Figure 21.2 Frequency of each symptom domain in FTD, SD, and AD groups (revised from [6]). The frequencies of all domains except swallowing problems were higher in FTD than in AD (P < 0.001). Patients with SD had more frequent changes in food preference and eating habits than patients with AD (P < 0.01) [9].

stress, particularly in a condition such as FTD where the diagnosis may be delayed [13]. In contrast to AD and vascular dementia (VaD), educational material for caregivers of FTD is usually scarce. Education should provide information regarding the diagnosis, prognosis, and the meaning and cause of specific behaviours. Once caregivers have a greater understanding of dementia, many of their anxieties and concerns are diminished [14]. For example, wandering and pacing are significant problems in AD while wandering (called roaming) in FTD is not a distressing behaviour for caregivers at least in early stages of the disease. Patients with FTD embark on long walks, usually involving the same route without getting lost owing to their relatively preserved memory and visuospatial abilities such as orientation in familiar surroundings. Sometimes caregivers will change the patient's environment based on their knowledge of specific behaviours. Some caregivers may find the use of day care with bathing services is helpful from an early stage. This is based on information that undressing and bathing frequently become serious obstacles at home in advanced FTD and putting it into their strict daily timetable from an early stage can help avoid this issue. Education is necessary prior to commencement of any intervention and in addition to advice from the treating physician, input from a clinical psychologist, occupational therapist or specialist nurse can be a very useful resource for caregivers.

FOCUSING ON TARGET BEHAVIOURS AND SPECIFIC NEUROCHEMICAL ABNORMALITIES

It is important to perform a detailed evaluation of the quality and severity of BPSD in FTD at the earliest possible time, so that the burden of caring can be reduced through tailored intervention. There is a wide range of BPSD in FTD such as disinhibition, impulsivity, aspontaneity, stereotypies, utilisation behaviours, and abnormal eating behaviour, and it is essential to determine the specific target symptoms for intervention in each patient. Patients may be overactive, restless, distractible, and disinhibited at the first medical referral. Those same patients may show little spontaneous activity when left to their own devices. Moreover, overactive patients may show increasing inertia [15].

Target symptoms might also vary in different disease stages. Target symptoms might be challenging behaviours which are often anti-social, risk for patients and/or cause profound distress for caregivers. These can result in the institutionalisation of sufferer. When overeating and hyperorality are present, dietary restrictions may be necessary to prevent excessive weight gain or eating non-edible foodstuffs [9]. Pharmacologic agents are indicated for challenging

behaviours where non-pharmachological interventions – such as environmental changes – are insufficient to alleviate the behavioural disturbance.

BPSD are thought to arise from complex changes in central neurotransmitter levels, with particular categories of symptoms linked to certain neurotransmitter abnormalities [16], though more research is needed as these relationships are largely based on speculation rather than empirical evidence in FTD at present. Aggression may be associated with raised levels of norepinephrine and reduced levels of serotonin, depression with low serotonin, psychosis with low acetylcholine and elevated dopamine, stereotypy and compulsivity with low serotonin, and apathy with low acetylcholine. Many features of FTD such as stereotypic behaviour, overeating, and impulsivity are thought to be compatible with serotonergic dysfunction. Thus, the choice of treatment should be based on the neurochemical target for each BPSD. Understanding the behavioural symptomatology of different dementias provides a rational strategy for the development of novel pharmacological treatments which target specific neurochemical abnormalities.

USING WELL-VALIDATED AND CAREFULLY SELECTED OUTCOME MEASURES

Objective assessment of any patient intervention – whether pharmacological, psychological, or environmental – is essential. Given the peculiar behavioural disturbances in patients with FTD, it is necessary to select an appropriate range of outcome measures that are sensitive to the effects of interventions on behaviour. Widely used behavioural assessment instruments, such as the Neuropsychiatry Inventory (NPI) [17] and BEHAVE-AD [18], may not be sufficiently sensitive to reliably detect improvement in challenging behaviours following an intervention, although they can distinguish FTD from AD to some degree [19, 20]. The NPI is a clinical rating instrument designed specifically to provide a comprehensive evaluation of neuropsychiatric symptomatology in demented patients and has been demonstrated to be sensitive to drug treatment effects in AD [21, 22]. However, this instrument does not adequately cover the range of compulsive, repetitive and bizarre stereotypic behaviours seen in FTD [23].

The Stereotypy Rating Inventory (SRI) (that can be used in conjunction with the NPI) is a validated instrument that efficiently and comprehensively assesses the stereotypic behavioural aspects of FTD [8]. The SRI assesses five distinctive stereotypic behavioural disturbances (eating and cooking behaviours, roaming, speaking, movements, daily rhythms) often seen in patients with FTD (Table 21.2).

The swallowing/appetite/eating habits questionnaire assesses the following five domains: swallowing problems, appetite change, food preference (including sweet food preference and food fads), eating habits (including stereotypic eating behaviours and decline in table manners), and other oral behaviours (including food cramming and indiscriminate eating) [9] (Table 21.3).

In summary, one is able to make a more comprehensive evaluation of the extent of psychopathological changes with the passage of time in patients with FTD by combining the NPI and these specific scales for FTD.

NON-PHARMACOLOGIC MANAGEMENT

Behaviour modification and environmental manipulation should be considered in the care of FTD before any pharmacologic treatment. Care of patients with FTD, without memory, apraxic or visuospatial disturbances, is potentially easier than care of AD patients, if stimulus-bound behaviours and stereotypies can be appropriately utilised in a positive sense [6].

EXPLOITING PRESERVED MEMORY FUNCTION

Using relatively preserved episodic and procedural memory is an important strategy in caring for patients with FTD. Fixing a specific nurse or occupational therapist for each FTD

Table 21.2 The Stereotypy Rating Inventory [8]

Daily rhythm

Does the patient live with a strictly fixed daily rhythm that looks like a timetable? Or does he/she do the same thing at a certain time everyday? Does he/she prefer to live with the fixed daily rhythm and dislike being disturbed from his/her daily rhythm?

No (If no, proceed to next screening question)
Yes (If yes, proceed to subquestions)

1. Is the patient concerned with going to bed and getting up at a certain time?
2. Is the patient concerned with watching TV at a certain time?
3. Is the patient concerned with taking a walk at a certain time?
4. Is the patient concerned with taking his/her meal at a certain time?
5. Is the patient concerned with doing other things at a certain time?

If the screening question is confirmed, determine the frequency and severity of the daily rhythm.

Frequency: 1. Often – about once per week
2. Moderately frequent – several times per week but less than everyday
3. Frequent – everyday (less than 5 times per day)
4. Extremely frequent – everyday (more than 5 times per day or almost all the time)

Severity: 1. Mild – stereotypic behaviours are notable but produce little interference with daily routines
2. Moderate – stereotypic behaviours are very evident; can be overcome by the caregiver
3. Marked – stereotypic behaviours are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress

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Table 21.3 Swallowing/appetite/eating habits questionnaire [9]

Food preference

	Frequency	Severity
1. Does he/she prefer sweet foods more than before?	0 1 2 3 4	1 2 3
2. Does he/she drink more soft drinks?	0 1 2 3 4	1 2 3
3. Does he/she drink more tea/coffee?	0 1 2 3 4	1 2 3
4. Has his/her 'taste' in food changed in another way (e.g. eats more meat, curries, fried foods)	0 1 2 3 4	1 2 3
Any comments _____		
5. Does he/she add more seasoning to their food (e.g. adds more salt)?	0 1 2 3 4	1 2 3
6. Has he/she developed other food fads?	0 1 2 3 4	1 2 3
Any comments _____		
7. Does he/she hoard sweets or other food?	0 1 2 3 4	1 2 3
8. Does he/she drink more alcohol?	0 1 2 3 4	1 2 3

If you have answered yes to any of these, when did the symptoms begin? _____

Frequency: 0. Never
1. Occasionally – less than once per week
2. Often – about once per week
3. Frequently – several times per week but less than every day
4. Very frequently – once or more per day or continuously

Severity: 1. Mild – changes in food preference or alcohol intake are present but easily controlled
2. Moderate – changes in food preference or alcohol intake are present, difficult to control and cause some problems in the family
3. Marked – obvious changes in food preference or alcohol intake causing considerable conflict, embarrassment, or other difficulties (e.g. drunkenness)

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patient in a day care unit or nursing home is effective to adjust them to program routines. Preserved episodic memory means that patients with FTD can easily identify their key-worker although they may seem indifferent to other staff members. This one-to-one approach is especially useful in the beginning of institutional care.

It can often be useful to program the daily activity for FTD patients in residential or day care based on each patient's premorbid hobbies or career. Knitting a muffler for a former housewife, even measuring blood pressures of staff members for a former physician, can be very effective to reduce their irritability and maladapted stereotypic behaviours [10, 24].

[Case] A 65-year-old right-handed retired office worker [10]
At 63 years old, he was referred for evaluation of inappropriate behaviour that had started 4 years earlier. He ate large amounts of sweet food, ate by stealth, and stole money from his family. Disinhibition and indifference were most conspicuous, and he was euphoric. In contrast to these behavioural changes there was scarce historical evidence of a primary impairment of language, perception, visuospatial skills or memory. Head CT revealed striking circumscribed bilateral fronto-temporal atrophy. In the ward, he frequently urinated or defecated in nearby beds of other patients. As a result, he was assaulted frequently. Based on information from his wife about his premorbid hobbies, he was offered a microphone for 'karaoke' in the ward recreation room. Being a music academy graduate, he sang several popular songs very well. After this intervention, he began to participate in recreational activities and always requested to sing. He became a popular person in the ward and troubles with other patients strikingly decreased.

POSITIVE USE OF STIMULUS-BOUND BEHAVIOUR AND STEREOTYPIC BEHAVIOUR

The stimulus-bound behaviour appears in various forms such as tracing figures, echo symptoms (echolalia, echopraxia, or echoreading), imitation behaviour, utilisation behaviour and the environmental dependency syndrome. This behaviour is thought to result from an imbalance between frontal and parietal lobe activity. Specifically, frontal lobe damage results in a loss of the normal negative feed-back on parietal lobe activity, rendering the patient unable to inhibit motor responses to any stimuli from the external environment [6, 25]. In patients who exhibit stimulus-bound behaviour, this phenomenon can be channeled to promote less disruptive daily activities. For instance, by conspicuously laying out items at the entrance to the rehabilitation room (knitting needles and wool, a jigsaw puzzle etc.), such stimuli can elicit the motor actions appropriate to those objects with an attendant reduction of less desirable behaviours.

Stereotypic behaviours range from simple to complex repeated actions. Simple stereotypies are defined as iterative actions such as palilalia, paligraphia and palikinesia (e.g. repetitive knee-rubbing) – also referred to as clonic perseveration. More complex stereotypic behaviour form part of the daily repertoire, such as roaming (strolling through precisely the same route each day) and clock-watching or adherence to a strict daily timetable [15]. These behaviours are thought to be due to an imbalance between the activity of the frontal cortex and the basal ganglia [6]. Patients become increasingly inflexible and often adopt a fixed daily routine. These fixed stereotypic behaviours may become incompatible with the patient's home environment, in which case, transfer to more adaptive stereotypic behaviours using short-term hospitalisation and/or SSRIs may be necessary.

[Case] A 71-year-old right-handed housewife [26]
At the age of 68 years, this lady began to show alterations in her personality and behaviour. She became increasingly restless and displayed flattening of affect. Her everyday routines

were repeated on a regular time schedule. At 69 years old, she was referred for evaluation because of her disinhibition, distractibility, and profound palilalia. MRI images revealed marked right fronto-temporal atrophy with left orbitofrontal atrophy. She ate large amounts of food and her weight had become a serious problem. At 71 years old, she was referred for hospital admission. In the dementia ward, she wandered into other patients' rooms in fixed order, stole meals of other patients, and ate non-edible things on the floor. However, it was known that knitting had been a favourite former hobby. The occupational therapist, therefore, left a ball of yarn and knitting needles ready beforehand on the table in the dayroom. Challenging behaviours disappeared during her periods of persistent knitting. It is considered that her tendency to respond easily to external stimuli (a ball of yarn and knitting needles) and her compulsive or repetitive tendency were successfully utilised.

SHORT-TERM HOSPITALISATION

The benefits of short-term hospitalisation into a special care unit are: (i) close observation and analysis of patients behaviour in order to develop strategies for behavioural therapy; (ii) provision of adequate instruction to caregivers on coping strategies for challenging behaviours that will reduce their burden; (iii) breaking anti-social daily routines and reconstructing more adaptive stereotypic behaviours; (iv) prompting by nurses or occupational therapists for improvement of aspontaneity and ambivalence; (v) to familiarise patients with the hospital environment and group activities thus enabling them to maintain regular visits to the hospital and utilise day care resources [27].

[Case] A 67-year-old right-handed housewife
At 63 years of age, she began to show profound alterations in her personality and behaviour. She was restless and would rapidly abandon activities that she had just commenced. She became incontinent of urine for which she showed no concern. Two years after onset of symptoms she began to embark on long walks, involving the same route. She strictly adhered to a practice of extinguishing her cigarettes on the floor of her own home – on one occasion causing a fire to break out. At the age of 67, while roaming her habitual route, she was caught stealing tomatoes from a nearby farm, causing the farmer to lodge a complaint. When her husband tried to interrupt her roaming, irritability or aggression was provoked which in turn exacerbated his distress. Thus an impasse had been reached in which she was unable to continue in her home environment and consequently, she was referred for admission to our dementia ward. Head CT revealed striking circumscribed atrophy of fronto-temporal lobes and amygdala. In the ward, she was unable to adhere to her destructive habits of smoking and stealing tomatoes. Her manner was disinhibited, restless, distractible, and puerile, however, 2 weeks after her admission an occupational therapist introduced her to the day care unit. While it took her more 2 weeks to adapt to the day care program, she was ultimately able to adapt to the strict daily timetable. Following discharge, she adhered to participation in the day care program 7 days per week. Her husband was relieved of both full-time caregiving responsibilities and of her anti-social stereotypic behaviours.

[Case] A 68-year old, right-handed housewife [28]
At the age of 53 years, this lady lost interest in her surroundings. Her behaviour became stereotyped, in that she cooked the same meal day after day without variation. Her everyday routines were repeated on a regular time schedule. At 57 years old, she was referred for evaluation because of her lack of initiation, difficulty in planning, and compulsive behaviour. MRI images revealed striking circumscribed atrophy of bilateral frontal lobes. We introduced education programs about preserved and deteriorating behaviours in FTD to her husband and occupational therapies such as string beads for a necklace to her once a week. With her husband's aid and initiative, functioning in the household, she was restored

to almost the same level as it had been premorbidly. With disease progression, her loss of volition dominated the clinical picture. By the age of 59 years, she was spending 2 h in the preparation of each meal in spite of her husband's aid. A further short-term hospitalisation was arranged during which her daily activities were improved by nurses and occupational therapists through one-to-one encouragement at the initiation of actions. This intervention led to her taking only 30 min to prepare each meal with her husband's encouragement. She remains at home and is fundamentally self-caring.

PHARMACOTHERAPY OF FTD

While several drugs, such as the cholinesterase inhibitors, have been shown effective for treatment of AD [29], few drugs have been evaluated for the treatment for FTD. Behavioural symptoms found in FTD have been associated with serotonin abnormalities [30, 31]. Following the finding that serotonin receptor binding is decreased in the brain of FTD patients [32], it was suggested that selective serotonin reuptake inhibitors (SSRIs) might improve behavioural symptoms of FTD patients [11]. In an open study, the use of sertraline, fluoxetine, or paroxetine improved behavioural symptoms in FTD although the outcomes of the treatments were not objectively measured. Given the abundant literature demonstrating the efficacy of SSRIs in such diverse conditions as obsessive-compulsive disorder and related disorders [33, 34], depression [35, 36], and eating disorders [37, 38], it is not surprising that treatment with SSRIs has been proposed as a candidate therapy for a wide range of psychiatric and behavioural symptoms in FTD patients, without causing any cognitive change. Unfortunately, after this early work, there have been only 4 systematic studies of SSRIs and related compounds. All these studies involve the symptomatic treatment of FTD.

At this moment, there is a general lack of evidence-based therapy and that even when a randomised, double-blind, placebo-controlled trial was done, the numbers were very small, making it hard to draw firm conclusions. It is difficult to do well-powered clinical trials for subjects with FTD. As indicated by the inclusiveness of diagnoses into the syndrome of FTD and/or FTLD, most clinical trials will have heterogeneous study samples. The wide range of neuropathological findings within FTD raises the possibility that including all subjects with FTD in one clinical drug trial, could mask a subpopulation of FTD patients who respond to the study drug. Given these problems, it would be preferable for future drug trials in FTD to be designed on multicentre protocols [39].

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Fluvoxamine maleate
Fluvoxamine is a monocyclic, specific serotonin reuptake inhibitor. There is one published study of fluvoxamine in the treatment of FTD and SD [40] (Table 21.4). Sixteen FTLD patients were treated with a fluvoxamine in an open-label 12-week trial. Treatment responses for stereotyped behaviour and other neurobehavioural symptoms were evaluated by the SRI and the NPI. The behavioural symptoms, especially stereotyped behaviours of FTLD, significantly improved after treatment. The Mini-Mental State Examination (MMSE) was not modified.

Tradozone
Tradozone is an atypical serotonergic agent that has moderate serotonin reuptake inhibition and a serotonergic antagonist effect with an active metabolite meta-chlorophenyl-piperazine (m-CPP). There is one randomised, double-blind, placebo-controlled, cross-over trial in FTD [41] (Table 21.5). Thirty-one FTD patients were included and treatment responses for neurobehavioural symptoms were evaluated by the NPI. Behavioural symptoms, especially eating disorders, agitation, irritability, and depression/dysphoria of FTD, significantly

Table 21.4 Fluvoxamine trial for FTD [40]

Design	Open, dose-finding
Subjects	Number = 16 (11 FTD, 5 SD)
	Mean age = 70.0
	M/F ratio = 6/10
Entry criteria	FTD and SD groups fulfilled the consensus clinical criteria for FTLD
Duration	12 weeks
Treatment	Started at a 50 mg/day. Dose was adjusted during the first regimen 8 weeks in increments of 50 mg/day
Main outcome	Primary: NPI, SRI. Secondary: MMSE

Table 21.5 Trazodone trial for FTD [41]

Design	Randomised, double-blind, placebo-controlled, cross-over
Subjects	Number = 31
	Mean age = 61.7
	M/F ratio = 15/16
Entry	Lund and Manchester criteria for FTD
criteria	Frontal Behavioural Dysfunction Scale >3
	NPI total scale >8 and a score >4 for one of subscale
Duration	6-week double-blind, then 6-week double-blind crossover
Treatment	Started at a 50–100 mg/day of tradozone or placebo for a week, regimen
Regimen	150 mg/day for 3 weeks, 300 mg/day for 3 weeks if patients had no side-effects
Maim outcome	Primary: NPI. Secondary: CGI-I, MMSE

Table 21.6 Paroxetine trial for FTD (1) [43]

Design	Open, randomised, uncontrolled
Subjects	Number = 16
	Mean age = 64.6
	M/F ratio = 6/10
Entry criteria	Lund and Manchester criteria for FTD, criteria of DSM-IV for dementia
Duration	14 months
Treatment	Paroxetine 20 mg/day or piracetam 1,200 mg/day
Regimen	Paroxetine was started at 10 mg/day and was titrated to the dose of 20 mg/day
Main outcome	NPI, the Clinical Insight Rating Scale (CIR), the Cornell Scale for depression, BEHAVE-AD, MMSE, The Ten Point Clock Test, the Proverb Interpretation Tasks, the Stroop Test

improved on active treatment. There was a mild to moderate improvement in clinical severity after the tradozone period, assessed by CGI-I scale [42]. The MMSE was not modified.

Paroxetine

Paroxetine is a selective and potent inhibitor of 5-HT re-uptake into serotoninergic neurons. There are two trials to evaluate the effects of paroxetine in FTD patients. The first was an open-labelled, randomised, uncontrolled study, with no crossover [43] (Table 21.6). Patients were randomised to receive paroxetine up to 20 mg/day ($n = 8$) or piracetam up to 1,200 mg/day ($n = 8$). At 14 months, the patients treated with paroxetine showed significant improvements in behavioural symptoms such as personal behaviour and social conduct, reflected by a reduction of caregiver stress. The second trial was a randomised, double-blind,

Table 21.7   Paroxetine trial for FTD (2) [44]

Design	Randomised, double-blind, placebo-controlled, cross-over
Subjects	Number = 10
	Mean age = 66.3
	M/F ratio = 7/3
Entry criteria	FTD fulfilled the consensus clinical criteria for FTLD
Duration	6-week double-blind, then 6-week double-blind crossover
Treatment	Started at a 20 mg/day of paroxetine or placebo for a week,
regimen	30 mg/day for a week, 40 mg/day for a month, reduced by 10 mg/day each week
Main outcome	NPI, Cambridge Behavioural Inventory, CANTAB, Paired association learning, Decision-making

placebo-controlled, cross-over trial [44] (Table 21.7). Doses of paroxetine were progressively increased to 40 mg daily (n = 10). The same regimen was used for placebo capsules (n = 10). Treatment responses for neurobehavioural symptoms were evaluated by the NPI and Cambridge Behavioural Inventory. Cognitive function was evaluated by a broad range of neuropsychological tests. On contrast to the results from the open-label trial, paroxetine did not significantly improve scores on behavioural assessments. Paroxetine therapy selectively impaired paired associates learning, reversal learning and delayed pattern recognition. This pattern of deficits closely resembles that seen after tryptophan depletion. The discrepancy between these two trials could be due to the procedural differences (open vs. double-blind with placebo-controlled) and/or paroxetine doses (20 mg vs. 40 mg). Forty milligram paroxetine/day is a relatively high dose. Whether low dose paroxetine (20 mg/day) could give the optimal balance between therapeutic and side effects awaits evaluation in a blinded, placebo-controlled trial.

OTHER AGENTS

Small doze of major tranquilisers such as risperidone or olanzapine might be indicated for disinhibition, aggressiveness, or stereotypic behaviours where above-mentioned non-pharmachological interventions or medications of SSRIs that do not have enough effectiveness for these challenging behaviours. However, all anti-psychotic drugs can be associated with increased drowsiness and falls. Multicentre trials of memantine for FTD are in progress, with the rationale that the neuroprotective effect of an N-methyle-D-aspartate antagonist could benefit patients with non-Alzheimer's neurodegenerative processes [39]. One randomised, double-blind, placebo-controlled, cross-over trial in FTD demonstrated the effectiveness of methylphenidate on the task of risk taking behaviour, with the rationale that methylphenidate would ameliorate reward-based deficits in FTD by stimulating dopaminergic transmission in orbitofrontal fronto-striatal circuit [45]. The amelioration of risk-taking behaviour carries important implications for rehabilitative approaches to disinhibition and impulsivity in patients with FTD. There is no evidence of benefits from acetyl-cholinesterase inhibitors such as donepezil, rivastigmine, or galantamine [14].

CONCLUSIONS

Neurodegenerative dementia is a chronic illness that is progressive and is associated with a range of behavioural and cognitive disturbance. For these patients there are still no drugs that can cure or retard the primary pathological process. Hence, the primary aim of treatment at present is to evaluate BPSD correctly, and at the earliest possible time, so that burden of care can be minimised through appropriate behavioural therapy or symptomatic drug treatment. This reduction is critical for the continuation of satisfactory home care and could also

benefit health economics. This is particularly relevant for FTD in that patients typically manifest marked behavioural disturbance in absence of major global cognitive deficits in its initial stages [46].

In addition to the above-mentioned BPSD, the early onset seen in FTD (often <65 years) can add to the burden and distress experienced by family members. Relative youth means patients are often employed and may have adolescent children at home. The young age of these patients is also problematic because many services designed for people with dementia are built around AD patients, who are usually much older. Many community dementia services are reluctant to accept young, physically healthy persons in their programs, particularly if that patient is male and is exhibiting problematic behaviours [47].

Not only physicians but other health-care professionals and also caregivers need to be aware of the features of FTD to provide appropriate and specific care and social support for this early onset dementia with striking BPSD.

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Functional neuroimaging in Alzheimer's disease

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Introduction

With increasing life expectancy across the world, the number of elderly people at risk of developing dementia is growing rapidly, and Alzheimer's disease (AD) remains the most common cause of dementia in all age groups. For almost three decades, positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to investigate functional alteration of the brain in patients with AD. Recent advances of instruments have enabled us to investigate functional alteration in fine structures of not only cortical but also subcortical areas with high spatial resolution. Moreover, development of computer-assisted analysis using three-dimensional stereotactic surface projection (3D-SSP)[1–3] or the easy Z-score imaging system (eZIS)[4,5] based on statistical parametric mapping (SPM)[6] afforded objective and more reliable assessment of functional abnormalities by means of stereotactic coordinates than visual interpretation of raw tomographic images. This stereotactic approach is

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voxel-by-voxel analysis in the stereotactic space to avoid subjectivity and to adopt the principle of data-driven analysis. Although an alternative approach by a regions of interest (ROI) technique has gained general acceptance, it is limited by the fact that selection of the sample depends on the observer's a priori choice and hypothesis and leaves large areas of the brain unexplored. Recent medications such as cholinesterase inhibitors (e.g., donepezil) has turned out to be able to delay the progression of AD.[7] This fact makes present studies on AD focus on an earlier diagnosis and longitudinal investigation to assess therapeutic effects. In this article I review recent progress in functional neuroimaging of AD using PET and SPECT.

Easy Z-score imaging system

We developed a method for automated diagnosis of brain perfusion SPECT and designated this method eZIS.[4,5] In this software program, voxel-based analysis was performed using a Z-score map calculated from comparison of a patient's data with the control database in the same manner as with a 3D-SSP method. Anatomical standardization of SPECT images into a stereotactic space was performed using SPM99. This program was made from the combination of 3D-SSP and SPM99. It has been reported that 3D-SSP with two-dimensional surface projection of cortical activities is less sensitive to artifacts derived from incomplete anatomical standardization of the brain with localized cortical atrophy.[8] However a 3D-SSP technique loses information on three-dimensional location, which SPECT images inherently possess. This program also has the advantage being able to incorporate SPM results into the automated

analysis of Z-score values as an ROI. A specific ROI can be determined by group comparison of SPECT images for patients with a neuropsychiatric disease with those for healthy volunteers using SPM.

Even if a center can construct a normal database with good quality comprising a large number of healthy volunteers, other centers have not been able to use this normal database because of differences between the gamma cameras, collimators, and physical correction algorithms used. Because SPECT exhibits greater variations in image quality than PET among different centers, conversion of SPECT images may be necessary for sharing a normal database. In this eZIS software, we incorporated a newly developed program for making it possible to share a normal database in SPECT studies.[4] A Hoffman three-dimensional brain phantom experiment was conducted to determine systematic differences between SPECT scanners. SPECT images for the brain phantom were obtained using two different scanners. Dividing these two phantom images after anatomical standardization by SPM99 created a three-dimensional conversion map. This conversion map was applied to convert an anatomically standardized SPECT image using one scanner to that using the other scanner. The SPM99 demonstrated adequate validity of this conversion in comparative analyses of these SPECT images with different scanners.[4] The present use of a conversion map obtained from SPECT images of the same phantom provided very similar SPECT data despite extreme differences between scanners. The present method may be useful for combining normal databases from different centers and greatly enhance the diagnostic value of brain SPECT imaging by standardization of data analysis using a common normal database.

Early diagnosis of AD

The context of subjects with memory complaints who do not yet match criteria for AD but who are at high risk of developing a full-blown dementia syndrome in the next few years has been recently noteworthy. This "at risk" state is commonly referred to as mild cognitive impairment (MCI).[9] In this prodromal stage of AD, decrease of regional cerebral blood flow (rCBF) as well as glucose metabolism in the posterior cingulate gyrus and precuneus has been reported using PET[10,11] or SPECT[12,13] (Fig. 1). Statistical image analysis using the 3D-SSP or SPM method has made these observations. We could hardly distinguish a slight decrease of rCBF or metabolism in this area in patients with early AD by visual inspection, as metabolic activity or rCBF in the posterior cingulate gyrus is as high as in the primary visual cortex in normal individuals at rest.[11] Reduced PET measures of glucose metabolism in AD remain even after accounting for partial volume effects; thus, it is more than just an artifact resulting from increased cerebral fluid space.[14] We reported the superiority of 3D-SSP analysis over visual

Fig. 1. Regional cerebral blood flow (rCBF) decrease at the very early stage of Alzheimer's disease (AD). Although visual interpretation of single-photon emission computed tomography (SPECT) images is quite difficult for differentiating AD at the mild cognitive impairment (MCI) stage from age-matched healthy volunteers, voxel-based statistical parametric mapping (SPM) after anatomic standardization between two groups demonstrated distinct rCBF decrease in the posterior cingulate gyrus (PCG) and precuneus
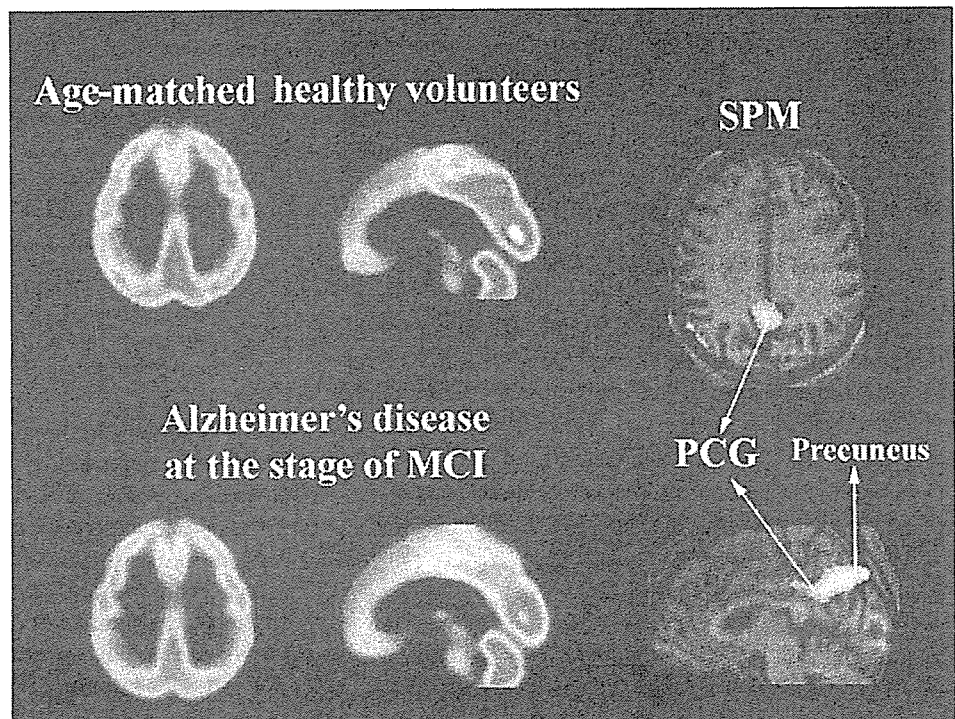
inspection in the discrimination of very early AD from controls using brain perfusion SPECT.[15] In this report, the Z-score in the posterior cingulate gyrus and precuneus gave better discrimination accuracy (86%) between AD and healthy controls than that in medial temporal areas, parietal association cortices, or temporal association cortices.

The observation that a metabolic reduction in this area predicts cognitive decline in presymptomatic persons indicates that the pathophysiologic process begins well before even mild or questionable dementia is recognized clinically.[16,17] PET measures of glucose hypometabolism reflect decreased synaptic activity due either to loss or dysfunction of synapses,[18] and regional metabolic deficits observed on PET may reflect projections from dysfunctional neurons in other brain lesions. In non-human primates, lesions of the entorhinal cortex, which is the first to be affected in AD,[19] cause significant and long-lasting metabolic decline in a small set of remote brain regions, especially in the inferior parietal, posterior temporal, posterior cingulate and associative occipital cortices, and posterior hippocampal regions.[20] Minoshima et al.[21] reported that epilepsy patients who have undergone medial temporal lobectomy have reductions in rCBF in the thalamus and posterior cingulate cortex. Mosconi et al.[22] reported functional connectivity between the entorhinal cortex and posterior cingulate gyrus in AD patients using fluorodeoxyglucose PET. These results suggest that rCBF or metabolic reduction in the posterior cingulate gyrus and precuneus indicates the earliest functional changes in AD as a remote effect. According to our longitudinal SPECT study,[12] rCBF decrease in the posterior cingulate gyrus and precuneus became ambiguous as the disease progressed. This may be due to more stability of flow in this area than that of other cortical areas as disease process.

The area of the posterior cingulate gyrus and precuneus is known to be important in memory.[23] A PET study revealed activation of the retrosplenial area of the posterior cingulate cortex during the episodic memory encoding task.[24] Clinical evidence of existence of brain tumor[25] or arteriovenous malformation[26] in the retrosplenial cingulate cortex supports the importance of this area in memory function. The retrosplenial cingulate cortex receives input from the subiculum and projects to the anterior thalamus, thus providing an alternative route between the hippocampus and thalamus. Medial temporal structures involved in memory receive anterior thalamic input directly via the cingulate bundle and indirectly through a relay in the retrosplenial cortex.[26] This thalamocortical portion of Papez' circuit[27] may be important in memory, and lesions of the cingulum and

retrosplenial cortex may cause memory dysfunction by disrupting this pathway.

The PET study also showed activation in the precuneus during the episodic memory retrieval task but not in the control or the semantic memory tasks.[23] Little is known concerning either the functions or connectivity of the precuneus. Anatomical evidence indicates prefrontal, temporal, occipital, and thalamic connections to the precuneus. Recent advances in functional MRI revealed significant contributions of the precuneus to episodic memory retrieval.[28]

Prediction of conversion from MCI to AD

Mild cognitive impairment comprises a heterogeneous group of disorders with a variety of clinical outcomes, and the patients are at risk for developing AD. The prediction of conversion from MCI to AD using the initial neuroimaging studies is an important research topic. A recent longitudinal fluorodeoxyglucose PET study reported a high predictive value of reduced uptake in the parietal association areas and a lower predictive value of that in the posterior cingulate gyrus.[29] Mosconi et al.[30] also reported that converters demonstrated reduced glucose metabolism in the inferior parietal cortex compared with nonconverters. These results strongly demonstrate the high predictive value of functional abnormality in the parietal association areas. However, two longitudinal studies[31,32] suggested a high predictive value for functional abnormality in the posterior cingulate gyrus.

Our investigation on a comparison between 52 converters and 24 nonconverters from MCI to AD at a 3-year follow-up showed reductions of rCBF in the bilateral parietal areas and the precunei in converters compared with that in nonconverters.[33] The logistic regression model revealed that reduced rCBF in the inferior parietal lobule, angular gyrus, and precunei has high predictive value and discriminative ability for converters and nonconverters. Our data suggest that the initial rCBF SPECT studies of individuals with MCI may be useful in predicting who will convert to AD in the near future.

Partial volume correction

The more limited spatial resolution of SPECT scanners compared with that of PET does not allow an exact measurement of the local radiotracer concentration in brain tissue, as partial volume effects cause underestimation of activity in small structures of the brain. Because

brain atrophy accentuates the partial volume effects on SPECT measurements, the actual rCBF could be underestimated in AD. It has been therefore obscure whether the reduction of rCBF observed in AD patients reflects an actual reduction of rCBF or partial volume effects. Recent advances in image analysis made partial volume correction (PVC) in SPECT images possible using three-dimensional volumetric T1-weighted magnetic resonance (MR) images.[34,35] In summary of the PVC method, the PVC was performed by dividing a gray matter SPECT image by a gray matter MR image that was segmented from an original MR image and further convoluted with equivalent spatial resolution to SPECT on a voxel-by-voxel basis.

Our previous SPECT study[36] in mild AD patients, the significantly decreased rCBF in the amygdala and hippocampus became normal after PVC. These areas have been reported to show marked atrophy from the early stage of AD.[37] Therefore partial volume effects would mostly affect these areas in SPECT images. Several previous reports on brain perfusion SPECT observed low rCBF in the hippocampus of probable AD patients.[38] However, recent investigations using PET scanners with better spatial resolution have not reported such a decrease in the hippocampus.[39] These observations suggest that the decreased rCBF in the hippocampus may be mainly attributable to the partial volume effects in SPECT images. The rCBF per unit volume may be maintained in the medial temporal areas in mild to moderate AD patients. This maintenance may result from a neuroplastic response in AD. The perforant path, arising from the entorhinal cortex, which has been reported to be the first to be affected in AD,[19] is the major cortical input to the hippocampus. It appears that the neuronal loss in the entorhinal cortex of AD patients acts as a stimulus similar to that of the lesion in the rat brain, where loss of one set of axons induces sprouting of the remaining afferents and replacement of the lost connections to maintain synaptic activity.[40] This compensatory response of reinnervation would result in milder functional changes than morphological changes. After PVC, selective rCBF decreases were bilaterally observed in the parahippocampal gyrus containing the entorhinal cortex. Measures of PET glucose metabolism in the entorhinal cortex were most accurate in differentiating those with mild cognitive impairment from normal subjects.[41] The selective rCBF decrease in the parahippocampal regions may be not due to incomplete PVC but, rather, to disclosure of accurate pathophysiology hindered by the limitation of SPECT's spatial resolution.

We also observed PVC effects in brain perfusion SPECT on discrimination between patients with prob-

able AD at the very early stage and age-matched controls.[5] Analysis of receiver operating characteristics curves for a Z-score discriminating AD and controls in the posterior cingulate gyrus showed that the PVC significantly enhanced the accuracy of the SPECT diagnosis of very early AD from 73.9% to 83.7%. From this point of view, it would be preferable to perform PVC in a SPECT study for early diagnosis of AD by overcoming the drawback of greater susceptibility to partial volume effects due to lower spatial resolution than PET.

## Differential diagnosis of AD and dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is the second most common form of degenerative dementia, accounting for up to 20% of cases in the elderly in Europe and United States. It has been increasingly diagnosed also in Japan as the development of neuroimaging techniques. It is characterized by the clinical triad of fluctuating cognitive impairment, spontaneous parkinsonism, and recurrent visual hallucinations. Consensus clinical criteria have been published and have been shown to have high specificity, but they may still lack sensitivity. Pathologically, DLB may be classified as a Lewy body disorder and/or an α-synucleinopathy. Although both DLB and AD show a reduction in presynaptic cholinergic transmission from the basal forebrain, in DLB there are also deficits in cholinergic transmission from brain stem nuclei. Postsynaptic cortical muscarinic receptors are more functionally intact in DLB, suggesting potential responsiveness to cholinergic enhancement. Accurate diagnosis of DLB is clinically important, as the management of psychosis and behavioral disturbances is complicated by sensitivity to neuroleptic medication. There is accumulating evidence to suggest that DLB may be particularly amenable to cholinergic enhancers.

Neuroimaging findings indicate relative preservation of medial temporal lobe structures and rCBF in DLB.[42,43] Defects in nigrostriatal dopamine pathways in DLB have been demonstrated with functional neuroimaging using ligands highlighting pre- and postsynaptic dopaminergic systems.[44] Several studies also indicate subtle differences in perfusion patterns on SPECT or fluorodeoxyglucose PET with a greater degree of occipital hypoperfusion or hypometabolism in DLB than in AD[45-47] (Fig. 2).

Effects of cholinesterase inhibitor on cerebral blood flow

Pharmacological, biochemical, and functional imaging observations implicate a cholinergic defect underlying

Fig. 2. Differentiation of AD and dementia with Lewy bodies (*DLB*) using positron emission tomography (PET) and SPECT. Both PET and SPECT revealed rCBF decrease or hypometabolism in occipital cortex of DLB as compared with AD (*arrows*). In contrast, DLB showed more preserved rCBF in the medial temporal area than AD (*arrowheads*)
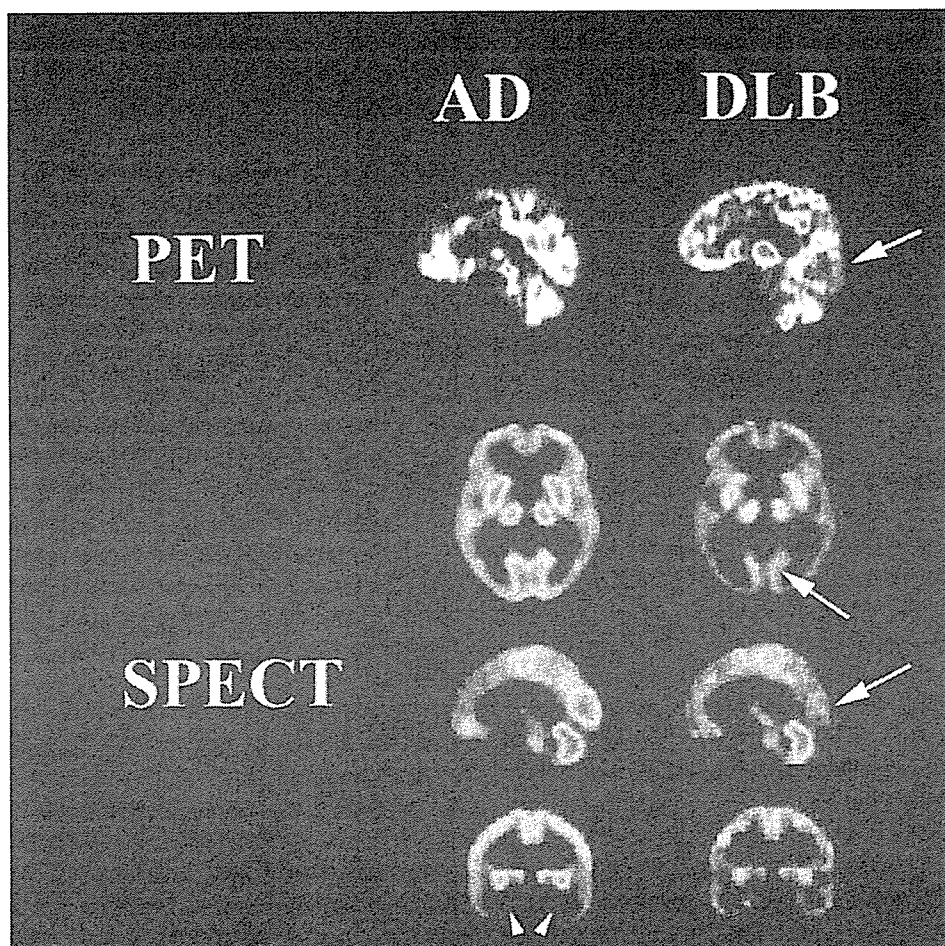
many behavioral abnormalities in AD.[48] Donepezil hydrochloride is a piperidine-based acetylcholinesterase inhibitor that is used clinically for the symptomatic treatment of mild to moderate AD.[49,50] Donepezil has been shown to improve cognition significantly and to maintain global function compared with placebo; it is also well tolerated.[50] The results of 24-week studies have indicated that the well-established benefits of donepezil on cognition may extend to improvement of the ability to perform complex activities of daily living.[49] Although donepezil has been approved in many countries for the treatment of patients with mild to moderate AD, its effect on cerebral blood flow or metabolism has not been fully investigated yet.

In a study using ^{99m}Tc-HMPAO SPECT with SPM analysis, Mega et al.[51] found that the presence of lower lateral orbital frontal and dorsolateral frontal perfusion suggested a good response to donepezil and was significantly related to behaviors of irritability, disinhibition, and eupholia. Staff et al.[52] also observed the most significant increase in frontal lobes as well as overall slight increase in global cerebral blood flow after donepezil treatment in AD patients.

Nobili et al.[53] compared the longuitidinal SPECT findings during 15.0 months on average between stabilized and nonstabilized groups under donepezil treatment. No significant difference was found between the baseline and repeated SPECT data in the stabilized group. In contrast, in the nonstabilized group a significant rCBF reduction was found in the frontal, temporal, and parietal superficial cortex, in the occipital precuneus in the right hemisphere, and in the frontal and mesial temporal cortex in the left hemisphere. On repeated SPECT, rCBF was significantly lower in a left frontal region in the nonstabilized group than in the stabilized group.

Ceravolo et al.[54] reported that SPM analysis showed significantly increased rCBF after short-term (4 months) acetylcholinesterase inhibitor therapy with respect to the baseline in the right anterior cingulate, dorsolateral prefrontal, and temporoparietal areas bilaterally. These data suggest that cognitive or behavioral benefits after

cholinesterase (ChE) inhibitor therapy are related to a clear increase of rCBF in crucial areas specifically involved in the attention and limbic networks.

Our longuitidinal study[55] before and 1 year after administration showed that the adjusted rCBF was significantly preserved in the right and left anterior cingulate gyri, right middle temporal gyrus, right inferior parietal lobules, and prefrontal cortex of 15 donepezil-treated AD patients compared with that in 20 placebo-treated AD patients. Treatment with donepezil for 1 year appears to reduce the decline in rCBF, suggesting preservation of functional brain activity.

Conclusion

PET and SPECT imaging for the assessment of rCBF and metabolism has played very important roles in diagnosing early AD at the MCI stage, the staging of AD, differentiation of AD and other dementias, prediction of conversion from MCI to AD, and assessing therapeutic indications and its effects. A recent advance in voxel-based statistical analysis of PET and SPECT images has remarkably raised the value of neuroimaging in dementia.

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Comparison of the diagnostic performance of FDG-PET and VBM-MRI in very mild Alzheimer's disease

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Abstract. *Purpose:* The aim of this study was to compare the diagnostic performance of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and voxel-based morphometry (VBM) on magnetic resonance imaging (MRI) in the same group of patients with very mild Alzheimer's disease (AD).

Methods: Thirty patients with very mild AD (age 67.0± 5.8 years; MMSE score 25.5±1.2, range 24–28), 32 patients with mild AD (age 67.0±4.5 years, MMSE score 22.1±0.8, range 21–23) and 60 age- and sex-matched normal volunteers underwent both FDG-PET and three-dimensional spoiled gradient echo MRI. Statistical parametric mapping was used to conduct voxel by voxel analysis and Z score mapping. First, the region of interest (ROI) maps of significant reductions in glucose metabolism and grey matter density in the mild AD patients were defined. Secondly, analysis of receiver operating characteristic (ROC) curves for Z scores in the ROI maps discriminating very mild AD patients and normal controls was performed.

Results: In mild AD patients, FDG-PET indicated significant reductions in glucose metabolism in the bilateral posterior cingulate gyri and the right parietotemporal area, while VBM analysis showed a significant decrease in grey matter volume density in the bilateral amygdala/hippocampus complex, compared with the normal control group. ROC analysis showed that in very mild AD patients the accuracy of FDG-PET diagnosis was 89% and

that of VBM-MRI diagnosis was 83%. The accuracy of the combination of FDG-PET and VBM-MRI diagnosis was 94%.

Conclusion: In very mild AD, both FDG-PET and VBM-MRI had high accuracy for diagnosis, but FDG-PET showed slightly higher accuracy than VBM-MRI. Combination of the two techniques will yield a higher diagnostic accuracy in very mild AD by making full use of functional and morphological images.

Keywords: Alzheimer's disease – FDG – PET – MRI – Voxel-based morphometry

Introduction

Alzheimer's disease (AD) is the most common type of dementia. Although no eradicative medicine exists, several drug therapies have been developed. Acetylcholinesterase inhibitors are commonly administered to slow the progression of AD, and early intervention is recommended, making early diagnosis important.

Using magnetic resonance imaging (MRI), structural measurements of brain atrophy in specific brain structures, such as the hippocampus, have been reported to detect the development of dementia early in the course of the disease [1–4]. On the other hand, using positron emission tomography (PET), functional measurements of brain activity (e. g. glucose metabolism) have revealed hypometabolism in the parietotemporal and posterior cingulate areas early in the disease course [5–7]. ^{18}F-fluorodeoxyglucose (FDG)

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PET is regarded as excellent in detecting very early neocortical dysfunction before atrophy appears.

Recently, voxel-based techniques have been used to analyse differences between two groups of subjects for both structural and functional imaging of the brain by analysing the pathophysiology of degenerative disease and disease-associated functional changes [6, 8]. Voxel-based morphometry (VBM) [9], permitting the comparison of local grey matter density at every voxel in an image, has been developed to quantify brain atrophy in AD and other degenerative diseases [10, 11] and has been used in a clinical study of mild AD patients [12].

We previously reported that in very mild AD, comparison of grey matter and metabolic reductions using VBM-MRI and FDG-PET studies in the same subjects showed that morphological change occurs in the medial temporal lobes, whereas metabolic changes occur in the posterior cingulate gyri and parietal lobule [13]. No reports have directly compared PET and MRI for the prediction of AD. In this study, PET and MR images were obtained in the same patients with very mild AD and the images were analysed using voxel-based techniques in order to assess the ability of the two modalities to detect AD-specific abnormalities.

Materials and methods

All procedures were approved by the Institutional Review Board at our institution. Written informed consent was obtained from subjects and patients or from patients' relatives. We studied 122 subjects, including 30 with very mild AD [age 67.0±5.8 years (mean±SD), 22 women and 8 men], 32 mild AD patients (age 67.0±4.5 years, 23 women and 9 men) and 60 healthy volunteers. All patients were examined by both neurologists and psychiatrists, and underwent MRI of the brain, MR angiography of the neck and head, electroencephalography and standard neuropsychological examinations. The inclusion criteria were: (i) diagnosis of probable AD using National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [14], (ii) no evidence of focal brain lesions on MR images. Three of the patients did not satisfy the NINCDS/ADRDA criteria because they were at a very early stage of AD at the time of the imaging procedure; however, 1 year later they were shown to fulfill those criteria for probable AD. The mean Mini-Mental State Examination (MMSE) [15] score was 25.5±1.2 for the very mild AD group and 22.1±0.8 for the mild AD group, and the mean Alzheimer's Disease Assessment Scale (ADAS) [16] score was 12.8±3.8 for the very mild AD group and 16.2±4.5 for the mild AD group.

Healthy volunteers, who served as control subjects, had no neurological signs or significant medical antecedents and no abnormal findings on MR images. None of the subjects in this study had diabetes mellitus. The 60 healthy volunteers were divided into two groups. The first group (age 66.6±5.8 years, 22 women and 8 men) was compared with the mild AD group to delineate regional metabolic reduction and area of grey matter loss and to produce region of interest (ROI) maps, while the second group (age 66.8±5.8 years, 22 women and 8 men) was compared with the very mild AD group to assess diagnostic utility using the ROI maps.

MR procedure

The MR scanner was a 1.5-T Signa Horizon (GE Medical Systems, Milwaukee, WI, USA). Sagittal, coronal and axial T1-weighted SE images [repetition time (TR, ms)/echo time (TE, ms) =550/15, two excitations, 5-mm thickness, 2.5-mm gap] and axial T2-weighted fast SE images (3,000/21,105, two excitations) were obtained for diagnosis. Then three-dimensional spoiled gradient echo (SPGR) imaging (TR 14 ms, TE 3 ms, flip angle 20°, 0.86×0.86 mm pixel size, 1.5-mm thickness by 124 slices) was performed in this study. MR images were obtained 0–28 days before PET examination.

PET procedure

The detailed PET procedure is described elsewhere [17]. In brief, FDG-PET images were obtained using a Headtome IV scanner (Shimadzu Corp., Kyoto, Japan). Before PET scans, all subjects received MR examinations for PET positioning. All subjects fasted for at least 4 h before PET scanning. Subjects were studied in resting conditions with the eyes closed and ears unplugged. After a transmission scan, a 12-min emission scan was started 60 min after intravenous injection of 185–370 MBq of FDG. Data were collected in 128×128 matrices. The slice interval was 6.5 mm when the z-motion mode was used. Images were reconstructed by filtered backprojection, resulting in an in-plane resolution of 6.0 mm full-width at half-maximum (FWHM).

Data analysis

Anatomical normalisation and statistical processing for PET and MR images were performed with SPM99 software (Wellcome Department of Cognitive Neurology, London, UK) [18–20] implemented on MATLAB 5.3 (Mathworks Inc., MA, USA). For PET, all the individual PET images were transformed into a standard stereotactic anatomical space. Then all images were smoothed using an isotropic Gaussian kernel of 12 mm to increase the signal-to-noise ratio and to compensate for the differences in gyral anatomy between individuals. Individual FDG images were adjusted by using proportional scaling to a mean value of 5.0 mg/100 ml per minute. For MRI, the VBM method [9] was performed after anatomical normalisation of brain images; images were automatically segmented using a cluster analysis technique. This process, based on prior probability maps about the relative distribution of tissue types, partitioned the brain into grey matter (GM), white matter (WH), cerebrospinal fluid (CSF)