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ORIGINAL PAPER

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Clinical characteristics of frontotemporal patients with symmetric brain atrophy

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Abstract In this paper we explored patterns of frontal and temporal asymmetry in frontotemporal dementia (FTD) and tried to isolate clinical correlates associated with asymmetry or lack thereof. Volumes of frontal and temporal lobes, hippocampus and entorhinal cortex were measured using magnetic resonance imaging (MRI) in 10 patients with FTD. Age- and cranial size-specific values were computed through linear regression analysis (W-scores). A subgroup of 3 patients with symmetric frontal and temporal atrophy was identified. When compared to patients with asymmetric atrophy, the former had younger age at onset of the disease ($p = 0.02$), greater overall frontotemporal ($p = 0.02$) and greater entorhinal atrophy ($p < 0.04$). Two of the three patients were apolipoprotein E ε4 carriers versus none of the asymmetric patients ($p = 0.02$). The lack of asymmetry in this small sample of FTD patients was associated with greater brain atrophy, younger age at onset, and presence of the ε4 allele of apolipoprotein E. The presence of the ε4 allele is consistent with the hypothesis of greater vulnerability of the brain in ε4 carriers.

Key words FTD · symmetry · MR · ApoE · dementia

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Introduction

One of the most typical features of frontotemporal dementia (FTD) is asymmetry. This is evident at both clinical and biological levels. At the clinical level, language can be affected early and disproportionately [23], indicating predominantly greater involvement of the left hemisphere. In other cases, behavioral disturbances predominate, which may indicate greater right hemisphere involvement [22]. At the biological level, strikingly asymmetric hypometabolism [19] and atrophy [19], as detected with *in vivo* imaging methods [12], have been repeatedly described, as well as an asymmetric distribution of lesions on pathological studies [5]. However, asymmetry may also be absent. Miller and Gearhart analyzed 15 FTD patients with single photon emission computerized tomography (SPECT) and magnetic resonance imaging (MRI), and observed symmetric hypoperfusion in 3, and symmetric atrophy in 7 of the subjects [19]. Filley and colleagues reported symmetric involvement in 2 of 4 FTD patients at pathological evaluation [5].

It is not known what the origin of the observed patterns of symmetry or asymmetry is, nor whether symmetric versus asymmetric FTD forms a further subgroup under the umbrella of frontotemporal dementias. Thus, the aim of this study was to explore clinical and imaging characteristics of symmetric versus asymmetric FTD patients.

Methods

Subjects and clinical assessment

The patients of this study have been described in detail elsewhere [6]. Here we summarize the characteristics of the FTD patients and the non-demented subjects who were used as controls for the volumetric analyses. Routine dementia assessment was carried out in all the FTD patients.

In the original series [6], the diagnosis of FTD was made on clinical grounds following clinical descriptions [8] and guidelines [17,

20]. The patients were retrospectively assessed and judged to fulfill the criteria for the diagnosis of frontotemporal lobar degeneration of FTD type [23], representing rather homogeneous clinical phenotype. The diagnosis of FTD was supported by SPECT with HM-PAO. Follow-up evaluations were carried out from a minimum of eight months to a maximum of three years. The persistence of the neuropsychological pattern of disproportionate language and behavioral symptoms with relative sparing of memory and orientation was regarded as confirmatory of the diagnosis. After excluding two patients with progressive aphasia in the absence of other cognitive and behavioral disturbances, one who displayed no deterioration in three years, and the subjects from whom compatible data for volumetric analysis were not available, 10 FTD subjects remained.

History, estimated onset of FTD, and information on basic and instrumental activities of daily living were taken from a knowledgeable informant. Laboratory studies, and clinical, neurological, and neuropsychological evaluations have been described elsewhere [6].

Disease duration was computed from the estimated onset to the date of MR imaging. Italian version of Folstein's Mini-Mental State Examination (MMSE) was used to assess cognition [18]. Global dementia severity was assessed with the Clinical Dementia Rating scale (CDR) [9].

Controls were patients' relatives (mostly spouses) without detectable cognitive deficit. They had a negative history of neurological disease, though some reported mild subjective memory problems which did not result in impairment of daily activities. All had the MMSE administered, and were judged not demented by a neurologist and a psychologist involved in the evaluation of the patients. Their mean age was 70 ± 8 years, percentage of men was 37 %, and they had received education for an average of 8 ± 3 years. Of the original 31 controls, 27 had MR images suitable for volumetric analyses of the present study.

The study was approved by the local ethics committee.

Brain measurements

MRI was performed with a 1.5 T Siemens Magnetom using a standard head coil. A 3D gradient-echo technique was employed for acquisition of T1-weighted images for volumetry (TR 10 ms; TE 4 ms; TI 300 ms; flip angle 10°; field of view 250 mm; acquisition 2; matrix 160×256). All volumetric measurements were made blind to the subjects' diagnostic category.

Frontal and temporal lobes

Prior to tracing of the lobar volumes, MR images were transferred to a Sun workstation (Sun Microsystems Inc., Mountain View, CA), and aligned to correct for head tilt, pitch, and rotation in 3D. The frontal and temporal lobe volumes were analyzed with the software QUANTA [3]. This software combines manual tracing of a crudely defined region of interest (ROI) with an automatic thresholding procedure separating CSF from brain pixels. The first frontal and temporal ROIs were traced on the slices where the brain matter appeared, and the most posterior ROIs on the slice where the Sylvian aqueduct appeared. In the posteriormost portions of the frontal lobe, the temporal lobe was separated from the frontal lobe with a line drawn from the angle of the medial temporal lobe where it is attached to the temporal stem to the midpoint of the operculum. The frontal and temporal horns were manually drawn within the brain matter in close proximity (about 2–3 mm) of the border of the horn. The intraclass correlation coefficient for intrarater reliability for the measurements ranged from 0.83 to 0.99.

Medial temporal lobe

The hippocampus and the entorhinal cortex were manually traced from contiguous coronal, 2.0 mm thick images oriented perpendicular to the intercommissural line. The hippocampus included the dentate gyrus, the hippocampus proper and the subicular complex. The rostral end of the hippocampus, when it first appears below the amygdala, was the anatomical starting point. The caudal end of the hippocampus was taken as the section in which the crura of the fornices depart from the hippocampal tail. The intraclass correlation coefficient for intrarater reliability for hippocampal volumes, measured from 10 subjects was 0.95.

The entorhinal volumes were traced according to the criteria by Insausti et al. [10]. The first slice measured was the one after the appearance of limen insula when the temporal lobe can be first appreciated to be attached to the rest of the brain when proceeding from anterior, and the last slice was the one where the uncus and gyrus intralimbicus could no longer be appreciated. The intraclass correlation coefficient for intrarater reliability for entorhinal volumes was 0.90.

Head size

The intracranial area (ICA), measured on a coronal section at the level of the anterior commissure, was used to normalize brain volumes [15].

Data management and statistical analyses

The combined effect of age [25] and brain size was controlled for with a multivariate approach by transforming crude volumes into W-scores according to the formula:

$$W = \frac{\text{(observed value)} - \text{(predicted age- and ICA-specific value in controls)}}{\text{standard deviation of residuals in controls}}$$

where age- and ICA-specific values and residuals in controls are computed by linear regression analysis [11]. W-scores are thus the distance in standard deviation units of an observed value from the expected age- and ICA-specific value.

Overall values of atrophy were computed by summing up the crude brain volumes, and correcting the obtained value, with the W formula, with respect to the sum of crude volumes of controls.

Symmetry of the frontotemporal atrophy was operationalized as the difference between right and left W-scores lower than 1 both in the frontal regions (mean between brain and horns) and in the temporal regions (brain and horns).

$$\frac{\Delta FB + \Delta FH}{2} < 1 \text{ AND } \frac{\Delta TB + \Delta TH}{2} < 1$$

where Δ indicates the difference between right and left.

If the patient had a difference higher than 1 (mean between brain and horn) in the frontal or in the temporal lobe, the patient was classified as asymmetric.

The significance of comparisons among groups was assessed with Mann-Whitney U and χ^2 tests. The level for statistical significance was set at 0.05.

Table 1 Clinical and demographic features of the 10 FTD patients

	FTD N = 10	Controls N = 27
Age, mean years (SD)	63 (5)	70 (8)[b]
Sex, number of men	7	10 (37 %)[b]
Education, mean years (SD)	7 (4)	8 (3)
Disease duration, mean months (SD)	30 (14)	–
Mini-Mental State Examination, mean score (SD)	16 (9)	29 (1)[b]
Clinical Dementia Rating 0/0.5/1/2–3 (no.)	0/4/2/4	27/0/0/0
Instrumental Activities of Daily Living, number of functions lost (SD)	3.0 (2.4)	0
ApoE ε4, n/total alleles (percentage)[a]	3/18 (17 %)	5/50 (10 %)

[a] ApoE genotyping was performed in 9 patients
[b] significant difference at non-parametric tests

Results

As summarized in Table 1, the FTD patients were of moderate disease severity. The frequency of the ε4 allele was not significantly higher than in the Italian population (0.17 vs. 0.10) [2].

One subject could not be categorized as either symmetric or asymmetric since the frontal brain was normal, frontal and temporal horns were smaller than in controls, and atrophy was limited to the temporal brain, and she was excluded from the following analyses. This patient had no ε4 alleles. Of the other 9 patients, 6 were asymmetric (Fig. 1).

Comparisons between the symmetric and asymmetric groups (Table 2) show that they are similar in sociodemographic features, disease duration and clinical severity. The symmetric group is, however, distinct from the asymmetric group for age at onset and genetic asset. The patients with symmetric atrophy had onset of dementia 9 years earlier compared with the asymmetric cases (53 ± 2.0 vs. 62 ± 2.5, exact $p = 0.02$), and higher prevalence of the ε4 allele of the apolipoprotein E (50 % vs. 0 %, $p = 0.02$).

The symmetric group also had greater atrophy of the frontal and temporal regions (Table 3). Moreover, medial temporal atrophy was absent, or rather minor in the asymmetric, and markedly greater in the symmetric pa-

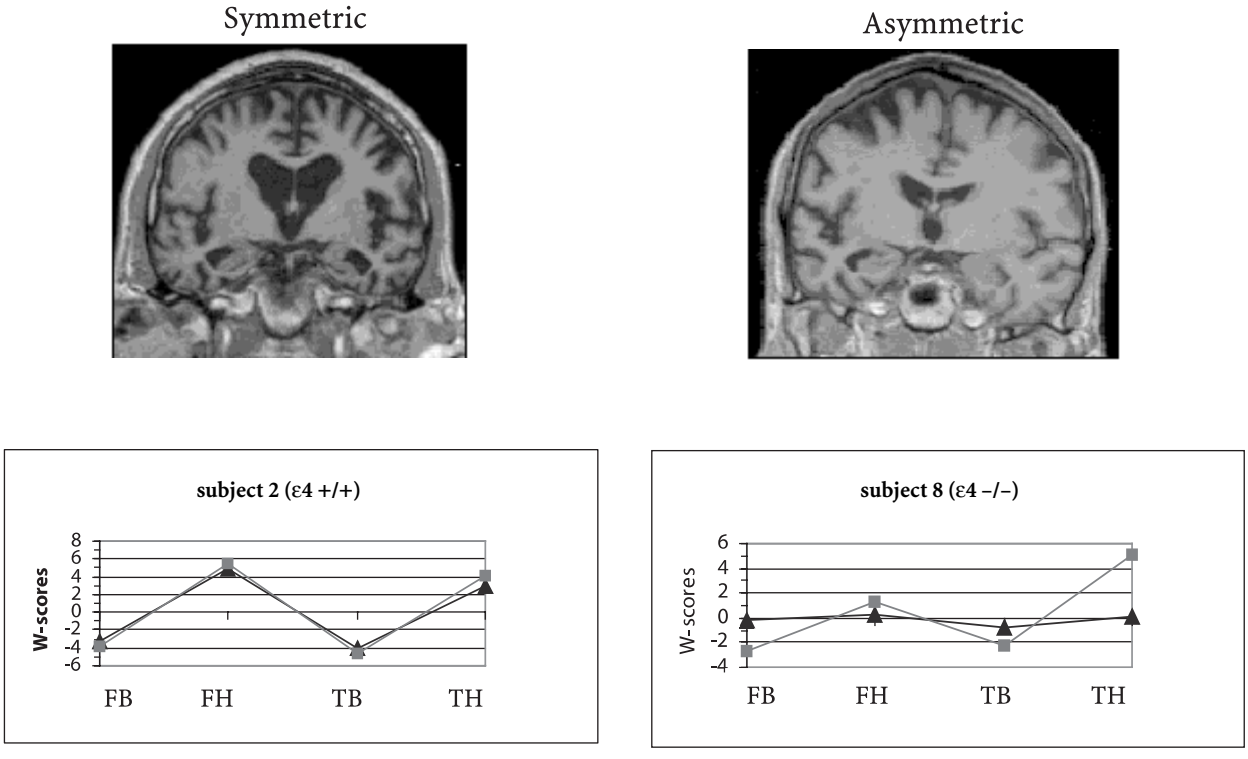

Fig. 1 Examples of symmetric and asymmetric patients with frontotemporal dementia. Upper part: MR scan. Lower part: quantification of atrophy with W-scores (see methods). *FB* frontal brain, *FH* frontal horn, *TB* temporal brain, *TH* temporal horn. ▲ = right, ■ = left. Negative W-scores indicate shrinkage, positive values indicate enlargement. Note different scales of atrophy

Table 2 Sociodemographic and clinical features of each FTD subject, divided in symmetric and asymmetric groups

Subtype	Age	Sex	Education	Disease duration	Age at onset	ε4	MMSE	CDR
Symmetric	54	M	5	24	52	2	18	1.0
Symmetric	59	F	5	40	55	1	4	2.0
Symmetric	56	M	5	36	53	0	19	2.0
Asymmetric	68	F	5	18	66	0	12	0.5
Asymmetric	64	M	8	24	62	0	23	0.5
Asymmetric	65	M	17	36	62	0	29	0.5
Asymmetric	66	M	5	60	61	0	0	3.0
Asymmetric	61	M	5	18	59	0	14	0.5
Asymmetric	65	M	3	12	64	–	13	1.0
P	0.02	n. s.	n. s.	n. s.	0.02	0.02	n. s.	n. s.

Table 3 Atrophy of frontal, temporal and medial temporal regions in the symmetric and asymmetric groups

Region		Symmetric n = 3	Asymmetric n = 6	p
Frontal region				
Brain	R	−3.78 (0.47)	−0.91 (1.70)	0.04
	L	−4.09 (0.32)	−2.20 (2.01)	n. s.
Horn*	R	−4.49 (1.33)	−1.41 (1.09)	0.04
	L	−5.03 (0.91)	−2.94 (1.52)	0.07
Temporal region				
Brain	R	−3.82 (0.17)	−1.38 (0.55)	0.02
	L	−4.07 (0.46)	−1.75 (2.11)	n. s.
Horn*	R	−5.43 (2.49)	−1.86 (2.29)	n. s.
	L	−5.22 (2.14)	−4.71 (3.53)	n. s.
Overall fronto-temporal atrophy		**−6.61 (1.05)**	**−2.72 (1.69)**	**0.02**
Medial temporal region				
Hippocampus	R	−2.87 (1.32)	−0.97 (1.18)	0.07
	L	−2.59 (1.83)	−0.82 (1.23)	0.07
Entorhinal cortex	R	−3.18 (0.26)	−0.76 (1.16)	0.02
	L	−2.38 (0.81)	−0.92 (1.03)	0.04
Overall medial temporal atrophy		**−3.46 (1.13)**	**−1.22 (1.16)**	**0.04**
Overall atrophy		**−3.66 (1.11)**	**−1.31 (1.19)**	**0.04**

Values denote mean (SD) values of atrophy expressed as W-scores. Overall values of atrophy are the W-score of the sum of crude right and left frontal and temporal brain and horns (overall frontotemporal), right and left hippocampus and entorhinal cortex (overall medial temporal, and of all brain regions considered in the study (overall atrophy).

* Polarized so that negative values indicate atrophy. *p* significance on Mann-Whitney U test

tients (Table 3). The difference between the two groups was close to statistical significance for the hippocampi, and significant for the entorhinal cortex. Global values of frontotemporal, medial temporal and overall atrophy indicate significantly greater atrophy in symmetric patients.

Discussion

In this study we describe some characteristics associated with the symmetric distribution of brain atrophy in FTD. First, the patients with symmetric atrophy had earlier onset of disease. Second, they presented with more severe global and medial temporal atrophy despite equal global clinical severity duration. Third, in the patients with asymmetric disease, only the left frontal and temporal regions were affected, while right frontotemporal and bilateral medial temporal regions were only mildly atrophic. Finally, the patients with symmetric presentation also had greater frequency of the ApoE ε4 alleles.

The asymmetric involvement of the brain in FTD is maintained as the cause of the wide variety of symptoms of this type of dementia (mainly linguistic or behavioral, considered to represent left and/or right involvement, respectively)[22]. Symmetric involvement would imply that both linguistic and behavioral symptoms are both present and severe, but lack of detailed data in our patients over the years does not allow us to test this hypothesis.

The genetic asset (the presence of ApoE ε4 allele) is consistent with a theory of greater brain vulnerability in the ε4 carriers. The greater frequency of the ε4 allele might be at least in part responsible for greater and symmetric atrophy, as well as younger age at onset. None of the cases with asymmetric FTD were ε4 carriers. Smaller brain volumes in normal and AD subjects carrying the ε4 allele have repeatedly been addressed [1], as well as reduced asymmetry [16]. In addition, the ε4 allele might contribute to the younger age at onset [1], although this effect in FTD is more controversial [21, 24], and indeed the identification of different polymorphisms of the ApoE itself suggests that the interaction of this gene with the clinical phenotypes might be particularly complex [27].

A more symmetric distribution of atrophy might be due to a very advanced stage of disease, and represent a floor effect. Our symmetric patients had a mean disease duration 5 months longer than the asymmetric. As the initial pattern of atrophy in degenerative dementias has been shown to remain unchanged as the disease progresses for at least 2–3 years [26], it does not seem likely that the minor difference of disease duration is responsible for the different distribution of atrophy in our groups.

Limitations of this study must be underlined. First, the small patient groups are not sufficient to guarantee generalizability of the results regardless of whether the findings were statistically significant. Second, a more detailed clinical assessment, including neuropsychological and behavioral evaluation, would have been of great importance to better investigate the clinical correlates of asymmetry or lack thereof. Third, pathologic evaluation was not available for our patients, but the follow-up allowed us to repeatedly verify the diagnosis (one subject was in fact excluded since he did not deteriorate over time), and this should increase reliability of the diagnoses.

Moreover, the clinical profile remained consistent with typical FTD and inconsistent with either AD or its frontal variant [13], thus excluding the possibility that the symmetric FTD might have been frontal variant AD. Moreover, for the known effect of apoE ε4 on the development of AD in the age window around 70 years [4], pre-senile onset of AD is characterized by a lower prevalence of ε4, which is inconsistent with that observed in our symmetric FTD patients.

In any case, these findings should be regarded as descriptive, trying to explain a phenomenon, and providing a platform to investigate the subject, until replicated or challenged in larger samples.

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References

1. Berg L, McKeel DW, Miller JP, et al. (1998) Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 55:326–335
2. Corbo RM, Scacchi R, Mureddu L, Mulas G, Alfano G (1995) Apolipoprotein E polymorphism in Italy investigated in native plasma by a simple polyacrylamide gel isoelectric focusing technique. Comparison with frequency data of other European populations. Ann Hum Genet 59:197–209
3. DeCarli C, Maisog J, Murphy DG, Teichberg D, Rapoport SI, Horwitz B (1992) Method for quantification of brain, ventricular, and subarachnoid CSF volume from MR images. J Comput Assist Tomogr 16:274–284
4. Farrer LA, Cupples LA, Haines JL, et al. (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278:1349–1356
5. Filley CM, Kleinschmidt-De Masters BK, Gross KF (1994) Non-Alzheimer frontotemporal degenerative dementia. A neurobehavioral and pathologic study. Clin Neuropathol 13:109–113
6. Frisoni GB, Beltramello A, Geroldi C, Weiss C, Bianchetti A, Trabucchi M (1996) Brain atrophy in frontotemporal dementia. J Neurol Neurosurg Psychiatry 61:157–165
7. Frisoni GB, Laakso MP, Beltramello A, et al. (1999) Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. Neurology 52:91–100
8. Gustafson L (1987) Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. Arch Gerontol Geriatr 6:209–223
9. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. Br J Psychiatry 140:566–572
10. Insausti R, Juottonen K, Soininen H, et al. (1998) MRI volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. Am J Neuroradiol 19:659–671
11. Jack CR Jr, Petersen RC, Xu YC, et al. (1997) Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. Neurology 49:786–794
12. Jauss M, Herholz K, Kracht L, Pantel J, Hartmann T, Jensen M, Essig M, Schröder J (2001) Frontotemporal dementia: clinical, neuroimaging, and molecular biological findings in 6 patients. Eur Arch Psychiatry Clin Neurosci 251:225–231
13. Johnson JK, Head E, Kim R, Starr A, Cotman CW (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. Arch Neurol 56:1233–1239
14. Jorm AF (1985) Subtypes of Alzheimer's dementia: a conceptual analysis and critical review. Psychol Med 15:543–553
15. Laakso MP, Soininen H, Partanen K, Lehtovirta M, Hallikainen M, Hänninen T, Helkala EL, Vainio P, Riekkinen PJ Sr (1998) MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. Neurobiol Aging 19:23–31
16. Lehtovirta M, Laakso MP, Frisoni GB, Soininen H (2000) How does the apolipoprotein E genotype modulate the brain in aging and in Alzheimer's disease? A review of neuroimaging studies. Neurobiol Aging 21:239–300
17. Lund and Manchester Groups (1994) Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 57:416–418
18. Magni E, Binetti G, Bianchetti A, et al. (1996) Mini-Mental State Examination: a normative study in an Italian elderly population. Eur J Neurol 3:198–202
19. Miller BL, Gearhart R (1999) Neuroimaging in the diagnosis of frontotemporal dementia. Dement Geriatr Cogn Disord 10 (suppl):71–74
20. Miller BL, Ikonte C, Ponton M, et al. (1997) A study of the Lund-Manchester research criteria frontotemporal dementia: clinical and single photon emission CT correlations. Neurology 48:937–942
21. Minthon L, Hesse C, Sjögren M, Englund E, Gustafson L, Blennow K (1997) The apolipoprotein E ε4 allele frequency is normal in fronto-temporal dementia, but correlates with age at onset of disease. Neurosci Lett 226:65–67
22. Mychack P, Kramer JH, Boone KB, Miller BL (2001) The influence of right frontotemporal dysfunction on social behavior in frontotemporal dementia. Neurology 56:S11–S15
23. Neary D, Snowden JS, Gustafson L, et al. (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546–1554
24. Pickering-Brown SM, Owen F, Isaacs F, et al. (2000) Apolipoprotein E ε4 allele has no effect on age at onset or duration of disease in cases of frontotemporal dementia with Pick- or microvacular-type histology. Exp Neurol 163:452–456
25. Reischies FM, Rossius W, Felsenberg D (2001) Brain atrophy parameters of very old subjects in a population-based sample with and without dementia syndrome. Eur Arch Psychiatry Clin Neurosci 251:99–104
26. Smith GS, de Leon MJ, George AE, Kluger A, Volkow ND, McRae T, Golomb J, Ferris SH, Reisberg B, Ciaravino J, et al. (1992) Topography of cross sectional and longitudinal glucose metabolic deficits in Alzheimer's disease. Pathophysiologic implications. Arch Neurol 49:1142–1150
27. Zill P, Engel R, Hampel H, et al. (2001) Polymorphisms in the apolipoprotein E (APOE) gene in gerontopsychiatric patients. Eur Arch Psychiatry Clin Neurosci 251:24–28