Although chronic fatigue syndrome (CFS) is not recognised as an independent syndrome by most neurologists and psychiatrists, this symptom complex is of enormous relevance for health economy. Estimations by the Centers of Disease Control (CDC) suggest that about 200 persons per 100 000 are affected. This would mean that in the USA alone nearly 500 000 people suffer from symptoms that fulfil the criteria for CFS.

According to the diagnostic criteria established by the CDC, CFS is characterised by a sudden onset of debilitating, persistent fatigue and loss of energy which lasts for more than six months and cannot be attributed to other medical or psychiatric conditions. Particular subjective complaints of patients are headache, sore throat, tender and painful lymph nodes, muscle and joint pain, and substantial impairment of short term memory and concentration. Depression and related symptoms are common comorbidities in CFS, and there are studies indicating that major depressive disorder is more prevalent in CFS than in other chronic medical illnesses. The aetiology of CFS remains unclear, although abnormalities in serological, immunological, and central nervous system function have been reported.

Up to now there have been no specific biomedical markers for the diagnosis of this disease. The diagnosis is exclusively based on patients' complaints and the fulfilment of a clinical case definition. Objective findings are lacking.

Functional neuroimaging, especially single photon emission computed tomography (SPECT) of regional cerebral blood flow, has been used to assess specific patterns of blood flow alteration in patients with CFS, but conflicting results have been obtained. Although most studies describe lowered regional cerebral blood flow in a variety of brain regions (mainly frontal and temporal), no consistency of findings can be observed across studies.

A positron emission tomography (PET) study by Tirelli et al examined cerebral glucose metabolism using $^18$F-fluorodeoxyglucose (FDG) and a region of interest based approach for data analysis. These investigators found significant hypometabolism compared with normal controls in the right mediofrontal cortex and the brain stem. They also compared CFS with depression and found hypometabolism bilaterally in the upper frontal regions in the latter.

So far there have been no PET studies using observer independent analytical approaches to determine regional changes in cerebral metabolism induced by CFS on a pixelwise basis. Furthermore, no attempts have been made to use PET or SPECT to correlate the neuropsychological alterations observed in CFS with regional impairments of glucose utilisation or regional cerebral blood flow.

Our aim in the present study was therefore to identify in an observer independent way individual alterations of glucose metabolism in a carefully selected population of CFS patients, in order to assess how often significant abnormalities occur among such patients and whether the abnormalities follow a specific pattern. In addition, we undertook a group analysis to correlate regional functional impairment with different neuropsychological alterations occurring in CFS patients.

**Abbreviations:** CDC, Centers for Disease Control; CFS, chronic fatigue syndrome; FDG-PET, $^{18}$F-fluorodeoxyglucose positron emission tomography; FWHM, full width half maximum; HADS, hospital anxiety and depression scale; HRQOL, health related quality of life; PET, positron emission tomography; SF-36, short form 36 item questionnaire; SCID, structured clinical interview for DSM-IV; SPECT, single photon emission computed tomography.
METHODS

Patients

A sample of 26 adults (mean (SD) age, 43 (9.3) years, range 26 to 61; 13 male; 13 female) was drawn from 74 consecutive referrals for the evaluation of CFS seen at the University Hospital Mainz. The 1992 CDC working case definition, together with the CDC exclusionary conditions and criteria for sub-grouping variables, was used by a neurologist (WAN) to diagnose CFS. All patients with presumptive CFS were admitted to hospital for one week, during which they underwent an extensive physical, electrophysiological, and psychological examination (including all standard blood tests, microbiology, a variety of neurological examinations, and various psychometric tests such as the “symptom checklist 90 revised” and other measures of somatic and psychological complaints). The fatigue scale, the hospital anxiety and depression scale (HADS), and the short form 36 item questionnaire (SF-36) were chosen for the analyses because they assess distinct aspects of neuropsychological function with minimal overlap. Patients who were found to have an organic disease (two with diabetes, one with gluten induced enteropathy, and one with multiple sclerosis) or a psychotic disorder (two cases) that explained the fatigue were excluded. Major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria was also a reason for exclusion. Recent morphological imaging (computed tomography (CT)/magnetic resonance imaging (MRI) (done within six months of the study) did not reveal substantial deficits or relevant atrophy in this sample.

Eagerness to participate in the PET study among the patients initially selected was low because they were worried about radioactivity, so in the end it was only possible to study 26 individuals. All these patients gave written informed consent after the PET study protocol was explained to them. For controls we referred to a normal database consisting of 18 volunteers (mean (SD) age, 38 (11.5) years, range 21 to 55; 12 male, six female). Neurological or psychiatric diseases were excluded in the normal controls by physical examination and extensive neuropsychological testing (SCID). Although the mean age of the control population was slightly lower, this difference was not significant (p > 0.05). The same was true for the balance between male and female subjects.

Psychometric tests

Before the PET scan was done, the patients completed a series of psychometric tests. The testing procedure took about 10 to 15 minutes. It contained, among others, a fatigue impairment scale, anxiety and depression scales, and a generic health related quality of life questionnaire. The fatigue scale used is the German version of a disability index originally developed by Buchwald and coworkers, comprising 16 visual analogue scales that refer to impairment in different domains of daily life (for example, household, job, leisure, partner) as a result of CFS. The construction of the scales is oriented towards the pain disability index, 11 widely used and validated measure. A single dimension was extracted through factor analysis (principal components analysis), which yielded a Cronbach’s α of 0.94 in the present sample. High values represent severe impairment.

Anxiety and depression were assessed using the hospital anxiety and depression scale (HADS-D). 12-14 The HADS is a widely used questionnaire containing seven items for each dimension and having good reliability (Cronbach’s α = 0.81 and 0.80, respectively). This questionnaire was chosen because its items were designed particularly to avoid any questions relating to somatic complaints, which may be difficult to assess in the context of CFS. High values represent high levels of anxiety or depression.

The SF-36 (short form) is a self rating questionnaire designed to assess generic health related quality of life (HRQOL). 15-16 It was derived from a much longer functional status measure used in the medical outcomes study to facilitate the assessment of health related quality of life in clinical and research settings. The SF-36 consists of eight sub-scales: physical functioning, role limitations caused by physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations caused by emotional problems, and emotional wellbeing. Raw values of the SF-36 were transformed into z scores based on population means and standard deviations, adjusted for age and sex, as described in the SF-36 manual (for details, see Hardt et al. 17). The eight domains were combined into two dimensions of health related quality of life—mental and physical—using a method described by Hays et al. 18 High values represent good health related quality of life.

PET scanning

All PET scans were done at the department of nuclear medicine of the University Hospital Mainz on a Siemens ECAT EXACT PET scanner (Siemens Co, Erlangen, Germany). Psychotropic drug treatment, which was taken only by a minority of the patients, was discontinued before the PET for a period determined by the plasma half life of the drug. All studies were done under identical standardised testing conditions with closed eyes and in dim ambient light.

The patients were placed on the PET scanner bed with the head parallel to the canto-meatal line, using a laser device. After a 10 minute transmission scan with a “Ga/Ge ring source to allow for proper attenuation correction, 330 to 410 MBq of 18fluoro-2-deoxy-D-glucose (FDG) were injected into an antecubital vein. Thirty minutes later, a 30 minute emission scan in cross sectional mode consisting of three frames of 10 minutes duration was acquired. Postprocessing included adding the three frames to a single frame. The data on the control population were acquired in an identical fashion. The PET camera has a field of view of 16 cm and a resolution of 6 mm full width half maximum (FWHM). Correction for dead time, scatter, and random coincidence was applied, and the images were reconstructed using filtered back projection with a 4 mm Hamming filter, resulting in images consisting of 47 slices with a slice thickness of 3.4 mm and a pixel size of 2 mm in a 128 × 128 matrix.

Image analysis

Image analysis was done two parts: the identification of patterns of abnormal glucose metabolism in individual patients, and group analysis to correlate regional impairment of glucose metabolism with various psychometric indices.

Patterns of abnormal glucose metabolism in individual patients

Individual comparisons with the normal controls were undertaken with an automated program (3D-SSP, Neurostat, University of Michigan, USA). This software package was chosen because it is dedicated to single subject analysis and has been extensively evaluated in various disorders, including dementia and epilepsy. 20-24

The analysis started with stereotactic normalisation to the standard brain atlas of Talairach and Tournoux, which was done on a SUN workstaton (SUN Microsystems Inc, Santa Clara, California, USA). In a second step, standardised individual three dimensional surface projections were generated and related to the thalamus as the reference region. That region was chosen because even at very low significance thresholds we did not detect any differences between the groups in thalamic activity (p < 0.05 not corrected for multiple comparison). We therefore felt justified in using the thalamus as the most robust reference region in our patient sample. The reliability of this reference region has been demonstrated in previous evaluations. 20-24 The surface projections were compared statistically on a pixelwise basis with the normal controls, resulting in parametric z score images reflecting the standard deviation of the individual index brain compared with the normal controls.
A relevant decrease in glucose metabolism was assumed if more than 50 adjacent pixels showed a value of > 2 in the resulting z score image. As this analysis requires no user interaction or a priori hypothesis, it can be regarded as observer independent.

An additional analysis based on proportional normalisation to the global mean was also undertaken. This analysis yielded similar results. Because some patients showed extensive cortical abnormalities, we felt that normalisation based on cortical activity was not adequate. Therefore these results are not reported here in detail.

Correlation of glucose metabolism with psychometric indices

In a second analytical step we aimed to identify in a group analysis areas where regional impairment of glucose metabolism was correlated with various psychometric indices. This was done using the SPM 99 software package (Wellcome Department of Cognitive Neurology, London, UK). Following stereotactic normalisation, this analysis started with a categorical group comparison between the patients in the CFS group (n = 26) and the normal controls (n = 18). This was done in order to identify the areas where glucose metabolism was most consistently impaired. Based on the entire CFS study population, we carried out correlation analyses (Spearman correlation, Fischer transformation) of regional glucose metabolism with the individual psychometric test scores measuring depression and anxiety (HADS), fatigue, and HRQOL. These analyses were restricted to voxels where the categorical comparison revealed differences (p < 0.05, uncorrected).

As it was the aim of this study to identify impairments that are specific for CFS in a sensitive manner, a generous significance threshold was applied (p < 0.001; uncorrected) for all correlation analyses.

RESULTS

Psychometric tests

The mean impairment resulting from CFS on the visual analogue scales was about 62. This corresponds to more than the 50% impairment required for the definition of CFS. Reported anxiety (HADS) was in the normal range, but values for depression were increased. There were negative z scores for HRQOL, implying a major decrease in the quality of life compared with the general population—that is, 2.45 SD below normal in the physical and 1.77 SD below normal in the mental components. As all psychometric tests showed a meaningful range in the present sample, their use in a correlational analysis was reasonable. A summary is given in table 1.

PET data

Individual comparisons with the normal database

Twelve of the 26 CFS patients (46%) showed no significant abnormalities in comparison with the healthy control group. In 12 of the 14 remaining patients we identified areas with decreased glucose metabolism in the cingulate gyrus and adjacent mesial cortical areas (Brodmann areas 32, 24, 31, and 23). Five of these 12 patients showed additional decreases in the orbitofrontal/frontobasal cortex (Brodmann area 11). Figure 1 presents the patient (No 22 in table 1) with the most pronounced abnormalities. This 41 year old man was one of the most severely affected. During the course of the disease he developed severe anxiety and an obsessive-compulsive disorder. The remaining two patients (mother and son) showed a different pattern of decreased glucose metabolism centred in

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Table 1 Summary of demographic data, positron emission tomography findings, and psychometric findings in 26 patients with chronic fatigue syndrome in individual comparisons with normal controls

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Mean 43 7.6 8.2 -2.5 -1.8 61.8
SD 9.3 4.2 3.8 0.9 1.0 19.4

*Missing data.
F, female; HRQOL, health related quality of life (short form 36); M, male; n, no; PET, positron emission tomography; y, yes.
the cuneus/precuneus region. Remarkably, these two patients had no abnormalities in the cingulate and orbitofrontal regions (fig 2).

Table 1 summarises the findings of the individual comparison of all 26 patients including demographic data.

**Group comparison**

The categorical comparison between the patient group and the 18 healthy controls showed areas of significantly decreased glucose metabolism only in the orbitofrontal cortex (15% decrease in the maximum pixel of this cluster) \( p < 0.001 \). When a more generous threshold was applied \( p < 0.05 \) the cingulate gyrus and the adjacent mesial cortical areas showed a decrease in glucose metabolism as well (8% in the maximum pixel of this cluster). These findings are in good agreement with the individual analyses.

**Correlation analyses**

The pixelwise correlation analyses between the decrease in glucose metabolism and the psychometric testing scales
showed the following results in the CFS patient group as a whole (n = 26).

**HADS depression scale**
We found correlations between the severity of depression and changes in the mesial orbitofrontal cortex on the right, the right temporal superior and medial gyrus, and the anterior cingulate gyrus, at z score levels of > 3.10 (p < 0.001) (fig 3, table2).

**HADS anxiety scale**
Anxiety was exclusively correlated with a bilateral decrease in glucose metabolism at the border between the mesial temporal cortex and the cerebellum. As the maximum significant pixel on both sides was located in the parahippocampal gyrus it seems reasonable to attribute the correlations to this structure (fig 3, table2).

**Fatigue scale**
Remarkably no correlation between regional decreases in glucose metabolism and the severity of perceived fatigue was observed.

**Health related quality of life**
Impairment in the mental component of HRQOL was very closely correlated with decreased glucose metabolism in the orbitofrontal region, mainly on the left side (z = 4.3; p < 0.0001). In addition, other areas with a less tight correlation were located in the mesial and dorsolateral prefrontal regions and in the mesial and superior temporal cortex. In contrast to this, no correlation between the physical component of HRQOL and regional impairment of glucose metabolism was found.

Table 2 gives an overview of the significant correlations between the psychometric test results and the regional decreases in glucose metabolism that were found.
DISCUSSION

The main finding of the individual comparisons in our study is that, in the patients fulfilling the diagnostic criteria for CFS, only about half the cases showed abnormalities of glucose metabolism detectable using an observer independent approach. In most of the abnormal cases the abnormalities were focused on the anterior cingulate gyrus/mesial frontal cortex and the orbitofrontal cortex. Two patients (relatives) showed a very distinct pattern, with decreased glucose metabolism centered on the cuneus/precuneus region.

As no consistent pattern of metabolic abnormality was detectable in this patient sample, this individual observer independent analysis does not support the assumption that CFS is a homogeneous disease entity.

The most homogeneous pattern detectable in our sample is in line with the results of the SPECT study on CFS by Schwartz et al. The observed results are also comparable with the findings of various other SPECT studies where significantly lowered regional cerebral blood flow was found in a several brain regions—mainly in the lateral frontal, lateral temporal, and medial temporal lobes—in CFS patients compared with normal controls (for a review, see Mayberg).

Additional abnormalities in the brain stem described by Costa et al. in a pilot study using region of interest analysis were not detectable in our patient sample. Even an exploratory analysis in our group comparison at a very low significance threshold (p < 0.05, not corrected) did not reveal significant changes. Owing to the stereotactic normalisation approach necessary for the pixelwise analyses in our study, subtle changes in small structures like the brain stem might not be detectable with the same sensitivity. On the other hand region of interest based analyses in this area are very sensitive to small changes in region size and location. Thalamic hyperperfusion in CFS, as described by MacHale et al., was also not apparent in our group analysis, even at a very low significance threshold (p < 0.05 not corrected for multiple comparisons). This might reflect differences in the methodology used (FDG-PET v regional cerebral blood flow SPECT) and patient selection (depressed patients were excluded by MacHale et al.).

Correlation analyses revealed region specific impairment of glucose metabolism for depression, anxiety, and the mental component of HRQOL, but not for the psychophysical abnormalities, reflecting the CDC diagnostic criteria for CFS (fatigue and impairment in the physical component of health related quality of life).

The loci of the area of decreased metabolism correlating with depression in our CFS patients has striking similarities to the region (the most anterior parts of the cingulate gyrus) described by Drevets as showing decreased blood flow and metabolism in patients with unipolar and bipolar depression. In line with these observations is the fact that the patterns detected in the majority of abnormal patients in our sample by individual comparison share similarities with results of PET and SPECT imaging in major depression. Resting state studies on patients with unipolar depression consistently describe hypofrontality, mainly in the dorsolateral prefrontal cortex and the anterior cingulate. This suggests that depression is one of the key factors inducing abnormalities of neuronal function in some CFS patients, detectable with functional imaging. The relation of the impairments in our CFS group to depression is also supported by findings of Tashiro et al., who described reductions in cerebral metabolism in cancer patients in similar areas (especially the anterior cingulate and dorsolateral prefrontal cortex) and related these to the degree of depression in these patients. Comparable changes in the frontal lobe have also been reported in patients with rheumatoid arthritis. However, attributing hypometabolism in anterior cingulate and frontal cortex in CFS patients to depression does not help to determine whether depression is a triggering factor for CFS or the result of chronic suffering from fatigue.

Additional dimensions of neuropsychological impairment in CFS patients were correlated with decreased cerebral glucose metabolism in other locations. Thus the severity of anxiety was mainly correlated with changes in glucose metabolism in the mesial temporal structures including the amygdalo-hippocampal complex. This area appears to be a key structure in a circuit that governs negative affect. The amygdala has been shown in animal experiments to be necessary for the development of conditioned fear and is said to be important in the expression of anxiety disorders in humans. Anxiety as a subcomponent of the CFS syndrome complex may make a major contribution to mesiotemporal changes observable with neurofunctional imaging.

A third area correlated mainly with subjective impairment in the quality of life was the orbitofrontal cortex. This area, as an element of the paralimbic belt, has also been found to be involved in various psychiatric disorders including anxiety, obsessive-compulsive disorder, addiction, and physiological states such as aversion. As perception of quality of life is clearly dependent on whether emotions experienced are rated as mainly positive or mainly negative, a correlation between subjective quality of life and the orbitofrontal cortex seems appropriate. It has been shown in an international comparison that were impairment of quality of life is a common finding in CFS patients. This is important, as our findings with respect to this impairment can be generalised and do not seem to be restricted to the specific patients or location under study. Dysfunction of the orbitofrontal cortex can also result from chronic stress experiences during childhood or later in life. This correlation was confirmed in an animal study, as well as in PET studies in patients with torture related post-traumatic stress disorder and in previously institutionalised Romanian orphans.

In contrast to these clear correlations, it is remarkable that objective impairment of quality of life and the severity of fatigue—both of which are CDC diagnostic criteria and were therefore present in all our CFS patients—did not have a metabolic correlate. Abnormalities of glucose metabolism in CFS thus do not seem to be specific for the syndrome but rather are correlated with different neuropsychological symptoms shown during the course of the disease. They can be observed in other clearly defined disorders with similar symptoms, so they may be an expression of the same mediating neuroanatomy underlying these symptoms rather than the reaction of neuronal lesions caused by CFS. Differences in the level of symptom expression could be responsible for the inconsistency of the results of previous PET/SPECT studies on CFS patients. However, it seems that disease severity is determined not by the level of symptom expression but rather by the symptom mix and by the number of individual symptoms. Our data therefore support the hypothesis that the CFS case definition does not define a single disease entity but rather recruits patients with different health problems but similar subjective complaints.

Conclusions

Although abnormalities in FDG-PET were only detectable in approximately half the CFS patients examined and no pattern specific for CFS could be determined, PET may provide valuable information in helping to separate patients with this condition into subpopulations with and without apparent alterations of the central nervous system.

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Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome

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