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ECD-SPECT Findings of Semantic Dementia and Fronto-temporal Dementia: Visual and Statistical Parametric Mapping Analysis

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Background: Semantic dementia (SD) and frontotemporal dementia (FTD) are two major variants of frontotemporal lobar degeneration (FTLD) which have unique clinical manifestations. We studied to determine the patterns of regional cerebral blood flow (rCBF) in SD and FTD. **Methods:** We observed characteristic patterns of rCBF in SD and FTD with statistical parametric mapping (SPM) analysis of ^{99m}Tc-ECD single photon emission computed tomography (SPECT). Five patients with SD and 5 patients with FTD as well as 12 age-matched normal controls underwent brain MRI and ECD-SPECT scan. We conducted an SPM analysis to identify brain regions with hypoperfusion in each of groups. **Results:** Visually, ECD-SPECT images of the SD patients showed decreased rCBF in bilateral anterior temporal lobes, more severe on the left and those of the FTD patients did in bilateral prefrontal and anterior cinglulate gyrus. SD group had more perfusion defect in the left temporal area than FTD group. FTD group showed more perfusion defect in the medial frontal, right prefrontal and anterior cingulate areas than SD group. **Conclusions:** In clinical syndromes of SD and FTD, two different patterns of rCBF were identified. SD and FTD are distinctive degenerative dementias with different cortical involvement which can be differentiated by ECD-SPECT study.

Key Words: *Semantic dementia, Frontotemporal dementia, Single photon emission computed tomography, Statistical parametric mapping*

INTRODUCTION

The most common and early symptom of frontotemporal dementia (FTD) is a decline in social interpersonal conduct. According to the Nearly criteria[4], the core clinical features of the FTD are insidious onset, early decline of the social interpersonal and personal conduct, emotional blunting, and loss of insight. Early features include loss of social awareness, loss of sense of what is proper and often with escalating impulsiveness[1-3]. However, FTD patients often have a preserved ability to manage routine daily activities and initially they may have intact or mildly impaired cognitive functions, such as memory, visuospatial function, understanding language and perceptual function. Some of the common features are disturbed eating behavior, changes in appetite and food preference. Some patients with FTD present with prevailing language dysfunction as an initial cognitive deficit. Additionally, two syndromes have been described. Some speak fluently with appropriate grammer and pronunciation, but appear to have lost the meaning of many words, exemplified in tasks, such as picture naming, category word fluency, word-to-picture matching and definitions. Structural brain imaging may show circumscribed temporal lobe atrophy, sometimes asymmetric with more pronounced atrophy in the left anterior area. This syndrome has been called semantic dementia (SD). Although in typical cases the patterns of cognitive impairment and behavioral changes are distinct between FTD and SD, cross-sectional and longitudinal studies have shown that patients with SD may develop behavioral disturbances at the beginning or during the course of their illness which are quite

similar to those seen in FTD, suggesting considerable overlap between the two groups. The FTD is the most common type of frontotemporal lobar degeneration (FTLD) but it is frequently combined with language problems and is often misdiagnosed as SD. Therefore, the differentiation between FTD and SD on clinical grounds including neuropsychological assessments and informant interviews may be difficult. Thus an accurate differentiation of FTD from SD should be important from the diagnosis and therapeutic points of view [3-6].

The degeneration of the frontal and anterior parts of the temporal areas in FTD has resulted in atrophy seen on brain CT or MR imaging and hypoperfusion or hypometabolism seen on Single photon emission computed tomography (SPECT) and Positron emission tomography (PET)[6-8]. Structural imaging using MRI has demonstrated that SD is associated with atrophy of the anterior temporal lobes which involves the polar and inferolateral regions. Quantification of brain atrophy using automated voxel-based morphography or manual volumetry has confirmed the involvement of the temporal pole, fusiform gyrus and inferolateral cortex[10].

Our aims are to know the characteristic patterns of regional cerebral blood flow (rCBF) in FTD and SD with statistical parametric mapping (SPM) analysis of ECD-SPECT to help differentiate two groups and to better define the specific cortical areas involved in each groups.

MATERIALS AND METHODS

1. Materials

Patients with FTLD were recruited at the dementia clinic in St. Mary's Hospital from 2003 to 2005. Of 15 patients included in this study, only 10 patients who underwent ECD-SPECT scans were enrolled. All subjects met the dementia criteria of the DSM-IV and modified Neary criteria of FTLD [4]. Five patients were diagnosed as FTD and 5 patients as SD (Table 1). According to the criteria, the core clinical features of the FTD are insidious onset, early decline of the social interpersonal and personal conduct, and emotional blunting and loss of insight. And the core clinical features of SD are fluent, empty spontaneous speech, loss of word meaning, semantic paraphasias and prosopagnosia[10]. Clinical diagnoses were based on information gathered from neurological examination, informant interview and psychiatric interview. All patients underwent neuropsychological evaluation using the Mini-Mental State Examination (MMSE) and comprehensive Seoul Neuropsychological Screening Battery (SNSB). It includes Digit span test-forward (DST-F) and Digit span test-backward (DST-B) for attention, Korean version of Boston naming test (K-BNT) for language function, Rey Complex Figure Test (RCFT) for visuoaspatial function, Seoul Verbal Learning Test (SVLT-immediate recall, delayed recall and recognition) for verbal memory, Rey Complex Figure Test (RCFT-immediate recall, delayed recall and recognition) for nonverbal memory, president naming for long-term memory and Contrasting program, Go-no-go test, Word fluency test-category (WFT-C), Word fluency test-letter (WFT-L) for frontal lobe function. Patients were excluded who fulfilled the diagnostic criteria for Alzheimer's disease, Lewy body disease and when had a history of stroke. Further exclusion criterias were intracranial tumor, hydrocephalus, epilepsy, alchoholism and psychiatric disorder like major depression. Cases of progressive non-fluent aphasia were also excluded from this study analysis. The age-matched 12 healthy subjects were recruited as normal controls. They had no history of neurologic and psychiatric disorders and did not complain about cognitive deterioration. They were interviewed to rule out dementia and all other diseases that were also excluded in the patients.

2. Methods

1) SPECT Imaging

The SPECT images were obtained 20 min after an intravenous injection of approximately 740-925 MBq of ^{99m}Tc-ECD and with using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) that was equipped with a low-energy, fan-beam collimator. The head unit consists of two rings of 59 probe-type detectors. The data were acquired on 128×128 matrices with a 20% symmetric window at 140 keV. The continuous transaxial tomograms of the brain were

Table 1. Characteristics of patients and controls

Particioants	FTD (n=5)	SD (n=5)	Controls (n=12)	*p*-values
Age (yr)	56.0±6.5	58.8±5.5	61.9±4.0	0.902
Sex (M/F)	1/4	1/4	7/5	0.005*
Educational level (yr)	9±6	9.6±6.1	11.0±4.4	0.501
MMSE score	19.3±6.2	19.5±6.1	27.8±1.6	0.627
CDR	1.6±1.1	1.3±1.0	0.2±0.1	0.399

Value are mean±Standard deviation. *P* values are calculated by t-test for the continuous variables and by using *Fisher's exact test for the categorical variables. MMSE, Mini-mental State Examnination.

reconstructed after the back projection was filtered with a Butterworth (cutoff frequency 0.4 cycles/pixel, order 5) to reduce the signal noise. The ^{99m}Tc-ECD SPECT images were corrected for tissue attenuation with using a standard commercial correction routine, which assumes uniform attenuation with the circular shape of the head.

2) Statistical parametric mapping

The software for the image manipulation included Matlab software, version 5.3 (Mathworks, Inc., Natick, MA) and SPM99 software (Institute of Neurology, University College of London, UK)[8]. The reconstructed SPECT data with attenuation and scatter correction were reformatted into the Analyze (Mayo Foundation, Baltimore, Md., USA) header format. The header format for the SPECT data included 348 bytes of header, 3.9 mm of x and y pixel size and a 3.9 mm slice thickness. The SPECT images of each subject were fitted into the same standard template with minimal changes of the 12 affine parameters that were associated with spatial distortion. All the slices of a brain image were sampled and averaged to arrive at the mean pixel intensity for that image. The intensity threshold was set at 80% of the whole-brain mean. The global cerebral blood flow rate was normalized to an arbitrary mean of 50 mL/100 mL of brain per minute by a group-wise analysis of covariance (ANCOVA)[9]. The data were then normalized to a SPECT template (Montreal Neurological Institution Template), and the data were next smoothed with an 8 mm full-width at half-maximum (FWHM) prior to the SPM99 analysis. The final image format was 16-bit, $79\times95\times68$ mm in size and it had a $2\times2\times2$ mm voxel size. For the graphic presentation, the results of the analysis were displayed on transverse MRI templates with a hot color map.

3) Image analysis

We used the simple regression SPM99 analysis between the SPECT images for each subjects, using four contrasts: 1) FTD vs. control, to test the brain region in FTD patients with relatively lower rCBF than in controls, 2) SD vs. control, to test the brain region in SD patients with relatively lower rCBF than in controls 3) SD vs. FTD and 4) FTD vs. SD to test the difference of brain CBF changes between two groups. The normalized SPECT data of the two subtypes of FTLD patients were separately compared to the data of the control subjects to evaluate the CBF patterns of each group with using a two sample t-test.

The results of the SPM analysis were considered significant if they reached the t (p) values 5.05 (voxel level corrected $p<0.05$). However, for display purposes, and to present the results in a comprehensive way, the less conservative threshold of t=3.35 (uncorrected $p<0.005$) was used. Only clusters with size greater than 100 voxels were considered.

For the visualization of the t-score statistics, the t-score voxel clusters of significance were projected onto the standard high-resolution MR images. To identify the precise anatomical location of the results, we entered the values of x, y and z for the statistically significant clusters into the software program (Talairach Daemon Database Software), and we finally obtained the anatomical locations and the Brodmann areas for the results (Table 2, 3).

RESULTS

The distributions of the subjects' age and the educational level between the patient group and the control group were not different, but the MMSE scores of the patients were significantly lower than those of the control subjects ($p<0.001$). The patients' age, gender, educational level, MMSE scores and CDR scores were not different between the two subtypes (Table 1).

When FTD was compared with controls, the relative rCBF was found to be significantly reduced in the bilateral prefrontal, medial frontal, orbital frontal, thalamic areas and anterior

Table 2. Brain areas, T values of the voxels and the coordinates of the significant clusters (corrected $p<0.05$) showing relative regional cerebral blood flow reduction in frontotemporal dementia compared with Semantic dementia patients

Brain region	BA	Stereotaxic coordinates (mm)			T value
		X	*Y*	*z*	
Right superior frontal gyrus	6	2	24	62	7.38
Right cingulated gyrus	24	12	4	48	6.32
Left cingulated gyrus	24	-8	4	46	6.31

BA, Broadmann area.

Table 3. Brain areas, T values of the voxels and the coordinates of the significant clusters (corrected $p<0.05$) showing relative regional cerebral blood flow reduction in Semantic dementia compared with frontotemporal dementia patients

Brain region	BA	Stereotaxic coordinates (mm)			T value
		X	*Y*	*z*	
Left inferior temporal gyrus	20	-54	-4	-32	7.20
Left inferior temporal gyrus	20	-40	-10	-38	7.10

BA, Broadmann area.

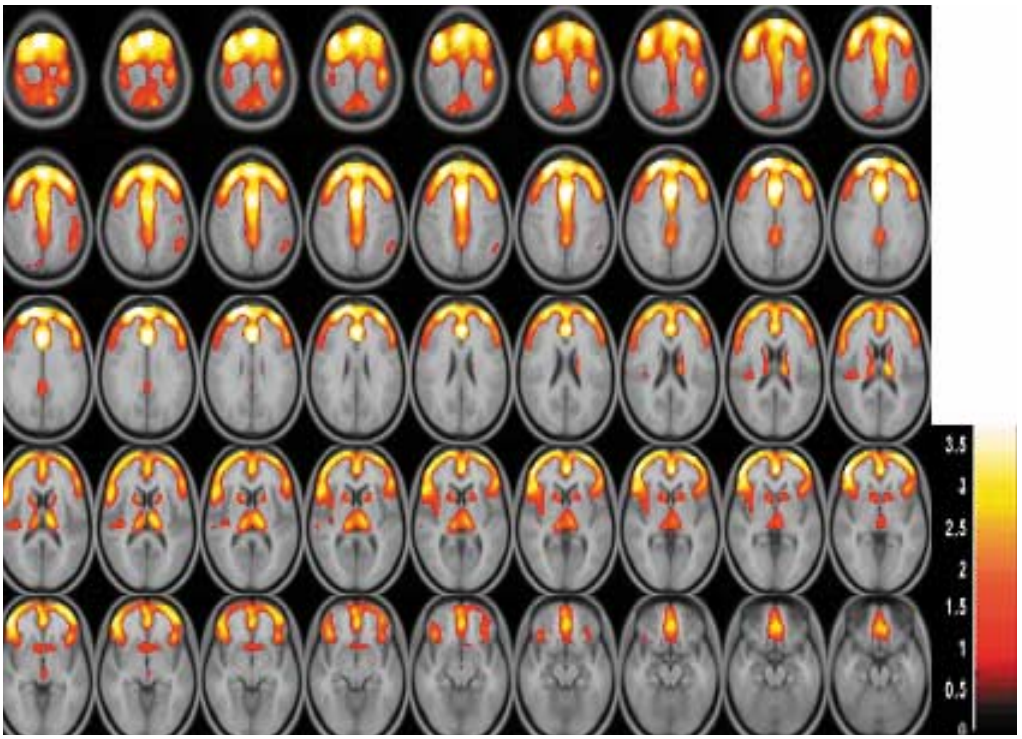

Fig. 1. SPM analysis between FTD and Controls (p=0.005 uncorrected). This is a fusion image of SPM analysis and axial MRI template, where it shows reduced rCBF in patients of FTD. rCBF is decreased in the bilateral prefrontal, medial frontal, orbital frontal, thalamic areas and anterior cingulate areas.

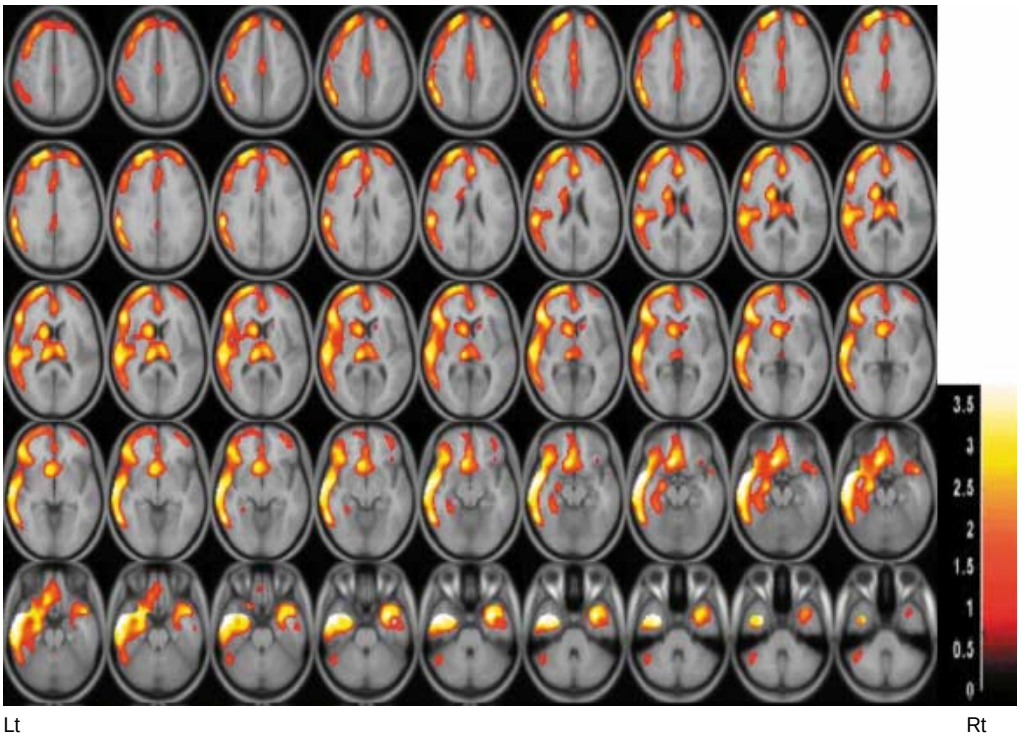

Fig. 2. SPM analysis between SD and Controls (p=0.005 uncorrected). rCBF is decreased in the left temporal, frontal, orbi-tal frontal, anterior cingulate and right temporal areas.

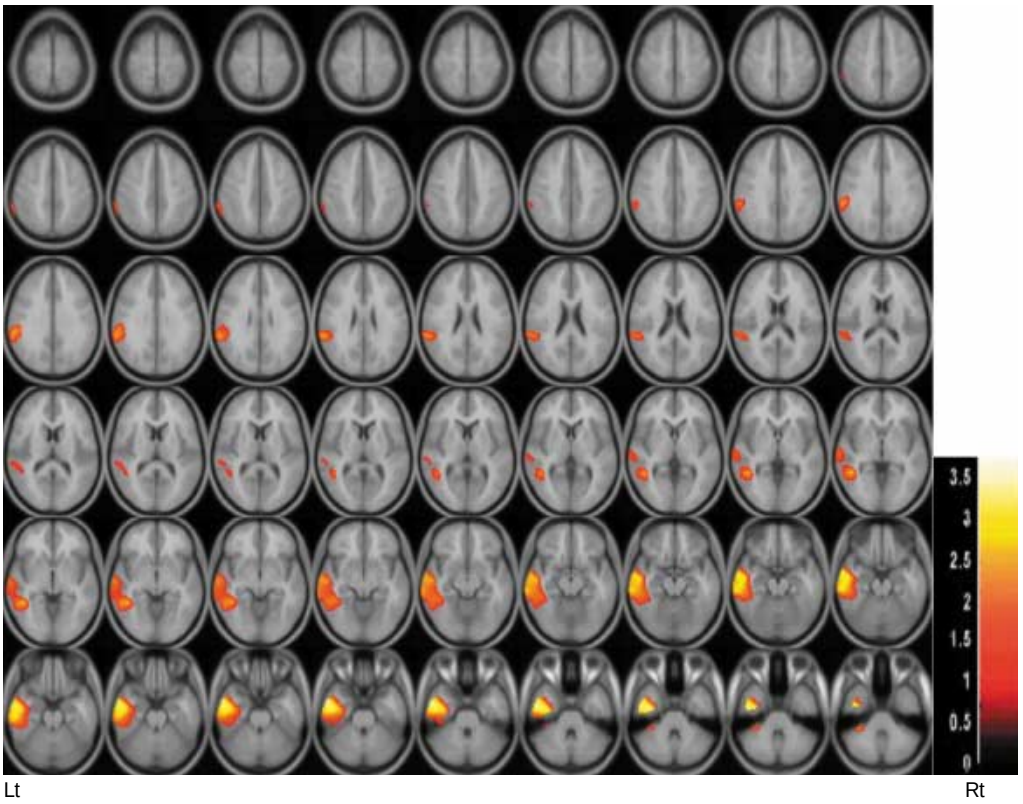

Fig. 3. SPM analysis between SD and FTD (p=0.005 uncorrected). This shows decreased rCBF in the SD when it compared to the FTD. rCBF is clearly decreased in the left inferior and middle temporal areas.

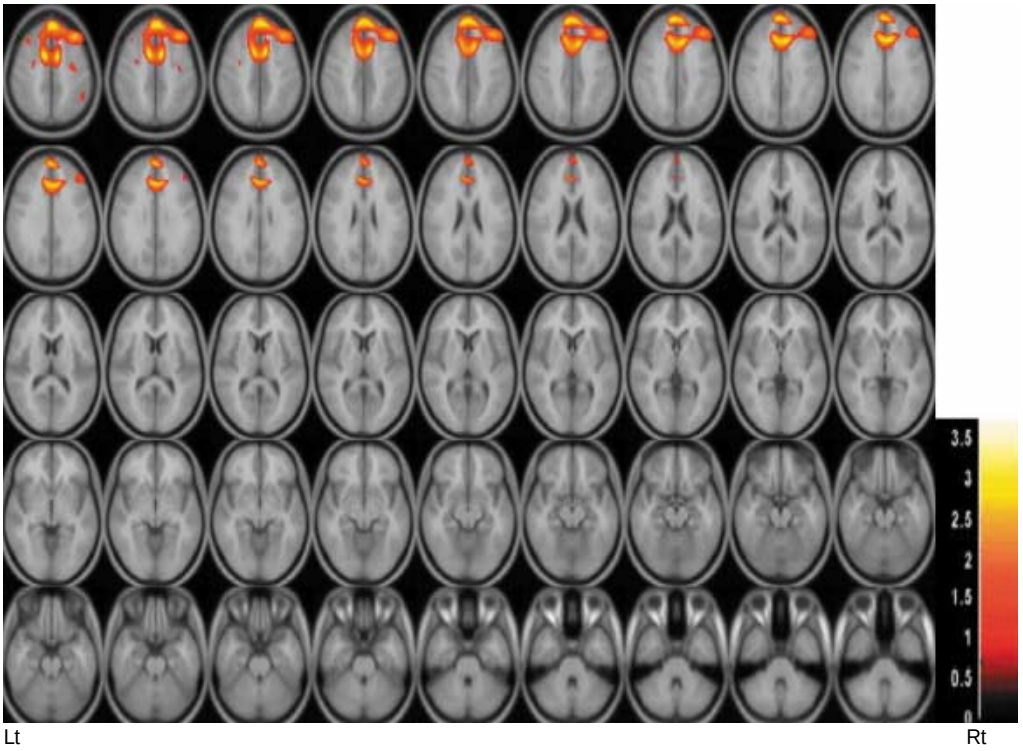

Fig. 4. SPM analysis between FTD and SD (p=0.005 uncorrected). This shows decreased rCBF in the FTD when it compared to the SD. rCBF is clearly decreased in the medial frontal, right prefrontal and anterior cingulate areas.

cingulate area (Fig. 1). When SD was compared with controls, the relative rCBF was found to be significantly reduced in the left temporal, frontal, orbital frontal, anterior cingulate and right temporal areas (Fig. 2).

When compared FTD to SD, rCBF was decreased in the medial and right prefrontal and anterior cingulate areas. In SD, compared to FTD, rCBF was clearly decreased in the left inferior and middle temporal areas (Fig. 3, 4).

DISCUSSION

In the present study we compared resting CBF among the patients of FTD, SD and age-matched cognitively healthy controls with SPM analysis of ECD-SPECT. Overall, the results showed that a preferential involvement of specific regions within the frontal cortex in FTD and within temporal cortex in SD. A decreased rCBF in the bilateral middle and inferior temporal gyri may be associated with cognition and behavior dysfunctions in SD. And a decreased rCBF in the bilateral frontal gyri may be associated with cognition and behavior dysfunctions in FTD.

These findings are consistent with other recent imaging studies using voxel-based morphometry. They found significant atrophy in the frontal in FTD. Also bilateral asymmetric atrophy of temporal lobe as well as atrophy of the left amygdala and of the parahippocampal, fusiform and inferior middle temporal gyri was identified in SD. However in previous SPECT studies, hypoperfusion of the frontal cortex, more marked in the orbitofrontal than in the dorsolateral frontal regions and of anterior temporal cortex has been reported in FTD[6-8]. In a PET study, they found a more generalized hypometabolism in FTD patients which not only involved the frontal region but extended to the temporal, parietal and subcortical regions, particularly to the corpus striatum and thalalmus[16-18]. All the results reported above were obtained by means of qualitative or semiquantitative analyses, using either visual rating or regional-of-intereast (ROI) approach. These methods can be subjective and require an extended time for analysis. In addition they are based on a priori hypothesis regarding the brain regions potentially involved in the disease. Recently, like this study, voxel-by-voxel statistical analysis has been successfully applied to identify the distribution of functional abnormalities in patients with dementia.

In this study we found that, compared with SD, FTD patients showed a significant rCBF reduction in the medial frontal, right prefrontal and anterior cingulate areas. The preferential involvement in FTD of regions interconnected with the limbic system and engaged in emotion and loss of drive (anterior cingulate). The prefrontal cortex, in particular the orbitofrontal region, plays a pivotal role in the regulation of social and aggressive behavior. The medial orbitofrontal cortex is considered as the limbic portion of the frontal association cortex and is intimately connected with the amygdala and the limbic system. It has long been known that the human orbitofrontal cortex plays a crucial role in the modulation of the expression of social and emotional behavior[11-13].

The role of orbitofrontal and prefrontal cortical areas in the evaluation of distinct negative and positive emotional situations have been supported by several functional brain studies in both healthy subjects and patients with psychiatric disorders. In particular, the ventromedial prefrontal cortex is involved in making judgements on the basis of the emotional balance of stimuli[14-19]. It would be interest to see that the thalamic involvement in the FTD compared to controls. The thalamus is positioned at the interface of frontal-subcortical circuits. Thus thalamic involvement might reflect a disruption of frontal-subcortical circuits[10].

We found that, compared with FTD, SD patients showed a significant relative rCBF decreased in the left inferior and middle temporal areas. The left posterior inferior temporal gyrus has direct connections to Wernicke's area. It has been shown that stimulation of this region may cause specific naming deficits[22]. The posterior medial temporal gyrus is contiguous with the basal temporal lobe though lies more anterior and dorsal. The posterior medial temporal gyrus is known to be activated by semantic tasks and is affected with aphasia plus a semantic deficit. So it is not surprising that rCBF in this region was lower in SD patients than in controls. Additionally, a decreased rCBF in the left frontal lobe was found in SD compared to controls. Several hypotheses about the role of the left inferior frontal gyrus have been proposed on the basis of functional neuroimaging data. Many authors have concluded that the left inferior frontal gyrus mediates the semantic processing (especially semantic retrieval)[22]. This is because the frontal lobe plays a major role for working memory, encoding semantic and episodic memory, and episodic memory retrieval[22-26]. But most of studies have a potential compound: The task associated with activation at or near left inferior frontal gyrus were more difficult than the non-semantic comparison task. Althought the role of it, in the semantic processing is under considerable debate, we suggest that the patients

of semantic impairment enhance the requirement for frontal involvement.

The functional meaning of rCBF is the balance between local excitatory and inhibitory synapses. The accepted explanations for decreases in rCBF are that they present functional deactivations and are due to a decreased excitation. Therefore, whether due to inhibition or a reduced excitatory input, the decreased rCBF is a true index of reduction of the functional activity in these cortical areas[11].

The present study has several limitations. First, diagnoses were not confirmed by post-mortem examination. However, we adhered to a very strict and careful inclusion of patients following the Neary criteria for FTLD. These criteria provide a mechanism for diagnosis and differentiation of dementias associated with FTLD. The core diagnostic criteria indicate the consensus of the group in identifying the key clinical aspects that differentiate FTD, progressive non-fluent aphasia, and SD[6]. Second, the patient sample was small because FTD and SD occur relatively rare. Finally, the longitudinal study is needed to find that the clinical progression of FTD and SD is accompanied by a region-specific decline in rCBF.

In conclusion, unique patterns of hypoperfusion in FTD and SD may help us to distinguish two subtypes of FTLD and distinguish FTD and SD from other degenerative dementia like Alzheimer's disease or other causes of dementia.

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