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Appendix A. Supplementary data

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