White Matter Damage in the Semantic Variant of Primary Progressive Aphasia

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ABSTRACT: *Background:* The semantic variant of primary progressive aphasia (svPPA) is a form of dementia, mainly featuring language impairment, for which the extent of white matter (WM) damage is less described than its associated grey matter (GM) atrophy. Our study aimed to characterise the extent of this damage using a sensitive and unbiased approach. *Methods:* We conducted a between-group study comparing 10 patients with a clinical diagnosis of svPPA, recruited between 2011 and 2014 at a tertiary reference centre, with 9 cognitively healthy, age-matched controls. From diffusion tensor imaging (DTI) data, we extracted fractional anisotropy (FA) values using a tract-based spatial statistics approach. We further obtained GM volumetric data using the *Freesurfer* automated segmentation tool. We compared both groups using non-parametric Wilcoxon rank-sum tests, correcting for multiple comparisons. *Results:* Demographic data showed that patients and controls were comparable. As expected, clinical data showed lower results in svPPA than controls on cognitive screening tests. Tractography showed impaired diffusion in svPPA patients, with FA mostly decreased in the longitudinal, uncinate, cingulum and external capsule fasciculi. Volumetric data show significant atrophy in svPPA patients, mostly in the left entorhinal, amygdala, inferior temporal, middle temporal, superior temporal and temporal pole cortices, and bilateral fusiform gyri. *Conclusions:* This syndrome appears to be associated not only with GM but also significant WM degeneration. Thus, DTI could play a role in the differential diagnosis of atypical dementia by specifying WM damage specific to svPPA.

RÉSUMÉ: **Des atteintes à la substance blanche du cerveau dans le cas de la variante sémantique de l'aphasie primaire progressive**. *Contexte:* La variante dite « sémantique » de l'aphasie primaire progressive (vsAPP) constitue une forme de démence de laquelle découlent principalement des troubles du langage. À l'inverse de l'atrophie de la substance grise associée à cette démence, on a été moins portés à décrire les atteintes à la substance blanche. Notre étude entend donc cerner l'étendue de ces atteintes au moyen d'une approche à la fois sensible et neutre. *Méthodes:* Nous avons effectué une étude intergroupe en comparant 10 patients ayant reçu un diagnostic clinique de vsAPP à 9 témoins en santé sur le plan cognitif. À noter que ces 10 patients ont été recrutés entre 2011 et 2014 dans un centre de soins médicaux tertiaires. C'est à partir de données obtenues grâce à l'imagerie par tenseur de diffusion (diffusion tensor imaging) que nous avons extrait, au moyen d'une approche privilégiant les statistiques spatiales basées sur les voies neuronales, des valeurs d'anisotropie fractionnelle (FA). Nous avons en outre obtenu des données volumétriques concernant la substance grise en utilisant l'outil de segmentation automatisée Freesurfer. Nous avons ensuite comparé ces deux groupes à l'aide de tests des rangs signés de Wilcoxon non-paramétriques, et ce, en veillant à appliquer une correction en vue de nombreuses comparaisons. *Résultats:* D'entrée de jeu, précisons que nos données démographiques ont révélé que les patients et les témoins étaient comparables. Comme il fallait s'y attendre, nos données cliniques ont montré, dans le cadre de tests de dépistage cognitif, que les résultats des patients atteints de vsAPP se sont révélés inférieurs à ceux des témoins. Des examens de tractographie ont par ailleurs montré une diffusion déficiente chez ces 10 patients, les valeurs de FA ayant surtout diminué dans les faisceaux longitudinaux et uncinés, dans le cingulum et la capsule externe. Quant à nos données volumétriques, elles ont révélé une atrophie notable chez les patients atteints de vsAPP, surtout dans les régions suivantes : cortex entorhinal gauche, amygdale, temporale inférieure, mésiotemporale, temporale supérieure, cortex temporo-polaires et lobules fusiformes bilatéraux. *Conclusions:* Le syndrome évoqué ci-dessus semble être associé non seulement à une dégénérescence de la substance grise mais aussi à une dégénérescence importante de la substance blanche. En précisant de manière spécifique l'atteinte à la substance blanche que sous-tend la vsAPP, l'imagerie par tenseur de diffusion pourrait donc être appelée à jouer un rôle dans l'établissement de diagnostics différentiels pour des démences atypiques.

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INTRODUCTION

Background/Rationale

Primary progressive aphasia[1] is a neurodegenerative disorder whose prominent feature is language impairment,[2] as opposed to early episodic memory or motor deficits that are predominant in other dementias. The semantic variant of primary progressive aphasia (svPPA), also called semantic dementia, is one of its three variants, alongside progressive non-fluent aphasia and logopenic progressive aphasia. These aphasias are forms or phenotypes of frontotemporal lobar degeneration,[3,4] a family of diseases that represent 10% of all dementias in adults <65 years old.[5,6] It has been often reported that logopenic PPA is most often Alzheimer's disease, and not a frontotemporal dementia per se.[7–9]

Clinically, features of svPPA include impairment in confrontation naming and single-word comprehension and may include surface dyslexia or dysgraphia, while repetition and speech production is preserved.[10] Pathologically, svPPA appears to be associated with ubiquitin and TDP-43.[4,11–13] Anatomically, changes in cortical grey matter (GM) have been well studied in svPPA, to the extent that imaging can be used as a supportive criterion for the diagnosis. These findings include the presence, on magnetic resonance imaging (MRI), of cortical atrophy located predominantly in the anterior temporal lobes, bilaterally but more severely in the left hemisphere, especially in its ventral and lateral regions.[14–19] In studies involving presymptomatic subjects, focusing on correlating genetics and imaging, researchers have found that GRN mutations are associated with GM changes in the striatum, insula and with early temporal and parietal atrophy, while MAPT mutations are associated mainly with temporal atrophy, particularly in its anteromedial portion.[20–23]

Comparatively, the extent of white matter (WM) damage in svPPA has been much less studied, in part due to the difficulty in recruiting large patient groups. Only a few reports[24–27] have addressed this topic (largest $N = 10$). They all made use of diffusion tensor imaging (DTI), a technique that allows the study of WM fibre tracts in MRI, and from which one can extract maps of fractional anisotropy (FA), a scalar value indicating the directionality of diffusion in axons, itself a proxy of microstructural damage in the brain.[28] These studies reported lower FA mostly lateralised in the left hemisphere[29] and affecting the postero-inferior longitudinal, uncinate and posterior cingulate fascicule,[24–27] in opposition to non-fluent primary progressive aphasia that appears to affect the left intrafrontal and frontostriatal fascicule.[30]

Furthermore, all of these cited WM studies but one used a region-of-interest rather than a tract-based statistical (TBSS)[31] approach to analyse FA maps. The latter is a whole-brain skeleton-based technique that is more sensitive than the ROI voxel-based technique, as demonstrated in a simulation study;[32] and hence that should provide a better resolution of WM damage in the brains of svPPA patients.

Objectives

We designed this study to increase our current knowledge of concurrent WM and GM damage in svPPA in a different study group. Our objectives were to localise and quantify cerebral GM and especially WM differences in patients with svPPA, compared with cognitively healthy controls, through automated cerebral segmentation and tract-based statistics of fractional anisotropy.

METHOD

Ethics

The ethics committee of the *Institut universitaire en santé mentale de Québec* approved the study (project #300-2012). Informed and free consent was obtained from each participant.

Study Design

We used a between-group experimental design, in which we compared patients with a diagnosis of svPPA with cognitively and neurologically healthy, age-matched control subjects. All participants were native French speakers from Quebec, Canada.

Setting and Participants

Patients – Ten patients who fulfilled current svPPA clinical criteria[1] and were being followed at *Clinique Interdisciplinaire de Mémoire* (*CHU de Québec*, Quebec City, Canada) between August 2013 and August 2014 were included in this study. These patients all had a diagnosis of svPPA confirmed by a neurologist, without family histories indicative of a possible genetic risk. Additionally, a comprehensive neuropsychological battery was administered to all participants. The most salient results of this battery included:

– Mild to moderate word production and anomia difficulties measured with a picture-naming task (Boston Naming Test)[33] and phonological, semantic and free fluency tasks (MEC Protocol);[34]
– Impaired verbal and non-verbal single-word comprehension, assessed with visual and oral word–picture matching tasks (BECLA battery)[35] and semantic association of pictures (pyramids and palm trees test);[36]
– Spared repetition (TEFREP)[37] and absence of apraxia of speech (PENO).[38]

Some of the patients also had impaired object recognition (object decision and object matching subtests, BORB battery)[39] with or without surface dyslexia (regular and irregular word and pseudoword reading test),[40] while others presented with surface dyslexia with unimpaired object recognition. They all were free of noticeable deficit on tests tapping other cognitive domains such as non-verbal episodic memory, visuospatial abilities (Rey-Osterrieth Complex Figure Test)[41] and working memory (forward and backward digit SPANs Wechsler Memory Scale IV).[42]

Controls – Cognitively healthy controls were recruited among patients' proxies and members of the community and were matched by age, gender, education and manual dominance to the svPPA patients. They were screened via telephone for inclusion criteria by means of a structured questionnaire. Then they went through the same neuropsychological battery as did the patients.

Neither patients nor controls had histories of either moderate or severe traumatic brain injury, cerebrovascular disease or intracranial surgery, encephalitis or meningitis. They had no history of a significant psychiatric syndrome, alcoholism or drug addiction or unstable medical or metabolic condition (e.g., uncontrolled diabetes, vitamin B12 or folic acid deficiency, hypothyroidism), nor any history of learning or reading

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Table 1: Demographic and clinical data for svPPA patients and controls

	Healthy controls (*n* = 9)	svPPA patients (*n* = 10)	*p*-value
Age	67 (67.1 ± 9.7)	68 (67.3 ± 9.1)	0.90
Gender (male)	77.8%	80.0%	0.94
Education (in years)	15 (15.9 ± 3.8)	16 (16.3 ± 5.0)	0.90
Manual dominance (right)	100%	100%	–
MoCA	25 (24.7 ± 1.8)	19 (18.9 ± 3.4)	0.001*
MMSE	28 (27.8 ± 1.5)	24 (23.7 ± 3.8)	0.01*

svPPA = semantic variant of primary progressive aphasia; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination.
*Statistically significant.
Results are presented as median (mean ± standard deviation).

difficulties. They were also screened for MRI compatibility by means of another questionnaire.

Data Sources and Measures

Above and beyond the tests previously mentioned, the demographic and clinical data included the presence or absence of semantic dementia, age, gender, education (in years), manual dominance, and global cognition assessed via the Montreal Cognitive Assessment Test (MoCA)[43] and Mini-Mental State Examination (MMSE).[44] Since both groups of participants were matched by age, gender, education and manual dominance, we did not make further sensitivity analyses. It would have been unlikely that the 10:9 ratio of patients and controls affected the volumetric or FA data.

MRIs were acquired within 4 weeks of the clinical assessment using the Canadian Dementia Imaging Protocol[45] (www.cdip-pcid.ca) on a 3-T magnetic resonance scanner (Philipps Medical Systems, Best, The Netherlands) at the IRM Québec radiology clinic in Quebec City. Specifically, the protocol included:

– An isotropic, 1 mm^3 3D T1-weighted sequence (TR = 7.3 ms; TE = 3.3 ms; flip angle = 9 degrees); and
– A 60-direction, 2 mm^3 isotropic diffusion imaging sequence (*b*-value = 1000).

For cerebral WM data, fractional anisotropy maps and tract-based statistics were obtained following these steps. First, we converted our native data from DICOM files to the NIFTI format using MRIcron (http://www.mricro.com/mricron). Then, we used FMRIB's Diffusion Toolbox[46] to create an FA image from the DTI data of each subject. This included eddy current correction, brain masking and diffusion tensor model fitting. Afterwards, we used the FMRIB Software Library 5.0.6[47] to perform voxel-wise analyses, following the TBSS approach.[31] There were five steps to this process: (1) pre-processing; (2) nonlinear alignment of all FA images to a standard-space image (FMRIB58_FA); (3) creation of the mean FA image and generation of its skeleton; (4) projection of every pre-aligned FA image on the study-specific template skeleton; and (5) generation of voxel-wise statistics with the Randomise tool, using the Threshold-Free Cluster Enhancement. The final output was a brain map in which we could identify voxels that were statistically different in FA between patients and controls. We used the Atlasquery tool to localise these voxels and

provide numerical FA values for each subject in each of the 48 regions of interest (ROIs) identified in the ICBM-DTI-81 WM labels atlas of the Laboratory of Brain Anatomical MRI at Johns Hopkins University.[48]

For GM analysis, we used an automated segmentation tool (*FreeSurfer*)[49,50] to segment the 3D T1-weighted image for all subjects, producing surfaces (mm), thicknesses (mm^2) and volumes (mm^3) for the whole brain and 44 different cortical and subcortical structures according to their atlases (DKT40 and ASEG[51]).

Statistical Methods

For all demographic, clinical and imaging data, we opted for non-parametric Wilcoxon rank-sum test to compare cases with controls, given the size of our sample and the robustness of the test. We used a significance level of *p*-value = 0.05, correcting for multiple comparisons using the false discovery rate (FDR) method.

Reporting

This study follows the recommendation of the STROBE Statement.[52]

RESULTS

Demographic and Clinical Data

Nineteen participants (10 svPPA and 9 controls) were recruited in this study. Every subject that was screened happened to be eligible for the study. Analysis of demographic data showed no significant difference between groups in age, gender, education or manual dominance. Clinical data showed significantly lower results for svPPA patients at both MoCA and MMSE tests, which was expected (see Table 1).

WM Analysis

Volumetric data showed that both groups had similar total WM volumes. Qualitative assessment of diffusion data demonstrated multiple WM regions where svPPA patients had significantly lower FA values, slightly more severely in the left hemisphere and temporal lobe. Statistical analysis of numerical FA values resulted in 16 out of 48 tract regions with significantly lower FA values in svPPA patients than in healthy controls, after FDR correction. The most significantly impaired regions were the right hippocampus and uncinate fasciculus tract regions, and the left external capsule and superior longitudinal fasciculus (see Table 2 and Figure 1).
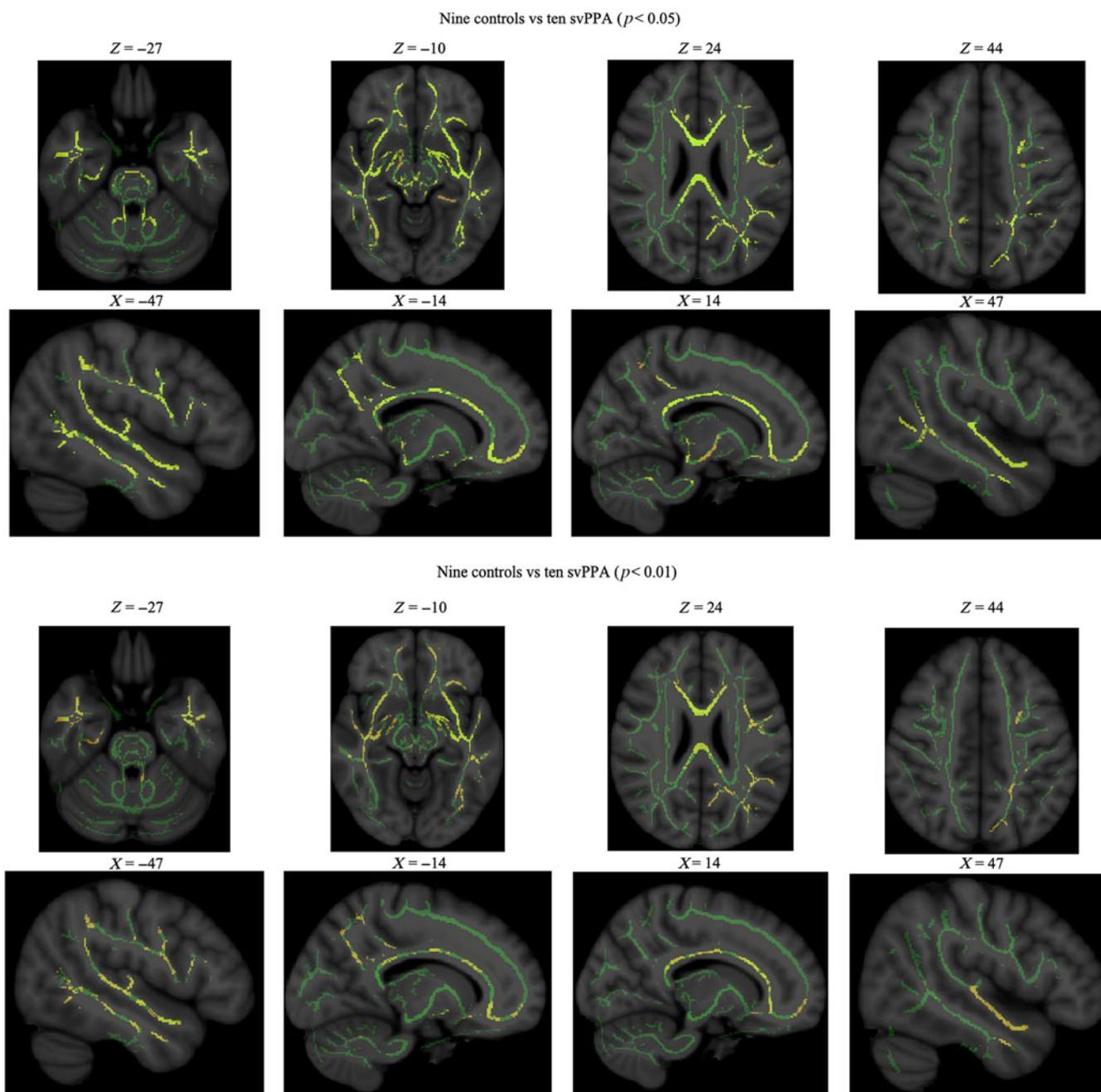
Nine controls vs ten svPPA ($p < 0.05$)

Nine controls vs ten svPPA ($p < 0.01$)

Figure 1: *WM maps: statistically significant differences in fractional anisotropy between svPPA patients and controls. svPPA, semantic variant of primary progressive aphasia.*

GM Analysis

Volumetric data showed that both groups had indistinguishable total intracranial capacity and total brain volumes. However, our group of svPPA patients had smaller subcortical and left hemispheric cortical GM volumes. When looking at specific ROIs, volumes were consistently lower in svPPA patients than in healthy controls, reaching significance in 22 of the 33 studied regions, after FDR correction. The most significant differences were noted in the left amygdala, entorhinal, fusiform, inferior temporal, middle temporal and superior temporal gyri, as well as in the temporal poles and right fusiform GM (see Table 3 and Figure 2).

Discussion

The semantic variant of primary progressive aphasia is a neurodegenerative disorder with language impairment as its hallmark. Previous literature reported cortical GM atrophy predominantly in the anterior temporal lobes, bilaterally but markedly in the left hemisphere. As for WM damage, literature is scant and based on a small number of studies and patients. Only a few reports have described abnormal diffusion, in one or more of the left postero-inferior longitudinal, uncinate, posterior cingulate fasciculi. Of these studies, only one used a more sensible tract-based approach instead of the ROI approach. We designed this study principally to address the knowledge gap we observed

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Table 2: WM study: fractional anisotropy data for svPPA patients and controls

WM tracts	Healthy controls	SD cases	*p*-value	FDR
Cingulum (right hippocampus)	0.48 (0.49 ± 0.03)	0.43 (0.42 ± 0.02)	0.0004	0.005*
External capsule (left)	0.43 (0.43 ± 0.02)	0.37 (0.37 ± 0.02)	0.0004	0.005*
Longitudinal fasciculus (left superior)	0.50 (0.51 ± 0.02)	0.47 (0.47 ± 0.02)	0.0004	0.005*
Uncinate fasciculus (right)	0.47 (0.48 ± 0.04)	0.41 (0.40 ± 0.04)	0.0004	0.005*
Cingulum (left cingulate gyrus)	0.58 (0.59 ± 0.03)	0.52 (0.52 ± 0.03)	0.001	0.010*
Cingulum (right cingulate gyrus)	0.54 (0.54 ± 0.04)	0.49 (0.49 ± 0.03)	0.002	0.012*
Fornix	0.38 (0.37 ± 0.09)	0.23 (0.24 ± 0.08)	0.002	0.012*
Uncinate fasciculus (left)	0.48 (0.48 ± 0.04)	0.39 (0.39 ± 0.04)	0.002	0.012*
Cerebellar peduncle (middle)	0.06 (0.06 ± 0.00)	0.06 (0.06 ± 0.00)	0.003	0.013*
Corpus callosum (genu)	0.65 (0.64 ± 0.02)	0.60 (0.60 ± 0.03)	0.003	0.013*
Fornix (left stria terminalis)	0.51 (0.51 ± 0.03)	0.46 (0.46 ± 0.02)	0.003	0.013*
Cerebellar peduncle (left superior)	0.63 (0.63 ± 0.02)	0.58 (0.57 ± 0.04)	0.009	0.029*
Cingulum (left hippocampus)	0.45 (0.46 ± 0.03)	0.41 (0.41 ± 0.02)	0.009	0.029*
External capsule (right)	0.40 (0.41 ± 0.02)	0.38 (0.38 ± 0.02)	0.009	0.029*
Sagittal stratum (right)	0.52 (0.53 ± 0.03)	0.49 (0.49 ± 0.02)	0.009	0.029*
Cerebral peduncle (right)	0.65 (0.65 ± 0.01)	0.63 (0.62 ± 0.03)	0.01	0.030*
Thalamic radiation (left posterior)	0.58 (0.57 ± 0.03)	0.53 (0.53 ± 0.03)	0.02	0.056
Cerebellar peduncle (left inferior)	0.17 (0.17 ± 0.01)	0.16 (0.15 ± 0.02)	0.03	0.072
Cerebellar peduncle (right inferior)	0.16 (0.16 ± 0.01)	0.15 (0.14 ± 0.02)	0.03	0.072
Cerebellar peduncle (right superior)	0.58 (0.57 ± 0.02)	0.54 (0.53 ± 0.04)	0.03	0.072
Sagittal stratum (left)	0.53 (0.54 ± 0.03)	0.50 (0.50 ± 0.03)	0.05	0.114
Cerebral peduncle (left)	0.67 (0.67 ± 0.02)	0.65 (0.64 ± 0.03)	0.07	0.146
Longitudinal fasciculus (right superior)	0.49 (0.48 ± 0.02)	0.48 (0.47 ± 0.02)	0.07	0.146
Corpus callosum (splenium)	0.74 (0.74 ± 0.02)	0.73 (0.73 ± 0.02)	0.08	0.154
Fornix (right stria terminalis)	0.50 (0.50 ± 0.04)	0.47 (0.46 ± 0.04)	0.08	0.154
Corpus callosum (body)	0.68 (0.67 ± 0.03)	0.61 (0.62 ± 0.03)	0.10	0.185
Internal capsule (left anterior limb)	0.55 (0.54 ± 0.03)	0.52 (0.53 ± 0.02)	0.12	0.213
Tapetum (left)	0.61 (0.58 ± 0.08)	0.53 (0.54 ± 0.06)	0.14	0.240
Corona radiata (left anterior)	0.43 (0.42 ± 0.03)	0.41 (0.40 ± 0.03)	0.16	0.256
Pontine crossing tract	0.27 (0.27 ± 0.01)	0.26 (0.27 ± 0.02)	0.16	0.256
Superior fronto-occipital fasciculus (left)	0.48 (0.48 ± 0.04)	0.51 (0.51 ± 0.04)	0.19	0.285
Tapetum (right)	0.56 (0.53 ± 0.08)	0.49 (0.49 ± 0.06)	0.19	0.285
Corona radiata (left superior)	0.49 (0.48 ± 0.02)	0.50 (0.51 ± 0.04)	0.25	0.343
Corticospinal tract (left)	0.36 (0.36 ± 0.02)	0.35 (0.35 ± 0.02)	0.25	0.343
Internal capsule (left retrolenticular)	0.57 (0.57 ± 0.02)	0.55 (0.55 ± 0.02)	0.25	0.343
Internal capsule (right anterior limb)	0.55 (0.54 ± 0.02)	0.51 (0.52 ± 0.03)	0.28	0.373
Thalamic radiation (right posterior)	0.56 (0.55 ± 0.03)	0.52 (0.53 ± 0.04)	0.32	0.415
Corona radiata (left posterior)	0.47 (0.47 ± 0.02)	0.48 (0.48 ± 0.03)	0.36	0.432
Corona radiata (right anterior)	0.42 (0.42 ± 0.03)	0.40 (0.41 ± 0.02)	0.36	0.432
Corona radiata (right superior)	0.47 (0.46 ± 0.02)	0.47 (0.48 ± 0.04)	0.36	0.432
Internal capsule (left posterior limb)	0.67 (0.67 ± 0.01)	0.68 (0.68 ± 0.04)	0.56	0.656
Medial lemniscus (left)	0.29 (0.29 ± 0.01)	0.29 (0.29 ± 0.02)	0.74	0.826
Medial lemniscus (right)	0.29 (0.29 ± 0.01)	0.29 (0.30 ± 0.02)	0.74	0.826
Corona radiata (right posterior)	0.47 (0.47 ± 0.02)	0.47 (0.47 ± 0.03)	0.81	0.864

(Continued)

Table 2: *(Continued)*

WM tracts	Healthy controls	SD cases	*p*-value	FDR
Internal capsule (right posterior limb)	0.64 (0.64 ± 0.02)	0.64 (0.65 ± 0.03)	0.81	0.864
Corticospinal tract (right)	0.35 (0.35 ± 0.01)	0.34 (0.34 ± 0.03)	0.87	0.908
Internal capsule (right retrolenticular)	0.55 (0.54 ± 0.02)	0.54 (0.54 ± 0.02)	0.93	0.930
Superior fronto-occipital fasciculus (right)	0.45 (0.45 ± 0.03)	0.45 (0.46 ± 0.05)	0.93	0.930

FDR = false discovery rate; svPPA = semantic variant of primary progressive aphasia; WM = white matter.
*$p < 0.05$ (false discovery rate corrected).Results are presented as median (mean ± standard deviation).
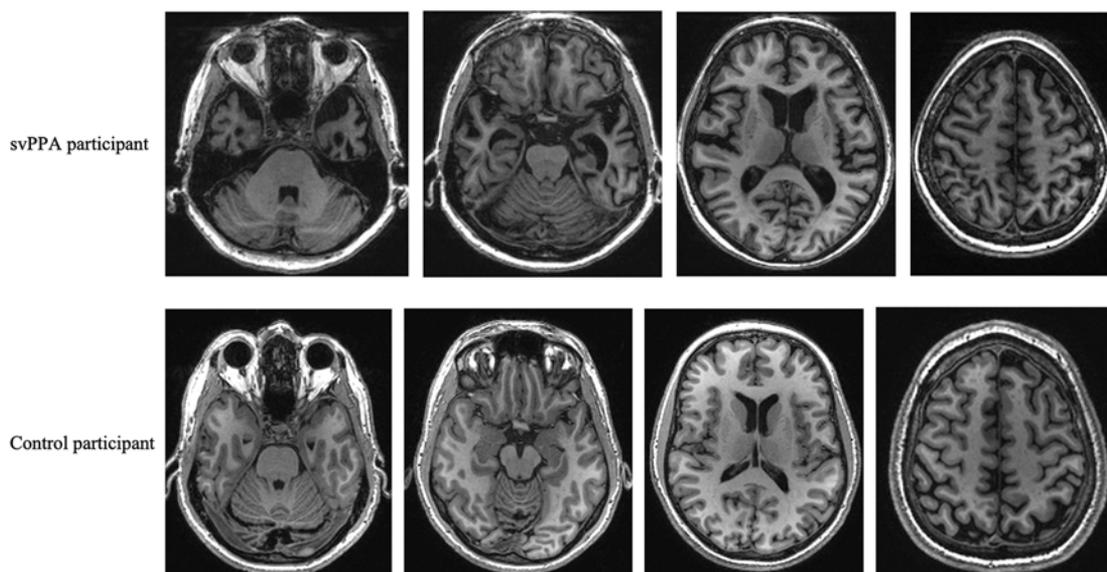

Figure 2: GM images: examples of atrophy in a svPPA patient compared with a cognitively healthy control. svPPA, semantic variant of primary progressive aphasia.

concerning WM damage in svPPA, in addition to validating the characterisation of GM atrophy. Our ultimate goal is to use such information to improve diagnosis, as we know that an early diagnosis might lead to earlier care and, in turn, decreased social difficulty.[10]

Our first aim was to characterise cerebral WM lesions in our cohort of svPPA patients, compared with cognitively healthy, age-matched control subjects. Using a tract-based whole-brain approach, we found FA differences between our two groups, including statistically lower FA in the right hippocampus and uncinate fasciculus tract regions, as well as the left external capsule and superior longitudinal fasciculus tracts. Our second aim was to characterise cerebral GM lesions in these same patients. Using volumetric tools, we found significant atrophy differences between patients and controls. Notably, larger GM atrophy in svPPA patients was found in the left amygdala, in the left entorhinal, fusiform, inferior temporal, middle temporal and superior temporal gyri, left temporal pole and right fusiform gyrus.

Findings

Our WM results showed a significant diminution of FA in different tracts, which is known to demonstrate microstructural damages in these fasciculi. In accordance with some of the few reports available, we found impairment of the longitudinal fascicule and some of the uncinate fascicule;[24,26,27,53]

however, we also found that the damage was more extensive and less clearly lateralised than previously thought, including more extensive than GM atrophy. The latter may constitute an interesting line of inquiry as to the longitudinal progression of the disease.

Our GM results showed a lateralisation of atrophy related to svPPA, as it was more severe in the left hemisphere. We also found significant atrophy in the temporal lobes. These results are in line with those previously described in literature.[40] This is also in accordance with fundamental neuroimaging studies on the cerebral regions associated with language,[40] which have shown that the left anterior temporal lobe is part of the semantic brain network, whereas other functions like syntax would be processed more in the posterior temporal or frontal lobes.

Hypotheses

Two different hypotheses have been proposed to explain the pattern of WM damage.[24,54–59] The first one posits an extrinsic cause. Following GM atrophy by neuronal loss, a process of Wallerian degeneration or axonal degeneration begins, hence causing WM loss. Considering the severity of GM damage that we also observed in our cohort, this hypothesis would explain why not only tracts close to the left temporal lobe, but also other connecting tracts that are located more distantly, are impaired. The second hypothesis is an intrinsic direct axonal pathology.[60] This explanation puts

Table 3: GM study: volumetric data for svPPA cases and controls

Anatomical regions	Healthy controls ($n = 9$)	svPPA cases ($n = 10$)	p-value	FDR
Inferior temporal (left)	9258 (9424 ± 791)	4688 (5155 ± 1238)	0.0003	0.003*
Entorhinal (left)	1077 (1127 ± 201)	633 (681 ± 157)	0.0004	0.003*
Temporal pole (left)	2304 (2257 ± 212)	904 (943 ± 195)	0.0003	0.003*
Middle temporal (left)	9948 (9943 ± 1314)	5091 (5151 ± 1137)	0.0003	0.003*
Superior temporal (left)	10299 (10510 ± 1078)	6920 (6949 ± 1336)	0.0004	0.003*
Parahippocampal (right)	1943 (2001 ± 260)	1437 (1417 ± 303)	0.001	0.004*
Amygdala (left)	1318 (1362 ± 229)	878 (840 ± 317)	0.0008	0.004*
Fusiform (left)	9472 (9724 ± 1200)	5415 (5661 ± 1323)	0.0006	0.004*
Fusiform (right)	9350 (9354 ± 1430)	6514 (6691 ± 1031)	0.0008	0.004*
Inferior temporal (right)	8993 (8997 ± 985)	6753 (6653 ± 724)	0.001	0.004*
Amygdala (right)	1554 (1602 ± 287)	1066 (1087 ± 248)	0.001	0.004*
Hippocampal (left)	3636 (3678 ± 425)	2429 (2435 ± 659)	0.001	0.004*
Entorhinal (right)	968 (938 ± 165)	621 (644 ± 140)	0.002	0.005*
Parahippocampal (left)	2066 (2136 ± 342)	1297 (1426 ± 390)	0.002	0.005*
Left cortical GM	205579 (203100 ± 16743)	172081 (172812 ± 15797)	0.002	0.005*
Temporal pole (right)	2091 (2110 ± 162)	1132 (1220 ± 452)	0.002	0.005*
Subcortical GM	58410 (59075 ± 5179)	48256 (49102 ± 6890)	0.003	0.008*
Middle temporal (right)	9778 (10775 ± 1511)	8403 (8019 ± 1518)	0.004	0.009*
Insula (left)	6465 (6220 ± 712)	4929 (5075 ± 654)	0.004	0.009*
Superior temporal (right)	10388 (10402 ± 1280)	7723 (8117 ± 1273)	0.005	0.011*
Total cortical GM	412642 (407724 ± 34596)	351598 (362632 ± 61407)	0.007	0.014*
Bankssts (left)	2505 (2362 ± 512)	1728 (1712 ± 366)	0.007	0.014*
Total GM	566007 (555670 ± 44013)	487394 (501518 ± 44157)	0.03	0.055
Corpus callosum (mid-ant)	395 (442 ± 135)	289 (301 ± 116)	0.03	0.055
Corpus callosum (mid-post)	316 (329 ± 69)	213 (229 ± 121)	0.04	0.068
Transverse temporal (left)	1051 (1042 ± 229)	885 (889 ± 119)	0.04	0.068
Right cortical GM	207062 (204623 ± 17927)	182927 (189819 ± 16269)	0.05	0.081
Hippocampal (right)	3761 (3666 ± 415)	2986 (3174 ± 694)	0.06	0.094
Insula (right)	6357 (6515 ± 859)	5488 (5746 ± 859)	0.07	0.106
Corpus callosum (anterior)	822 (799 ± 223)	542 (496 ± 381)	0.08	0.117
Lingual (left)	6162 (6212 ± 649)	5244 (5436 ± 1114)	0.1	0.142
Corpus callosum (posterior)	854 (805 ± 241)	702 (557 ± 424)	0.14	0.193
Corpus callosum (central)	340 (353 ± 80)	295 (271 ± 105)	0.16	0.213
Bankssts (right)	2308 (2327 ± 426)	1908 (2052 ± 419)	0.19	0.232
Brain (without ventricles)	1031325 (101514 ± 86458)	886917 (940821 ± 108507)	0.19	0.232
Inferior parietal (left)	10365 (10771 ± 1378)	9947 (9664 ± 1640)	0.19	0.232
Left cortical WM	215561 (215029 ± 21759)	190731 (201804 ± 30910)	0.21	0.250
Total brain	1050500 (1046374 ± 94260)	945580 (1004021 ± 120333)	0.32	0.371
Transverse temporal (right)	730 (802 ± 223)	792 (778 ± 81)	0.36	0.406
Inferior parietal (right)	13239 (12956 ± 1717)	12312 (12388 ± 1495)	0.41	0.451
Total cortical WM	437685 (432584 ± 44871)	395650 (415799 ± 64891)	0.51	0.534
Total intracranial	1464158 (1445800 ± 157761)	1499366 (1514466 ± 167622)	0.51	0.534
Right cortical WM	222124 (217554 ± 23147)	204918 (213994 ± 34068)	0.68	0.696
Lingual (right)	6155 (6082 ± 622)	5938 (6026 ± 724)	0.74	0.740

GM = grey matter; svPPA = semantic variant of primary progressive aphasia; Bankssts = banks of the superior temporal sulcus; WM = white matter.
*$p < 0.05$ (false discovery rate corrected). Results are presented as median (mean ± standard deviation). Units are mm^3.

forward that intrinsic brain networks propagate WM disease, either by means of a process of neuroinflammation or by a cascade of misfolded proteins (prion-like),[61] an hypothesis put forward recently in a case of a novel prion protein variant in a patient with svPPA.[62]

Since our study is purely descriptive and cross-sectional, we cannot support firmly either hypothesis; however, the significantly large extent of WM atrophy would tend to support the intrinsic theory. Longitudinal studies are needed to understand the evolution of GM and WM damage in the brain, and hence confirm or infirm either hypothesis.

Strengths and Limitations

Compared with similar studies in the literature, and given the prevalence of svPPA in the population, the number of patients that we were able to recruit is a strength insofar as it allows us to compare directly with other studies of similar, or smaller, sizes, even though it still implied the use of non-parametric tests, with their inevitably lower statistical power. Furthermore, our inclusion and exclusion criteria prevented confounding factors from altering the internal validity of our results, while maximising participant recruitment. Finally, the whole-brain TBSS approach has many advantages such as correcting for misalignment, registration and smoothing, and removing the need to determine *a priori* ROI for the analysis, which would imply the use of a yet-incomplete knowledge of connectomics.

In contrast, there were some limitations arising from these same measurement techniques. The first comes from the use of DTI, as it is known that the diffusion tensor model has limited sensitivity to crossing fibres. Future studies could use high-angular-resolution diffusion imaging[63] to alleviate this problem. The second limitation relating to the technique comes from the choice of FA as our sole metric to evaluate WM microstructural changes. The use of apparent diffusion coefficient, or axial, radial and mean diffusivity, could have improved the sensitivity of our study. It is indeed known that FA is a scalar value, and that different combinations of diffusion tensor eigenvalues that have changed concurrently could generate identical FA values.[54] However, FA is a known, oft-reported metric that captures the essential changes related to WM integrity; employing other techniques could only uncover further areas or a deeper level of WM damages. Equally, TBSS will also be subject to reduced sensibility whenever fibres cross, for similar reasons as mentioned previously. Finally, the atlas used to extract numerical values remains composed of rather large structures that may end up masking small, sub-regional effects. The Human Connectome Project[64] aims to improve our knowledge of WM tracts and is currently addressing this issue.

Our results in a French-speaking population are comparable with previous studies conducted on native speakers of other languages, mostly English. This means that, in terms of external validity, language does not seem to be a concern. This could lead to multicentric studies, without language barriers, involving a higher number of subjects in future studies, especially those on a longitudinal basis and those correlating clinical, anatomical and pathological data. As well, to better understand the notions of cerebral lateralisation and brain plasticity, it would also be of interest to include, as much as available, left-handed patients to assess if findings differ for this group.

CONCLUSION

In summary, our study confirms known GM atrophy in svPPA patients, as well as validates WM damage using a more sensitive and unbiased approach than previously reported. MRI and DTI appear to have the potential to occupy an important place in the initial investigation of dementia and could eventually be very useful in the differential diagnosis of atypical dementia, to characterise, as precisely as possible, the cerebral damage in one patient and to link it to a specific disease through its imaging signature.

DISCLOSURES

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

LOB: Study conception and design, analysis and interpretation of data, manuscript drafting and approval for publication.

MAW: Contribution to conception and design of study, interpretation of data, critical revision of manuscript for important intellectual content, and approval for publication.

RL: Patient recruitment, interpretation of data, critical revision of manuscript for important intellectual content, and approval for publication.

SD: Contribution to conception and design of study, interpretation of data, critical revision of manuscript for important intellectual content, and approval for publication.

All authors agree to be accountable for all aspects of the work.

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