RESEARCH PAPER

Acta Neurobiol Exp 2025, 85: 29–37
DOI: 10.55782/ane-2025-2621

Regional cerebral blood flow correlated with aphasia in dementia of the Alzheimer's type and frontotemporal lobar degeneration

Miho Ota[1]*, Yuko Koshibe[1], Ayako Kitabatake[2], Masashi Tamura[1], Takumi Takahashi[1], Kiyotaka Nemoto[1], Tetsuaki Arai[1]

[1] Department of Psychiatry, Division of Clinical Medicine, Institute of Medicine, University of Tsukuba, Ibaraki, Japan
[2] Department of Clinical Psychology, University of Tsukuba Hospital, Ibaraki, Japan
**Email: ota@md.tsukuba.ac.jp*

Individuals with neurocognitive disorders such as dementia of the Alzheimer's type (DAT) and frontotemporal lobar degeneration sometimes show characteristic language dysfunctions. As neurocognitive disorders progress, different types of aphasia may present. To evaluate the disease-related changes of language functions, and to determine the correlation between the regional cerebral blood flow (rCBF) and language dyfunctions in patients with DAT or the behavioral variant of frontotemporal dementia (bvFTD) or semantic dementia (SD), we used a scale for speech and reading impairment in Japanese (the Standard Language Test for Aphasia [SLTA]), and perfusion single photon emission computed tomography, and we analyzed the relationships among them. Significant differences were identified among the DAT, SD, and bvFTD groups in the SLTA subscales concerning *kanji* (morphographic) words. There were positive correlations between the SLTA subscales concerning *kanji* words and the rCBF in left temporo-occipital regions. The patients with bvFTD showed relative rCBF preservation in the posterior cerebrum compared with the DAT and SD patients. Our results indicate that aphasia for Japanese *kanji* words might be related to the dysfunction of temporo-occipital regions, and they suggest that in patients with bvFTD, preserving the CBF in the posterior cerebrum might help maintain the ability to handle morphographic words such as *kanji*.

Key words: aphasia, behavioral variant frontotemporal dementia, cerebral blood flow, dementia of the Alzheimer's type, semantic dementia

INTRODUCTION

Neurocognitive disorder is a general term that means clinical syndromes of cognitive dysfunction involving functions such as memory, thinking, comprehension, and language. Regarding language, a classification has been proposed based on the clinical features of primary progressive aphasia (PPA) and its three main subtypes: nonfluent/agrammatic variant, semantic variants, and logopenic variants (Gorno-Tempini et al., 2011). The syndrome of nonfluent/agramm variant PPA is characterized by expressive agrammatism and/or apraxia of speech. Impaired naming and single-word comprehension are the core clinical features of semantic variant PPA, and anomia are the feature of logopenic variant PPA. Among these language classifications, the nonfluent/agrammatic-variant and semantic-variant PPAs have been regarded as frontotemporal lobar degeneration (FTLD) (Neary et al., 1998), whereas the logopenic variants have sometimes been observed during the course of dementia of the Alzheimer's type (DAT) (Gorno-Tempini et al., 2011). FTLD refers to a group of disorders caused by progressive nerve cell loss in the frontal and temporal lobes, and FTLD differs from DAT (The Lund & Manchester

Received 11 September 2024, accepted 10 March 2025

Groups, 1994). FTLD consists of semantic dementia (SD), progressive non-fluent aphasia (PNFA), and behavioral-variant FTD (bvFTD), the latter of which is characterized by disinhibition, emotional blunting, apathy, and compulsive or ritualistic behaviors. Non-fluent/agrammatic variant PPA is the main feature of PNFA, and semantic variants PPA is the core symptom of SD. Several neuroimaging studies that focused on the disease-related changes of the human brain revealed that bvFTD involves atrophy and hypometabolism in the prefrontal cortex and anterior temporal lobes, with relative sparing of more posterior regions, and SD is characterized by asymmetrical anteroposterior gradient atrophy and hypometabolism in anterior temporal regions (Whitwell, 2019; Planche et al., 2023; Ward et al., 2023). The discrimination of these diseases is clinically important, and the utility of both MR imaging and ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) in the diagnosis of FTLD has already been well established (Ward et al., 2023). However, it is sometimes difficult to distinguish bvFTD from SD by the atrophic pattern visualized by MRI. In addition, some patients with DAT have shown asymmetrical atrophy in the temporal lobe and difficulty in speaking (Herholz, 2022). Further, as neurocognitive disorders progress, different types of aphasia may become mixed.

We conducted the present study to clarify the differences among these disease-related clinical symptoms, e.g., cognitive impairment and aphasia, in patients with neurocognitive disorders (SD, DAT, or bvFTD). We also assessed the disease-related changes in our subjects' regional cerebral blood flow (rCBF) by using ^{99m}Tc-ethyl cysteinate dimer (ECD) single photon emission computed tomography (SPECT), and evaluated the correlation between rCBF and dysfunctions. We hypothesized that the rCBF in the left temporo-occipital region would be correlated with morphographic ability, which is often detected in patients with SD.

METHODS

Patients

We enrolled patients who had been diagnosed with DAT (n=19, all patients were right handed), bvFTD (n=16, all patients were right handed), or SD (n=16, all patients were right handed) by trained psychiatrists (M.O, M.T, T.T, or T.A.). The diagnostic criteria for DAT outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). The criteria for bvFTD were those developed by the International Behavioural Variant FTD Criteria Consortium (Rascovsky et al., 2011), and the criteria used to diagnose SD were described elsewhere (Neary et al., 1998; Gorno-Tempini et al., 2011). The patients' characteristics are summarized in Table 1.

All of the patients had completed the Mini-Mental State Examination (MMSE) for cognitive functions (Folstein et al., 1975) and the Standard Language Test of Aphasia (SLTA) for language functions (Mimura et al., 1998; Takaya et al., 2020). Each patient underwent an examination by ^{99m}Tc-ECD SPECT for the evaluation of their rCBF volume. The mean duration between the SLTA and SPECT scan was 34.3±52.7 days. After the study was explained to each patient, his or her written informed consent for participation in the study was obtained. The study was approved by the Medical Ethics Committee of the University of Tsukuba Hospital, Japan (reference no. H29-315).

Language evaluation

The SLTA is a aphasia assessment tool containing 26 items and was designed to classify and evaluate the severity of aphasia of Japanese speakers, examining factors such as naming, auditory comprehension, reading, writing, and the dictation of *kana* (the Japanese syllabary) and *kanji* (the Japanese morphogram) letters and sentences (Table 2).

Table 1. Demographic and biochemical parameters of the patients with Alzheimer's disease and frontotemporal lobar degeneration.

	DAT	bvFTD	SD	ANOVA
	n=19	n=16	n=16	p-value
Age (years)	74.0 ± 6.1	69.1 ± 7.9	72.1 ± 7.6	0.14
Men / women	9 / 10	8 / 8	7 / 9	0.94
Duration of illness (years)	3.7 ± 3.5	3.5 ± 3.2	3.3 ± 2.6	0.90
Education (years)	13.1 ± 2.7	13.3 ± 2.5	14.1 ± 3.1	0.52
MMSE total	17.7 ± 5.8	22.6 ± 7.6	21.6 ± 5.8	0.07

The data are mean ± std. deviation. DAT: dementia of Alzheimer's type; bvFTD: behavior variant frontotemporal dementia; SD: semantic dementia; ANOVA: analysis of variance; MMSE: mini mental state examination.

Table 2. Scores of cognitive tests in patients with Alzheimer's disease and frontotemporal lobar degeneration.

		HC	DAT	bvFTD	SD	ANCOVA
Standard Language Test for Aphasia		Mean ± SD	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	*P* value
(1)	Auditory comprehension of words (to point at pictures)	10.0 ± 0.2	10.0 ± 0.2 (10–9)	10.0 ± 0.0 (10–10)	9.3 ± 1.7 (10–5)	0.114
(2)	Auditory comprehension of short sentences (to point at pictures)	9.5 ± 0.8	9.1 ± 1.6 (10–4)	8.8 ± 1.7 (10–4)	8.6 ± 1.9 (10–4)	0.769
(3)	Follow verbal commands	9.6 ± 0.7	7.4 ± 2.7 (10–1)	7.5 ± 2.7 (10–1)	4.8 ± 4.0 (10–0)	0.053
(4)	Auditory comprehension (to point at Kana letters)	10.0 ± 0.1	9.7 ± 0.8 (10–7)	9.4 ± 1.8 (10–3)	10.0 ± 0.0 (10–10)	0.534
(5)	Speaking object naming	19.6 ± 0.8	16.0$^{\$}$ ± 4.7 (20–4)	17.1* ± 4.9 (20–1)	10.1$^{\$*}$ ± 5.8 (19–0)	0.001
(6)	Word repetition	10.0 ± 0.1	9.9 ± 0.4 (10–8)	9.6 ± 1.0 (10–6)	10.0 ± 0.0 (10–10)	0.228
(7)	Explain behavior in pictures	9.9 ± 0.4	9.0 ± 1.7 (10–3)	8.7 ± 2.7 (10–1)	7.5 ± 2.4 (10–2)	0.234
(8)	Verbal explanation of picture story	5.8 ± 0.6	5.0 ± 0.9 (6–3)	4.2 ± 1.4 (6–1)	4.5 ± 1.4 (6–1)	0.440
(9)	Sentence repetition	4.5 ± 0.8	3.3 ± 1.1 (5–1)	3.9 ± 1.3 (5–1)	3.6 ± 1.2 (5–1)	0.564
(10)	Verbal fluency	12.6 ± 4.5	7.4 ± 4.7 (21–0)	8.0 ± 5.6 (16–0)	4.8 ± 5.0 (13–0)	0.219
(11)	Reading aloud Kanji words	5.0 ± 0.4	4.8 ± 0.5 (5–3)	4.8 ± 0.5 (5–3)	4.2 ± 1.3 (5–0)	0.053
(12)	Reading aloud Kana letters	10.0 ± 0.2	10.0 ± 0.0 (10–10)	9.8 ± 0.8 (10–7)	9.7 ± 0.8 (10–7)	0.404
(13)	Reading aloud Kana words	5.0 ± 0.1	5.0 ± 0.0 (5–5)	5.0 ± 0.0 (5–5)	5.0 ± 0.0 (5–5)	
(14)	Reading aloud short sentences	4.9 ± 0.3	4.8 ± 0.8 (5–2)	4.7 ± 0.8 (5–2)	4.8 ± 0.8 (5–2)	0.988
(15)	Reading comprehension of Kanji words (to point at pictures)	9.9 ± 0.8	10.0 ± 0.0 (10–10)	9.9 ± 0.3 (10–9)	9.0 ± 2.7 (10–0)	0.122
(16)	Reading comprehension of Kana words (to point at pictures)	10.0 ± 0.1	10.0 ± 0.0 (10–10)	10.0 ± 0.0 (10–10)	9.3 ± 2.1 (10–3)	0.135
(17)	Reading comprehension of short sentences (to point at pictures)	9.6 ± 1.0	9.6 ± 1.2 (10–5)	9.2 ± 2.0 (10–2)	8.7 ± 2.6 (10–0)	0.452
(18)	Reading comprehension (to obey written commands)	9.4 ± 0.5	7.7 ± 3.0 (10–0)	7.8 ± 3.1 (10–1)	6.6 ± 3.6 (10–0)	0.639
(19)	Writing words with Kanji (to represent pictures)	4.2 ± 1.1	2.6 ± 1.5 (5–0)	3.8* ± 1.5 (5–0)	2.4* ± 1.9 (5–0)	0.017
(20)	Writing words with Kana (to represent pictures)	4.8 ± 0.7	3.7 ± 1.9 (5–0)	4.0 ± 1.5 (5–0)	3.6 ± 1.9 (5–0)	0.833
(21)	Narrative writing	5.2 ± 1.1	4.3 ± 1.7 (6–1)	4.4 ± 1.8 (6–0)	4.1 ± 1.5 (6–1)	0.745
(22)	Dictation of Kana letters	9.7 ± 1.1	8.7 ± 2.7 (10–0)	9.6 ± 1.0 (10–6)	9.9 ± 0.3 (10–9)	0.129
(23)	Dictation of Kanji words	4.3 ± 1.0	2.7 ± 1.6 (5–0)	3.9* ± 1.5 (5–0)	3.0* ± 1.5 (5–0)	0.028
(24)	Dictation of Kana words	4.8 ± 0.8	4.2 ± 1.4 (5–0)	4.3 ± 1.4 (5–0)	4.8 ± 0.4 (5–4)	0.378
(25)	Dictation of short sentences	4.8 ± 1.5	3.9 ± 1.8 (5–0)	3.7 ± 1.9 (5–0)	4.4 ± 1.0 (5–2)	0.603
(26)	Calculation	16.3 ± 4.2	11.6 ± 5.1 (19–0)	12.4 ± 5.7 (20–1)	15.4 ± 3.7 (20–9)	0.143

HC: healthy controls; DAT: dementia of Alzheimer's type; bvFTD: behavior variant frontotemporal dementia; SD: semantic dementia; ANCOVA: analysis of covariance; $^{\#}$: The difference between DAT and bvFTD reached $p<0.05$ after *post hoc* t test; $^{\$}$: The difference between DAT and SD reached $p<0.05$ after *post hoc* t test; *: The difference between bvFTD and SD reached $p<0.05$ after *post hoc* t test.

SPECT data acquisition and analysis

For the measurement of rCBF, the patient received an intravenous injection of 600 MBq of ^{99m}TC-ECD and was then scanned by a multidetector SPECT machine (E.CAM; Siemens Medical, Malvern, PA) and a high-solution collimator (LEHR; Siemens Medical). The details have been described (Boku et al., 2022).

For the normalization of each patient's rCBF data, we first normalized the individual rCBF images by using statistical parametric mapping 12 (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2021b (MathWorks, Natick, MA), using the reference template 'SPECT.nii', which is the standard image for SPM12. Each normalized image was smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 6-mm.

Statistical analyses

We first assessed the differences in the patients' cognitive and language functions among the three diagnostic groups (SD, DAT, and bvFTD) by performing an analysis of covariance (ANCOVA) adjusting for age, gender, and education, and we used the Bonferroni correction for a multiple comparison test. The statistical analyses were performed using SPSS Statistics for Windows 27.0 software (SPSS Japan, Tokyo).

We next evaluated the differences the three groups' rCBF data using the SPM12 toolbox, controlling for age, sex, and education. Results were considered significant if a single-voxel p threshold <0.001 (uncorrected) and a cluster size-level threshold of p<0.05 (uncorrected) were obtained. We then analyzed the correlations between rCBF volumes and MMSE and SLTA subscale scores in all of the participants by using the SPM12 toolbox and considering the impacts of age, sex, and education. The results were interpreted as significant if a single-voxel p threshold<0.05 (family-wise error corrected) and a cluster size-level threshold of p<0.05 (uncorrected) were obtained.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the DAT, SD, and bvFTD groups. There were no significant differences among the groups in any of these characteristics, including global cognitive function calculated by the MMSE total score, although the patients' MMSE subscale scores, i.e., 'orientation (time)' and 'recall' scores were differed significantly among the groups, as shown in Table 3. The patients' SLTA subscale scores differed significantly among the groups, as shown in Table 2. The averages of subscales listed in the SLTA manual are also presented in Table 2. Regarding the SLTA, the SD patients' naming scores

Table 3. Scores of cognitive tests in patients with Alzheimer's disease and frontotemporal lobar degeneration.

	DAT	bvFTD	SD	ANCOVA	
MMSE	Mean ± SD	Mean ± SD	Mean ± SD	*F* value	*P* value
Orientation (time)	2.8# ± 1.6	3.9 ± 1.9	4.3# ± 0.9	4.0	0.025
Orientation (place)	3.2 ± 1.6	4.0 ± 1.3	3.4 ± 1.6	1.4	0.264
Registration	2.5 ± 1.0	2.7 ± 0.6	2.9 ± 0.3	0.7	0.481
Attention / calculation	1.9 ± 1.8	2.7 ± 2.2	3.1 ± 2.0	1.5	0.231
Recall	0.2# ± 0.5	1.6# ± 1.3	0.8 ± 1.2	6.6	0.003
Naming	1.8 ± 0.5	1.9 ± 0.5	1.6 ± 0.8	1.1	0.351
Repetition	0.5 ± 0.5	0.8 ± 0.4	0.8 ± 0.4	1.8	0.185
Three-stage verbal command	2.4 ± 1.1	2.8 ± 0.6	2.3 ± 1.0	0.8	0.447
Written command	0.8 ± 0.4	0.8 ± 0.4	0.9 ± 0.3	0.9	0.416
Writing	0.7 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.4	0.671
Construction	0.8 ± 0.4	0.8 ± 0.4	0.9 ± 0.3	1.0	0.378

DAT: dementia of Alzheimer's type; bvFTD: behavior variant frontotemporal dementia; SD: semantic dementia; MMSE: mini mental state examination; ANCOVA: analysis of covariance; #: p value <0.05 (*post-hoc* t tests of ANCOVA controlling for age, sex, and education after Bonferroni correction).

were significantly lower than those of the DAT and bvFTD groups. The bvFTD group's scores for 'Writing words with *kanji* (to represent pictures) ' and 'dictation of *kanji* words' were higher than those of the SD patients. On the MMSE, the time-orientation score of the DAT patients was significantly lower than that of the patients with SD, and the DAT group's recall score was significantly lower than that of the bvFTD group too.

In the neuroimaging analyses, our evaluation of the relationships between rCBF and language functions revealed significant positive correlations between the rCBF values in the left lateral temporal region and the SLTA 'naming' scores (Fig. 1A), the 'writing words with *kanji* (to represent pictures)' scores (Fig. 1B), and the 'dictation of *kanji* words' scores (Fig. 1C).

Concerning disease-related differences among the three groups, compared to the DAT group, the patients with bvFTD showed significantly lower rCBF volumes in the right lateral frontal and medial frontal regions, and significantly higher rCBF volumes in the bilateral lateral temporal regions and the left angular region (Fig. 2A, B). When we re-analyzed the differences between these two groups using the conservative threshold (p<0.05), we observed that the patients with bvFTD showed higher rCBF values in the parietal, temporal and occipital lobes compared to the DAT group (Fig. 2C). As can be seen in Fig. 3A and 2B, the patients with bvFTD showed significantly lower rCBF in bilateral lateral frontal regions, and significantly higher rCBF in bilateral temporal regions and left insula compared to the values of the SD patients. When we re-analyzed the differences between these two groups using the conservative threshold (p<0.05), the patients with bvFTD showed higher rCBF in bilateral occipito-temporal regions compared to SD group (Fig. 3C). Compared to the patients with SD, the rCBF values of the patients with DAT were significantly higher in the bilateral nucleus accumbens and the right amygdala (Fig. 4A) and significantly lower in the bilateral parietal regions and the left frontal region (Fig. 4B).

DISCUSSION

We observed the disease-related clinical symptoms of aphasia and changes of rCBF in patients with SD, DAT, or FTLD, and we detected relationships between the patients' rCBF and their language dysfunctions. Based on our findings, we speculate that the lack of inability to handle morphograms (e.g., *kanji*) among patients with bvFTD might be derived from the preservation of rCBF in temporo-occipital regions. Most notably, our analyses revealed the brain regions related to aphasia for morphographic letters in patients with FTLD or DAT.

Individuals with DAT show hippocampal and/or parietotemporal atrophy and hypoperfusion (Herholz, 2022; Ward et al., 2023). Temporal hypoperfusion

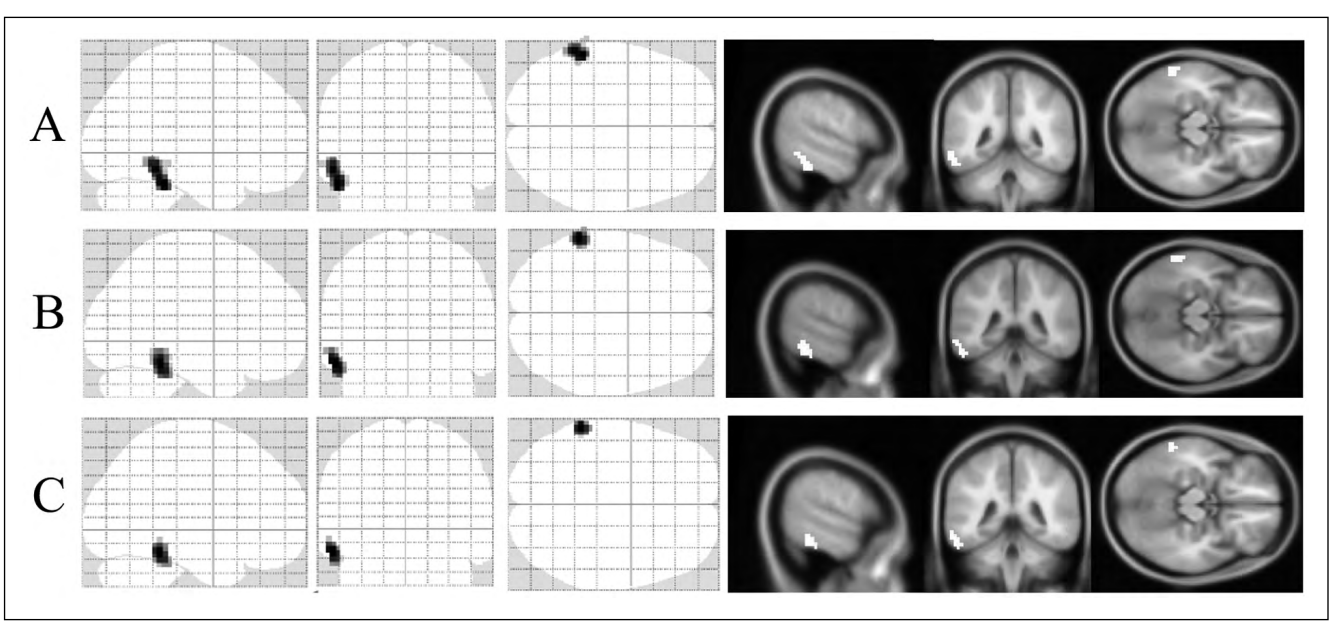

Fig. 1. The relationships between the regional cerebral blood flow (rCBF) and language functions of patients with dementia of the Alzheimer's type (DAT), the behavioral variant of frontotemporal lobar degeneration (bvFTD), or semantic dementia (SD). There were significant positive correlations between the SLTA 'naming' score and rCBF in the left superior-middle temporal region (A), between the SLTA score for 'writing words with kanji (to represent pictures)' and rCBF in the left lateral temporal region (B), and between the SLTA score for 'the dictation of kanji words' and the rCBF in the left lateral temporal (C).

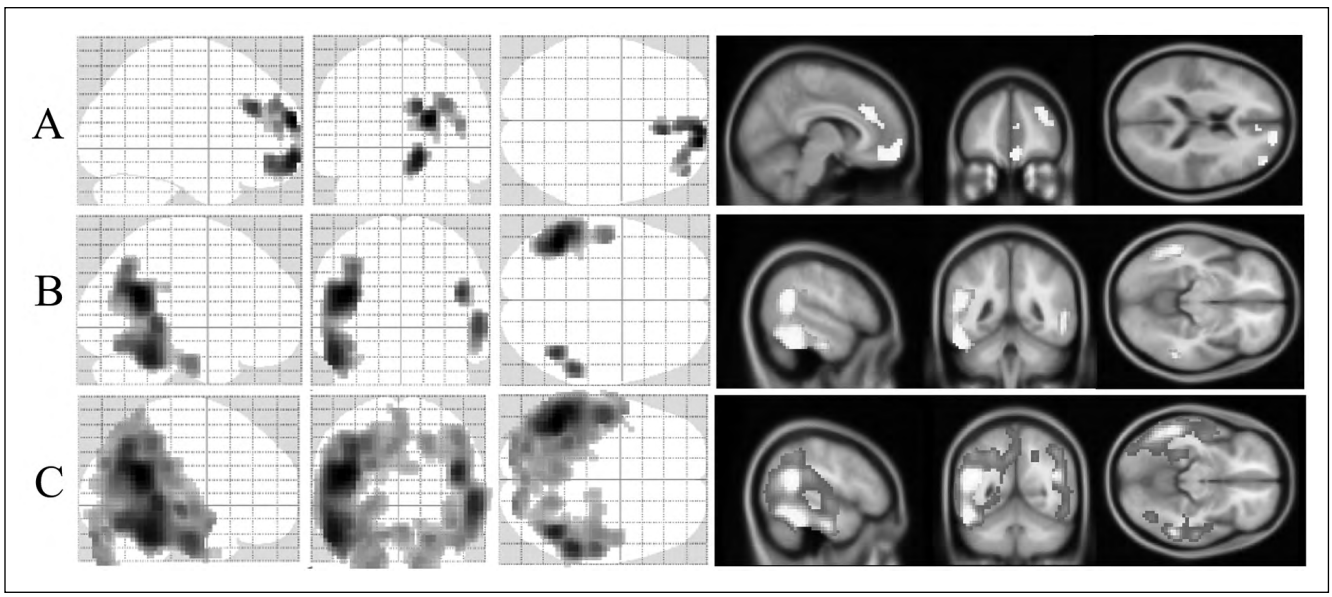

Fig. 2. The differences in the regional cerebral blood flow (rCBF) between patients with dementia of the Alzheimer's type (DAT) and those with the behavioral variant of frontotemporal lobar degeneration (bvFTD). The rCBF volumes of the patients with DAT were significantly higher in the medial and lateral frontal regions compared to those of the bvFTD patients (A). The rCBF volumes of the patients with DAT were significantly lower in the bilateral parietotemporal and lateral temporal regions compared to those of the bvFTD patients (B). When we used the conservative statistical threshold (voxel-level $p<0.05$), the rCBF of the DAT group was significantly lower in bilateral parieto-occipito-temporal regions compared to that of the bvFTD group (C).

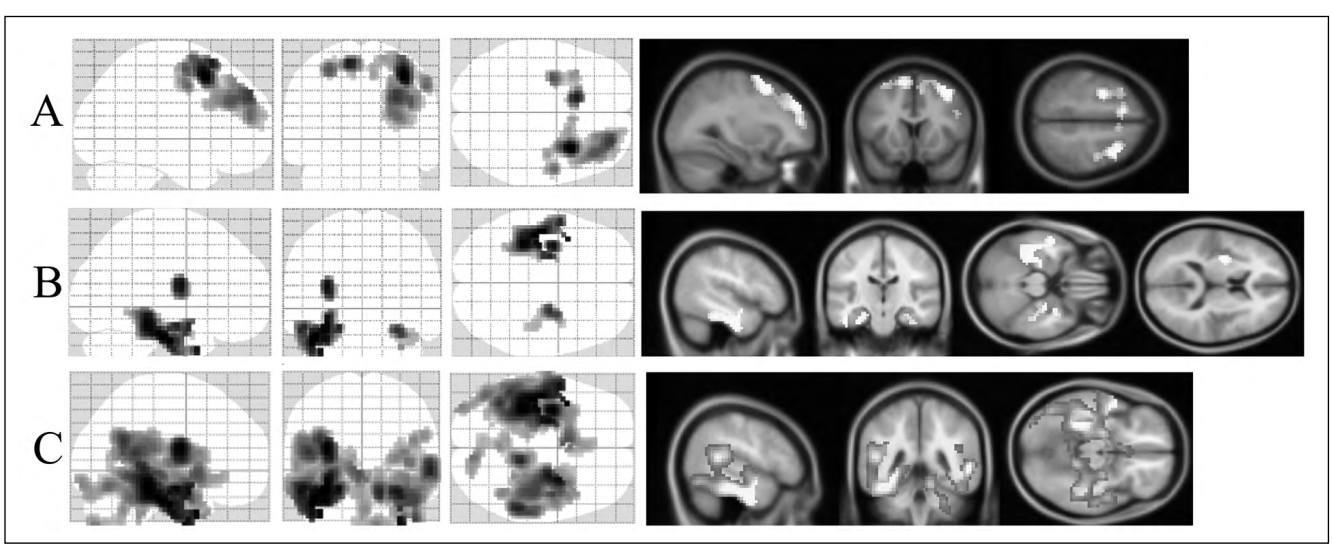

Fig. 3. The differences in the rCBF between the patients with semantic dementia (SD) and those with bvFTD. The rCBF volumes of the patients with SD were significantly higher in the bilateral lateral frontal regions compared to those of the bvFTD patients (A). The rCBF volumes of the SD group were significantly lower in the bilateral temporal and lateral temporal regions and the left insula compared to those of the bvFTD group (B). When we applied the conservative statistical threshold (voxel-level $p<0.05$), the rCBF volumes of the SD group were significantly lower in the bilateral occipito-temporal regions compared to those of the bvFTD group (C).

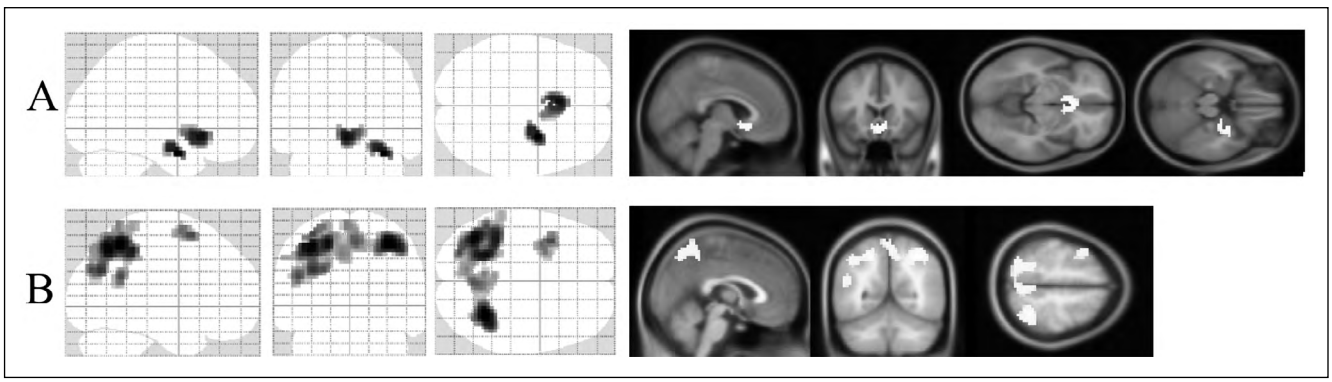

Fig. 4. The differences in rCBF between the patients with DAT and those with SD. The rCBF volumes of the DAT patients were significantly higher in the bilateral nucleus accumbens compared to those of the SD patients (A). The rCBF volumes of the patients with DAT were significantly lower in the bilateral parietal regions and the left frontal region compared to those of the SD patients (B).

is often observed in SD patients, and frontotemporal hypoperfusion is common among patients with bvFTD (Whitwell, 2019; Planche et al., 2023; Ward et al., 2023). We also observed that patients with bvFTD showed relatively preserved functions in temporo-occipital regions. Our findings are congruent with these prior reports. The utility of ^{18}F-FDG-PET in the diagnosis of FTLD is well established (Ward et al., 2023). Compared to SPECT, PET has a higher spatial resolution and allows more detailed studies, however, SPECT radioisotopes are more readily available, and SPECT is less expensive than PET. In this regard, the clarification of the associations between SPECT data and aphasia might provide a significant contribution to clinical medicine. In addition, although three accumulative radioligands, (^{123}I-labeled N-isopropyl-p-iodoamphetamine [IMP], ^{99m}Tc-labeled hexamethylpropyleneamineoxime [HMPAO], and ^{99m}Tc-ECD) have been developed for use as CBF tracers for SPECT, the mechanism of retention in the brain differ for each of these radioligands, and this causes the differences in their regional distribution in the brain. A SPECT study showed that the retention of ^{99m}Tc-ECD in the occipital region was higher than those of ^{123}I-IMP, and ^{99m}Tc-HMPAO, and it revealed lower retention of ^{99m}Tc-ECD in the thalamus and brain stem, compared to those of ^{123}I-IMP, and of ^{99m}Tc-HMPAO (Ito et al., 2006). Future analyses using ^{123}I-IMP, and ^{99m}Tc-HMPAO are necessary to reveal the precise relationship between the brainstem and thalamic areas and aphasia.

Regarding the aphasia observed in DAT, bvFTD, and SD, individuals with DAT are known to experience word-retrieval difficulties and repetition impairment, and those with SD have trouble with naming and understanding the meaning of words, in addition to surface alexia and agraphia (Gorno-Tempini et al., 2011). Patients with bvFTD have shown deficits in word fluency, naming, auditory comprehension, and oral expression (Hardy et al., 2016; Mamouli et al., 2022). Ikeda et al. (2011) used the SLTA and reported that the performance of Japanese patients with very mild SD was considerably better at the processing of *kana* (phonographic words) than *kanji* (morphographic words), and those authors considered that this dysfunction of *kanji* processing was similar to the mechanism of surface alexia, i.e., impairment in reading irregular words, especially when these items were of low frequency. Our present investigation revealed that the patients with SD had lower *kanji*-processing scores compared to the patients with DAT or bvFTD, which is consistent with previous findings.

It has been pointed out that lateral temporo-occipital regions play a central role in the processing of morphographic words, and lateral temporo-occipital dysfunction might cause alexia with agraphia for morphographic words (Lee, 2004; Sakurai, 2011). A functional MRI (fMRI) study demonstrated that the brain's lateral temporo-occipital regions are relevant to object recognition (Schultz et al., 2000), and another fMRI study revealed a relationship between the visual naming and left lateral temporal region (Hamberger et al., 2014). Our present analyses identified correlations between the reading and writing of morphographic words (*kanji*), and visual naming and the rCBF volume in the left lateral temporo-occipital regions of patients with DAT, SD, or bvFTD. In light of these points, we speculate that it may be possible that the disease-related clinical symptoms were caused by disease-related changes of brain functions.

This study has some limitations to address. The sample size was somewhat small, but our findings were significant after the multiple comparisons. Further research with large sample sizes might help identify the foci of responsibility for aphasia. In addition, we

did not observe a correlation between subscales of the SLTA and the rCBF in the angular gyrus, which is deeply involved in language function (Dejerine, 1892). Several investigations have shown that the reading of syllabograms is processed in the dorsal pathway *via* the angular gyrus or inferior occipital gyrus (Iwata, 1984; Lee et al., 2003; Sakurai, 2011), and the left angular gyrus is related to syllabogram–sound association (Lee et al., 2003). Our present patients did not show language dysfunctions dealing with a syllabary as we first evaluated, and these points might have obscured a correlation between the SLTA subscales and the rCBF in left angular gyrus. We also did not consider medications being used by the patients. Anti-dementia drug use has been reported to increase the CBF (Kanaya et al., 2012; Li et al., 2012). Some of our participants used anti-dementia drugs, but we evaluated the association not with brain structure but with brain function visualized by SPECT, and the effect of anti-dementia drugs were already taken into account.

CONCLUSION

We investigated the disease-related language dysfunctions and rCBF changes among patients with DAT, bvFTD, and SD, and we detected significant differences in the patients' rCBF at regions where the specific clinical symptoms of aphasia are relevant. Our findings might be useful to distinguish bvFTD from SD and DAT and may contribute to the understanding of the features of surface alexia and agraphia.

REFERENCES

American Psychiatric Association, DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc. https://doi.org/10.1176/appi.books.9780890425596

Boku, Y., Ota, M., Nemoto, M., Numata, Y., Kitabatake, A., Takahashi, T., Nemoto, K., Tamura, M., Sekine, A., Ide, M., Kaneda, Y., Arai, T. (2022) Effects of a multicomponent day-care program on cerebral blood flow in patients with mild cognitive impairment. *Psychogeriatrics,* 22(4), 478-484. https://doi.org/10.1111/psyg.12847.

Dejerine, J. (1892) Contribution à l'étude anatomopathologique et clinique des différentes variétés de cécité verbale. *Compt Rend Séances Mém Soc Biol*, 4, 61–90 (in French).

Folstein, M., Folstein, S., McHugh, P. (1975) 'Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician. *J Psych Res*, 12(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M. (2011) Classification of primary progressive aphasia and its variants. *Neurology*, 76(11), 1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6.

Hamberger, M.J., Habeck, C.G., Pantazatos, S.P., Williams, A.C., Hirsch, J. (2014) Shared space, separate processes: Neural activation patterns for auditory description and visual object naming in healthy adults. *Hum Brain Mapp*, 35(6), 2507-2520. https://doi.org/10.1002/hbm.22345.

Hardy, C.J., Buckley, A.H., Downey, L.E., Lehmann, M., Zimmerer, V.C., Varley, R.A., Crutch, S.J., Rohrer, J.D., Warrington, E.K., Warren, J.D. (2016) The language profile of behavioral variant frontotemporal dementia. *J Alzheimers Dis,* 50(2), 359–371. https://doi.org/10.3233/JAD-150806.

Herholz, K. (2022) Imaging clinical subtypes and associated brain networks in Alzheimer's disease. *Brain Sci*, 12(2), 146. https://doi.org/10.3390/brainsci12020146.

Ikeda, M., Kitamura, I., Ichimi, N., Hashimoto, M., Lambon Ralph, M.A., Komori, K. (2011) Gogi aphasia: The early description of semantic dementia in Japan. *Acta Neuropsychologica*, 9(2), 133–140.

Ito, H., Inoue, K., Goto, R., Kinomura, S., Taki, Y., Okada, K., Sato, K., Sato, T., Kanno, I., Fukuda, H. (2006) Database of normal human cerebral blood flow measured by SPECT: I. Comparison between I-123-IMP, Tc-99m-HMPAO, and Tc-99m-ECD as referred with O-15 labeled water PET and voxel-based morphometry. *Ann Nucl Med.* 20(2), 131–138. https://doi.org/10.1007/BF02985625.

Iwata, M. (1984) Kanji versus kana: Neuropsychological correlates of the Japanese writing system. *Trends Neurosci*, 7(8), 290–293. https://doi.org/10.1016/S0166-2236(84)80198-8.

Kanaya, K., Abe, S., Sakai, M., Fujii, H., Koizumi, K., Iwamoto, T. (2012) Efficacy of a high dosage of donepezil for Alzheimer's disease as examined by single-photon emission computed tomography imaging. *Psychogeriatrics* 12(3), 172-178. https://doi.org/10.1111/j.1479-8301.2011.00399.x.

Lee, H.S., Fujii, T., Okuda, J., Tsukiura, T., Umetsu, A., Suzuki, M., Nagasaka, T., Takahashi, S., Yamadori, A. (2003) Changes in brain activation patterns associated with learning of Korean words by Japanese: An fMRI study. *Neuroimage*, 20(1), 1–11. https://doi.org/10.1016/s1053-8119(03)00254-4.

Lee, K.M. (2004) Functional MRI comparison between reading ideographic and phonographic scripts of one language. *Brain Lang*, 91(2), 245–251. https://doi.org/10.1016/j.bandl.2004.03.004.

Li, W., Antuono, P.G., Xie, C., Chen, G., Jones, J.L., Ward, B.D., Franczak, M.B., Goveas, J.S., Li, S.J. (2012) Changes in regional cerebral blood flow and functional connectivity in the cholinergic pathway associated with cognitive performance in subjects with mild Alzheimer's disease after 12-week donepezil treatment. *Neuroimage*, 60(2), 1083-1091. https://doi.org/10.1016/j.neuroimage.2011.12.077.

Mamouli, D., Stavrakaki, S., Iakovou, I., Parisis, D., Karacostas, D., Papanastasiou, E., Ioannidis, P. (2022) SPECT analysis and language profile in Greek speaking patients with subtypes of frontotemporal dementia. *Hell J Nucl Med*, 25(1), 43–56. https://doi.org/10.1967/s002449912436.

Mimura, M., Kato, M., Kato, M., Sano, Y., Kojima, T., Naeser, M., Kashima, H. (1998) Prospective and retrospective studies of recovery in aphasia. Changes in cerebral blood flow and language functions. *Brain*, 121(Pt 11), 2083–2094. https://doi.org/10.1093/brain/121.11.2083.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F. (1998) Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology*, 51(6), 1546–1554. https://doi.org/10.1212/wnl.51.6.1546.

Planche, V., Mansencal, B., Manjon, J.V., Tourdias, T., Catheline, G., Coupé, P., (2023) Frontotemporal Lobar Degeneration Neuroimaging Initiative and the National Alzheimer's Coordinating Center cohort. Anatomical MRI staging of frontotemporal dementia variants. *Alzheimers Dement*, 19(8), 3283–3294. https://doi.org/10.1002/alz.12975.

Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C, Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M.,

Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L. (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, 134(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179.

Sakurai, Y. (2011) Lesion localization of non-aphasic alexia and agraphia. *Clin Neurol,* 51(8), 567–575. https://doi.org/10.5692/clinicalneurol.51.567.

Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D.J., Gore, J.C. (2000) Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Arch Gen Psychiatry*, 57(4), 331–340. https://doi.org/10.1001/archpsyc.57.4.331.

Takaya, M., Ishii, K., Kubota, I., Shirakawa, O. (2020) The Landscape Montage Technique for diagnosing frontotemporal dementia starting as primary progressive aphasia: A case report. *J Med Case Rep*, 14(1), 5. https://doi.org/10.1186/s13256-019-2338-7.

The Lund and Manchester Groups. (1994) Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psych*, 57(4), 416–418. https://doi.org/10.1136/jnnp.57.4.416.

Ward, J., Ly, M., Raji, C.A. (2023) Brain PET imaging: Frontotemporal dementia. *PET Clin*, 18(1), 123–133. https://doi.org/10.1016/j.cpet.2022.09.010.

Whitwell, J.L. (2019) FTD spectrum: Neuroimaging across the FTD spectrum. *Prog Mol Biol Transl Sci*, 165, 187–223. https://doi.org/10.1016/bs.pmbts.2019.05.009.