ELSEVIER

Neuroscience Letters 335 (2002) 139–143

Neuroscience Letters

www.elsevier.com/locate/neulet

Amygdaloid atrophy in frontotemporal dementia and Alzheimer's disease

M. Boccardi[a], C. Pennanen[b], M.P. Laakso[b,c], C. Testa[a], C. Geroldi[a], H. Soininen[b], G.B. Frisoni[a,1,*]

[a]*Laboratory of Epidemiology and Neuroimaging, IRCCS San Giovanni di Dio-FBF, via Pilastroni 4, 25125 Brescia, Italy*
[b]*Department of Neurology, Kuopio University Hospital, Kuopio, Finland*
[c]*Department of Clinical Radiology, Kuopio University Hospital, Kuopio, Finland*

Received 5 April 2002; received in revised form 24 September 2002; accepted 4 October 2002

Abstract

Crude and corrected amygdaloid volumes were computed from magnetic resonance scans in ten patients with frontotemporal dementia (FTD), 25 patients with Alzheimer's disease (AD) and 27 controls. Amygdaloid atrophy was present in FTD ($P < 0.005$) compared to controls, and a trend for increasing atrophy from controls, through FTD to AD (P for trend <0.00005) showed that FTD amygdaloid volumes were intermediate between controls and AD. Behavioral and Klüver–Bucy-like symptoms, characteristic of FTD, cannot be explained by amygdaloid atrophy alone.

Keywords: Dementia; Frontotemporal dementia; Imaging; Amygdala; Morphology; Magnetic resonance; Alzheimer

Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by a wide set of behavioral disturbances. A number of these disturbances, including disinhibition, hyperorality and hypersexuality (Klüver–Bucy-like symptoms), which are characteristic for FTD as defined by the consensus criteria [18], might indicate amygdaloid involvement underlying the symptoms.

However, the few previous imaging studies on the amygdalae in FTD and related conditions have provided unexpected and controversial results. A study with positron emission tomography could not find different metabolism of the amygdala in FTD without motor neuron disease (MND) as compared to controls [10], but found amygdaloid hypometabolism in FTD with MND as compared to controls and to FTD without MND [10]. Amygdaloid volumes of FTD patients have been recently investigated in vivo in a volumetric magnetic resonance (MR) imaging study [19]. The authors detected amygdaloid atrophy in semantic dementia but not in FTD, confirming previous findings on semantic dementia [4]. However, in Pick's disease, pathologic studies have also found amygdaloid damage [5]. In Alzheimer's disease (AD), the amygdala has been demonstrated to be atrophic compared to healthy elderly controls [12].

Given the paucity of data and the controversies concerning the amygdaloid involvement in FTD, the aim of this study was to measure amygdaloid volumes with MR in FTD, and compare them to those of AD patients and nondemented controls.

The patients and controls have been extensively described previously [8]. Controls were patients' relatives with no detectable cognitive deficits, a negative history of neurological disease, and judged not demented by a neurologist and a psychologist (Table 1). MR images were suitable for volumetry in ten patients with FTD (seven men), 25 patients with AD (four men), and 27 controls (ten men). FTD patients fulfilled the criteria for frontotemporal lobar degeneration of FTD type [17,18]. One of them had FTD associated with motor neuron disease. The AD patients met the NINCDS-ADRDA criteria for probable AD [16]. Apolipoprotein E (ApoE) genotyping was performed in 25 controls, in 24 patients with AD and nine with FTD. The study was approved by the local ethics committee.

MR was performed with a 1.5 Tesla unit (Siemens, Magnetom) and a standard head coil with a 3D gradient-echo was employed for image acquisition (repetition time 10 ms; echo time 4 ms; inversion time 300 ms; flip angle

* Corresponding author. Tel.: +39-030-3501-361; fax: +39-027-0043-5727
E-mail address: papers@centroAlzheimer.it (G.B. Frisoni).
[1] http://www.centroAlzheimer.it

0304-3940/02/$ - see front matter
PII: S0304-3940(02)01169-2

Table 1
Sociodemographic features of patients and controls[a]

	Sociodemographic features						
	Age	Disease duration (months)	MMSE	CDR, n (%)			
				0	0.5	1	2–3
Controls	*70 (8)	–	29 (1)	27 (100)	0 (0)	0 (0)	0 (0)
FTD	63 (5)	30 (14)	*16 (9)	*0 (0)	4 (40)	2 (20)	4 (40)
AD	*74 (8)	43 (26)	*21 (4)	*0 (0)	7 (28)	10 (40)	8 (32)

[a] Values denote mean (standard deviation) unless otherwise specified. * Significant difference from the unmarked group on Mann–Whitney *U*-test.

10°; field of view 250 mm; acquisition two; matrix 160×256).

The amygdalae were manually traced by a single rater (C.P.) blind to the study groups using a custom-made software for a standard Siemens' work console. Volumes of the entire amygdalae were traced from contiguous, coronal 2.0 mm thick slices oriented perpendicular to the intercommissural line. The anterior starting point was where the amygdala starts to form the typical bulk in the medial temporal lobe. The tracing continued by avoiding the hippocampus and the rhinal cortices until the disappearance of the amygdala above the hippocampus. The intraclass correlation coefficient for intra-rater reliability was 0.93.

The tracing of the frontal lobes has been accurately described elsewhere [1]. This was carried out on a Sun workstation with the software QUANTA [6] that combines manual tracing of the crudely defined region of interest, traced in each slice in which it is visible, with an automatic thresholding procedure separating cerebrospinal fluid from brain pixels. The intraclass correlation coefficient for intra-rater reliability for the lobar measurements ranged from 0.83 to 0.99.

Intracranial area (ICA), measured on a coronal section at the level of the anterior commissure, was used for normalization [8].

Pearson's correlation was used to assess the effect of possible confounding variables. The effect of cranial size was accounted for with the formula: (volume/ICA $\times$ 100). Further correction was necessary for the frontal lobes and all computations that included this structure, since age had a significant effect on their volume. This correction was carried out with the computation of standardized measures of change (W-scores) [12] computed by dividing, for each subject, the difference between the expected value (based on age and cranial size) and the observed value, by the standard deviation of residuals in controls [1].

The standardized ratio between frontal and amygdaloid volumes was computed by dividing the mean right and left frontal by the mean right and left amygdaloid volumes, and then correcting this ratio for age according to the W-scores formula. Volume loss was defined as the percentage difference of patients' volume with respect to the mean of control subjects (set at 100). Significance of between group comparisons was assessed by the Kruskall–Wallis analysis of variance, and Mann–Whitney U test. Proportions were compared with the χ^2 test. The test for trend used to assess the significance of increasing atrophy among groups consisted in a regression model with group (group coding mirroring increasing atrophy: zero for controls, one for FTD two for AD) as independent variable, and volumes as dependent variable.

FTD patients were 11 years younger and more often men than AD patients, these differences reaching statistical significance. No significant effect of age and gender was found in amygdaloid volumes in the control group, while a significant effect of age was present in the frontal lobes ($r = -0.48$, $P < 0.012$ on the right, $r = -0.64$, $P < 0.0005$ on the left frontal brain). The two patients groups did not differ for disease duration ($P = 0.21$) and dementia severity (Table 1). The prevalence of the ApoE $\varepsilon 4$ alleles was 3/18 (17%) in the FTD patients, 18/48 (37%) in the AD patients, and 5/50 (10%) in the control group.

The normalized volumes of the amygdalae were different from control values in both demented groups: FTD vs. controls ($P < 0.005$), AD vs. controls ($P < 0.0005$), but not between the two patient groups ($P > 0.15$) (Table 1). However, there was a trend for increasing atrophy from controls, through FTD, to AD (P for trend <0.00005).

The comparisons of the FTD amygdaloid volumes were also carried out without the subject with FTD associated to motor neuron disease. Normalized volumes of this subject were 0.726 and 0.632 for right and left amygdala, and the results of comparisons among groups did not change.

Although the crude volumes of the frontal lobes were not dissimilar in FTD and AD patients, age-corrected volumes were smaller in FTD (Table 2) as well as the ratio between frontal lobes and amygdaloid volumes ($W = 0.6 \pm 1.4$ vs. 2.1 ± 2.0; $P = 0.04$), the latter value indicating larger frontal relative to amygdaloid volume in AD patients.

Previous studies on amygdaloid volumes did not detect amygdaloid involvement in FTD [10,19]. This finding, that does not seem compatible with the typical FTD symptoms [18], is not confirmed by our work, indicating a tissue loss of about 20% in the amygdalae of the FTD group. Moreover, the amygdaloid atrophy tended to be greater in AD patients, up to 30%.

Table 2
Crude and corrected amygdaloid and frontal volumes[a]

	Amygdalae						Frontal lobes					
	Crude values, cm^3		Normalized values		Loss, %		Crude values, cm^3		Normalized values (W-scores)		Loss, %	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Controls	1.16 (0.18)	1.11 (0.17)	0.91 (0.13)	0.87 (0.11)	0.0	0.0	196 (19)	193 (19)	ref	ref	0.0	0.0
FTD	0.96 (0.26)	0.88 (0.19)	*0.74 (0.21)	*0.69 (0.16)	18.6	21.6	180 (31)	170 (25)	* − 1.7 (2.0)	† − 2.6 (1.9)	12	17
AD	0.77 (0.17)	0.78 (0.20)	*0.64 (0.15)	*0.64 (0.18)	30.2	26.3	172 (23)	170 (21)	* − 0.9 (1.2)	* − 0.8 (1.2)	7	6

[a] * Significant difference from the unmarked group on Mann–Whitney *U*-test and † between groups. Normalized values are volumes corrected for cranial size (amygdalae) or for cranial size and age (frontal lobes). Percent loss is computed with respect to the mean normalized volumes of the control subjects. W-scores are obtained by dividing the difference between the observed volume and the expected volumes for a subject of the same age and cranial size by the standard deviation of residuals in controls. Expected values and residuals are computed in controls with a linear regression analysis where age and cranial size are independent variables. By definition, the W-scores of controls are equal to zero and negative values indicate shrinkage.

After the observations of Klüver and Bucy on monkeys, symptoms like hyperorality, hypersexuality, absence of fear have been related to amygdaloid involvement in man as well [11,14,15]. The fact that amygdaloid atrophy is lesser in FTD than in AD in our study is not consistent with the clinical observation that symptoms considered to be largely due to amygdaloid damage are more frequent in FTD than in AD [7,16,18]. A possible explanation might be that these symptoms are not due to amygdaloid damage per se, but to disruption of a neural system including this structure. This might include the frontal lobes, particularly damaged in FTD [1,9] and in close connection with the amygdalae [21]. This view is supported by the greater frontal/amygdaloid ratio in AD as compared to FTD patients, indicating a disproportionate frontal preservation in AD compared to FTD. Such explanation of Klüver–Bucy-like symptoms is based on results obtained through mathematical modeling of the frontal/amygdaloid ratios in order to account for the effect of younger age in FTD patients, and needs to be replicated in age-matched groups.

However, the hypothesis is consistent with findings of other authors, who, contrary to expectations, found Klüver–Bucy-like symptoms in patients without amygdaloid involvement, and attributed them to disruption of fronto-limbic connections [3,22].

Overall, this hypothesis is still speculative. As we have not systematically recorded behavioral and Klüver–Bucy-like symptoms in our patients, the hypothesis cannot be tested systematically. However, the clinical criteria that we used to isolate patients with FTD are devised in way that they indirectly lend support to this hypothesis. The typical Klüver–Bucy symptoms comprise bulimia, hyperorality, hypersexuality, irresistible impulse to touch objects, and loss of normal fear and anger [13,14]. Most of these are included in clinical criteria for FTD [18], and it is accepted that these patients show these symptoms early [3,18] while in AD patients they take place only later in the disease course [7]. Therefore, it is very likely that our FTD patients had more Klüver–Bucy symptoms than AD, although accurate recording is lacking in our study.

Finally, it should be noted that attributing a particular cluster of symptoms to lesions of a single brain structure implies a localizationist approach that has serious limits in the light of recent findings in neurosciences [2], and involvement of a circuit can better account for such a set of symptoms.

An issue to bear in mind when interpreting these data is that the observed amount of amygdaloid volume loss does not necessarily reflect amygdaloid function. The amygdala may be more dysfunctional in FTD despite lesser volume loss since the amygdala consists of at least 13 subnuclei [5,20], and the two dementias may selectively affect different nuclei, which are not possible to be evaluated separately by using current MR technologies. In a similar manner, this study cannot say whether or not the patterns of atrophy in FTD and AD are regionally different in the functionally heterogeneous frontal lobes. Histopathological studies are needed to shed light on these issues. What can be concluded based on this study, and the previous studies not finding amygdaloid atrophy in FTD [10,19] is that, in terms of volumetric atrophy or lack thereof, the amygdaloid involvement alone cannot explain behavioral symptoms in FTD.

Some caveats of the study must be underlined. First, the small number of subjects, especially in the FTD group, prompts caution in the generalization of the results. Second, lack of pathological confirmation prevents to draw final conclusions about the specificity of our findings. Future research might study the involvement of neural networks and systems rather than single structures in neurodegenerative dementias.

This study was supported by the Research Council for Health of the Academy of Finland.

[1] Boccardi, M., Laakso, M.P., Bresciani, L., Galluzzi, S., Geroldi, C., Beltramello, A., Soininen, H. and Frisoni, G.B., The MRI pattern of frontal and temporal brain atrophy in frontotemporal dementia, Neurobiol. Aging, (2002) in press.
[2] Brett, M., Johnsrude, I.S. and Owen, A.M., The problem of functional localization in the human brain, Nat. Rev. Neurosci., 3 (2002) 243–249.
[3] Carroll, B.T., Goforth, H.W. and Raimonde, L.A., Partial Klüver–Bucy syndrome: two cases, CNS Spectrums, 6 (2001) 329–332.
[4] Chan, D., Fox, N.C., Scahill, R.I., Crum, W.R., Whitwell, J.L., Leschziner, G., Rossor, A.M., Stevens, J.M., Cipolotti, L. and Rossor, M.N., Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease, Ann. Neurol., 49 (2001) 433–442.
[5] Cummings, J.L. and Duchen, L.W., Klüver–Bucy syndrome in Pick's disease: clinical and pathologic correlations, Neurology, 31 (1981) 1415–1422.
[6] DeCarli, C., Maisog, J., Murphy, D.G., Teichberg, D., Rapaport, S.I. and Horwitz, B., Method for quantification of brain, ventricular, and subarachnoid CSF volume from MR images, J. Comput. Assist. Tomogr., 16 (1992) 274–284.
[7] Förstl, H., Burns, A., Levy, R., Cairns, N., Luther, P. and Lantos, P., Neuropathological correlates of behavioural disturbance in confirmed Alzheimer's disease, Br. J. Psychiatry, 163 (1993) 364–368.
[8] Frisoni, G.B., Laakso, M.P., Beltramello, A., Geroldi, C., Bianchetti, A., Soininen, H. and Trabucchi, M., Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease, Neurology, 52 (1999) 91–100.
[9] Fukuy, T. and Kertesz, A., Volumetric study of lobar atrophy in Pick complex and Alzheimer's disease, J. Neurol. Sci., 174 (2000) 111–121.
[10] Garraux, G., Salmon, E., Degueldre, C., Lemaire, C. and Franck, G., Medial temporal lobe metabolic impairment in dementia associated with motor neuron disease, J. Neurol. Sci., 168 (1999) 145–150.
[11] Gerstenbrand, F., Poewe, W., Aichner, F. and Saltuari, L., Kluver–Bucy syndrome in man: experiences with posttraumatic cases, Neurosci. Biobehav. Rev., 7 (1983) 413–417.
[12] Jack Jr, C.R., Petersen, R.C., Xu, Y.C., Waring, S.C., O'Brien, P.C., Tangalos, E.G., Smith, G.E., Ivnik, R.J. and Kokmen, E., Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease, Neurology, 49 (1997) 786–794.

[13] Klüver, H. and Bucy, P.C., Preliminary analysis of functions of the temporal lobes in monkeys, J. Neuropsychiatry Clin. Neurosci., 9 (1997) 606–620.
[14] Lilly, R., Cummings, J.L., Benson, D.F. and Frankel, M., The human Kluver–Bucy syndrome, Neurology, 33 (1983) 1141–1145.
[15] Marlowe, W.B., Mancall, E.L. and Thomas, J.J., Complete Klüver–Bucy syndrome in man, Cortex, 11 (1975) 53–59.
[16] McKhann, G., Drachman, D., Folstein, M.F., Katzman, R., Price, D. and Stadlan, E.M., Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease, Neurology, 34 (1984) 939–944.
[17] McKhann, G.M., Albert, M.S., Grossman, M., Miller, B., Dickson, D. and Trojanowski, J.Q., Clinical and pathological diagnosis of frontotemporal dementia, Arch. Neurol., 58 (2001) 1803–1809.
[18] Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J. and Benson, D.F., Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria, Neurology, 51 (1998) 1546–1554.
[19] Rosen, H.J., Gorno-Tempini, M.L., Goldman, W.P., Perry, R.J., Schuff, N., Weiner, M., Feiwell, R., Kramer, J.H. and Miller, B.L., Patterns of brain atrophy in frontotemporal dementia and semantic dementia, Neurology, 58 (2002) 198–208.
[20] Swanson, L.W. and Petrovich, G.D., What is the amygdala? Trends Neurosci., 21 (1998) 323–331.
[21] Szesko, P.R., Robinson, D., Alvir, J.M.J., Bilder, R.M., Lencz, T., Ashtari, M., Wu, H. and Bogerts, B., Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder, Arch. Gen. Psychiatry, 56 (1999) 913–919.
[22] Takahashi, N. and Kawamura, M., Oral tendency due to frontal lobe lesions, Neurology, 57 (2001) 739–740.