Neuroanatomy of a neurobehavioral disturbance in the left anterior thalamic infarction

Yoshiyuki Nishio,1 Mamoru Hashimoto,2 Kazunari Ishii,3 Etsuro Mori1

ABSTRACT

Background and purpose Cognitive and behavioural symptoms represent primary clinical manifestations of anterior thalamic infarcts (ATIs) in the tuberothalamic artery territory. The aim of the study is to understand the pathomechanism of cognitive and behavioural disturbances in left ATI (LATI).

Methods Six patients with isolated LATIs were investigated using neuropsychological assessments, MRI stereotactic lesion localisation and positron emission tomography.

Results The patients were characterised clinically by verbal memory impairment, language disturbances dominated by anomia and word-finding difficulty and apathy. The ventral anterior nucleus (VA) proper, magnocellular VA (VAmc), ventral lateral anterior nucleus (VLa), ventral lateral posterior nucleus (VLp) and mammillothalamic tract were involved in all patients. Compared with healthy controls, the regional cerebral blood flow was lower in the thalamus, the dorsolateral, medial and orbital frontal lobes, the anterior temporal lobe, the inferior parietal lobule and the occipital lobe of the left hemisphere.

Conclusions The authors propose that the Papez circuit disruption at the mammillothalamic tract and possibly thalamomedial temporal disconnection at the VA region is responsible for memory impairment and that the thalamo-anterior temporal disconnection is associated with language disturbance in LATI, respectively.

INTRODUCTION

Clinical observations have documented that the thalamus participates in a great variety of cognitive functions and mental activities, including memory, language, perception and emotion. However, the precise functional attributes of the individual thalamic nuclei and fibre systems remain to be elucidated. Clinicopathological investigations of thalamic infarctions, in which only subsets of thalamic structures are involved, have been one of the best ways to study the functional anatomy of the human thalamus. The inference of the function of individual thalamic structures on the basis of their anatomical connectivity with other brain regions has also played an important role. Here we highlight the left anterior thalamic infarction (LATI) resulting from occlusion of the left tuberothalamic artery, in which cognitive and behavioural symptoms represent primary clinical manifestations. Using neuropsychological evaluations, MRI stereotactic lesion localisation and positron emission tomography (PET), we attempted to delineate neurobehavioral and neuroanatomical profiles of LATI.

METHODS

Subjects

We recruited six right-handed patients (mean age, 76±7.4 years; two women; mean years of education, 9.2±2.9) with a subacute phase of isolated LATI. They were consecutive patients admitted to the Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD), a research-oriented dementia clinic, from 1993 to 2001. All of them presented to the institute with sudden onset of cognitive or behavioural problems, such as forgetfulness, loss of spontaneity and dysomnol. Duration between onset of symptoms and start of examination ranged from 1 to 4 weeks (mean, 3±1.3 weeks). Their past medical history included hypertension, diabetes mellitus and rheumatoid arthritis. The inclusion criteria were as follows: (1) sudden onset of symptoms; (2) presence of circumscribed infarction in the anterior portion of the thalamus with a lack of lesions elsewhere on MRI; (3) no severe stenosis or occlusion of the major cerebral arteries on MR angiography; (4) no history of other neurological and psychiatric diseases and (5) no history of premorbid cognitive impairment or behavioural abnormalities. The clinical diagnosis was made based on an examination by behavioural neurologists and psychiatrists and compared with MRI findings. All procedures used in this study were approved by the ethics committee of the HI-ABCD. Written informed consents were obtained from both patients and their relatives or from the control subjects.

Neuropsychology and behaviour

Neuropsychological assessments were performed within 2 weeks before and after neuroimaging investigations. The batteries and tests used in the study comprised the Mini Mental State Examination, the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Wechsler Memory Scale-Revised (WMS-R), the Western Aphasia Battery, the 100-word object naming, verbal fluency (animals/initial letter), Raven’s Coloured Progressive Matrices, the Weigl’s Colour-Form Sorting Test and Luria’s executive/motor performance tests (list-edge-palm test, 2-1 tapping test and alternative pattern drawing). These tests represent the domains of general intelligence, anterograde episodic memory, language/semantic knowledge, perceptual organisation/construction and executive function (concept formation, psychomotor speed and executive/motor control). Retrogade episodic memory and the presence and types of behavioural abnormalities were assessed based on interviews of patients and their close family members and a bedside examination. The correspondence between the cognitive...
domains and the neuropsychological measures are indicated in table 1.

**Stereotactic lesion localisation on MRI**

Coronal three-dimensional T1-weighted SPCR images (TR, 14 ms; TE, 5 ms; flip angle, 20°; resolution, 1.5×0.86×0.86 mm) were obtained using a 1.5-T GE Signa Horizon system. The images were reconstructed into 1.0 mm isotropic transverse sections and then normalised to the Montreal Neurological Institute (MNI) T1 template using the affine transformation algorithm implemented in the SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) software application. The lesions of each patient were traced on normalised images. The detailed localisation of the thalamic and adjacent structures involved was determined on transverse sections using an electronic version of the Schaltenbrand–Wahren (S–W) atlas.15 The correspondence of the transverse sections between the MNI-T1 template and the S–W atlas was determined by scaling the z-axis with reference to the intercommissural distance, the distance between the top of the thalamus and the AC–PC plane. In-plane two-dimensional linear coregistration was performed with reference to the intercommissural distance, interepituminal distance and contour of the thalamic.

**Positron emission tomography**

PET images were obtained from the six patients and six healthy subjects (75.2±9.0 years; six females) under resting conditions with their eyes closed using a Shimadzu Headtome-IV scanner. The regional cerebral blood flow (rCBF) was determined using a steady-state technique. The subjects continuously inhaled O₂ at 500 MBq/200 ml/min during a 10-minute scanning session.16 Arterial blood samples were collected to measure the blood radioactivity concentrations. Data were collected in 128×128 matrices, and the slice interval was 6.5 mm when the z-motion mode was used.17 The scan did not include the top of the frontal and parietal lobes and the inferior portion of the cerebellar hemispheres. Image preprocessing and statistical analyses were carried out using SPM5. The ventromedial prefrontal region was masked because of the presence of artefacts due to gas inhalation. The obtained images were reconstructed into 2 mm cubic voxels and then normalised to the SPM-PET template using affine transformation. The resultant images were smoothed with 12 mm full width at half maximum. Threshold masking was applied with a criterion of 80% of the mean global value. Proportional scaling was used to control the individual variation in the global CBF. Two-sample t-tests were used for a voxelwise group comparison between the patient and control groups. T-contrast maps were created with a height threshold of uncorrected p<0.001 and an extent threshold of 50 voxels (400 mm³). As the small number of the subjects could cause underestimation of group difference in rCBF, we additionally analysed the PET data on individual subject basis using regions of interests (ROIs). Twenty-one pairs with their eyes closed using a Shimadzu Headtome-IV scanner. The regional cerebral blood flow (rCBF) was determined using a steady-state technique. The subjects continuously inhaled O₂ at 500 MBq/200 ml/min during a 10-minute scanning session. Arterial blood samples were collected to measure the blood radioactivity concentrations. Data were collected in 128×128 matrices, and the slice interval was 6.5 mm when the z-motion mode was used. The scan did not include the top of the frontal and parietal lobes and the inferior portion of the cerebellar hemispheres. Image preprocessing and statistical analyses were carried out using SPM5. The ventromedial prefrontal region was masked because of the presence of artefacts due to gas inhalation. The obtained images were reconstructed into 2 mm cubic voxels and then normalised to the SPM-PET template using affine transformation. The resultant images were smoothed with 12 mm full width at half maximum. Threshold masking was applied with a criterion of 80% of the mean global value. Proportional scaling was used to control the individual variation in the global CBF. Two-sample t-tests were used for a voxelwise group comparison between the patient and control groups. T-contrast maps were created with a height threshold of uncorrected p<0.001 and an extent threshold of 50 voxels (400 mm³). As the small number of the subjects could cause underestimation of group difference in rCBF, we additionally analysed the PET data on individual subject basis using regions of interests (ROIs). Twenty-one pairs

<table>
<thead>
<tr>
<th>Cognitive and behavioural domains</th>
<th>Tests</th>
<th>Patients</th>
<th>Normative data</th>
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<td></td>
<td></td>
<td>1</td>
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<tr>
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<td></td>
<td>WAIS-R</td>
<td>68*</td>
<td>78*</td>
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<td></td>
<td>PIQ</td>
<td>85</td>
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<td>Visual memory</td>
<td>72*</td>
<td>93</td>
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<td>Attention/concentration index</td>
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<td>84*</td>
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<td>Delayed recall index</td>
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<td>&lt;50*</td>
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<td>69.2*</td>
<td>90.8*</td>
</tr>
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<td>Spontaneous speech (/20)</td>
<td>12*</td>
<td>17*</td>
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<tr>
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<td>Auditory comprehension (/10)</td>
<td>7.2*</td>
<td>9.8</td>
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<td>Naming (/10)</td>
<td>8.9*</td>
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<td></td>
<td>Repetition (/10)</td>
<td>5.5*</td>
<td>9</td>
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<td>6.7*</td>
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<td>Writing (/10)</td>
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<td>Animal fluency (/min)</td>
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<td>Initial fluency (/min)</td>
<td>0*</td>
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<td></td>
<td>Picture Naming (/100)</td>
<td>74*</td>
<td>97</td>
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<td>6*</td>
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<tr>
<td></td>
<td>Vocabulary SS</td>
<td>5*</td>
<td>7</td>
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<tr>
<td></td>
<td>Comprehension SS</td>
<td>2*</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Similarities SS</td>
<td>4*</td>
<td>5*</td>
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<td>WAIS-R7</td>
<td>Picture completion SS</td>
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<td>Block design SS</td>
<td>5*</td>
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<td>Weig's colour-form sorting13</td>
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<td>Psychomotor speed</td>
<td>WAIS-R Digit symbol SS12</td>
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<tr>
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<td>Executive/motor control</td>
<td>Fist-edge-palm14</td>
<td>2-1 tapping14</td>
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<td>Behaviour</td>
<td>Apathy</td>
<td>(+)</td>
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of 8 mm spherical ROIs of each hemisphere were determined on
the mean normalised PET image of the 12 subjects using the
MarsBar toolbox (http://marsbar.sourceforge.net/). Left/right
asymmetry indices (calculated as (mean voxel value of left ROI)/
(mean voxel value of right ROI)) of each patient were compared
to 95% CIs of that obtained from the six control subjects.18 19

RESULTS
Neuropsychology and behaviour
The results of the neuropsychological tests and behavioural
observations are summarised in table 1.

General intelligence
The verbal intelligence quotient (VIQ) of the WAIS-R was
less than 85 (−1 SD of the normative mean) in four of the six
patients, whereas the performance IQ was within the normal
range in all patients except Patient 4.

Episodic memory
All patients showed impairments in the verbal memory index
(MI) of the WMS-R (<85, −1 SD). Their verbal MI was disprop-
orportionately lower than their VIQ in the WAIS-R (verbal MI —
VIQ≥10).18 Retrograde memory was preserved in all patients.

Language/semantic knowledge
The spontaneous speech score was impaired in all patients due
to poor information content and word-finding difficulties.
Semantic paraphasias were occasionally observed in some
patients. Articulatory errors and phonological paraphasias were
not observed. All patients excluding Patient 2 showed anomia in
the naming subtest of the Western Aphasia Battery and/or in the
picture naming test of 100 words. Apparent reading and writing
disabilities were observed in two patients (Patients 1 and 4). All
the patients were impaired (<7) in at least one of the subtests
of the WAIS-R: Information, Vocabulary, Comprehension and
Similarities.

Perceptual organisation/construction
Five of the six patients performed at normal levels on the Picture
Completion and Block Design subtests of the WAIS-R.

Executive function (concept formation, psychomotor speed and
executive/motor control)
Although all patients excluding Patient 6 were impaired in at
least one of the executive function tests, no consistent tendency
in the test categories showing impairment was found in the
patient group.

Behaviour
Apathy was observed in all patients. Lack of spontaneity,
reduced emotional response and psychomotor retardation were
observed in Patients 1 and 4. In the other four patients, their
apathy was milder and consisted only of lack of spontaneity.
Other behavioural alterations that have been associated with
frontal lobe damage, such as disinhibition, irritability and
repetitive behaviours, were not observed.

Stereotactic lesion localisation
The results are shown in figure 1 and table 2. Designations of the
thalamic nuclei were according to Hirai and Jones.20 The ventral
anterior proper (VA proper; also referred to as the parvocellular
VA or just the VA), magnocellular ventral anterior nucleus
(VAmc), ventral lateral anterior (VLa), ventral lateral posterior
(VLp), reticular (R) nuclei and mammillothalamic tract (MTT)
were involved in all patients. The anterior nuclei (AN) were
preserved in all patients. The mediodorsal nucleus (MD) was
involved only in Patient 4. The internal medullary lamina (IML)/
central medial nucleus (CeM) was affected in three patients
with lesions that were located medially (Patients 2, 4 and 5). The
genu of the internal capsule (ICg) was damaged at the site
ventral to the thalamus in Patients 3, 4 and 5.

Positron emission tomography
A voxelwise group comparison revealed significant rCBF reduc-
tions in the anterior temporal lobe (ATL), thalamus, orbital
frontal lobe (OFL) and middle frontal gyrus (MFG) of the left
hemisphere in the patients with LATI compared to the control
subjects (figure 2). A relative increase in rCBF was detected in
the right precuneus and right lingual gyrus. An ROI analysis
showed decreased left/right asymmetry index (lower rCBF in the
left side compared to the right side) in the anterior cingulate
gyrus, inferior temporal gyrus, inferior parietal lobule, calcarine

Figure 1 Transverse images from the Schaltenbrand—Wahren (S–W) atlas are shown in the left column. The structures involved in left anterior thalamic infarction are coloured. Images showing lesions (red) superimposed on the Montreal Neurological Institute (MNI) template are indicated in the right column. The voxels that overlapped in more patients are coloured in brighter red. CeM, central medial nucleus; IML, internal medullary lamina; MTT, mammillothalamic tract; VA, ventral anterior
nucleus proper; VAmc, magnocellular ventral anterior nucleus; VLa, ventral lateral anterior nucleus; VLp, ventral lateral posterior
nucleus; VLP, ventral lateral posterior nucleus.
and the VIQ of the WAIS-R suggested that our patients had deficits in the memory function itself. A hypothesis has been recently proposed that selective or predominant memory impairment of verbal materials in left temporal lobe pathology arises from concomitant deficits in semantic processing and protosemantic components of episodic memory. The same perspective may be applicable to material-specific memory impairment in thalamic damage.

The language disturbances in our patients were characterised by word-finding difficulty and anoma. The articulation and phonological aspects were well preserved. Anoma and poor performance in the naming tests and the Information, Vocabulary, Comprehension and Similarities subtests of the WAIS-R suggested that the lexical-semantic impairment was the core deficit responsible for their language symptoms. This interpretation is supported by previous reports investigating a variety of lexical-semantic deficits, including category-specific anoma, proper name anoma and degraded knowledge of object use, in patients with LATI. The nomenclature for the thalamic nuclei is according to Hirai and Jones and Hassler.

### DISCUSSION

#### Clinical features of LATI

In agreement with previous reports of LATI, the symptoms of our patients were characterised primarily by memory impairment, language disturbances and apathy. Although previous studies of acute LATI have reported a perseverative behaviour (palipsychism) and mild sensorimotor deficits, we did not observe these symptoms.

The memory impairment was restricted to the anterograde domain and dominant in the verbal materials. Although the concomitant deficits in language, attention and executive function may partly explain the memory impairment observed in our patients, the dissociation between the verbal MI of the WMS-R and the VIQ of the WAIS-R suggested that our patients had deficits in the memory function itself. A hypothesis has been recently proposed that selective or predominant memory impairment of verbal materials in left temporal lobe pathology arises from concomitant deficits in semantic processing and protosemantic components of episodic memory. The same perspective may be applicable to material-specific memory impairment in thalamic damage.

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### Cortical diaschisis in LATI

Using CBF diaschisis, we demonstrated that the connections of the thalamus with the dorsolateral, medial and orbital frontal lobes, the ATL, the inferior parietal lobe and the occipital lobe were disrupted in LATI. Compared to patients with paramedian thalamic infarction (PTI), the extent of hypoperfusion regions in our patients was relatively restricted. This difference in PET findings is well correspondent with that in clinical manifestations; patients with PTI develop more severe behavioural symptoms compared with those that had anterior thalamic infarction (ATI), for example, coma, akinetic mutism and confusion. The involvement of the intralaminar nuclei, which project broadly to the cerebral cortex, and/or their projecting fibres probably causes extensive cortical dysfunction in PTI. A previous single-case PET study of LATI reported restricted rCBF reductions in the ipsilateral amygdala and posterior cingulate cortex. The disagreement between this and our studies is probably related to difference in affected thalamic structures and in neuroimaging analysis.

### Neuroanatomical basis of memory impairment

The neural circuit that arises from the hippocampus via the fornix, mammillary body (MB), MTT, AN and posterior cingulate cortex and then projects back to the hippocampus is known.
In contrast with this view, however, our PET analysis did not detect diaschisis in the medial temporal lobe and other regions, such as the Papez or Delay–Brion circuit. This circuit has long been considered to play a central role in memory. In addition, the significance of the rhinal/parahippocampal-MD-prefrontal network has been recently recognised.25 Because the AN and MD are spared in the majority of patients with ATI,2 29 the disconnection of these neural networks at the intrathalamic white matter structures, namely the MTT and IML, have been considered critical in memory impairment in ATI.2 29 31 In the present case series, the MTT was consistently involved, whereas the IML was affected only in half of the patients, suggesting the significance of Papez circuit disruption. In addition, we propose a possible role of lesions in the VA region, which is penetrated anteriorposteriorly by the inferior thalamic peduncle, the bundle carrying the fibres from the rhinal/parahippocampal cortex to the MD.20 In contrast with this view, however, our PET analysis did not detect diaschisis in the medial temporal lobe and other components of the Papez circuit. Two possible factors may be associated with this negative result: diaschisis is presumably hard to be observed in the disruption of polysynaptic connections;24 for example, the connection between the MTT and the posterior cingulate cortex via the AN; rCBF reduction in the left anterior cingulated gyrus was observed in our patients. In the original formulation of the frontal-subcortical circuits,25 disinhibited behaviour is linked to disruption of the orbitofrontal circuit. However, none of our patients developed such kind of behavioural alteration in spite of diaschisis in the OFL. Previous studies have suggested that disinhibition syndrome occurs after right-lateralised lesions.41 42 The lack of disinhibited behaviour in our patients is presumably associated with the laterality of the lesions.

### Table 3 Left/right asymmetry indices obtained from the regions of interest (ROI) based positron emission tomography analysis

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls (n = 6)</th>
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<tbody>
<tr>
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<td>1</td>
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<tr>
<td>Inferior frontal</td>
<td>0.79</td>
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<td>Middle frontal</td>
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<td>0.93</td>
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<tr>
<td>Frontal operculum</td>
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<tr>
<td>Lateral orbital frontal*</td>
<td>0.80</td>
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<tr>
<td>Anterior cingulate*</td>
<td>0.78</td>
<td>0.87</td>
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<tr>
<td>Central</td>
<td>1.16</td>
<td>0.97</td>
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<tr>
<td>Temporal pole*</td>
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<td>0.86</td>
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<td>Inferior temporal*</td>
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<td>Inferior parietal*</td>
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<td>Cuneus*</td>
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<tr>
<td>Fusiform</td>
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<tr>
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<td>Posterior striatum</td>
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<td>1.19</td>
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<tr>
<td>Thalamus*</td>
<td>0.66</td>
<td>0.80</td>
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</table>

Indices lower and than 95% CI of the controls are shown in bold and italic, respectively. *and † indicate ROIs in which laterality indices are lower and than 95% CI of the controls in four or more patients, respectively.

### Neuroanatomical basis of language disturbance

It is noteworthy that diaschisis was observed in the ATL, which is a region that is putatively involved with the integration of lexical and semantic information.34 35 Both LATI and left ATL damage have been linked to semantic-lexical deficits, including category-specific anoma and proper name anoma.34 36 37 This symptomatic similarity suggests the presence of functional relationships between these two regions. Connectional anatomical studies in monkeys have shown anatomical connections between the VAmc, a thalamic structure consistently involved in ATI, and the anterior temporal neocortex.30

We propose that thalamo-anterior temporal disconnection plays a significant role in the language disturbances observed in LATI. Some investigators have speculated that the disruption of the intralaminar nuclei-inferior thalamic peduncle-prefrontal system is critical in the language disturbances observed in LATI.59 Although the IML was involved only in half of our patients, diaschisis in the dorsolateral prefrontal cortices was demonstrated in our PET analysis. The thalamo-dorsolateral prefrontal disconnection may also be related to the linguistic symptoms.

### Behavioural symptoms and their relevance to cortical diaschisis

Apathy is the most common behavioural feature in the current and previously reported cases of LATI.3 21 Although apathy can result from lesions in various locations,40 it has been particularly associated with anterior cingulate damage. Consistently, rCBF reduction in the left anterior cingulated gyrus was observed in our patients. In the original formulation of the frontal-subcortical circuits,2 disinhibited behaviour is linked to disruption of the orbitofrontal circuit. However, none of our patients developed such kind of behavioural alteration in spite of diaschisis in the OFL. Previous studies have suggested that disinhibition syndrome occurs after right-lateralised lesions.41 42 The lack of disinhibited behaviour in our patients is presumably associated with the laterality of the lesions.

### Limitations of the study

The first limitation of the study is the small sample size. Age, disease duration, subclinical neurodegenerative pathologies and individual differences in functional lateralisation among others, may have had a large effect on the clinical presentation and neuroimaging results. Clinical-PET correlation analyses were unavailable also due to the small number of subjects. Although much larger sample sizes are needed to overcome these problems, it would be quite difficult to recruit a sufficient number of subjects from a single institution due to the rarity of isolated ATI. A meta-analysis of studies that have performed detailed neuroimaging investigations would be valuable. Also, the probable selection bias on the neuropsychological and behavioural findings should be noted. Since we performed the study in a dementia department, only patients with cognitive problems mimicking dementia may have been referred to us. Lack of sensorimotor deficits and perseverative behaviours21 and relatively long-lasting cognitive impairment may be associated with such kind of bias. Finally, as it took a long time, over 7 years, to recruit the patients, we failed to update the neuropsychological tests. Therefore, we could not incorporate new cognitive theories, such as the recollection/familiarity components of episodic memory.43

There are a number of methodological limitations to our neuroimaging investigations. The precision of lesion localisation on MRI is limited by image distortion due to magnetic field inhomogeneity, inaccuracy of spatial normalisation and image co-registration, difficulty in defining exact lesion boundaries and so forth. In the PET analyses, the proportional scaling probably led to underestimation of the spatial extent and strength of hypoperfusion and to spurious hyperperfusion. The ROI-based left/right asymmetry analysis is unable to detect bilateral rCBF changes.19 Lastly, inhalation artefacts precluded the evaluation of the ventromedial frontal regions, which are reported to have dense interconnections with the thalamic structures.20.

Research paper

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Competing interests None.

Ethics approval This study was conducted with the approval of the Hyogo Institute for Aging Brain and Cognitive Disorders.

Provenance and peer review Not commissioned; externally peer reviewed.

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