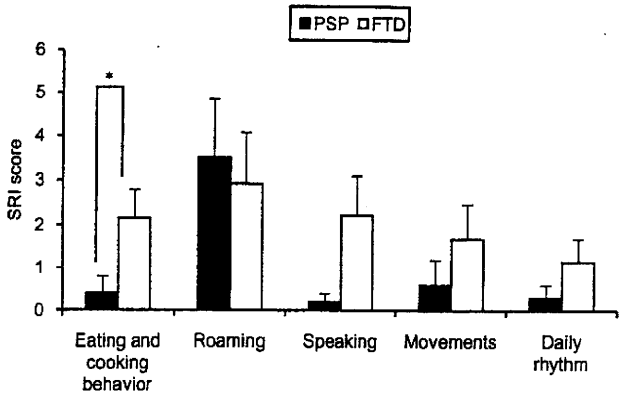

Figure 2 The scores of the Stereotypy Rating Inventory (SRI) subscale in the progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) groups. *$P < 0.05$.

Table 2 Frequency of specific antisocial behavior in progressive supranuclear palsy and frontotemporal dementia groups

	PSP *n* (%)	FTD *n* (%)	*P*-value
Stealing	0/10 (0)	0/13 (0)	—
Neglect of the traffic rules	3/10 (30)	3/13 (23)	1.000
Physical assault	3/10 (30)	2/13 (15)	0.618
Hypersexuality	3/10 (30)	0/13 (0)	0.068
Public urination	1/10 (10)	2/13 (23)	1.000
Any of antisocial behaviors	5/10 (50)	6/13 (47)	1.000

FTD, frontotemporal dementia; PSP, progressive supranuclear palsy.

Table 2 shows the frequency (on a present/absent basis) of specific antisocial behaviours between the two groups. A total of 50% of patients with PSP and 46% of patients with FTD showed at least one of the antisocial behaviours. The PSP group had a history of physical assault (30%), hypersexuality (30%), neglect of the traffic rules (30%) and public urination (10%). The FTD group had a history of neglect of traffic rules (23%), public urination (15%) and physical assault (15%). In our cohort, no patients in either group presented stealing. Hypersexuality was more common in the PSP group than in the FTD group, although the differences did not reach statistical significance ($P = 0.068$).

DISCUSSION

This is the first study to systematically investigate neuropsychiatric symptoms based on the data from consecutive patients with PSP in a dementia clinic and directly compare them with those in the FTD group. The feature of neuropsychiatric symptoms showed quite a similar pattern in both diseases, except for the profile of stereotypical behaviour represented by the SRI. Namely, apathy was one of the most predominant neuropsychiatric symptoms following aberrant motor behaviour and disinhibition. Delusions, hallucinations and depression were unusual in both diseases. It was surprising that the prevalence of antisocial behaviours in PSP (50%) was equal to those in the FTD (46%) in a dementia clinic.

Thus, we found a close resemblance in psychiatric symptoms and behavioural disturbances between PSP and FTD. Previous reports have shown that not only FTD,[22,23] but also PSP,[24,25] show hypoperfusion of frontal regions, although there is no study to directly compare the brain functional imaging between PSP and FTD. In the present study, the background of cerebral blood perfusion in both diseases was consistent with these previous studies.[22–25] The similarity of the neuropsychiatric symptoms in both diseases might be explained by frontal hypoperfusion. Furthermore, PSP and corticobasal degeneration (CBD) are considered to be the same spectrum as FTLD and are known as a single term, 'Pick complex', by some researchers because there are clinical, pathological, genetic and biochemical overlaps.[26] In recent years, PSP and CBD, together with tau-positive FTD, were included in FTLD-tau as neuropathological subtypes of FTLD.[27] The results in the present study support the validity of regarding PSP as FTLD from a clinical viewpoint to some extent, although there is an objection to including PSP, which has been recognized as a movement disorder in FTLD, which is recognized as a cortical dementia syndrome in clinical practice.

In the present study, patients with PSP showed apathy, aberrant motor behaviour and disinhibition, but rarely psychosis and depression. The feature of the neuropsychiatric symptoms in our PSP cohort was almost consistent with several previous studies.[7–9] Litvan *et al.*[7] investigated neuropsychiatric features in the patients with PSP using the NPI, and found that apathy and disinhibition were common, whereas delusions, hallucinations and depression were uncommon. Aarsland *et al.*[8] and Kulisevsly *et al.*[9] also reported the same pattern of BPSD in their PSP cohorts. The present study and these previous reports[7–9] were based on data from a dementia clinic. In contrast, Borroni *et al.*[28] showed that by using the NPI, that the patients with PSP in a movement disorder clinic had

more depression and less apathy. The difference among these studies,[7–9,28] including ours, could be explained by the location of the studies. The patients with PSP are mainly diagnosed and treated for movement disorders by neurology services. However, the first medical contact is sometimes with psychiatry services or dementia clinics, because cognitive impairment and behavioural change is quite often seen in patients with PSP and might appear before the neurological signs.[29]

In contrast to the similar results of the NPI, there were several differences in stereotypical behaviour between the patients with PSP and FTD. As shown by the SRI, the patients with PSP were less marked than those in the FTD group in stereotypical behaviour, especially stereotypical eating and cooking behaviour. Bozeat *et al.*[12] suggested that only stereotypical behaviour, changes in eating preference, disinhibition and features of poor social awareness reliably distinguished between FTD and AD. Our results also suggest that the lack of stereotypical eating behaviour might help to differentiate PSP from FTD. Furthermore, it is noteworthy that 30% of patients with PSP presented hypersexuality, whereas no patients with FTD presented hypersexuality in our cohort. Bathgate *et al.* showed that 58% of patients with FTD showed hyposexuality, whereas 19% of FTD showed hypersexuality.[30] To our knowledge, there is no study to investigate sexual behaviour in PSP. There is a possibility that the existence of frontal syndrome with sexually disinhibited behaviour suggests the diagnosis of PSP, but not FTD, although this suggestion requires further examination.

There are a few methodological issues that should be taken into consideration to appreciate our results fully. First, although we diagnosed all patients according to clinical consensus criteria[2,10] with brain MRI or CT and SPECT, diagnosis was not confirmed by autopsy. Second, the statistical evaluation was limited by the small number of patients. Third, as we described earlier, the present study was based on the data from a dementia clinic rather than population-based. It can be claimed that selection bias affected our results. Fourth, we assessed specific antisocial behaviour using a checklist that has not yet been standardized, because there is no standardized measurement for antisocial behaviours in dementia. As a result of these limitations, the findings in the present study might not be applied to all patients with PSP.

Despite these limitations, we believe that our findings are quite meaningful, because the present study based on the data from consecutive patients in a dementia clinic highlighted the variety of clinical manifestations in PSP. In a dementia clinic, the BPSD profile in patients with PSP closely resembled those in the FTD. Furthermore, the absence of stereotypical eating behaviour and the presence of hypersexuality might be useful for differential diagnosis between PSP and FTD, although further investigation with a larger sample is warranted. Clarifying the underlying mechanism of these symptoms should be also carried out using a method of neuroimaging analysis. We emphasize that PSP should be considered as not only a movement disorder, but also a disorder with a wide range of neuropsychiatric symptoms.

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連載 Focus

認知症の診断における症候学の重要性

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その物忘れは本当に認知症か ―鑑別の重要性

認知症が疑われる高齢者の診察では，主な愁訴である物忘れが認知症に基づくものであるかどうかを慎重に検討する必要があり，特に正常な老化による物忘れ，うつ病，せん妄などとの鑑別が重要である（表1）。病初期に認知症を発見することは，その後の治療・介護に大きな効果をもたらすことになる。

アルツハイマー病（Alzheimer's disease；AD）では，病識の欠如が正常な老化との決定的な違いになる。軽度認知障害（mild cognitive impairment；MCI）であれば病識はかなり保たれるが，AD患者では多くの場合欠如している。受診理由を尋ね，病識への認識に関して介護者と患者との間に乖離が認められれば，ADを念頭において診察を進める。

老年期うつ病は認知症との鑑別が難しい。老年期うつ病では抑うつ感情や悲哀感が少なく，心気的・身体的な訴えが中心となり認知機能障害を伴いやすいため，従来は仮性認知症などと称されることもあった。これらの患者はMMSE（Mini-Mental State Examination）などで，初期のAD患者と同等のスコアを示す場合が多く，しかもADやレビー小体型認知症（dementia with Lewy bodies；DLB）では40%程度が初期に抑うつ状態を伴うため，鑑別がより難しい。ただし，血管性認知症（vascular dementia；VaD）や前頭側頭葉変性症（frontotemporal lobar degeneration；FTLD）では抑うつ状態は少なく，これらの疾患で抑うつに類似する症状がみられた場合にはアパシー（意欲低下）が推測される。アパシーはほぼすべての認知症患者で高頻度に認められるため，アパシーと抑うつとの見極めも鑑別ポイントになる。

せん妄状態も認知症との見極めを要するが，せん妄で多発する幻視は，DLB以外の認知症ではあまり発現しない。このため幻視があればせん妄を疑い，次にDLBを疑うことができる。

症候学を用いた背景疾患の診断・治療・予防

認知症と鑑別できれば，背景疾患の診断を行う。背景疾患は，①治療が可能な疾患，②予防が重要な血管障害性の疾患，③治療困難な神経変性疾患に大きく分類される（表2）。約半数はADであり，以下VaD，DLB，FTLDが続く。

1．根治的治療の可能性がある認知症

慢性硬膜下血腫では，転倒などで硬膜下に生じた血腫が脳を圧迫して認知機能障害を生じる。一例を挙げると，自立が保たれていた軽度AD患者において，2ヵ月半前の転倒をきっかけに症状が急速に悪化し，受診時には歩行不可能，傾眠傾向でMMSEが6点であった。本症と診断され脳外科で手術を行った結果，術後1週間で退院し，3ヵ月後にはMMSEが19点に回復していた。

このように治療の可能性がある認知症には経過が早いという特徴がある。ADをはじめとする神経変性疾患では，症状が緩やかに悪化する。またVaDでは，数年をかけて脳梗塞が起こるたびに症状が段階的に悪化する。これに対して慢性硬膜下血腫のような疾患では，受診2～3ヵ月前から症状が急速に悪化することが多い（図1）。身体疾患と同様であるが，早い経過には早急な対応が必要であり，問診から経過を正確に把握することが治療の決め手となる。神経学的な所見を得たらすぐに画像診断を行うべきであり，発症後半年以内が勝負である。

2．予防が重要な認知症

主な疾患はVaDであるが，血管障害の発症部位や数に応じて症状は多彩であり，認知症の背景疾患の中でも特に診断が難しい。典型的なVaDでは図1のように症状の悪化が階段状に認められ，介護者への問診でこれが確認できれば，ADと鑑別することができる。ちなみに，介護が奏効すると症状が改善する場合もある。

日本人を含めアジア人では，多発性小梗塞によるVaDが圧倒的に多く，大脳基底核，深部白質の小梗塞が蓄積すると前頭葉の血流が二次的に減少し，アパシーをきたす。この場合には，病初期であっても社会生活の範囲に狭小化が生じる。たとえば，今まで熱心に参加していた老人会に急に行かなくなった，あるいは一人では家事ができなくなったといった例では，アパシーや遂行機能障害が推測される。記憶障害などの道具的機能は病初期には比較的維持されているので，周囲が患者の変化に気づき，患者の活動性を上げることができれば，回復は十分可能である。しかしこのような状況が続くと，廃用症候群に関わる悪循環(図2)が形成されてしまう。現在，わが国の高齢者の7割は高齢夫婦世帯か独居であり，家庭内でこの悪循環を断ち切ることが難しく，患者は2～3ヵ月で重度の認知症や寝たきりに至る可能性が高い。このため周囲が介護保険を利用して患者の環境調整を行い，デイサービス，デイケアなどで患者の活動性を徹底的に高める必要がある。

さらに，VaD患者の大部分は糖尿病や高血圧など血管障害の危険因子をもつため，精神科医が内科のかかりつけ医と連携をとり，危険因子の管理を行うことも重要である。

表1　「認知症」とは何か―「認知症」と「正常老化による物忘れ」との違い

	認知症	正常老化による物忘れ
原　因	病気により生じる	加齢により生じる
自覚(病識)	**低　下**	**あ　り**
記憶障害	**経験自体を忘れる**	**喘喋に思い出せない**
社会生活	営むのが困難	支障がない
精神症状や行動障害	伴うことが多い	な　し

表2　認知症の原因疾患

●治療が困難な疾患
- **アルツハイマー病，レビー小体型認知症，前頭側頭葉変性症(ピック病)**，脊髄小脳変性症などの変性性疾患

●予防が重要な疾患
- **多発性脳梗塞**，脳出血，ビンスワンガー病などの血管障害

●治療が可能な疾患
- **正常圧水頭症，慢性硬膜下血腫**，脳腫瘍などの外科的疾患
- 甲状腺機能低下症，ビタミン欠乏症などの代謝性疾患
- 脳炎，髄膜炎などの炎症性疾患
- 廃用症候群(これは他の認知症に合併することが多いので注意が必要)

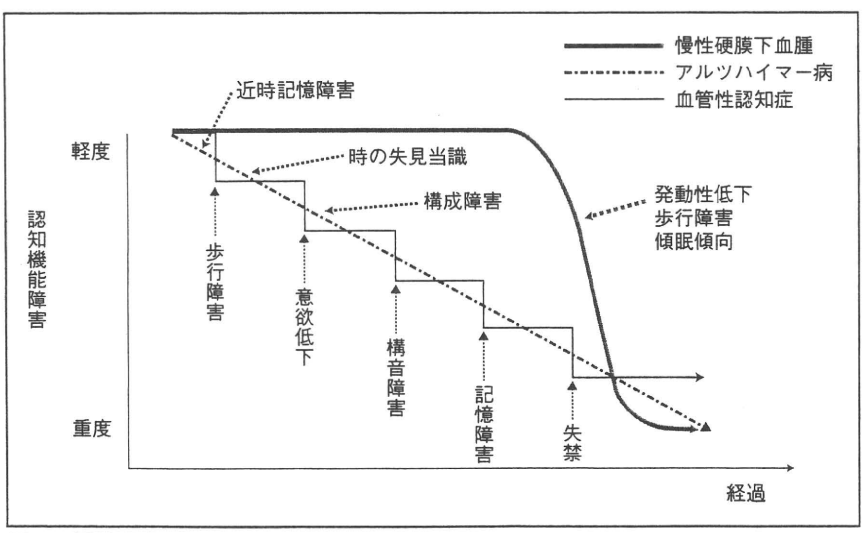

図1　慢性硬膜下血腫の経過

(池田学．認知症－専門医が語る診断・治療・ケア．東京，中央公論新社，2010より引用)

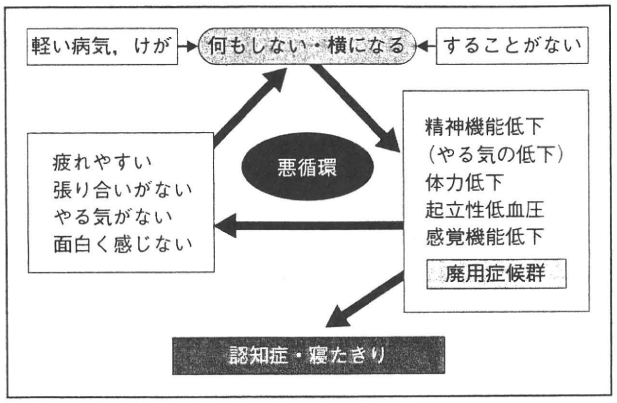

図2　廃用症候群とは

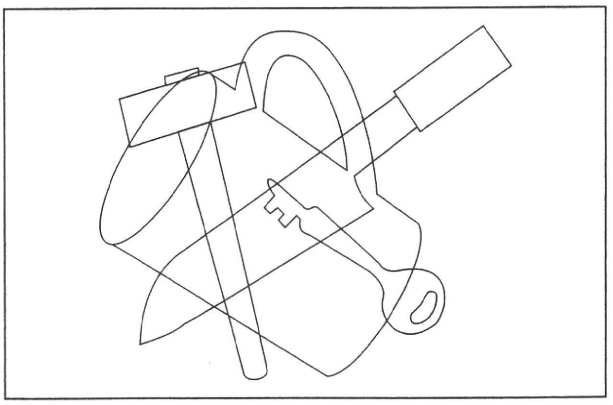

図3　錯綜図
（日本高次脳機能障害学会 編．標準高次視知覚検査（VPTA）．東京，新興医学出版社，2003より引用）

治療困難な認知症でも症候学が診断・ケアの手がかりに

1．アルツハイマー病

ADでは患者の大半が近時記憶障害から発症するので，これを確実に把握することが早期診断に直結する。ただし，ADに限らずすべての認知症に共通するが，認知機能障害のみに捉われると的確な診断ができない場合が多い。認知機能障害とともに精神症状，行動特徴に注目することで診断感度やケアの効果が高まる。

たとえば，初期のADでは「取り繕い反応」が特徴的に認められ，物忘れについて高齢などを理由に取り繕う患者が多い。アパシーと抑うつも，多くのAD患者で認められる症状である。

妄想も約半数のAD患者で発現し，「物盗られ妄想」はそのうち75%程度でみられる。物盗られ妄想では患者の主たる介護者が攻撃の対象になりやすく，また比較的病初期のADL(activity of daily living)がほぼ自立している段階で起こる。このため，発現前に適切な介入ができれば，患者はADLを保ちつつ家庭生活を継続することができるが，介入に失敗するとADLがほぼ自立した時期から長期の入院や入所を余儀なくされる。介護者に前もって物盗られ妄想が起きる可能性があり，妄想が始まったら受診するように伝えておくことができれば，3割程度の介護者は精神的な余裕をもって妄想に対処できる。ただし物盗られ妄想は非常に激しく，約6割の介護者では単独での対応が難しいとされる。その場合は介護保険を活用してデイサービス，デイケアを毎日利用し，介護者と患者の接触時間を減らすという環境調整を行うと，妄想を分散できる場合が多い。それでも解決できなければ，リスペリドンなどの非定型抗精神病薬を用いた薬物療法を検討する。

ADの根治的治療法はまだ確立されていないが，症候学により早期発見ができれば，進行を抑制するさまざまな対応が可能になる。

2．レビー小体型認知症

DLBでは症状の変動が特徴であるが，その確認は簡単ではない。介護者から症状の変動を聞き出すとともに，毎回の外来診察や検査では患者の変化を見逃さないことが重要である。さらに次のような点も鑑別の手掛かりとなる。認知機能障害としては視覚認知，視覚構成，視覚性注意の障害が生じるのに対し，記憶・見当識はADに比べると比較的保たれる。視覚認知障害の検査に用いられる錯綜図（図3）では，DLB患者の場合ごく初期の患者でもこの図の中に何が隠されているかを言い当てることが困難であるが，ADやFTLD，VaD患者では容易である。

DLBにおいても，精神症状や行動特徴は診断の重要な手掛かりになる。特に抑うつは，AD患者とほぼ同等に病初期から認められ，しかも初発症状となる場合が多い。難治性のうつ病として治療に難渋する例で後から幻覚や妄想が出現し，DLBが明らかになることもある。幻覚，妄想はAD以上に多く，70%近くで認められる。なかでも「誤認妄想」が高頻度に認められ，「亡くなった家族がずっと2階に住んでいる」などの誤認をきたす。また幻覚の中では幻視が

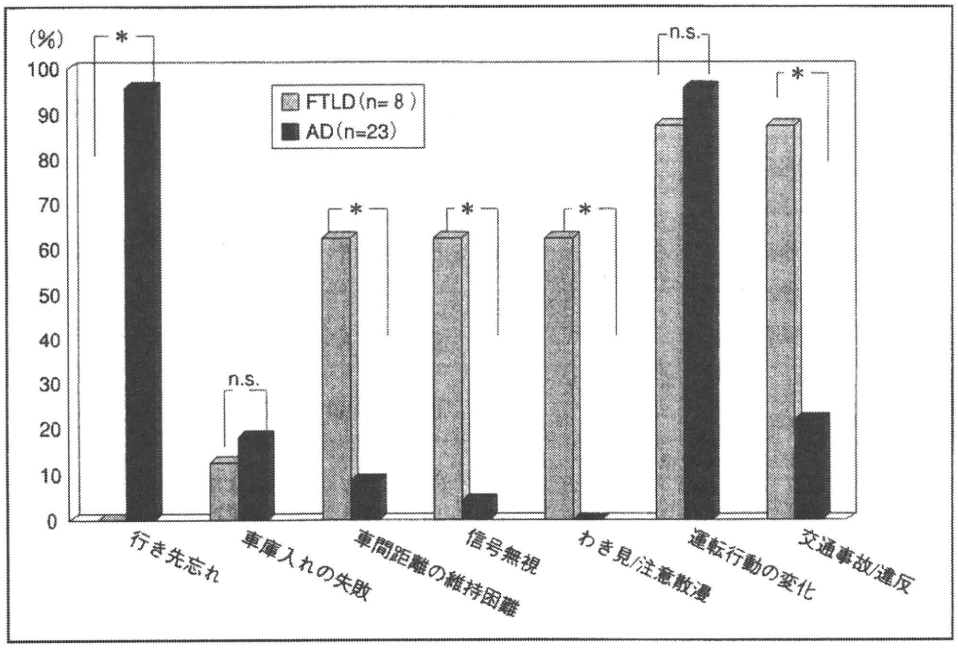

図4　認知症の疾患別による運転行動・交通事故の危険性
*p<0.001，Fisher's exact test
（上村直人．厚生労働省長寿科学総合研究事業 痴呆性高齢者の自動車運転と権利擁護に関する研究［主任研究者 池田学］，平成15～17年度総合研究報告書．2006より引用）

圧倒的に多いが，幻聴も10%程度で認められている。さらにREM睡眠行動障害もDLBの特徴であり，介護者が夜中に目覚めるほどの激しい寝言がみられることも多い。

3．前頭側頭葉変性症

FTLDの典型例では，形態画像で前頭葉あるいは側頭葉前方部の萎縮が顕著に認められる。主症状は前頭葉症状であり後方症状はほとんどみられず，初期には記憶障害，視空間認知障害はなく，ADLもほぼ保たれるが，脱抑制，反社会的行動，常同行動，食行動異常，失語などの症状が多発する。

認知症疾患別の自動車運転行動調査によれば，ADでは目的地忘れや現在位置の失認によるパニック状態が多く，一方FTLDでは前頭葉症状により目前の刺激へ反応するため，前方車両への追従による車間距離の維持困難，信号無視，わき見，逆走などが多数認められた（図4）。

食行動異常もFTLDの特徴であり，過食，甘/辛い物を好む嗜好の変化，さらに同じ物ばかり食べるという常同的な食行動の変化が，FTD患者の約90%で認められる。このため，食行動の問診だけでもADとおおよその鑑別が可能となる。なお，常同行動は食行動に限らず，滞続言語や同コースを同時刻に歩くような徘徊も認められるため，これらが確認できればVaDやADなどとの鑑別が容易になる。

FTLDの介護や治療では，ほぼ保たれているADLを激しい精神症状に惑わされずにどのように維持するか，という点がポイントになる。さらに，異常行動をケアにうまく応用することができる。たとえば，常同行動を考慮し，自宅で入浴可能なごく病初期からデイケア，デイサービスを利用して週2回程度の入浴習慣をつければ，言語的なコミュニケーションが困難になる5～6年後でも入浴の継続が可能になる。

認知症診療における症候学の意義

認知症の診断法としては，画像診断やバイオマーカーの開発が急速に進んでいる。しかし上述のとおり，現時点では症候学に基づく臨床診断が高い感度を有する。認知機能障害に加え，行動特徴や精神症状を正確に見極められれば，早期診断の大きな手掛かりになるとともに，病初期からの有用な治療，ケアの実施に直結する。行動特徴や精神症状は日常生活の中で捉えやすいので，介護者から正確な情報を聞き取ることが必須である。

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False item recognition in patients with Alzheimer's disease

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ABSTRACT

Recent evidence suggests that patients with Alzheimer's disease (AD), as compared with normal individuals, exhibit increased false recognition by stimulus repetition in the Deese–Roediger–McDermott (DRM) task or associative recognition memory tasks, probably due to impaired recollection-based monitoring. However, because of possible alternative explanations for the findings of these previous studies, the evidence for impaired recollection-based monitoring in AD patients remains inconclusive. In this study, we employed stimulus repetition in old/new recognition judgments of single-item picture memory without a factor of association between the stimuli and examined whether AD patients showed increased false item recognition as compared with healthy controls. AD patients and healthy controls studied single-item pictures presented either once or three times. They were later asked to make an old/new recognition judgment in response to (a) Same pictures, pictures identical to those seen at encoding, (b) Similar lures, novel pictures similar to but not identical to those seen at encoding, and (c) Dissimilar lures, novel pictures not similar to those seen at encoding. For Same pictures, repeated presentation of stimuli increased the proportion of "old" responses in both groups. For Similar lures, repeated presentation of stimuli increased the rate of "old" responses in AD patients but not in control subjects. The results of the present study clearly demonstrated elevated false recognition by stimulus repetition in single-item recognition in AD patients. The present findings strongly support the view that AD patients are impaired in their ability to use item-specific recollection in order to avoid false recognition.

1. Introduction

One of the more prominent cognitive problems observed in Alzheimer's disease (AD) is the decline in episodic memory (Salmon and Bondi, 2009), the type of memory that allows one to remember past occurrences in one's life (Tulving, 2001). The episodic memory impairments observed in AD patients are mainly characterized by the failure to retrieve desired information, but at times, AD patients also suffer from memory distortion. The memory distortion in AD patients can sometimes be extreme, as in syndromes of delusional misidentification (e.g., Abe et al., 2007; for review, see Forstl et al., 1994). Therefore, an understanding of memory distortion in AD patients is clinically important; however, the underlying mechanisms remain to be fully elucidated.

One approach to evaluating memory distortion is assessment of false recognition in cognitive memory tasks. False recognition is a process whereby people incorrectly claim that they have recently seen or heard a stimulus that they have not actually encountered (Underwood, 1965). One of the most common tasks for assessment of false recognition is the Deese–Roediger–McDermott (DRM) task (Deese, 1959; Roediger and McDermott, 1995; for review, see Gallo, 2010) in which false recognition of non-studied lures is elicited by having subjects study lists of associates. For example, using a modified version of the DRM paradigm in which study and test trials were repeated five times, Budson, Daffner, Desikan, & Schacter (2000) reported that false recognition increased in AD patients, decreased in young adults, and fluctuated in older adults.

The findings of Budson et al. (2000) can be interpreted as indicating that impaired retrieval monitoring processes in AD patients would cause memory distortion (Schacter, Norman, & Koutstaal, 1998a). More specifically, recall-to-reject processes, where recall (or recollection) opposes familiarity in recognition memory tasks (see Yonelinas, 2002), might be impaired in AD patients. Here, "recall" refers to the ability to retrieve previously experienced information in response to some retrieval cue, and recollection is defined as the mental reinstatement of experienced events during which unique details of memory are recalled. Familiarity is a mental awareness that an event has been experienced previously without the unique details or mental reinstatement of the event (Gardiner,

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1988; Jacoby, 1991; Mandler, 1980; Skinner and Fernandes, 2007). In the study of Budson et al. (2000), owing to the multiple study/test sessions, control subjects may have increased their recollection of the studied items, determined that the related lures were not presented, and hence rejected these lures as non-studied items. AD patients might be unable to use such a recollection-based monitoring process to reduce false recognition. In line with this idea, some previous studies have reported that AD patients have impaired recall or recollection relative to familiarity. For instance, Bartok et al. (1997) reported that AD patients tend to be impaired more in recall than in recognition tests. Dalla Barba (1997) showed that recollection-based recognition is more affected than familiarity-based recognition in AD patients. These findings suggest that AD patients perform poorly on tasks in which recall or recollection is necessary to oppose familiarity-based false recognition.

However, as Gallo, Sullivan, Daffner, Schacter, & Budson (2004) have pointed out, there are other possible explanations, such as impairment of source memory (e.g., Dalla Barba, Nedjam, & DuBois, 1999; Multhaup and Balota, 1997; Smith and Knight, 2002). In the repeated study/test sessions, the subject needs to monitor several sources of information, including whether the related lure was in the study list, in the test list, or whether it was only imagined (Budson et al., 2002; Kensinger and Schacter, 1999; Schacter, Verfaellie, Anes, & Racine, 1998b). Another possible explanation would be the impairment in remembering the associations between items and list-contexts. If the subjects can successfully remember the list-context in which they studied the item, they may reject the unstudied related lures more effectively.

To test the impaired recall-to-reject hypothesis for false recognition in AD patients without contamination of deficits in source memory, Gallo et al. (2004) used an associative recognition memory task in which subjects studied pairs of unrelated words and were later asked to distinguish between these same studied pairs (intact) and new pairs that contained either rearranged studied words (rearranged) or non-studied words (non-studied). During the study period, the pairs were presented either once or three times. The results showed that repetition increased the hits to intact pairs in both AD and control groups, but repetition increased false alarms to rearranged pairs only in the AD group. Gallo et al. (2004) suggested that repetition increases the familiarity of the words in both rearranged and intact pairs; however, only the control subjects were able to counter this familiarity by recalling the originally studied pairs, which is consistent with the recall-to-reject hypothesis.

As Gallo et al. (2004) noted, however, their findings may also be explained by an impaired memory for associations, although they did not ascribe their findings to deficits in source memory. Repetition of word pairs during a study task may enhance familiarity for test words in both intact and rearranged pairs, such that the discrimination between intact and rearranged pairs depends on the memory for the specific association formed during the task. More specifically, in the task used by Gallo et al. (2004), subjects need to recollect associations between two words in order to make an accurate recognition memory judgment. Here, it should be noted that both of the tasks used in Budson et al. (2000) and Gallo et al. (2004) required the subjects to recollect some kind of associations, namely, item-to-list-context association in Budson et al. (2000) and item-to-item associations in Gallo et al. (2004). Thus, from the previous studies on false recognition in AD patients, the evidence for impaired recollection-based monitoring in AD patients remains inconclusive due to possible alternative explanations, especially associative memory account.

To provide strong evidence supporting the impaired recall-to-reject hypothesis, we investigated false recognition in AD patients using a different kind of item-recognition task from those used in previous studies. Prior studies have used semantically related word lists (Budson et al., 2000), phonologically related word lists (Budson, Sullivan, Daffner, & Schacter, 2003b), or categorized color photographs (Budson et al., 2003a). In the present study, we used previously presented pictures (Same pictures), novel pictures similar to previously presented pictures (Similar lures), and novel pictures not similar to previously presented pictures (Dissimilar lures) as experimental stimuli for the recognition memory task. The experimental paradigm using these stimuli, which have often been reported in previous studies (e.g., Garoff, Slotnick, & Schacter, 2005; Kensinger, Garoff-Eaton, & Schacter, 2007a, 2007b; Kensinger and Schacter, 2007), was suitable for our investigation because it allowed us to measure changes in the ability to discriminate Same pictures from Similar lures (i.e., item-specific recollection) by stimulus repetition without the element of source memory or associative memory. The aim of the present study was to determine whether AD patients would show increased false recognition in response to Similar lures by stimulus repetition and to provide strong evidence supporting the impaired recall-to-reject hypothesis in AD patients.

Table 1
Demographic data (mean ± SD) for the AD patients and the healthy controls.

	AD patients ($n = 18$)	Controls ($n = 18$)	p-Value
Age	74.5 (4.6)	74.8 (4.2)	$p > 0.1$
Sex (female/male)	14/4	11/7	$p > 0.1$
Education	10.7 (2.1)	10.9 (1.8)	$p > 0.1$
MMSE	24.4 (2.1)	28.0 (1.7)	$p < 0.001$

The chi-squared test was used for the gender ratio, and the t-test was used for the remaining variables. Standard deviations are in parentheses. MMSE, Mini-Mental State Examination.

2. Materials and methods

2.1. Participants

Eighteen patients with a clinical diagnosis of probable AD (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria; McKhann et al., 1984) and 18 healthy elderly adults participated in the experiment. AD patients were recruited from the clinical population at Tohoku University Hospital. Each of these patients was assessed by one or more board-certified neurologists with expertise in diagnosing dementia. Elderly adults who had no history of neurological or psychiatric diseases were recruited from the local community via an advertisement. The exclusion criteria for both groups were a medical history of neurological disease (e.g., stroke, head injury, and epilepsy) or psychiatric illness (e.g., schizophrenia and manic depression) and a documented or suspected history of alcohol or drug abuse. In addition, because we intended to study patients with mild AD, patients who scored less than 20 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) were excluded. Healthy participants who scored less than 24 (a cutoff level for a diagnosis of dementia) on the MMSE were also excluded. All participants had normal or corrected-to-normal vision. At the time of the study, none of the patients was being or had been treated with specific medication, such as anti-acetylcholinesterase agents. The elderly adults were matched to the patients for gender (4 male and 14 female patients vs. 7 male and 11 female elderly adults), age (patient mean = 74.5 years, range = 67–87 years; elderly adult mean = 74.8 years, range = 67–82 years), and education (patient mean = 10.7 years, range = 8–14 years; elderly adult mean = 10.9 years, range = 8–14 years). The study was approved by the Ethical Committee of Tohoku University and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their caregivers when appropriate. The demographic data of each group are summarized in Table 1.

2.2. Stimuli

We prepared color photographs of 120 common living things and 120 common inanimate objects, which were used in our previous study (Hashimoto et al., in press). These photographs consisted of 60 pairs of different photographs of the same living things and 60 pairs of different photographs of the same inanimate objects. These pairs were divided into three sets (i.e., 40 pairs each) of an equal number of animate and inanimate stimuli. The first members of two sets (80 stimuli) were used as study items in the study phase, and the first members of the other set (40 stimuli) were used as distracters in the test phase. The assignment of these three stimuli sets to either study or to the test phase was counterbalanced across subjects. Of the two sets used in the study phase, the first members of one set (40 stimuli)

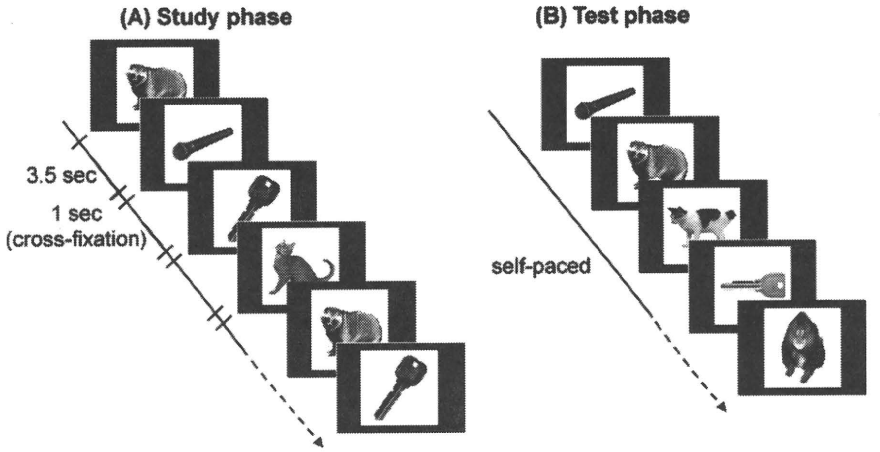

Fig. 1. The experimental design, which involved (A) a study phase and (B) a test phase. (A) During the study phase, participants were asked to judge whether each photograph represented a living or a non-living thing and to memorize each photograph. Half of the stimuli were presented once, and the remaining stimuli were presented three times. (B) During the test phase, participants were asked to judge whether each stimulus was new or old. They were requested to indicate "old" if the stimulus was presented as it was during the study phase and "new" if the stimulus was a non-studied object or was presented with different perceptual details from the studied object.

were used as target items to be recognized later in the test phase (for the "Same" condition, see below for details), whereas the second members of the other set (40 stimuli) were used as target items to induce false recognition in the test phase (for the "Similar" condition, see below for details). The assignment of the first and second members of the stimulus sets to either the "Same" or the "Similar" condition was also counterbalanced across subjects.

2.3. Procedure

The experiment consisted of an intentional study phase followed by the recognition memory test phase that required the participants to indicate whether the presented stimulus had been studied. Before the experiment, the participants were given a thorough explanation of the task procedure and were familiarized with the task by completing a short practice session. To ensure that the participants comprehended the task procedure, they were required to explain the instructions to an experimenter in their own words.

During the study phase (Fig. 1A), the subjects were presented with a total of 80 stimuli. Each stimulus was presented for 3.5 s with an interstimulus interval of one second during which a fixation point (a cross) was constantly presented. Half of these 80 stimuli were presented once, and the other half were presented three times. Therefore, the total number of trials was 160. The stimuli were presented one by one in a randomized order. The subjects were then asked to indicate whether the stimulus represented an animate or inanimate object by pressing buttons and were asked to memorize each stimulus for the later recognition memory test.

During the test phase, the subjects performed an old/new recognition task in a self-paced manner (Fig. 1B). Five different kinds of stimulus type were presented: (a) 20 stimuli that had been presented once during the study phase (Same-1× stimuli), (b) 20 novel stimuli similar to the 20 that had been presented once during the study phase (Similar-1× stimuli), (c) 20 stimuli that had been presented three times during the study phase (Same-3× stimuli), (d) 20 novel stimuli similar to the 20 that had been presented three times during the study phase (Similar-3× stimuli), and (e) 40 novel stimuli not similar to the 80 that had been presented during the study phase (Dissimilar stimuli). These stimuli were presented one by one in a randomized order. The subjects were asked to indicate whether they had studied each stimulus by pressing buttons. After each trial, the experimenter initiated the next trial by pressing a button.

3. Results

3.1. Demographic data

Comparisons of demographic data between the two groups were performed using the χ^2 test for gender ratio and the t-test for other components (Table 1). There were no significant differences in age ($t(34)=0.227$, $p>0.1$), gender ($\chi^2=1.178$, $p>0.1$) or education ($t(34)=0.260$, $p>0.1$). On the MMSE scores, the AD patients scored significantly lower than the healthy controls ($t(34)=5.621$, $p<0.001$).

3.2. Recognition memory test

The mean proportion of "old" responses for all types of stimuli in the two groups is summarized in Table 2. First, we performed a 2 (stimuli: Same and Similar) × 2 (repetition: 1× and 3×) analysis of variance (ANOVA) for the AD patient data. We found significant main effects of stimuli ($F(1,17)=145.040$, $p<0.001$) and repetition ($F(1,17)=55.148$, $p<0.001$) with no interaction between the two factors ($F(1,17)=0.491$, $p>0.1$). This indicates that the repeated presentation of stimuli increased the rate of "old" responses to both Same pictures (true recognition) and Similar lures (false recognition) in AD patients.

We then performed a 2 (stimuli: Same and Similar) × 2 (repetition: 1× and 3×) ANOVA for the healthy control data. We found significant main effects of stimuli ($F(1,17)=141.760$, $p<0.001$) and repetition ($F(1,17)=25.159$, $p<0.001$) with a significant interaction between the two factors ($F(1,17)=38.597$, $p<0.001$). Post-hoc tests revealed a significant difference in the proportion of "old" responses for Same pictures between the single and repeated presentations ($t(17)=9.301$, $p<0.001$), whereas there was no significant difference for Similar lures between the single and repeated presentations ($t(17)=0.452$, $p>0.1$). This indicates that the repeated presentation of stimuli increased the rate of "old" responses to Same pictures (true recognition) but not to Similar lures (false recognition) in control subjects.

To further compare performance across the groups, two types of memory indices were calculated: memory for items and memory for perceptual details. The memory index for items (MI) was calculated as the difference between hits to Same pictures and false alarms to Dissimilar lures. This difference reflects the participants' ability to correctly discriminate Same pictures from Dissimilar lures. The memory index for perceptual details (MD) was calculated

Table 2
Mean proportions of "old" responses for each stimulus type.

Stimulus type	AD patients ($n=18$)	Controls ($n=18$)
Same-1×	70.0 (19.7)	75.3 (11.6)
Same-3×	87.5 (13.0)	95.8 (5.5)
Similar-1×	50.3 (19.8)	43.1 (13.5)
Similar-3×	65.0 (18.9)	44.4 (14.7)
Dissimilar	30.3 (20.3)	10.8 (7.2)

Standard deviations are in parentheses.

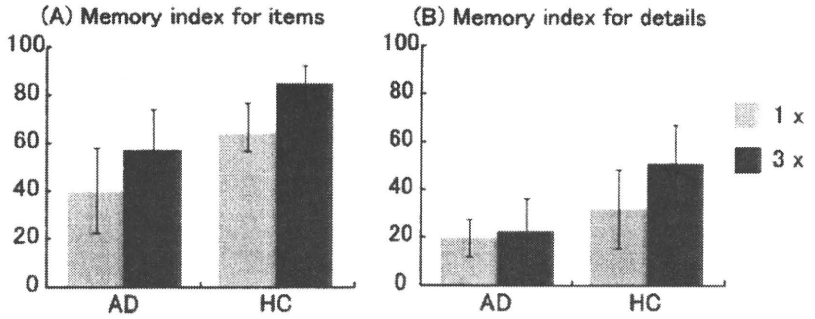

Fig. 2. Two memory indices for recognition memory in the two groups. (A) The memory index for items was calculated as the difference between the proportion of hits to Same pictures and the proportion of false alarms to Dissimilar lures. (B) The memory index for details was calculated as the difference between the proportion of hits to Same pictures and the proportion of false alarms to Similar lures. Error bars represent standard deviations. AD, patients with AD; HC, healthy controls.

as the difference between hits to Same pictures and false alarms to Similar lures. This difference reflects the participant's ability to correctly discriminate Same pictures from Similar lures. These measures were used over other measures of discrimination (d' or A') because they tend to be more sensitive (Snodgrass and Corwin, 1988) and because they may be more appropriate for recognition memory tests that investigate recall-to-reject processes (e.g., Gallo et al., 2004). These measures are also useful in that they reflect a subject's memory regardless of whether he or she has a liberal or conservative response bias (i.e., extremely high rate of "old" or "new" responses) derived from individual differences.

Fig. 2 shows the MI and MD for each group. A 2 (group: AD patients and healthy controls) × 2 (repetition: 1× and 3×) ANOVA was conducted separately for each type of memory index. For the MI, there were significant main effects of group ($F(1,34) = 34.994$, $p < 0.001$) and repetition ($F(1,34) = 94.150$, $p < 0.001$) without an interaction between the two factors ($F(1,34) = 0.607$, $p > 0.1$). The lack of interaction indicates that the ability of the AD patients and the healthy controls to discriminate Same pictures from Dissimilar lures was affected by stimulus repetition in a similar manner.

A different pattern emerged in the analysis of the MD. There were significant main effects of group ($F(1,34) = 27.806$, $p < 0.001$) and repetition ($F(1,34) = 19.079$, $p < 0.001$) with a significant interaction between the two factors ($F(1,34) = 10.641$, $p < 0.005$). Post-hoc tests revealed that AD patients did not show a difference between the single and repeated presentations ($t(17) = 0.701$, $p > 0.1$), whereas the healthy controls showed a higher index in the repeated presentation than in the single presentation ($t(17) = 6.213$, $p < 0.001$). This indicates that the ability of the AD patients and the healthy controls to discriminate Same pictures from Similar lures was differentially affected by stimulus repetition.

Finally, we examined whether AD patients were less susceptible to similarity-based false recognition than were healthy controls, especially in the Similar-1× condition. This analysis was inspired by previous findings that AD patients were less susceptible to false recognition in response to lure stimuli after a single list exposure in the DRM paradigm than were healthy controls (Balota et al., 1999; Budson et al., 2000). To control for response bias, we calculated the corrected false recognition rates that were obtained by subtracting the proportion of "old" responses to Dissimilar lures from the proportion of "old" responses to Similar lures. The corrected false recognition rates for Similar-1× and Similar-3× were 20.0 (SD = 16.2) and 34.7 (SD = 16.3) for AD patients and 32.2 (SD = 13.0) and 33.6 (SD = 13.0) for healthy controls, respectively. We found a significant difference in the corrected false recognition rate for Similar-1× between AD patients and healthy controls ($t(34) = 2.494$, $p < 0.05$). There was, however, no significant difference in the corrected false recognition rate for Similar-3× between AD patients and healthy controls ($t(34) = 0.227$, $p > 0.1$). This indicates that AD patients were originally less susceptible to similarity-based false recognition than were healthy controls, but stimulus repetition canceled out this effect.

4. Discussion

In the present study, we used an item-recognition memory paradigm to investigate false recognition in AD patients and healthy controls. Specifically, we focused on whether the repeated presentation of stimuli differentially affected the ability to discriminate the targets and the lures perceptually similar to the targets between these two populations. The results showed that the repeated presentation of stimuli increased the proportion of "old" responses to Same pictures in both groups and to Similar lures in the AD patients but not in control subjects. Further analysis revealed that repeated presentation of the stimuli raised a memory index for items in both groups, whereas unlike the healthy controls, repeated presentation of the stimuli did not show an improvement in the memory index for perceptual details in AD patients. The present study provides clear evidence to support the impaired recall-to-reject hypothesis in AD patients in a single-item recognition task, which excludes the factor of associative memory.

The present findings showing that false recognition was increased in an item-recognition paradigm by stimulus repetition in AD patients have provided strong support for the impaired recall-to-reject hypothesis in AD patients. As mentioned in the Introduction, Budson et al. (2000) used a modified version of the DRM task to argue that impaired item-specific recollection increases familiarity-based false recognition in AD patients. Similarly, Gallo et al. (2004) used an associative recognition task to argue that impaired recall-to-reject processes lead to an elevated level of familiarity-based false recognition in AD patients. However, the evidence for impaired recollection-based monitoring in AD patients from these studies was inconclusive because of the possible alternative explanations that could not be ruled out in these previous studies, namely, certain kinds of associative memory deficits. To avoid these possible confounding factors, we used stimuli consisting of photographs that were semantically concordant but perceptually distinct as Similar lures. We found an increased false item recognition in response to Similar lures by stimulus repetition in AD patients, but not in healthy controls. The pattern of these results is in line with the previous studies (Budson et al., 2000; Gallo et al., 2004) and is highly consistent with the impaired recall-to-reject hypothesis in AD patients.

One might think that, if the repeated presentation of the stimulus increases recollection of studied items and this increased recollection is used to more effectively reject Similar lures, then the healthy controls should show decreased "old" responses to Similar lures in the repeated condition relative to the single presentation

condition. However, our results were against this idea. The proportion of "old" responses to Similar lures remained unchanged between the single and repeated presentation conditions in the healthy controls. One possible reason is that the control subjects were also susceptible to similarity-based false recognition induced by stimulus repetition. Repetition increased the concept-based familiarity of Similar lures, which should have increased false recognition, but it also increased the ability to recall the original stimuli and thus to reduce false recognition by a recall-to-reject strategy (Kelley and Wixted, 2001). These two opposing processes canceled out on average, which indicates a lack of effect of repetition. In fact, Kelley and Wixted (2001) used a manipulation similar to Gallo et al. (2004)'s study and reported no effects of repetition in younger adults. Gallo et al. (2004) also reported no effects of repetition in their control subjects matched in age with AD patients. Budson et al. (2000) also reported a fluctuating pattern in their elderly subjects. The present findings indicate that control subjects were relatively more likely than were AD patients to use a recall-to-reject process to overcome similarity-based false recognition.

Our results also revealed a lower rate of corrected false recognition in the Similar-1× condition for AD patients relative to healthy controls. This suggests that AD patients were originally less susceptible to similarity-based false recognition than were healthy controls in the task using single-item picture memory, possibly as a result of decreased sensitivity to the semantic gist for the visually presented stimuli. Stimulus repetition, however, canceled out this effect. This pattern indicates that the repeated presentation of pictures created an increasingly robust representation of the semantic gist for presented pictures; AD patients showed elevated false recognition due to the lack of item-specific recollection, but healthy controls used recollection to counteract the gist representation. These results are highly consistent with previous works using the DRM paradigm in AD patients (Balota et al., 1999; Budson et al., 2000) and with data from amnesic patients (Schacter, Verfaellie, & Anes, 1997; Schacter et al., 1998b; Schacter, Verfaellie, & Pradere, 1996). Expanding on these previous studies, the present study has provided strong evidence that AD patients are initially less susceptible (but not after stimulus repetition) to similarity-based false recognition, regardless of the experimental paradigms used.

The precise neural dysfunctions accounting for why AD patients are impaired in the ability to use item-specific recollection to reduce false recognition are unknown. We speculate that this impairment in AD patients is associated with dysfunctions in two major areas: (1) in the hippocampus, causing recollection deficits, and/or (2) in the prefrontal cortex, causing disrupted post-retrieval processes. It is widely known that AD patients show both structural and functional abnormalities in the medial temporal lobe (Dickerson and Sperling, 2008; Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). Among the subregions within the medial temporal lobe, the hippocampus has been reported to be closely linked to recollection processes (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Mugikura et al., 2010; Vilberg & Rugg, 2007). It is also known that, even in the early stage of the disease, AD pathology might involve the prefrontal cortex, as neuropsychological and neuroimaging studies have demonstrated frontal lobe dysfunction in AD patients (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Dalla Barba et al., 1999). In addition, there is considerable evidence that frontal lobe lesions may produce disruptions in the processes that check for memory errors (Janowsky, Shimamura, & Squire, 1989; Johnson, O'Connor, & Cantor, 1997). Further studies are needed to obtain data that directly elucidate the relationship between neural disruption and false recognition.

In conclusion, the results of the present study strongly support the view that AD patients are impaired in their ability to use item-specific recollection in order to avoid false recognition. One of the questions to be pursued is whether the memory deficits in AD patients observed in previous studies are caused by deficits during the retrieval phase or during the encoding phase. It remains possible that the degraded encoding of stimuli causes the subsequent deficits in the recollection of perceptual details. It is worth investigating whether experimental manipulation during encoding can alter the pattern of task performance in AD patients; on the basis of such findings we may be able to infer whether the encoding deficits are relevant to subsequent false recognition. Alternatively, a study using functional magnetic resonance imaging, which assesses neural responses during the actual performance of a task, may enable us to better assess how the brain dysfunction associated with AD gives rise to these memory impairments.

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Research paper

Neuroanatomy of a neurobehavioral disturbance in the left anterior thalamic infarction

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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 6 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.[1–3] However, the precise functional attributes of the individual thalamic nuclei and fibre systems remain to be elucidated. Clinicoanatomical 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.[3] 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.[3] Using neuropsychological evaluations, MRI stereotactic lesion localisation[4 5] 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 dysnomia. 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,[6] the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[7] the Wechsler Memory Scale-Revised (WMS-R),[8] the Western Aphasia Battery,[9] 100-word object naming,[10] verbal fluency (animals/initial letter),[11] Raven's Coloured Progressive Matrices,[12] the Weigl's Colour-Form Sorting Test[13] and Luria's executive/motor performance tests (fist-edge-palm test, 2-1 tapping test and alternative pattern drawing).[14] 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). Retrograde 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 SPGR images (TR, 14 ms; TE, 3 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 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, interputaminal distance and contour of the thalamus.

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 O_2 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 mm^3). 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 1 Results of the neuropsychological tests

Cognitive and behavioural domains	Tests		Patients 1	2	3	4	5	6	Normative data
General intelligence	MMSE (/30)		25	27	27	16*	24	22*	≥24
	WAIS-R[7]	VIQ	68*	78*	88	65*	81*	89	≥85
		PIQ	85	106	93	66*	91	91	≥85
Episodic memory	WMS-R[8]	Verbal memory index	<50*	64*	61*	<50*	50*	64*	≥85
		Visual memory index	72*	93	118	68*	114	100	≥85
		Attention/concentration index	66*	84*	94	55*	77*	97	≥85
		Delayed recall index	<50*	<50*	69*	<50*	71*	83*	≥85
	Retrograde amnesia		(−)	(−)	(−)	(−)	(−)	(−)	
Language/semantic knowledge	WAB[9]	AQ	69.2*	90.8*	86.4*	71*	83.6*	87.6*	97.7±3.0
		Spontaneous speech (/20)	13*	17*	17*	12*	16*	16*	19.7±0.6
		Auditory comprehension (/10)	7.2*	9.8	7.7*	7.2*	9*	9.5*	9.8±0.1
		Repetition (/10)	8.9*	9.6	9.9	9.2	9.9	10	9.9±0.3
		Naming (/10)	5.5*	9	8.6*	7.1*	6.9*	8.3*	9.5±0.6
		Reading (/10)	6.7*	10	8.9	4.1*	7.2*	7.7*	9.5±0.8
		Writing (/10)	6.4*	9.7	9.9	4*	9.1	8.9	9.6±1.0
	Animal fluency (/min)		4*	10	9	4*	4*	12	11.8±4.4
	Initial fluency (/min)		0*	3*	1*	1*	2*	7	6.8±3
	Picture Naming (/100)[10]		74*	97	84	66	86	89	98.2±2.3
	WAIS-R[7]	Information SS	6*	6*	10	5*	6*	8	≥7
		Vocabulary SS	5*	7	7	5*	6*	9	≥7
		Comprehension SS	2*	7	5*	2*	7	5*	≥7
		Similarities SS	4*	5*	8	4*	8	6*	≥7
Perceptual organisation/ construction	WAIS-R[7]	Picture completion SS	8	11	9	5*	8	9	≥7
		Block design SS	5*	13	9	4*	12	11	≥7
Concept formation	RCPM (/36)[12]		25	30	23	14*	32	26	26.9±5.4
	Weigl's colour-form sorting[13]		✓	✗	✓	✗	✓	✓	
Psychomotor speed	WAIS-R Digit symbol SS[7]		6*	8	9	4*	7	8	≥7
Executive/motor control	Fist-edge-palm[14]		✗	✗	✗	✓	✗	✓	
	2-1 tapping[14]		✗	✓	✓	✓	✓	✓	
	Alternative pattern drawing[14]		✓	✓	✓	✓	✓	✓	
Behaviour	Apathy		(++)	(+)	(+)	(++)	(+)	(+)	

*Score below −1 SD of the normative data.[8–12]
✓, passed; ✗, failed.
AQ, aphasia quotient; MMSE, Mini-Mental State Examination; PIQ, performance intelligence quotient; RCPM, Raven's coloured progressive matrices; SS, scaled score; VIQ, verbal intelligence quotient; WAB, Western Aphasia Battery; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

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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 disproportionately lower than their VIQ in the WAIS-R (verbal MI − VIQ≥10)[8]. 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)

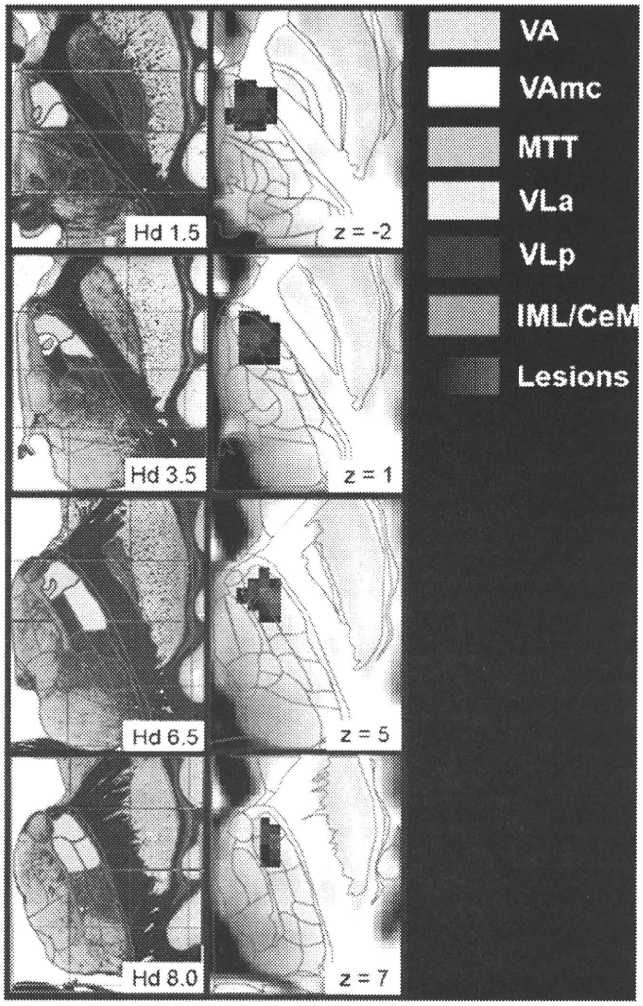


Figure 1 Transverse images from the Schaltenbrand–Wahren (S–W) atlas are shown in the left column. The structures involved in left anterior thalamic infarction are coloured. Images showing lesions (red) superimposed on the Montreal Neurological Institute (MNI) template are indicated in the right column. 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.

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 reductions 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

Table 2 The thalamic and adjacent regions affected in the patients

Thalamic regions		Patient No.						No. of patients
Hirai and Jones'	Hassler's	1	2	3	4	5	6	
VA proper	Lpo	(+)	(+)	(+)	(+)	(+)	(+)	6
VAmc	Lpo.mc	(+)	(+)	(+)	(+)	(+)	(+)	6
VLa	Zo	(+)	(+)	(+)	(+)	(+)	(+)	6
	Voa	(+)	(+)	(+)	(+)	(+)	(+)	
	Vop	(−)	(−)	(−)	(−)	(+)	(−)	
	Doe	(+)	(+)	(+)	(+)	(+)	(+)	
VLp	Voi	(+)	(+)	(+)	(+)	(+)	(+)	6
	Doi	(+)	(+)	(+)	(+)	(+)	(+)	
VM	Vom	(−)	(+)	(−)	(−)	(−)	(−)	1
MD	Mfa	(−)	(−)	(−)	(+)	(−)	(−)	1
IML/CeM	Lam	(−)	(+)	(−)	(+)	(+)	(−)	3
R		(+)	(+)	(+)	(+)	(+)	(+)	6
MTT		(+)	(+)	(+)	(+)	(+)	(+)	6
ICg		(−)	(−)	(−)	(+)	(+)	(+)	3
H		(−)	(−)	(−)	(+)	(+)	(−)	2
STN		(−)	(−)	(−)	(+)	(−)	(−)	1

The nomenclature for the thalamic nuclei is according to Hirai and Jones and Hassler. CeM, central medial nucleus; H, fields of Forel; ICg, genu of the internal capsule; IML, internal medullary lamina; MD, mediodorsal nucleus; MTT, mammillothalamic tract; R, reticular nucleus; STN, subthalamic nucleus; VA, ventral anterior nucleus; VAmc, magnocellular ventral anterior nucleus; VLa, ventral lateral anterior nucleus; VLp, ventral lateral posterior nucleus; VM, ventral medial nucleus.

gyrus and cuneus in addition to the ATL, thalamus, OFL, and MFG. Increased left/right asymmetry index was observed in the precuneus (table 3).

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.[1 3 4 21] Although previous studies of acute LATI have reported a perseverative behaviour (palipsychism) and mild sensorimotor deficits,[21] 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.[22] The same perspective may be applicable to material-specific memory impairment in thalamic damage.

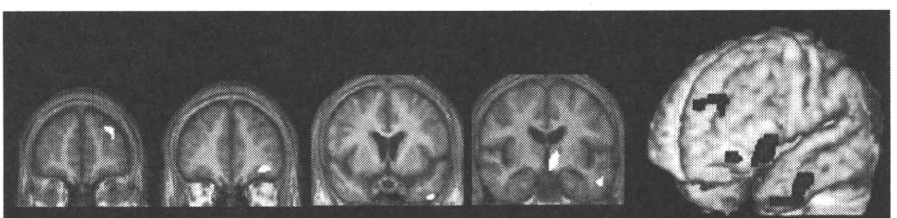
The language disturbances in our patients were characterised by word-finding difficulty and anomia. The articulation and phonological aspects were well preserved. Anomia and poor performance in the naming tests and the Information, Vocabulary, Comprehension and Similarities subtests of the WAIS-R suggested that the lexical-semantic impairment was the core deficit responsible for their language symptoms.[4] This interpretation is supported by previous reports investigating a variety of lexical-semantic deficits, including category-specific anomia, proper name anomia and degraded knowledge of object use, in patients with LATI.[5 23–25]

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 lobule and the occipital lobe were disrupted in LATI. Compared to patients with paramedian thalamic infarction (PTI),[26] 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.[3 26] The involvement of the intralaminar nuclei, which project broadly to the cerebral cortex,[20] and/or their projecting fibres probably causes extensive cortical dysfunction in PTI.[3 4] A previous single-case PET study of LATI reported restricted rCBF reductions in the ipsilateral amygdala and posterior cingulate cortex.[27] 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



Contrasts	Regions	Cluster size (voxels)	Cluster-level corrected p values	T value	Voxel-level corrected p values	MNI coordinates x	y	z
LATI < Controls	Anterior temporal lobe L	223	0.103	6.58	0.465	−42	6	−40
	Thalamus L	235	0.090	5.39	0.828	−6	−12	−6
	Lateral orbital frontal lobe L	64	0.637	5.26	0.863	−36	42	−8
	Middle frontal gyrus L	84	0.514	4.71	0.964	−28	48	32
Controls < LATI	Precuneus R	104	0.409	5.34	0.844	4	−68	48
	Lingual gyrus R	56	0.691	5.04	0.912	12	-98	−14

Figure 2 Results of the voxelwise group comparison of positron emission tomography. Regions with regional cerebral blood flow (rCBF) reduction are superimposed on the mean normalised MRIs of the patients. The table indicates relative decrease and increase in rCBF in patients with left anterior thalamic infarction compared to controls. The height and extent thresholds were $p<0.001$ uncorrected and 400 mm^3, respectively. LATI, left anterior thalamic infarct.

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

	Patients						Controls (n=6)	
	1	2	3	4	5	6	95% CI	
Inferior frontal	**0.79**	1.03	0.91	**0.82**	**0.71**	0.88	0.84	1.37
Middle frontal	**0.80**	0.93	0.93	1.01	**0.76**	**0.82**	0.86	1.25
Frontal operculum	1.08	1.13	1.01	1.03	0.88	**0.85**	0.86	1.29
Lateral orbital frontal*	**0.80**	**0.92**	1.14	**0.90**	**0.69**	**0.85**	0.97	1.20
Anterior cingulate*	**0.78**	**0.87**	**0.94**	0.99	**0.80**	**0.79**	0.95	1.18
Central	*1.16*	0.97	1.04	**0.85**	**0.77**	**0.80**	0.87	1.11
Temporal pole*	**0.86**	**0.86**	**0.87**	**0.92**	**0.80**	**0.89**	0.95	1.17
Inferior temporal*	1.15	**0.92**	1.02	**0.94**	**0.93**	**0.81**	0.95	1.21
Middle temporal	1.05	0.86	0.87	1.03	*1.07*	1.02	0.85	1.05
Superior temporal	1.05	1.20	1.14	**0.77**	1.04	0.89	0.87	1.20
Medial temporal	*1.36*	1.00	*1.08*	*1.24*	0.83	0.90	0.89	1.05
Inferior parietal*	**0.84**	**0.88**	1.17	**0.89**	**0.67**	**0.87**	1.00	1.27
Posterior cingulated	0.94	1.04	1.03	1.00	*1.41*	0.93	0.86	1.10
Precuneus†	*1.17*	*1.18*	*1.17*	0.95	*1.16*	**0.84**	0.91	1.08
Cuneus*	**0.82**	**0.85**	1.12	**0.94**	**0.93**	1.07	1.05	1.25
Calcarine*	1.11	**0.79**	**0.81**	**0.87**	**0.85**	**0.82**	0.91	1.16
Lingual	1.24	1.14	0.96	0.94	1.12	0.96	0.88	1.38
Fusiform	0.95	0.98	**0.93**	1.02	0.97	0.95	0.95	1.09
Anterior striatum	1.07	*1.22*	0.90	**0.82**	0.85	0.98	0.83	1.13
Posterior striatum	1.18	1.19	1.14	0.94	**0.45**	0.94	0.92	1.21
Thalamus*	**0.66**	**0.80**	**0.86**	**0.77**	**0.57**	**0.75**	0.92	1.19

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

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.[28] Because the AN and MD are spared in the majority of patients with ATI,[3 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.[5 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 anteroposteriorly 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,[26] for example, the connection between the MTT and the posterior cingulate cortex via the AN; rCBF reduction is an 'insensitive measure to detect medial temporal dysfunction.[32 33] This issue should be addressed using different neuroimaging modalities, such as fluorodeoxyglucose PET and diffusion tensor tractography, in future studies.

Neuroanatomical basis of language disturbance

It is noteworthy that diaschisis was observed in the ATL, which is a region that is putatively associated 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 anomia and proper name anomia.[24 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.[38] 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.[39] 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 behaviours[21] 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 44]

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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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Regular Article

Hyperperfusion in primary somatosensory region related to somatic hallucination in the elderly

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Aim: The purpose of the present study was to investigate the regional cerebral blood flow (rCBF) of patients with delusional disorder, somatic type (DDST) exhibiting somatic hallucination.

Methods: Five patients diagnosed with DDST, as well as 20 control subjects, were examined. All subjects underwent technetium-99*m* ethyl cysteinate dimer brain perfusion single-photon emission computed tomography. Statistical analysis was performed with SPM5, using a two-sample *t*-test model to test the regional population effect on rCBF.

Results: Patients with DDST had a significant increase in perfusion in the left post-central gyrus and the right paracentral lobule, both of which are involved in somatic sensory processing.

Conclusion: Somatic hallucination might be associated with increased perfusion in the primary somatosensory regions.

Key words: somatic hallucination, somatosensory cortex, technetium-99*m* ethyl cysteinate dimer.

SOMATIC HALLUCINATION INVOLVES the perception of a physical experience with the body.[1] Among the subtypes of delusional disorders, the somatic type (DDST) is unique in that patients may experience somatic hallucinations as well as somatic delusions. The prevalence of delusional disorder in the USA is estimated to be around 0.03% and its onset is usually at a late age.[2–4] The somatic type is rare among subtypes of delusional disorder.

It is well accepted that brain lesions can cause somatic hallucinations. Braun *et al.* reviewed a large number of case studies of post-lesion hallucinations. They reported that a lesion is almost always located in the brain pathway of the sensory modality of the hallucination and suggested that compensatory overactivation of the nearby brain tissue is the cause of the hallucinosis. It has been speculated that the parietal cortex and thalamus are involved in the development of somatic hallucinations.[5]

Neuroimaging has the potential to provide perspectives that help us better appreciate the biological underpinning of major mental disorders.[6] At present there are only a few case reports on the functional abnormality in patients who have experienced somatic hallucinations in the absence of brain lesions.[7] Shergill *et al.* studied a 36-year-old patient, diagnosed with schizophrenia and experiencing both auditory and somatic hallucinations, using functional magnetic resonance imaging to identify the differences in brain activation underlying the two phenomena.[8] That study showed that somatic

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