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Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia

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Abstract

In a multicenter study, FDG-PET images in a population of 29 patients with frontotemporal dementia (FTD) were compared to controls with similar age from each center. A conjunction analysis led to identification of the ventromedial frontopolar cortex as the single region affected in each and every FTD patients. This precise regional metabolic impairment should be integrated with recent neuropsychological researches, such as those showing that the ventromedial frontal cortex is critically involved in decision-making processes based on personal experience, feelings of rightness or social knowledge, processes that are characteristically impaired in FTD.

Introduction

Frontotemporal dementia (FTD) is clinically characterized by prominent alteration of personal and social judgment. However, FTD is also a heterogeneous degenerative disease, from both a clinical and a neuropathological viewpoint (Jackson and Lowe, 1996). Different stages have been described in the evolution of the disease and different clinical syndromes have been reported. For example, a distinction has been made between apathetic and disinhibited syndromes, or between frontal and temporal variants of FTD (Constantinidis et al., 1974; Edwards-Lee et al., 1997; Neary et al., 1998; Hodges et al., 1999). The neuropsychological picture is heterogeneous, and patients do not systematically perform poorly on tests which are assumed to depend on frontal functions (i.e., "executive" tests). On neuroimaging, frontal involvement constitutes a characteristic diagnostic criterion for this dementia. A widespread decrease of frontal activity is classically reported when using functional imaging in populations of FTD patients. However, the clinical heterogeneity suggests that frontal metabolic impairment might be variable between patients. We used a conjunction analysis of metabolic brain images from 29 FTD subjects studied in different positron emission tomography (PET) centers in an attempt to define cerebral regions that were consistently involved in all these patients.

Patients and methods

Patients

Patients were selected according to international clinical criteria (Lund and Manchester, 1994); data-from these patients were pooled in a retrospective multicenter European study (Network for Efficiency and Standardisation of Dementia Diagnosis or NEST-DD). Twenty-nine patients with FTD (15 males and 14 females) were studied in three different PET centers (6, 7, and 16 patients, respectively). Mean age was 61.5 ± 9.1 years, mean minimental state exam (MMSE) score was 21.5 ± 4.9, and mean disease duration was 2.7 ± 1.6 years. Table 1 shows that demographic variables were not significantly different between

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Table 1
Demographic variables of FTD patients

Center	Population	Age (year)	MMSE	Duration (year)	M/F	*n*
c1-Cologne	FTD	56.5 (11.8) Range: 44–76	23.6 (3.1) Range: 20–28	1.8 (1.3) Range: 0–3	2/4	6
	CTL	56.9 (9.2)			16/10	26
c2-Milan	FTD	63.4 (8.3) Range: 52–75	21.4 (5.3) Range: 14–27	3.0 (1.8) Range: 1–6	4/3	7
	CTL	63.8 (7.9)			4/3	7
c3-Liege	FTD	62.5 (8.3) Range: 46–74	20.7 (5.2) Range: 9–27	2.8 (1.6) Range: 1–7	9/7	16
	CTL	62.4 (8.8)			19/6	25

Note. Values are expressed as mean and (standard deviation); M = male; F = female; FTD = frontotemporal dementia; CTL = control population; *n* = size.

centers (one-way ANOVA for age, MMSE, and duration, every $P > 0.3$). One patient had a family history of FTD. Three patients had mild associated signs of motor neuron disease. Although more recent diagnostic criteria were not used in this retrospective study, we did not include subjects with primary progressive aphasia nor semantic dementia (Neary et al., 1998). Cerebral glucose uptake was studied with the (^{18}F) fluorodeoxyglucose method (FDG-PET). Neither significant cerebral vascular lesions nor extreme atrophy were reported after visual inspection of anatomical imaging in these early cases. Because of the retrospective nature of this study, digital structural images were not available for voxel-based morphometry. Patients were compared to a population of elderly controls (CTL) with similar age from their own center (Table 1; one-way ANOVA for age in all groups, $P = 0.12$). Controls had no history of neuropsychiatric problems or memory difficulty; diabetes was an exclusion criterion, but pathological conditions such as gastric ulcer, mild hypertension, osteoarthritis, thyroid disease, or angina pectoris were accepted if adequately treated. Informed consent was obtained at each center according to local Ethics Committee requirements.

PET acquisition

We capitalized on a previous report that discussed the methodology for the analysis of PET images gathered from different centers in our NEST-DD project (Herholz et al., 2002). Data were acquired with PET scanners that differed with respect to field of view and spatial resolution (Herholz et al., 2002). Studies were acquired during quiet wakefulness with eyes closed and ears unplugged after intravenous injection of 110 to 370 MBq ^{18}F-2-fluoro-2-deoxy-D-glucose. Images of tracer distribution in the brain were used for analysis; the required minimum scan starting time was 30 min after tracer injection. Scan duration was generally 20 min. Images were reconstructed using filtered backprojection including correction for measured attenuation and scatter using standard software as supplied by the various scanner manufacturers.

Image processing and data analysis

Basic image processing and voxel-based data analyses were performed using SPM99 routines (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA). In the coordinating center (Cologne), all data were checked and spatially normalized by affine 12-parameter transformation using the SPM99 standard brain template. Normalized images were represented on a $79 \times 95 \times 68$ matrix with $2 \times 2 \times 2$ mm voxel size. Images were transferred to the FTD task force center (Liege) and smoothed using a 12-mm FWHM isotropic kernel. Areas of significant metabolic changes between conditions of interest (FTD and controls) were estimated according to the general linear model using linear contrasts; global activity adjustment was performed using proportional scaling. In a pilot analysis, a "paired *t*-test"-like analysis compared patients to an age- and sex-matched control from the same center, using, respectively, 6, 7, and 14 pairs of scans (design: multigroup, conditions, and covariates, pretending each pair of scans was a subject, and treating FTD scan as condition 1 and age-matched CTL scan as condition 2). A comparison between FTD patients and controls was performed for each center with a subtraction analysis. Then a conjunction analysis using data from these three centers was performed with a masking procedure (the contrasts between FTD and CTL in each center were taken as inclusive masks, with an uncorrected mask *P* value < 0.05), in an attempt to reveal a consistent metabolic impairment common to three different FTD populations. We also performed a between-centers interaction analysis, to prove that comparisons between FTD patients and CTL were not significantly different in the three groups. In a second analysis, each patient was compared with the entire control population from his own center (design: single subject, conditions, and covariates, pretending controls constitute a single condition with different scans, and each patient corresponds to one condition with a single scan). A subtraction analysis identified brain regions where glucose metabolism was significantly lower in a patient than in the

Table 2
Hypometabolic areas in three FTD populations

	x	*y*	*z*	*Z*
		Conjunction (c1, c2, c3)		
Medial frontopolar	0	56	0	6.97
Anterior cingulate	−2	36	20	6.04
Subcallosal gyrus	0	18	−16	6.02
Left frontopolar	−14	60	22	5.96
Left middle frontal gyrus	−22	24	46	5.15
Left inferior frontal sulcus	−46	18	30	5.29
Left inferior temporal gyrus	−64	−20	−22	5.59
Left caudate	−10	10	2	5.08
		Interaction (c1 versus c2 and c3)		
Left cingulate gyrus	−6	28	−12	3.85
		Interaction (c2 versus c1 and c3)		
Nihil				
		Interaction (c3 versus c1 and c2)		
Right superior temporal gyrus	58	8	−12	3.73

Note. The analysis in each centre corresponded to a paired *t*-test, where each patient was compared to an age-matched control (see Fig. 1). Coordinates correspond to *x*, *y*, and *z* (in mm) in MNI standard space; c = center; $P < 0.05$ corrected for the conjunction analysis, $P < 0.001$ uncorrected for the interaction analyses.

respective center-defined CTL group. A conjunction analysis was then performed taking each individual comparison ($n = 29$) into account, to emphasize brain regions where activity was impaired in each and every subject (Laureys et al., 1999). The resulting set of voxel values for each analysis constituted a map of the T statistic (SPM[T]), thresholded at $P < 0.05$ corrected for multiple comparisons in conjunction analyses, and $P < 0.001$ uncorrected for multiple comparisons in subtraction and interaction analyses. Brain coordinates for SPM results correspond to the Montreal Neurological Institute (MNI) standard space.

Results

Reliability of the metabolic pattern for FTD between three centers was assessed in the pilot analysis. Only 14 patients could be matched to an elderly volunteer in center 3. Results are illustrated in Fig. 1. Decrease of frontal metabolism was observed in each center (subtraction analysis, $P < 0.001$ uncorrected). Between-center conjunction analysis revealed that hypometabolism predominated in medial frontal regions (Fig. 1 and Table 2). Remember that in this conjunction analysis, a masking procedure (an inclusive mask-taking individual contrasts in all three centers into account) ensured that the pattern was present in each center. An interaction analysis showed that there were only a few differences in metabolic decrease between centers (Table 2).

Between-patient conjunction analysis showed a regional decrease of metabolism common to all 29 subjects in the ventromedial and anterior portion of the frontal lobe (MNI coordinates: 4, 62, −6; $Z = 7.03$). This region was situated above the supraorbital sulcus, in the right frontopolar gyrus (Fig. 2).

Discussion

The principal aim of this study was to use new statistical analyses to precisely characterize frontal metabolic impairment in FTD: there was consistent medial frontal involvement in our FTD populations, with all patients showing a decrease in ventromedial frontopolar activity.

Methodological considerations

Drawbacks of functional imaging analysis have been discussed in most reports on PET in dementia (Garraux et al., 1999; Herholz et al., 2002). Despite using different PET scanners, most of the brain volume was comprised in the field of view, with this clearly being the case for the frontal regions. Patients were in a relatively early stage (mean disease duration 2.7 ± 1.6 years); anatomical imaging did not show extreme atrophy, and frontotemporal metabolism was sufficient to allow satisfactory spatial normalization in a common stereotactical space. All normalizations were performed in a single coordinating center and required careful inspection to avoid distortion. The conjunction analysis

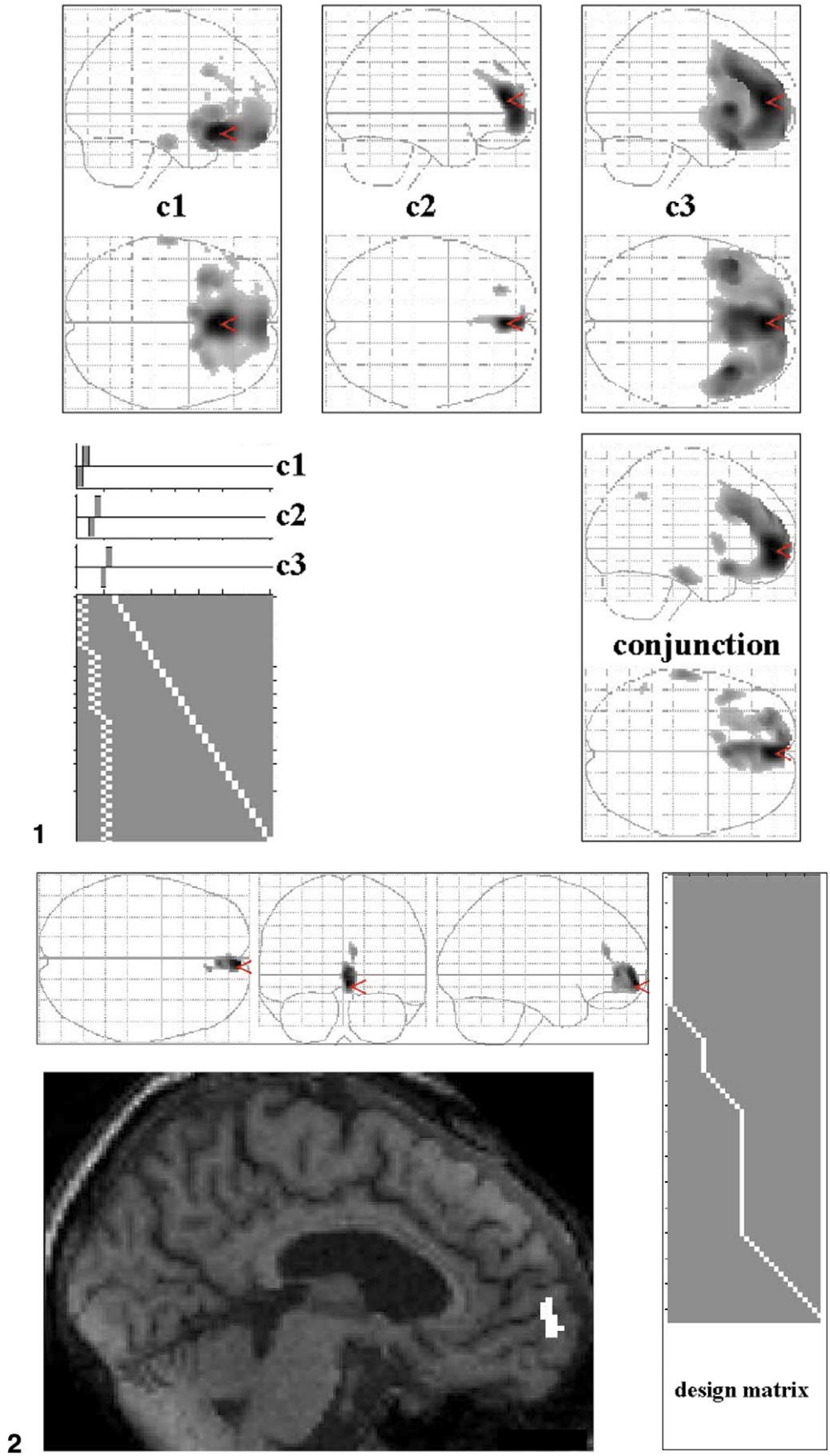

Fig. 1. For three centers, a subtraction analysis was performed comparing brain metabolic images between patients and an age- and sex-matched volunteer from their own center (see the design matrix). The conjunction analysis showed reliable, significant decreases of metabolic activity in medial frontal regions in three FTD populations ($P < 0.05$, corrected for multiple comparisons).

Fig. 2. Sagittal view of ventromedial frontopolar hypometabolism in FTD. Metabolic image from each patient was compared to the control group from his own center. A conjunction analysis demonstrated voxels with significant decreases of metabolism in each and every patient from the entire study population ($P < 0.05$, corrected for multiple comparisons), superimposed on anatomical MRI of one FTD subject.

between three centers confirmed that the use of different PET scanners and our normalization processes gave reliable results across the different FTD populations. The differences in metabolic activity might result from both functional and anatomical changes. A similar analysis of magnetic resonance imaging (MRI) scans was not possible in this retrospective study; preliminary voxel-based morphometric data indicate that atrophy might also occur in the medial frontal cortex of FTD patients (Boccardi et al., 2002); however, significant atrophy has been reported in more posterior ventromedial frontal cortex, in the subcallosal gyrus (Rosen et al., 2002a). Functional and anatomical changes might not be superimposable in FTD.

Clinical considerations

Previous studies using simple comparison of mean values between populations showed a widespread decrease of frontal activity in FTD (see, for example, Garraux et al., 1999). In the present article, voxel-based processing and conjunction analysis allowed us to identify the ventromedial frontopolar cortex as the single area involved in all our FTD patients, irrespective of age, sex, disease duration, family history, or severity of dementia. Our results apply to patients with a clinical phenotype of FTD: we did not have pathological confirmation, but clinical criteria of FTD have a high specificity (Rosen et al., 2002b).

A discussion on the role of this ventromedial frontopolar region and its relationship to FTD symptomatology can only be speculative at the present time, because we can only refer to clinical behavioral diagnostic criteria used to select our populations, and because the literature do not refer to such a precise location as the ventromedial frontopolar area.

Patients with adult-onset brain lesions in the ventromedial frontal region (extending to mesial orbital cortex) have been shown to have specific clinical disturbances including inappropriate affect, impairment in decision making, social inappropriateness, disturbance in goal-directed behavior, and loss of insight (Barrash et al., 2000). Accordingly, our FTD patients were selected following standard clinical diagnostic criteria, which include inappropriate social behavior, loss of insight, and emotional unconcern (Lund and Manchester, 1994). It is of interest that a correlation has already been reported between frontal lobe -related behavioral abnormalities assessed in different pathologies (including FTD) and decreased metabolism in a ventromedial prefrontal region of interest (Sarazin et al., 1998).

Patients with inferior medial frontal lesions frequently understand the requirements of standard neuropsychological tests of frontal lobe function; performance is then only impaired in more complex, unstructured situations. Referring to a theoretical cognitive framework, ventromedial and orbital frontal cortices have been implicated in decision-making processes (the somatic marker hypothesis) (Damasio, 1996). The literature suggests that patients with ventromedial and orbital frontal lesions would fail to integrate somatic markers (emotional values) and personal judgment (based on experience) with an unimpaired cognitive analysis of information to guide self-generated, goal-directed behavior (Damasio, 1996). Interestingly, patients with mild frontal variant of FTD have been reported to show risk-taking behavior in a decision-making paradigm (Rahman et al., 1999). Another concept related to behavioral neurology is the "theory of mind" (ToM). According to this concept, there are different stages of ability to make inference about others' mental states. Patients with lesions to ventromedial and orbital frontal cortex have shown impaired detection of deception and social "faux pas" (Stuss et al., 2001; Stone et al., 1998). FTD patients were reported to be impaired on tests of ToM, but not all patients failed faux pas tests, and a relationship was established between ToM performances and a posterior medial orbitofrontal atrophy (Gregory et al., 2002). The ventromedial frontopolar region was the single brain area where significant metabolic impairment was found in each and every FTD patients from our populations, and related clinical consequences should also be found (at any degree) in each FTD patient. Metabolic impairment in other frontal areas is much more variable, consistent with the heterogeneity of performances in frontal neuropsychological tests and with the diversity of clinical syndromes in FTD.

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