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Decomposition of metabolic brain clusters in the frontal variant of frontotemporal dementia

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Previous studies that measured brain activity in frontotemporal dementia (FTD) used univariate analyses, examining each region of interest separately. We explored in a multicenter European research program the principal brain clusters characterized by a common variability in cerebral metabolism in FTD. Seventy patients with frontal variant (fv) FTD were selected according to international clinical recommendations; principal component analysis (PCA) was performed on FDG-PET metabolic images, looking for covariance clusters in this large population. A first metabolic cluster included most of the lateral and medial prefrontal cortex, bilaterally; PC1 scores correlated with performances on memory and executive neuropsychological tasks. Moreover, FDG-PET images in fv-FTD were further characterized by a metabolic covariance in two clusters comprising the subcallosal medial frontal region, the temporal pole, medial temporal structures and the striatum, separately in the left and in the right hemisphere. The study provides original data-driven arguments for metabolic involvement of separate brain clusters in the rostral limbic system, corresponding to pathological poles differentially affected in each FTD patient.

Introduction

Frontotemporal dementia (FTD) is a heterogeneous disease (Lund and Manchester, 1994; McKhann et al., 2001). From a neuropathological viewpoint, the frontal or temporal distribution of regional cortical atrophy, neuronal loss and gliosis is variable in intensity, sometimes associated with subcortical lesions or with characteristic neuronal inclusions as in Pick's disease (Jackson and Lowe, 1996). From a clinical viewpoint, a classification has been proposed in the literature that distinguishes the frontal variant of FTD (fv-FTD) from primary progressive aphasia and semantic dementia (Neary et al., 1998). Different clinical stages have been described in FTD, various behavioral syndromes exist (for example, predominant apathy or prominent disinhibition) and the neuropsychological performances are quite variable among patients (Constantinidis et al., 1974; Grossman, 2002).

Functional imaging constitutes an independent diagnostic criterion for FTD, showing heterogeneous decrease of activity in association frontal, insular and anterior temporal cortices (Garraux et al., 1999; Mummery et al., 1999; Nestor et al., 2003). Brain atrophy and glucose metabolism or blood flow impairment are more important in orbital and ventromedial frontal regions than in the lateral prefrontal cortices in fv-FTD (Boccardi et al., 2005; Salmon et al., 2003; Starkstein et al., 1994). Moreover, patients with FTD often present with an asymmetric (left/right) frontotemporal impairment that is associated with differential clinical symptoms (Boone et al., 1999; Miller et al., 1993; Mychack et al., 2001; Rankin et al., 2004; Razani et al., 2001). Capitalizing on the literature, one may anticipate a metabolic variability among fv-FTD patients, i.e. a heterogeneous involvement of a dorsolateral prefrontal network and an orbitofrontal one, and of left- and right-sided metabolic networks (Cummings, 1993; Sarazin et al., 1998). Previous reports suggesting the involvement of multiple functional networks in FTD used univariate relationships between activity in separate brain regions and abnormal behavior (Sarazin et al., 2003). However, a univariate analysis assesses each region of interest or image voxel separately,

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which is not suited to document network dysfunction. On the contrary, we used a novel principal component analysis (PCA) for multivariate 3D voxel-based mapping of FDG-PET images (Zuendorf et al., 2003). This method is data-driven (and not hypothesis-driven) and considers all regions in brain images simultaneously. It was applied to identify, among brain voxels, patterns of covariance that would correspond to separate pathological poles in a group of 70 patients with a clinical phenotype of fv-FTD. This large sample was gathered retrospectively and prospectively in a European multicenter study (Network for Efficiency and Standardisation of Dementia Diagnosis or NEST-DD).

Population, materials and methods

Subjects

FTD patients were recruited in five European centers (Cologne, Dresden, Florence, Liege, Milan) according to international clinical criteria. A description of brain metabolism compared to age-matched controls was previously reported in 29 FTD patients selected according to Lund and Manchester criteria (Lund and Manchester, 1994; Salmon et al., 2003). In a prospective study, 41 FTD subjects were further recruited according to more recent diagnostic criteria (Neary et al., 1998). The diagnosis was based on a clinical interview with the patient and a caregiver on neurological and neuropsychological examinations. For exclusion criteria, clinical history, general medical examination and laboratory results were taken into account. Main exclusion criteria were major depression, education lower than 4 years, epilepsy, head trauma with permanent brain lesion and major systemic disease with disturbance of brain function. Only two patients were excluded from the prospective study after a 6-month follow-up: one finally met a diagnosis of psychosis and the other showed symptoms and signs consistent with Lewy body dementia. All patients presented with the frontal variant of FTD; the retrospective and prospective FTD groups showed a characteristic pattern of frontal and temporal decrease of metabolism compared to control populations. Patients with semantic dementia or progressive aphasia were not included in the study. The total population comprised of 70 FTD subjects (35 men and 35 women) whose principal demographic and clinical data are presented in Table 1. Mean age was 63.1 years, but, in four patients, dementia was recognized above 75 years of age. A familial history of dementia was present in 12 patients. Informed consent was obtained in each center according to local Ethics Committee requirements.

Clinical data

A common set of neuropsychological tests could be obtained in the prospective part of the study only (see Table 1 for main selected data in the prospective subset of 41 FTD patients). Moreover, the tests were not specific for FTD; for example, we did not introduce tests of emotion recognition (Rosen et al., 2004) in this multicenter study. All clinical variables were tentatively used for the clinical–metabolic correlations reported in the results section. Global cognition was assessed with mini-mental state examination or MMSE (Folstein et al., 1975), global dementia was evaluated using clinical dementia rating or CDR (Hughes et al., 1982), and instrumental activities of daily living or IADL were rated in percentage of the maximal possible difficulties in activities performed by each patient (Lawton and Brody, 1969). Most patients were in a very mild to moderate stage of dementia; two subjects had severe dementia but could perform the neuropsychological testing. Neuropsychological assessment comprised of the California Verbal Learning Test or CVLT (Delis et al., 1987), Rey's figure copy and delayed recall (Spreen and Strauss, 1998), naming (Huber et al., 1984), semantic and phonemic verbal fluencies (scores were normalized using z score to take age into account), digit span (Wechsler, 1997), mental control (Wechsler, 1997) and Trail Making Test or TMT (Reitan, 1955). Mood and behavior were evaluated by the 21-item Hamilton scale (Hamilton, 1967) and the Neuropsychiatric Inventory (Cummings et al., 1994). The specific clinical symptoms identified as diagnostic criteria (present or absent) for fv-FTD (Neary et al., 1998) were tentatively used for clinico-metabolic correlations, but it was not possible to introduce more recent behavioral evaluations because they were not standardized for a multilingual, multicenter study.

Table 1
Demographic and selected clinical data for FTD patients

Data for all 70 FTD patients		
Age (years)	63.1 (8.7)	Range: 43–80
Sex	35 males and 35 females	
Education (years)	9.4 (3.8)	Range: 5–23
Duration (months)	32.4 (20.5)	Range: 6–96
MMSE	22.5 (4.9)	Range: 3–30
Data for a subset of 41 prospectively studied FTD patients		
CDR	1.2 (0.7)	Range: 0.5–3
CVLT long delay free recall	4.9 (3.5)	Range: 0–12
CVLT long delay cued recall	6.4 (3.4)	Range: 0–13
Semantic fluency (z score)	−1.99 (1.11)	Range: −3.69 to 0.87
Phonological fluency (z score)	−1.36 (1.14)	Range: −2.75 to 2.80
Frontal atrophy	1.47 (0.99)	Range: 0–3
Temporal atrophy	1.29 (1.00)	Range: 0–3

MMSE = mini-mental state examination; CDR = clinical dementia rating; CVLT = California Verbal Learning Test.

Neuroanatomical data

Brain CT or magnetic resonance imaging (MRI) was required prior to inclusion in the protocol, and these data were examined to rule out major vascular lesions. Leucoaraiosis was mild and never sufficient to constitute an exclusion criterion in this study. Global, frontal and temporal atrophy was visually rated (none = 0, mild = 1, moderate = 2 and severe = 3) in each center by an investigator who attended a consensus meeting on rating. For most patients, mild to moderate or rarely severe atrophy was similar in frontal and temporal cortices. Frontal and temporal atrophy were essentially symmetrical. We entered the three atrophy scores obtained with visual rating as variables of interest in our correlations with the principal components of metabolic images in the FTD population.

Positron emission tomography acquisitions

We capitalized on a previous study of Alzheimer's disease to gather PET images from 5 different centers (Herholz et al., 2002). Data were acquired with PET scanners that differed with respect to

their field of view and spatial resolution (Herholz et al., 2002). For example, the field of view in Liege was 10.5 cm, so that the upper part of the brain (mainly the uppermost motor cortex) and the lower part of the cerebellum were not comprised in the metabolic image. Studies were performed during quiet wakefulness with eyes closed and ears unplugged after intravenous injection of 110 to 370 MBq 18F-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 softwares as supplied by the various scanner manufacturers.

Functional images processing and analysis

In the coordinating center (Cologne), all data were checked and spatially normalized to the standard MNI brain template by non-linear and affine 12-parameter transformations using the SPM2 routines (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA). Normalized images were represented on a 79 × 95 × 68 matrix with 2 × 2 × 2 mm voxel size. Images were smoothed using a 12 mm FWHM isotropic kernel. Images were scaled to the same global mean value. To accommodate for differences in field of view between centers, a binary mask was created from an average image of normalized PET acquisitions from Liege using a fixed threshold with additional manual editing to remove the remaining extracerebral voxels. The mask included gray and white matter tissues as well as the ventricles (except some areas in the superior motor cortex and some areas of the cerebellum): the number of voxels retained in the brain of all subjects was 200,668.

PCA described our entire metabolic data set in terms of few cerebral clusters with maximal variance in metabolic activity. Each principal component illustrated a component of image covariance comprising of two poles (called “positive” and “negative” by pure convention). Principles and validation of PCA for PET images were previously described (Zuendorf et al., 2003). In summary, PCA was applied to the entire set of n images (n = 70), each comprising of p voxels (p = 200,668). Images were centered by removing the mean and scaled by square root(n − 1). Thus, the mean removed data set (X) entered the PCA as an (n × p) matrix. The output data of the PCA were:

1. PC: principal components, which were new 3D image data sets, each comprising p voxels. The total number of PCs equals the number of original images (n). Only the first 3 PCs, which explained most of the variance, were retained for the final description (see the Results section). PCs correspond to eigenvectors and can be regarded as the axes of a new orthogonal coordinate system.
2. L: eigenvalues of the (p × p) covariance or correlation matrix of the data matrix X in decreasing order, giving the variance explained by each PC.
3. PC scores: projections of the original images (observations) onto the PCs, being the coordinates of the observations in the new space. Each FTD subject, denoted by index j (j = 1 to n), had one PC score (i, j) for each PC, denoted by index i (i = 1 to n).

One important property of the PCs is the following (Jackson, 1991): for each PC_i, R_i = PC_i * square root(L_i) / S, where S is the standard deviation of the centered matrix X. R_i represents the correlation coefficients between the voxels in the original data set (X) and the corresponding PC scores. This property allowed an absolute representation of the axes (see figures in the Results section), and therefore a corrected threshold ($P < 0.05$) could be set taking into account the multiple comparison problem. The correction used was based on the so-called random field theory method as implemented in SPM. This method takes into account the fact that neighboring voxels are not completely independent observations due to different spatial operations applied prior to the analysis such as spatial smoothing. For comparison, the most severe Bonferroni correction was also applied (which assumes that all voxels are independent observations), but there was no significant difference between the clusters surviving both thresholds for the first three PCs retained.To assess the robustness of the PCA, three measures were carried out:

1. The T^2 Hoteling test looking for outliers;
2. The Q statistic was used to test the residuals after some PCs were retained to test whether the data set was sufficiently explained or not;
3. The individual contribution of an observation to each PC was carried out using the formula: (1 / (n − 1)) * (PC score (i, j))^2 / Li. A big value (>25%), especially for the first PCs, might be an indication that the PCA was not stable, and removing the corresponding observation might change the result (Saporta, 1990).

It is of major importance to emphasize that PCA highlights independent (orthogonal) cerebral clusters with the greatest metabolic variance within the FTD image data set.

Once the few PCs explaining most of the variance in the entire set of metabolic data were identified, we tentatively looked for relationships between these PCs and the clinical data obtained in the 41 prospectively recruited FTD subjects. We also verified that PCs were not confounded by effects of age or scanner resolution (Zuendorf et al., 2003). For those regression analyses, we used a statistical threshold $P < 0.01$ (uncorrected for multiple comparisons) to consider all reasonable clinical interpretations of the independent cerebral clusters observed in PCs.

Results

Ten principal components allowed to explain 76% of the total variance in the metabolic brain distribution of our 70 FTD patients (Fig. 1). Thus, the dimension of our data set was reduced from about 200,000 voxels to 10 PCs, losing only 24% of the information. T^2 test showed that there were only two outliers in our FTD population ($P < 0.01$ threshold). Those two patients did not differ clinically from the entire group. Moreover, PCA was robust since removing those two scans only slightly modified statistical significance for the third principal component. Therefore, the original images represent a homogeneous set, reflecting the quality of the selection process of FTD patients among centers. Residual Q statistic showed low (residual) values for 67 patients when ten PCs were taken into account, reflecting that ten PCs were sufficient to correctly describe the data set. No patient contributed more than 20% to any PC, confirming that the analysis was stable. Each of the seven last PCs accounted for less than 5% of the total variance, and we concentrated our description on the first three PCs, which accounted for 50% of the total variance.

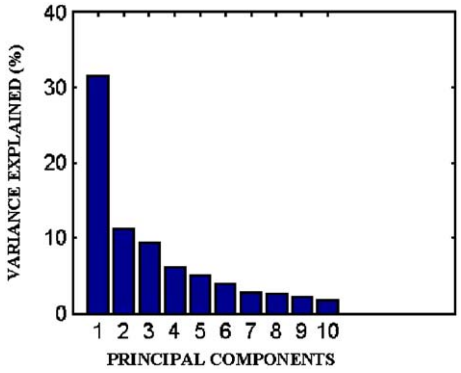

Fig. 1. Percentage of variance in metabolic images expressed by the first 10 principal components of the principal component analysis.

First principal component

The first component (PC1) image was characterized by an extensive bilateral frontal contribution to one pole. Regions with significant weight included superior, middle and inferior frontal gyri, dorsomedial prefrontal cortex (BA 6/8), anterior cingulate (BA 32), frontal poles and anterior ventromedial prefrontal cortex. There was also a limited (i.e. only few voxels) contribution of bilateral insula (Fig. 2 shows 3 planes displaying most of those structures). The opposite pole comprised of cerebellum, occipital lobe, lingual and fusiform gyri, cuneus, precuneus and posterior cingulate and peri-rolandic cortices. Thus, the first image nicely illustrated the two poles of a principal component: the variance of brain metabolic involvement in a large bilateral frontal pathological pole in our FTD population was accompanied by metabolic covariance in an "opposite", relatively preserved, cluster of posterior brain regions.

From a cognitive viewpoint, PC1 scores were positively correlated to several performances at CVLT (mean recall for list A, long delay cued recall, short delay free and cued recall) and to performances in an executive task (phonological fluency). Thus, for all those cognitive tasks, performance was better in patients with higher PC1 scores (corresponding to higher metabolism in the bilateral frontal cluster). PC1 was negatively correlated to visual assessment of atrophy in the frontal lobe, so that frontal atrophy did participate to the important metabolic variability in the frontal cluster. The correlations were relatively weak (with a range of r values from 0.42 to 0.49). They were observed between PC1 scores obtained in 70 patients and the clinical variables obtained in 41 prospectively selected subjects, but we verified that PC1 was similar in the prospective and in the entire (retrospective plus prospective) patient group. Then, we kept data obtained in the whole group because PCA is more robust when more scans are included (Zuendorf, personal communication).

Second principal component

The second component (PC2) image consisted in a positive pole comprising right frontal, parietal and posterior temporal cortices, along with supplementary motor area (SMA) and precuneus. More interestingly, for our purpose, the negative pole comprised of left medial temporal structures (amygdala, hippocampus, parahippocampal gyrus), the left uncus, the left temporal pole and also left posterior orbitofrontal and subcallosal medial prefrontal cortices (Fig. 2). Left ventral striatum, putamen, caudate and left thalamic nuclei were also included in this pathological pole.

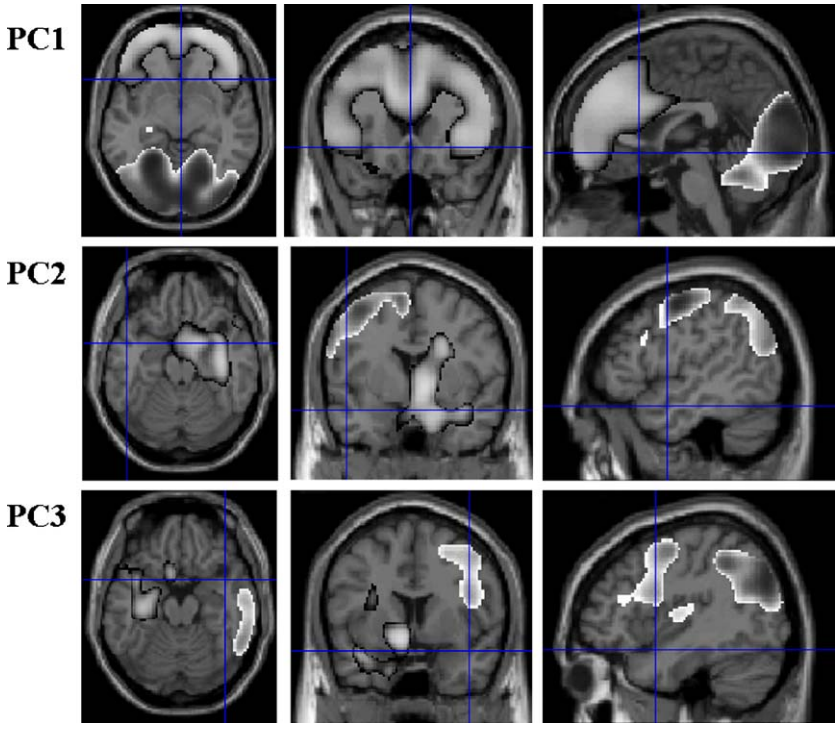

Fig. 2. Tridimensional representation of the first 3 principal components (PC) describing metabolic variance in FDG-PET images of FTD patients. For each component, there are two poles, respectively black- or white-edged, projected on a SPM2 reference MRI image. Only voxels with significant weight in each PC are shown ($P < 0.05$ corrected for multiple comparisons).

None of the neuropsychological, clinical, behavioral and anatomical data collected in our multicenter study was significantly related to the strictly data-driven PC2.

Third principal component

The third PC image showed a positive pole comprising of right medial temporal structures (amygdala, hippocampus, parahippocampal gyrus), the right uncus, the right temporal pole and the right subcallosal medial prefrontal cortex (Fig. 2). The right ventral striatum, putamen, globus pallidus, caudate and pulvinar were also included. There was a limited right insular contribution. The opposite pole included of left-sided precentral, parietal, occipital and temporal cortices.

There was no significant correlation between data-driven PC3, and the limited clinical data collected in our multicenter study.

Note that PC2 and PC3 appeared to represent relatively similar but independent clusters that were organized in a roughly symmetrical fashion.

Variability of metabolic clusters involvement in FTD patients

Fig. 3 illustrates the centered distribution of the PC scores among the FTD patients. There is a large heterogeneity in the involvement of the three different pathological poles in each patient, demonstrating that PCs are separate metabolic clusters differentially damaged in fv-FTD patients. Scores are widely distributed along all PC axes, and the same variability is observed on a graph with PC1 versus PC3 axes (data not shown).

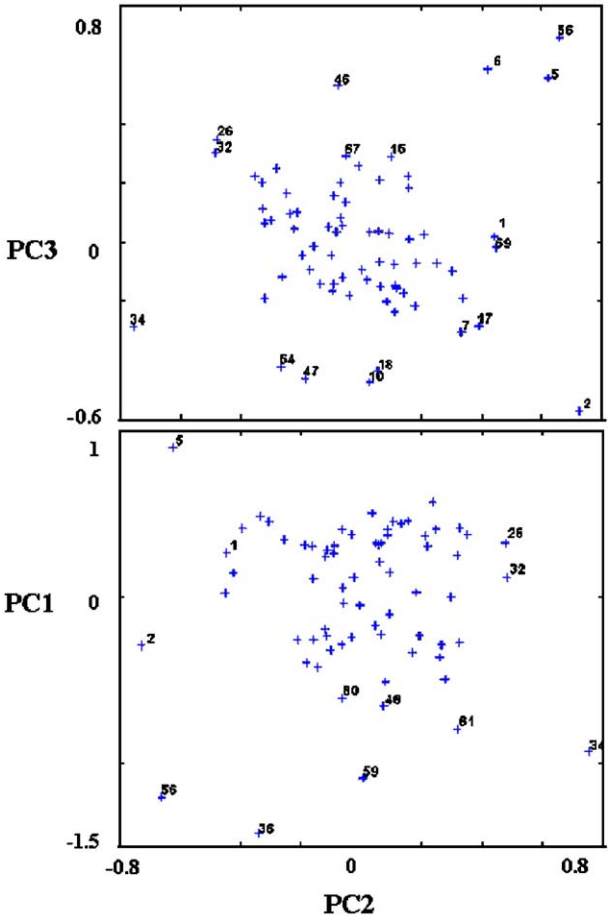

Fig. 3. Centered distribution of PC scores for the three main metabolic clusters (presented two by two). Each cross corresponds to 1 of the 70 FTD patients.

Discussion

In this study, a voxel-based principal component analysis was performed on FDG-PET obtained in a large sample of FTD patients with the frontal variant phenotype. The data-driven method of analysis showed that 50% of the metabolic variance was observed in three separate (orthogonal) clusters of brain regions. This report is the first to directly document the involvement of different ensembles of brain regions in fv-FTD. Previous reports suggested that FTD is a neural system disease (Boccardi et al., 2005), and rostral limbic involvement was demonstrated using conjunction analysis between data from different centers (Salmon et al., 2003); however, those studies were hypothesis-driven, searching for general metabolic differences between fv-FTD and control groups. On the contrary, PCA is a multivariate analysis, considering all regions in brain images simultaneously and searching for covariance in independent (orthogonal) ensembles of voxels. A high covariance of brain metabolism was observed in a first cluster (PC1) comprising of most prefrontal regions bilaterally (i.e. bilateral frontal convexity and anterior ventromedial prefrontal cortex) and in two lateralized clusters comprising of subcallosal medial prefrontal cortex, temporal pole, medial temporal structures and striatum (on the left in PC2 and on the right in PC3). The clusters corresponded to different pathological poles that were variably impaired in each FTD patient.

Methodological issues

A large sample of scans was required to ensure a robust PCA (Zuendorf et al., 2003), and the results were obtained with a high statistical significance. The contribution of individual patients to each PC was well distributed, so that PCs were not weighted by atypical metabolic images. The first three principal components already explained 50% of the variance among thousands of voxels in PET images. The approach provides data that complete previous comparisons of brain metabolic distribution between FTD and control subjects (Garraux et al., 1999; Salmon et al., 2003).

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 analysis, with this clearly being the case for the relevant frontal and temporal regions. To obtain a large enough sample for robust multivariate analysis, we combined FDG-PET images from different centers and from patients with different ages and education levels, with or without familial story of dementia; noteworthy, we checked in a preliminary analysis that none of these technical (i.e. scanner resolution) or demographic variables was correlated with our PC images, so they cannot be considered as confounders. We did not obtained pathological confirmation of the diagnosis in our patients, but strict inclusion criteria were followed that should ensure a good diagnostic accuracy (Rosen et al., 2002b). Moreover, a test for detecting outliers (T^2 test) suggested that inclusion criteria were consistent among the participating centers.

As expected, the distribution of metabolic covariance in FTD was quite different from that previously observed in control subjects (Zuendorf et al., 2003). In a normal population, voxels with a high

weight in PC1 were located in and around the cerebral ventricles, while PC2 had high positive loading in frontal and parietal cortex. Those two first PCs were related to age, but there was no correlation with gender nor with scanner resolution (Zuendorf et al., 2003). In the present study, PCs were not related to age, gender or scanner resolution. The clinical variables were not ideal to explain our PCs, but we used an intuitive approach to get a first result by calculating correlations separately, knowing that most confounding variables were included in the analysis.

Frontal metabolism in FTD

A decrease in frontal activity on functional images (or frontal atrophy on structural neuroimaging) is considered as a supportive diagnostic feature for FTD (Gustafson et al., 1992; Neary et al., 1998). Previous imaging studies essentially emphasized a mean decrease of activity (or volume) in large portions of the frontal lobes in groups of FTD patients compared to reference populations (Boccardi et al., 2003; Garraux et al., 1999; Ishii et al., 1998; McMillan et al., 2004; Rosen et al., 2002a). Although the distribution of brain activity between the positive and the negative pole in PC1 reproduced a pattern of affected frontal and insular regions versus relatively preserved posterior cortices, our results more precisely highlighted a covariance in the involvement of most prefrontal regions in FTD (with the exception of the subcallosal medial prefrontal cortex). Thus, PC1 image corresponded to a very symmetrical large-scale cluster, indicating a close metabolic coupling between both frontal hemispheres, even if FTD patients may frequently present with relatively lateralized decrease of frontal metabolism.

We could not perform PCA on structural imaging, but we observed a correlation between scores at PC1 and a visual assessment of frontal atrophy. This is consistent with a participation of brain atrophy to metabolic impairment in dementia. The objective of this study was to extract ensembles of brain regions commonly involved in FTD, and correction for brain atrophy effects was not implemented in the PCA analysis.

Most patients were in a relatively early stage of the disease, but their neuropsychological performances were quite variable (see Table 1), as already reported in the literature (Hodges et al., 1999). Metabolic variability was previously highlighted in a group of 29 FTD patients included in the present report, studied with a voxel-based comparison analysis using matched control subjects (Salmon et al., 2003). In that sample, the metabolic patterns were relatively heterogeneous between FTD groups studied in different centers, and there was a single ventromedial prefrontal region commonly involved in each and every patient.

In the present study, the clinical–metabolic correlations showed that the metabolic variability in PC1 cluster (expressed by the PC1 scores) was related to the heterogeneity of performances on memory and executive neuropsychological tests in FTD. This is consistent with the literature on the contribution of frontal lobes in retrieval from long-term memory (Fletcher and Henson, 2001; Wheeler et al., 1997). Moreover, it has already been emphasized that long-term memory difficulties in FTD would not be related to retrieval only, but also to failure to implement sophisticated (frontal related) organizational strategies during learning (Glosser et al., 2002; Pasquier et al., 2001). Accordingly, our results demonstrate (1) that providing a category as a cue for word retrieval did not dramatically improve memory performance (see Table 1), (2) that cued recall (and not only free recall) performance in FTD was related to prefrontal activity and (3) that difficulties already appeared at short delay (Swick and Knight, 1996).

Lateralized clusters with metabolic covariance in the frontal variant of FTD

The second and third PCs reflected metabolic covariance in two independent clusters, both comprising of subcallosal medial prefrontal cortex, temporal pole, medial temporal structures and striatum (including the nucleus accumbens).

Thus, PCA demonstrated that the medial (and orbital) prefrontal cortex can be pathologically dissociated into an anterior ventral and a posterior subcallosal component in FTD. We have seen that the anterior part is metabolically linked to the lateral and dorsomedial prefrontal cortex since they metabolically covary in PC1. Atrophy in posteroventral prefrontal cortex was previously reported in FTD using voxel-based morphometry (Rosen et al., 2002a), and lesions in mediotemporal structures (including the amygdala and the hippocampus) have been described in the pathological and neuroimaging literature on FTD (Boccardi et al., 2002; Constantinidis et al., 1974; Dickson, 1998; Kril and Halliday, 2004; Mann and South, 1993). They correspond to paralimbic structures centered on a paleocortical system (Mesulam and Mufson, 1982), and they form a functional complex (Tucker et al., 1995). Those regions have been related to behavioral and emotional symptoms frequently reported in FTD (Franceschi et al., 2005; Rankin et al., 2004; Rosen et al., 2004; Sarazin et al., 2003), but not specifically assessed in our study. It is noteworthy that the anterior and posterior parts of the ventral prefrontal cortex were respectively related, in the literature, to different symptoms characteristic of FTD (Sarazin et al., 2003), to specific processing of emotion (Morris and Dolan, 2004; Schaefer et al., 2003) and to various components of the theory of mind (Gregory et al., 2002; Vogeley et al., 2001). We were more disappointed than surprised by the low number of correlations in our study. The main explanation is that the PCA was data-driven, and not hypothesis-driven as in most previous reports. Although we did not obtain significant correlations between our PCs and behavioral data, the results were consistent with a recent voxel-based univariate analysis of brain metabolism in fv-FTD (Franceschi et al., 2005). The authors contrasted brain glucose metabolism in a priori selected FTD patients with predominant apathy or disinhibition; they reported anterior orbitofrontal and dorsolateral prefrontal hypometabolism in the apathetic subgroup and bilateral involvement of posterior orbitofrontal, medial temporal and inferior temporal cortex and of nucleus accumbens in the disinhibited subgroup. Note that the overlap is not complete between those hypothesis-driven bilateral metabolic networks and our data-driven clusters, confirming that we identified separate pathological poles with another type of metabolic variability that needs to be specified in further studies.

Moreover, our PCA demonstrated that the left- and right-sided clusters could be metabolically dissociated. The clusters must be distinguished from the left and right temporal variants of FTD since only patients with frontal variant FTD were included in our population. For a posteriori correlations with the individual PC scores, our multicenter European study did not allow to record appropriate impairments of emotional or social behaviors in fv-FTD (Gregory et al., 2002; Ikeda et al., 2002; Rosen et al., 2004) due to the lack of adequate validated scales in the different centers. It is also probable that several abnormal behaviors depend on disorganized functional connectivity between different frontal and tempo-

ral regions in FTD, and not on impaired integrity of a single pathological pole (Eslinger, 1998).

Conclusion

Using PCA as an original data-driven method of analysis of FDG-PET, we highlighted separate pathological poles in FTD, as defined by high covariance of metabolism within different clusters of brain areas. The first component comprised of most parts of the prefrontal cortices. Then, two independent, clearly lateralized clusters (PCs) were observed, including the subcallosal medial prefrontal cortex, the temporal pole, medial temporal structures and striatum. Those results complete previous data showing both unity and diversity of brain damage in FTD: a common involvement of the rostral limbic system was reported in the disease (Boccardi et al., 2002; Salmon et al., 2003), while heterogeneity of impairment of this cerebral system was demonstrated by correlations with clinical symptoms in hypothesis-driven studies (Franceschi et al., 2005; Miller et al., 2001; Sarazin et al., 2003). Our data-driven results confirm and specify our working hypotheses, showing a metabolic independence of the anterior and posterior part of the ventromedial prefrontal cortex, and of the left and right subcallosal frontal regions. Those constitute pathological poles in the rostral limbic system that are variably involved in different FTD patients.

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