ORIGINAL ARTICLE

"Functional" or "psychosomatic" symptoms, e.g. a flu-like malaise, aches and pain and fatigue, are major features of major and in particular of melancholic depression

Michael Maes
Maes Clinics, Antwerp, Belgium.

Correspondence to: Prof. Dr. Michael Maes, MD., PhD.
Director of the Maes Clinics
Groenenborgerlaan 206, 2610 Wilrijk, Antwerp, Belgium.
tel: 32-3-4809282; fax: 32-3-2889185; e-mail: crc.mh@telenet.be

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Abstract

BACKGROUND: Major depression is characterized by multifarious symptoms and symptoms clusters, such as the melancholic and anxiety symptom clusters. There is a strong comorbidity and a biological similarity between major depression and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).
OBJECTIVE: The aim of the present study was to examine "psychosomatic" symptoms reminiscent of ME/CFS in major depression.
METHODS: Toward this end, we examined the 12-item Fibromyalgia and Chronic Fatigue Syndrome Rating (FF) Scale and the Hamilton Depression Rating Scale (HDRS) in 103 major depressed patients by means of multivariate pattern recognition methods.
RESULTS: Our findings support the existence of two factors, i.e. a fatigue and somatic (F&S) factor, i.e aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, irritable bowel, headache, and a subjective experience of infection; and a depression factor, i.e. sadness, irritability, sleep disorders, autonomic symptoms, and a subjective experience of infection. Cluster analysis performed on the 12 FF items found two different clusters, which were separated by highly significant differences in the F&S items, the most significant being a subjective experience of infection, aches and pain, muscular tension, fatigue, concentration difficulties and failing memory. Multivariate analyses showed that the differences between both clusters were quantitatively, and not qualitatively, and reflected the severity of the F&S dimension. There was a strong association between the F&S symptoms and melancholia and chronic depression. Treatment resistant depression was characterized by higher scores on the depression factor score. There was a strong correlation between the HDRS score and the FF items, fatigue, a subjective experience of infection, and sadness. Our findings show that F&S symptoms are a major feature of depression and largely predict severity of illness, and chronic and melancholic depression.
CONCLUSIONS: It is concluded that the diagnostic criteria of depression and melancholia and rating scales to measure severity of illness should be modified to include the F&S symptom profile.

INTRODUCTION

The APA has provided operational criteria for the classification of depressed patients in categories, e.g. major depression with and without melancholia and or psychotic features (American Psychiatric Association, 2000). Cluster analytical studies performed on depressive symptoms have provided strong evidence for the descriptive utility of the melancholia category, which is characterized by a distinct quality of depressed mood, non-reactivity, early morning awakening, anorexia-weight loss, and cognitive and psychomotor disturbances (Maes *et al.* 1990a; 1990b; 1992). It was also shown that major depression patients may be divided according to another dimension into two qualitatively distinct groups, i.e. depression with severe versus minimal anxiety (Maes *et al.* 1994). Multivariate analyses showed that six "anxiety" symptoms significantly discriminated these depression subgroups, i.e. tension, behavior at interview (general or physiological), and respiratory, genito-urinary and autonomic symptoms. The DSM-IVR, however, does not include anxiety as a major feature of depression and does not adequately indicate that both anxiety and depression may merge with one another (Maes *et al.* 1994; Mountjoy and Roth, 1982a; 1982b; Fawcett and Kravitz, 1983).

In addition to the abovementioned symptoms, major depressed subjects often experience fatigue, muscular symptoms, somatic complaints, and aches and pain. Most psychiatrists consider this type of symptoms as "psychosomatic" or "functional", that is as a "somatic expression of their psychic problems" (Linde, 2007). This is exemplified by the status of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Maes and Twisk, 2009; Twisk and Maes, 2009). Most psychiatrists consider this biological disorder to be a "functional condition" – not even an illness – characterized by "somatoform" symptoms. Likewise, most psychiatrists and even governmental organizations adopt to a "psychosocial" model of ME/CFS, which is based on the premises that personality traits, "causal attributions", inactivity, kinesiophobia and somatizing are the etiological and maintaining factors for ME/CFS (Twisk and Maes, 2009). Nevertheless, ME/CFS is a World Health Association (WHO) established illness, characterized by chronic fatigue lasting for at least 6 months; substantial impairment in short – term memory or concentration; sore throat; tender cervical and axillary lymph nodes; muscle pain; multi – joint pain without selling or redness; headache of new type; unrefreshing sleep; and post exertion malaise lasting more than 24 hours (Fukuda *et al.* 1994).

There is a strong degree of "comorbidity" between depression and ME/CFS. At the symptomatic level there is a significant overlap between both disorders. While fatigue is one of the key symptoms of major depression, depression frequently occurs during ME/CFS (Maes *et al.* 1990a; Skapinakis *et al.* 2003; 2004). Because up to three-quarters of patients with fatigue syndromes have comorbid mood or anxiety disorders, it is even suggested that chronic fatigue is a "form fruste" of depression (Roy-Byrne *et al.* 2002). There are, however, symptomatic differences and other differentiating variables between ME/CFS and depression, showing that depression and ME/CFS are different, albeit overlapping, disorders (Griffith and Zarrouf, 2008; Hawk *et al.* 2006). The abovementioned comorbidity and similarities between both disorders may be explained by similarities in the pathophysiological pathways underpinning these disorders. Indeed, both depression and ME/CFS are characterized by an induction of inflammatory and oxidative and nitrosative stress (IO&NS) pathways, such as increased levels of pro-inflammatory cytokines; a lowered antioxidant status; and increased oxidative stress (Maes, 2009; Maes *et al.* 2009d; 2007a; 2007b; 2007c; 2007d; 2008a; 2008b; 2009a; 2009b). There is also evidence that the "psychosomatic" symptoms described by psychiatrists as "functional" are in fact the expression – not of "intrapsychic conflicts" – but of intracellular inflammatory processes. Thus, systemic inflammation causes a central neuroinflammation with increased levels of pro-inflammatory cytokines, which may remain elevated for several months and which induce specific "psychosomatic" symptoms, such as anorexia, soporific effects, disturbances of locomotor activity and exploration, and anhedonia (Goshen *et al.* 2008; Qin *et al.* 2007). There is a strong symptomatic similarity between those "psychosomatic" or "vegetative" symptoms of depression and inflammation-induced depressive behaviour (Maes *et al.* 1993). Cytokine-based immunotherapy in humans induces two overlapping syndromes, i.e. fatigue and somatic symptoms, including pain, appearing early after starting treatment; and depressive symptoms, occurring some weeks later (Martin *et al.* 2007; Wichers *et al.* 2005). The degree of fatigue one week after starting cytokine treatment predicts the severity of depression some weeks later (Wichers *et al.* 2005). In ME/CFS, there is evidence that "functional" symptoms, such as aches and pain, muscular tension and fatigue and malaise are the clinical expression of upregulated IO&NS pathways, e.g. increased intracellular inflammation and damage by O&NS (Maes, 2009). Also, decreased plasma levels of specific antioxidants, such as coenzyme Q10 (CoQ10) may explain fatigue and other "psychosomatic symptoms" in ME/CFS and depression as well (Maes *et al.* 2006; 2009a; 2009b; 2009c).

The present study was conducted to examine whether there is an association between major depression with and without melancholia and the abovementioned "psychosomatic" or "functional" symptoms; and whether major depression may be divided into meaningful subclasses according to these symptoms.

PATIENTS AND METHODS

Patients

One hundred and three patients participated in this study; all were depressed outpatients admitted to the Maes Clinic, Antwerp, Belgium. The diagnosis of major depression was made using the DSM-IV-R criteria (American Psychiatric Association, 2000), by means of a semistructured interview. Severity of depression was measured by means of the Hamilton Depression Rating Scale (HDRS) score (Hamilton, 1960). The primary outcome measure in this study was the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF scale) (Zachrisson *et al.* 2002). This scale measures 12 symptoms reminiscent of ME/CFS, i.e. pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances, irritable bowel, headache, and subjective experience of infection. The total sum on the FF scale is computed.

Classification of patients as suffering from TRD was based on criteria by Thase and Rush (1995). Patients were classified to suffer from TRD when they fulfilled the following criteria: a) nonresponse to two adequate trials with antidepressant agents from different classes, e.g. tricyclics (TCSs) or selective serotonin reuptake inhibitors (SSRIs); b) the previous stage (stage a) plus a failure to respond to one augmentation therapy; c) the previous stage plus failure to respond to two augmentation strategies; and d) the previous stage plus a nonresponse to electroconvulsive treatment. When the actual depressive episode lasted longer than 2 years, patients were classified as suffering from chronic major depression. The number of depressive episodes was registered. The presence of ME/CFS was assessed by means of the Center for Disease Control and Prevention (CDC) criteria (Fukuda *et al.* 1994). Although the CDC criteria rule out the possibility of the diagnosis "ME/CFS" when melancholia is present, we employed the CDC criteria to delineate the presence of the ME/CFS symptom complex. The criteria are as follows: a) the patient has to suffer from severe chronic fatigue for at least six months; and b) at least four of the following symptoms should be present: substantial impairment in short – term memory or concentration; sore throat; muscle pain; multi – joint pain without selling or redness; headache of new type; unrefreshing sleep; and post exertion malaise lasting more than 24 hours.

We excluded the following patients: a) those with life-time diagnoses of psychiatric DSM IV-R disorders, e.g. psychotic, substance use and organic mental disorders; b) those with abnormal blood tests, such as alanine aminotransferase (ALT), alkaline phosphatase (ALP), thyroid stimulating hormone (TSH) and total protein; c) those with medical illnesses, e.g. inflammatory bowel disorders, diabetes type 1 or type 2, hypertension, and arteriosclerosis; c) those with infections the two last months prior to the study; d) those subjects who had been treated with anti-psychotic drugs, anticonvulsants or mood stabilizers. Patients and controls gave written informed consent; the study has been approved by the local ethical committee.

Statistics

Differences among treatment means were analyzed by means of analysis of variance (ANOVA). Stepwise linear discriminant analysis (LDA) with an F-to-enter of p=0.05 was used in order to assess the symptom profiles of different groups. Correlations between variables were measured by means of Pearson's product-moment correlation coefficients, simple regression analyses, complete or stepwise automatic multiple regression analyses (with an p–to-enter of p=0.05), and canonical correlation analyses. The independence of classification systems was checked by means of analysis of contingence Tables (χ^2-test) or Fisher's exact probability test. The diagnostic performance was checked by means of ROC (receiver operating characteristics) analysis with computation of the area under the ROC curve, sensitivity, specificity and predictive value of a positive test result (PV+) and with κ statistics (Zweig and Campbell, 1993). The significance was set at α=0.05 (two tailed).

Factor analysis followed by orthogonal (quartimax, varimax) and non-orthogonal (oblimin) rotations were employed as an aid in the interpretation of the data structure in the 12 FF items. Loadings ≥ 0.300 were used for interpretation of the factors. We used Kaiser's criterion, retaining components with eigenvalues greater than 1, to delineate the number of factors. The scores on the first two factors subtracted from the data set were employed in a two-dimensional display method to map the patients on a two-dimensional plane. This method allows to observe the similarities among the patients, as defined by the factor scores.

Cluster analysis was used on the FF data set as a tool to classify the patients in useful clusters (Maes *et al.* 1990a; 1990b, 1992). This method is used to delineate the properties of a group of patients – characterized by their qualitative or quantitative characteristics – via measurements taken of the patients and without making a priori assumptions about the data (Sharaf *et al.* 1986; Derde and Massart, 1982). This technique will partition a set of patients into two or more clusters, such that the patients in the same cluster are similar to each other and dissimilar from those in another cluster. In the present study, we have assessed our data set by different clustering techniques, including hierarchical and non-hierarchical methods. Here we report on the results of Forgy's centroid method, which is a non-hierarchical, iterative, partioning clustering technique (Maes *et al.* 1990b; 1992; Massart and Kaufman, 1983). Forgy's method entails the selection of an a priori number of clusters (we used 2-3-4- a priori clusters); computation of the cluster centroids and the distances of each subject to these centroids; assignments of each patient into the cluster with the nearest centroid, calcu-

lation of new cluster centroids; and restarting the procedure from the beginning until convergence occurs, that is until the same clustering occurs in two successive assignment steps. We have assessed the underlying clustering structure by means of ANOVAs performed on the mean item-profiles of the derived clusters; the predictive value for a positive (PV+) test result; and complete and stepwise automatic LDA, with an p-to-enter of $p<0.05$. The classification ability of the solutions generated by means of LDA was checked by means of the Jackknife method.

Cluster analysis methods will divide any data set into clusters that have little overlap along the variables being used to create the clusters. Therefore, it is necessary to test the generalizability of the cluster solution against external criteria (Aldenderfer and Blashfield, 1986). In this study we have externally validated our cluster solution by using variables which were not used to generate the clusters, e.g. the HDRS score, the melancholia diagnosis, chronicity of depression and TRD. In order to check whether a substantial clustering structure may be found in the 12 FF data an external validating technique was employed, i.e. statistical isolinear multiple component analysis or soft independent modelling of class analogy (SIMCA). SIMCA is a pattern recognition method that is based on modelling each group, i.e. in this study the clusters generated by cluster analysis, by a separate model. In the present study, we have used SIMCA in order to examine the differences between the cluster-analytically formed classes. Toward this end, a Principal Component Analysis (PCA) model is fitted to each group separately and confidence envelopes are constructed around the model to contain all data points. As the first few PCs explain the greatest part of the variance within a group, the similarities between the subjects of each class can be estimated in a reduced hyperspace. Thus, SIMCA is a class-modelling technique that describes the similarities between the patients in the same group. Once these groups are modelled, the distances between these models can be computed and expressed in SDs. Values higher than 2 SDs indicate real, qualitative differences between the groups, which have been delineated by the similarities of the patients. A distance close to 0 S.D. indicates that there are no significant (qualitative) differences between the groups (Maes *et al.* 1990b; 1992; Derde and Massart, 1982; Massart and Kaufman, 1983).

RESULTS

The mean (±SD) age of the patients was 43.6 (11.7) years and the male/female ratio was: 47/56. There were 45 patients with TRD, 27 patients with a chronic depression (duration of the actual episode longer than 2 years) and 21 with melancholic depression. Fifty patients fulfilled the criteria for ME/CFS.

Results of factor analysis

Table 1 shows the first two varimax-rotated factors obtained by exploratory factor analysis performed on the 12 FF symptoms. The first two factors explained 71.4% of the total variance in the data set. The first varimax-rotated factor loaded highly on: pain, muscular tension, fatigue, concentration difficulties, failing memory, irritable bowel, headache, and a subjective experience of infection. Because of the presence of typi-

Tab. 1. Results of factor (FA) and cluster analysis (CA) performed on the 12 items of the FibroFatigue scale in 103 depressed patients.

FF items		Results of FA		Results of CA		Results of ANOVAs	
		Factor 1*	Factor 2*	Cluster 1**(n=62)	Cluster 2**(n=41)	F values***	*p*-values
1.	Aches and pain	**0.784**	-0.052	3.48 (1.14)	1.37 (1.04)	90.9	$<10^{-5}$
2.	Muscular tension	**0.767**	-0.03	3.64 (1.07)	1.95 (1.16)	57.6	$<10^{-5}$
3.	Fatigue	**0.557**	0.216	4.77 (0.88)	3.56 (1.21)	35	$<10^{-5}$
4.	Concentration difficulties	**0.609**	**0.374**	3.72 (0.98)	2.51 (1.00)	37.2	$<10^{-5}$
5.	Failing memory	**0.673**	**0.308**	2.93 (1.02)	1.71 (0.98)	36.8	$<10^{-5}$
6.	Irritability	0.178	**0.404**	4.02 (1.00)	3.56 (1.16)	4.5	0.03
7.	Sadness	-0.033	**0.538**	5.05 (1.03)	4.88 (0.84)	0.8	0.6
8.	Sleep disturbances	0.074	**0.55**	4.06 (1.24)	3.56 (0.98)	4.8	0.03
9.	Autonomic disturbances	0.238	**0.446**	3.76 (1.05)	3.19 (1.23)	6.2	0.01
10.	Irritable bowel	**0.303**	0.213	2.95 (1.57)	1.90 (1.43)	11.8	0.001
11.	Headache	**0.356**	0.066	2.50 (1.38)	1.54 (1.29)	12.7	0.0009
12.	Subjective experience of infection	**0.65**	**0.311**	4.43 (0.86)	1.98 (1.19)	147.5	$<10^{-5}$

*Factor loadings on the first two varimax-rotated factors obtained by FA. The significant loadings (> 0.300) are shown in bold.**Shown are the mean (±SD) values of the FF items in the two cluster-analytically derived clusters.***Results of analyses of variance (ANOVAs) performed on the 12 FF items with the two cluster-analytically derived clusters as treatments (all tested at df=1/101).

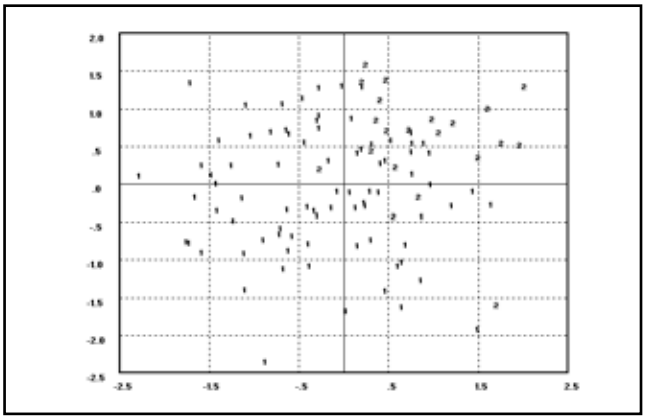

Fig. 1. The factor score plot showing the first two factors subtracted by means of factor analysis. This two-dimensional graph of the multidimensional data set indicates patients with (2) and without (1) melancholic depression.

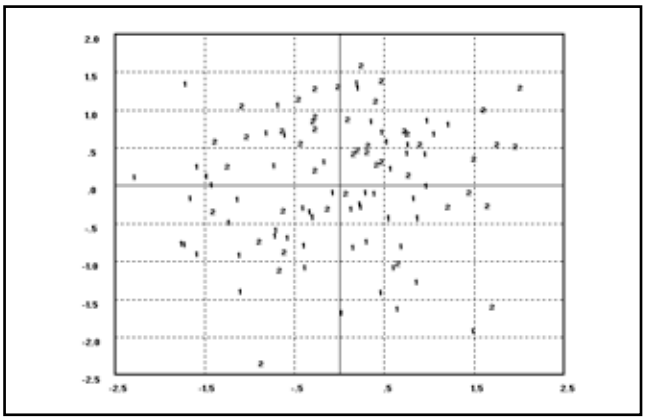

Fig. 2. This factor score plot shows the first two factors subtracted by means of factor analysis and the patients with (2) and without (1) treatment resistant depression.

cal fatigue and somatic symptoms reminiscent for ME/CFS we described this factor as the fatigue-somatic (F&S) factor. The second factor loaded highly on concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances and a subjective experience of infection. Because the first six symptoms are, reportedly, prevalent in depression, we labeled this second factor as the "depression" factor.

Consequently, we computed the factor scores and used these in other statistical analyses. The HDRS score was significantly correlated to the F&S (r=0.42, p=0.00003) and depression (r=0.45, p=0.0003) factor scores. Regression analysis showed that both the F&S (F=21.9, p=0.00006) and depression (F=26.2, df=0.00002) factor scores were significantly (F=26.6, df=2/100, $p<10^{-5}$) related to the HDRS score. Likewise, there was a strong correlation between the HDRS score and the total FF score (R^2=41.7%, F=17.5, df=4/98, $p<10^{-5}$) and significant correlations between the HDRS score and almost all FF items, in order of importance: fatigue (r=0.49, p=00001); a subjective experience of infection (r=0.45, p=0.00003); sadness (r=0.41, p=0.00009); memory disturbances (r=0.39, p=0.0002); concentration disorders (r=0.36, p=0.0005); muscle tension (r=0.33, p=0.0009); autonomic symptoms (r=0.30, p=0.002); aches and pain (r=0.28, p=0.005); irritability (r=0.28, p=0.005); sleep disorders (r=0.22, p=0.03); and gastro-intestinal symptoms (r=0.20, p=0.04). No significant correlation was found between the HDRS score and headache (r=0.12, p=0.2). There was no significant correlation between the number of depressive episodes and either the F&S (r=0.14, NS) or the depression (r=0.15, NS) factor score. Because – by definition – the factor scores derived from factor analysis are orthogonal, we have calculated the correlations between the first PC subtracted from the actual FF symptoms belonging to the F&S and depression factor. There was a significant and positive correlation between the first PCs subtracted from the F&S and depression factors (r=0.58, $p<10^{-5}$).

The factor score plot

Figure 1 shows the factor score plot, i.e. the first two factors subtracted by means of factor analysis. This two-dimensional graph of the multidimensional data set indicates that no outliers are observed in this data set; and that all patients group together with no boundaries between them. In this plot, we have displayed the patients with melancholic depression. It can be seen that the latter assemble in the upper-right quarter of the graph, indicating that the melancholia diagnosis is determined by higher scores on both the F&S and depression factor scores. LDA showed that the F&S (F=29.9, df=1/101, p=0.00001) and the depression factor score (F=13.5, df=1/101, p=0.0007) significantly discriminated (Wilks λ=0.64, F=23.3, df=2/100, p=0.000002) patients with melancholia from those without melancholia. ANOVAs showed significant differences in the items between patients with melancholia and those without; in order of significance: memory disturbances (F=35.5, p=0.00005); a subjective experience of infection (F=21.9, p=0.00006); concentration disorders (F=19.0, p=0.0001); muscle tension (F=16.4, p=0.0002); fatigue (F=13.9, p=0.0005); aches and pain (F=13.6, p=0.0006); sleep disorders (F=9.2, p=0.003); sadness (F=7.5, p=0.007) and headache (F=4.9, p=0.03).

In Figure 2 we show the same factor plot and the patients divided according to TRD. TRD patients assemble in the upper-half of the plot although there is considerable overlap between both groups. These results show that the diagnosis TRD is principally determined by the depression score. LDA showed that the depression (F=9.6, df=1/101, p=0.003), but not the F&S (F=3.5, df=1/101, p=0.06), factor score significantly discriminated (Wilks λ=0.89, F=6.2, df=2/100, p=0.003) patients with TRD from those without TRD. ANOVAs showed significant differences in FF items between patients with TRD and those without, in order of significance: memory disturbances (F=8.8, p=0.004); concentration disorders (F=5.3, p=0.02); sleep disorders (F=5.2, p=0.02); and autonomic symptoms (F=4.4, p=0.04).

In Figure 3 we show the classification of the patients into those who suffer from chronic depression and those who do not. Patients with chronic depression assemble in the upper-right quarter of the factor plot, which indicates that chronicity of depression is principally determined by the severity of the F&S and depression dimensions. LDA showed that the F&S (F=8.4, df=1/101, F p=0.005) and the depression (F=18.8, df=1/101, p=0.0001) factor score significantly discriminated (Wilks λ=0.78, F=12.8, df=2/100, p=0.00004) patients with chronic depression from those without chronic depression. ANOVAs showed significant differences in FF items between patients with chronic depression and those without, in order of significance: memory disturbances (F=11.6, p=0.001); a subjective feeling of infection (F=11.5, p=0.001); sleep disorders (F=11.3, p=0.001); sadness (F=10.9, p=0.002); concentration disorders (F=8.5, p=0.005); fatigue (F=7.7, p=0.006); and gastro-intestinal symptoms (F=5.7, p=0.02).

In Figure 4 we show the classification of the patients into those with and without ME/CFS. Patients with ME/CFS assemble at the right side of the factor plot, which indicates that ME/CFS in depression is determined by the severity of the F&S dimension only. LDA showed that the F&S (F=73.6, df=1/101, $p<10^{-5}$), but not the depression (F=2.2, df=1/101, p=0.1), factor score significantly discriminated (Wilks λ=0.57, F=37.5, df=2/100, $p<10^{-5}$) patients with ME/CFS from those without ME/CFS. ANOVAs showed significant differences in FF items between patients with ME/CFS and those without, in order of significance: aches and pain (F=51.6, $p<10^{-5}$); fatigue (F=44.9, $p<10^{-5}$); a subjective experience of infection (F=31.4, p=0.00001); concentration disorders (F=29.1, p=0.00001); memory disturbances (F=27.4, p=0.00002); muscle tension (F=24.8, p=0.00003); and gastro-intestinal symptoms (F=7.4, p=0.008).

Results of cluster analysis

We have employed cluster analysis in order to reorganize our data set – the 12 FF items – into relatively homogeneous groups. Toward this end, we have examined different cluster solutions, i.e. 2, 3 and 4 clusters, formed by Forgy's method. These analyses showed that the 2 cluster solution yielded the most meaningful results. The first cluster comprised 62 subjects and the second cluster 41 subjects; no outliers were detected. There were no significant differences in age between both clusters (F=3.5, df=1/101, p=0.06), although patients allocated to cluster 1 (mean=45.4±11.4 years) tended to be older than those allocated to cluster 2 (mean=41.0±11.9 years). There were no significant differences in the male/female ratio (χ^2=0.2, df=1, p=0.06) between cluster 1 (30/32) and cluster 2 (17/24).

Figure 5 shows the results of the cluster analysis, i.e. the memberships to cluster 1 and 2 are shown in the factor plot. This figure shows that those patients allocated by cluster analysis to the first cluster assemble at the right site of the graph, whereas the patients allocated to cluster 2 assemble at the left site of the graph. It can be seen that there are no clear boundaries between those two clusters. This means that Forgy's cluster analysis has delineated two groups that form a continuum along the severity of the F&S dimension.

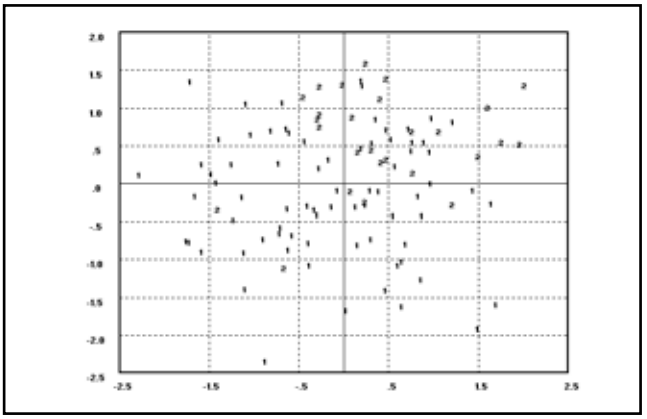

Fig. 3. This factor score plot shows the first two factors subtracted by means of factor analysis and the patients with (2) and without (1) chronic depression.

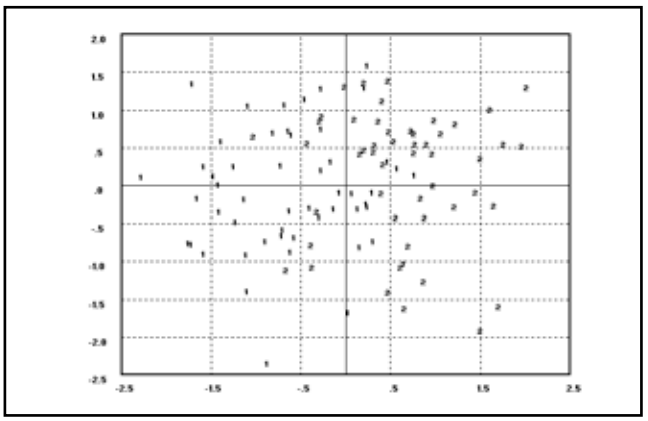

Fig. 4. This factor score plot shows the first two factors subtracted by means of factor analysis and the patients with (2) and without (1) ME/CFS.

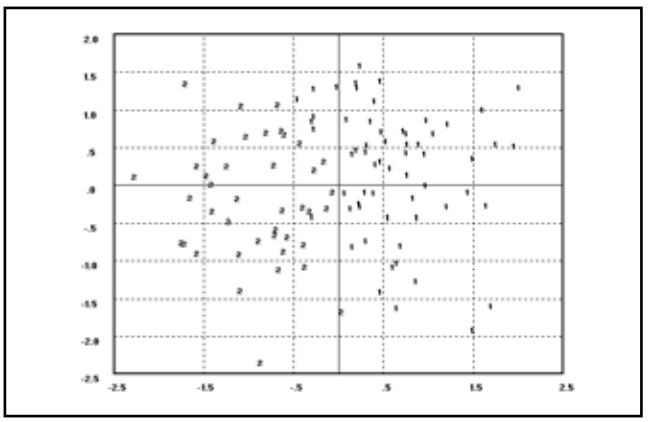

Fig. 5. Results of the cluster analysis which shows memberships to cluster 1 and cluster 2 (the F&S cluster) in the factor plot.

In order to detect the characteristics of the cluster-analytically derived groups we have performed ANOVAS on the HDRS, the total FF score, and the 12 FF items; and LDA on the 12 FF items with the clusters as treatments. ANOVA showed a significantly higher (F=15.2, df=1/101, p=0.0003) HDRS score in cluster 1 (mean=23.1±2.40) as compared to cluster 2 (mean=21.3±1.97). The total FF score was significantly higher (F=152.5, df=1/101, $p<10^{-5}$) in cluster 1 (mean=45.3±5.4) than in cluster 2 (mean=31.7±5.6). Table 1 shows that most FF items were significantly higher in cluster 1 than in cluster 2, except sadness. Irritability, and sleep and autonomic disturbances yielded only a very weak significance in contrasting both clusters. Thus, the symptoms belonging to the depression factor were not very significant in separating both clusters, whereas all symptoms belonging to the F&S factor were highly significantly different between both clusters. By means of LDA performed on the 12 FF items, a significant discrimination between both clusters was obtained (Wilks λ=0.26, F=69.9, df=4/98, $p<10^{-5}$); the distance between the centroids of both clusters was 3.41 SDs. Four FF items had a significant discriminatory power, i.e. the subjective experience of infection (loading on the LDA score=0.89), aches and pain (loading=0.80), muscle tension (loading=0.70) and concentration disorders (loading=0.60). Jackknife cross-validation showed a hit rate of 96.1% (mean of 7 different cross-validations). The LDA score performed well in separating both clusters: the area under the ROC curve was 96.1%. At the optimal cut-off value, the diagnostic performance was: sensitivity 97.6%, specificity 95.2% and PV+ 93.0% (κ=0.92, t=20.31, $p<10^{-5}$). By means of LDA with the F&S and depression scores as discriminatory variables, a significant separation of both clusters was obtained (F=201.9, df=1/101, $p<10^{-5}$); we found that the F&S factor was a highly significantly discriminatory variable (loading=0.98), whereas the depression score had only a very weak discriminatory power (loading=0.30). The distance between the centroids of both groups was 2.86 SDs. Jackknife cross-validation showed a hit rate of 95.1% (mean of 7 different cross-validations). The LDA score performed well in separating both clusters: the area under the ROC curve was 97.7%. At the optimal cut-off value, the diagnostic performance was: sensitivity 95.1%, specificity 96.8% and PV+ 95.1% (κ=0.92, t=23.13, $p<10^{-5}$).

SIMCA, using all FF items as modelling variables, showed that the distance between the class envelopes (constructed by means of PCA) of the two cluster-analytically generated classes was only 1.17 standard deviations. Only some FF items has a significant discriminatory power, i.e. a subjective experience of infection (0.562), aches and pain (0.357), gastro-intestinal symptoms (0.356), autonomic symptoms (0.345) and memory disturbances (0.331). Altogether, these results show that both the F&S and depression scores can be used as measures of severity of illness along two different dimensions and that the clusters are quantitatively different groups shaped by differences in the severity of the F&S factor. As cluster 1 was characterized by F&S symptoms we label this cluster the F&S cluster.

Significantly (χ^2=14.2, df=1, p=0.0002) more patients with chronic depression than those without were allocated to the F&S cluster 1, i.e. 25/37 versus 2/39. Significantly (χ^2=29.1, df=1, $p<10^{-5}$) more patients with than without ME/CFS were allocated to the F&S cluster, i.e. 44/18 versus 6/35 patients. There were no significant differences (χ^2=1.9, df=1, p=0.2) in the ratio between patients with and without TRD between patients allocated to the F&S cluster (31/31) versus those allocated to cluster 2 (14/27). Significantly (χ^2=11.7, df=1, p=0.0006) more patients with melancholia than without melancholia were allocated to the F&S cluster, i.e. 20/42 versus 1/40 patients.

Since our results might be biased by the fact that many of the patients who visit the Maes outpatient polyclinic suffer from ME/CFS and since the most severe melancholic and psychotic depression do no visit our clinic, we have rerun the cluster analysis on major depressed patients without ME/CFS symptoms (n=53). This cluster analysis solution allocated 27 patients to a first cluster and 26 to a second. ANOVAs performed on the 12 FF items in these 53 patients showed that patients allocated to cluster 1 scored significantly higher on all 12 FF items than those allocated to cluster 2. There was a very strong association between these two clusters generated in those 53 patients and the cluster solution generated in the 103 subjects ($p<10^{-7}$ by Fisher's exact probability test). Moreover, in the total study group (n=103) we have run another cluster analysis on the 12 FF items and 4 other variables as well, i.e. chronicity of depression, TRD, melancholia and ME/CFS. We found that this analysis generated exactly the same clusters as the analysis performed on the 12 items alone. The first cluster was characterized by higher scores on all FF items and higher frequencies of patients with melancholia, chronic depression and ME/CFS, but not TRD (see figures above).

Table 2 shows the results of a canonical correlation analysis with both the F&S and depression factors as the first set of variables, and TRD, chronic depression, melancholia, ME/CFS and cluster membership as the second set of variables. We found two significant canonical eigenvectors (χ^2=146.6, df=10, p=0.00001; and χ^2=16.0, df=4, p=0.003). The first showed a significant correlation between the F&S score, on the one hand, and cluster membership, ME/CFS; melancholia and chronicity, on the other. The second canonical eigenvector showed a significant correlation between the depression factor score, on the one hand, and chronicity; TRD; and melancholia on the other.

DISCUSSION

The major findings of this study are that two different dimensions may be retrieved in the data set and that the depressed patients may be divided into two quantitatively distinct groups which respect to the severity of "psychosomatic" symptoms.

The first factor had high loadings on specific "functional" symptoms such as pain, muscular tension, fatigue, concentration difficulties, failing memory, irritable bowel, headache, and a subjective experience of infection and, therefore, we called this factor the fatigue & somatic (F&S) dimension. The second factor loaded highly on concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances and a subjective experience of infection. This factor was labeled the depression factor. The strong correlation between the HDRS score, on the one hand, and the F&S dimension, and FF symptoms, such as fatigue and a subjective experience of infection, shows that F&S symptoms are important determinants of the overall severity of illness. This shows that the severity of depression is in fact determined by the combined effects not only of melancholic (non-reactivity, anhedonia, diurnal variation, etc) and anxiety features (psychic anxiety, agitation, tension, etc), but also by the severity of F&S symptoms.

Symptomatic dimensions consisting of "psychosomatic" symptoms have previously been found in depression. For example, one psychic anxiety and two somatic "anxiety" factors have been found in depressed patients (Hamilton, 1959; Beneke, 1987). In other studies, three relevant varimax-rotated factors were detected with amongst others a somatic factor (Mountjoy and Roth, 1982a; 1982b). Other authors even describe a "somatiform" depressive disorder, a type of depression with somatoform depressive symptoms, such as pain, paraesthesiae, anergy, chronic fatigue, irritable bowel, sexual inhibition, and vertigo (Alonso Fernandez, 2001). "Somatic depression" is associated with high rates of pain, and increased rates of anxiety and chronic dysphoria (Silverstein, 2002). Rating scales constructed to measure the severity of illness, e.g. the HDRS and the Beck Depression Inventory (BDI) (Beck *et al.* 1961), contain some F&S items. Thus, the HDRS considers two somatic items, i.e. somatic symptoms general, that is muscle aches, fatigue and loss of energy, etc; and hypochondriasis, that is bodily self-absorption. Another HDRS item is somatic anxiety, that is sweating, autonomic symptoms, headache, etc. However, the HDRS does not considers that symptoms such as "autonomic symptoms" and "sweating", for example, may be the consequence of other underlying pathophysiological mechanisms that have nothing to do with anxiety. In addition, the HDRS includes the psychodynamically-derived item "hypochondriasis" in stead of a description of the actual somatic complaints, which have a biological basis (see further). Another commonly used rating scale for depression, i.e. the BDI contains only two F&S items, i.e. fatigue and loss of energy. The Montgomery-Asberg Rating Scale (MADRS) (Montgomery and Asberg, 1979) does not rate any of the F&S symptoms. Thus, it is clear that most commonly used rating scales for depression do not adequately incorporate the F&S symptoms. One can wonder about the validity of rating scales for depression that do not give sufficient loading to the F&S symptoms, which reflect an important part of depression severity.

Tab. 2. Results of canonical correlation analysis performed on both the fatigue & somatic (F&S) and depression factor scores, as the first set of variables, and treatment resistant depression (TRD), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), chronicity of depression, melancholia and cluster membership (all entered as dummy variables), as a second set of variables.

variables	first canonical eigenvector	second canonical eigenvector
F&S factor	**0.964**	0.266
depression factor	0.359	**0.933**
TRD	0.284	**0.566**
ME/CFS symptoms in depression	**0.736**	–0.239
chronicity of depression	**0.415**	**0.731**
melancholic depression	**0.614**	**0.411**
cluster membership	**0.925**	–0.123
canonical correlation coefficient	r=0.88	r=0.38

The significant loadings (>0.400) are shown in bold.

A second major finding of this study is that "depression" may be divided into two clusters: one cluster with severe F&S symptoms, the F&S cluster, and another cluster with minimal F&S symptoms. The most significant items separating those two clusters are a subjective experience of infection, aches and pain, muscle tension, fatigue, and concentration and memory disorders. Importantly, membership to the F&S cluster significantly predicted overall severity of depression, chronicity of depression and melancholic depression. Treatment resistant depression, on the other hand, was characterized by higher scores on the depression, but not the F&S, factor. The strong association between melancholia and F&S symptomatology shows that F&S symptoms are not only important determinants of illness severity but are also major features of melancholic depression.

However, by means of SIMCA analysis it was shown that the F&S cluster and the non-F&S cluster do not differ qualitatively and, thus, that there are only quantitative differences between these groups. These quantitative differences are shaped along two dimensions of illness severity, i.e. most of all by the F&S symptoms. In any case, there is no indication that the F&S items should be employed in a diagnostic algorithm to describe a new diagnostic class. This contrasts with

our previous findings that symptomatic clusters made up by melancholic or anxiety features are qualitatively different and should, therefore, be regarded as separate diagnostic classes (Maes *et al.* 1990b; 1992; 1994). Nevertheless, we think that the number of DSM-IV criteria for a major depressive episode should contain not only fatigue but also other F&S symptoms, such as the subjective experience of infection, aches and pain, etc., in order to optimize the classification rule for major and melancholic depression. This will allow pharmacological research to analyse the effects of new antidepressant drugs on the different depressive dimensions, including the F&S dimension.

It is interesting to note that some FF symptoms loaded highly on both the F&S and the depression factor, one of these being a subjective experience of infection. The finding that this symptom was highly significantly correlated to the total HDRS score suggests that a subjective experience of infection is a major feature of major depression. However, a "subjective experience of infection" is not a good description and in stead we would propose to employ "flu-like malaise", which better describes the symptoms the patients are suffering from, i.e. the overall ill feeling, malaise, chills, heat flushes, etc.

Previously, we have shown that this symptom is an expression of inflammatory processes in ME/CFS. Indeed, significant correlations were established between this symptom and inflammatory markers, such as an increased production of nuclear factor kappa B (NFκB), cyclo-oxygenase (COX-2) and inducible NO synthase (iNOS), increased IgA-mediated immune responses against LPS of gram-negative enterobacteria (indicating leaky gut) and lowered serum zinc (Maes and Leunis, 2008; Maes *et al.* 2006; 2007a; 2007b; 2007c). Also, the other symptoms belonging to the F&S factor have been shown to correspond to inflammatory responses in ME/CFS. Thus, we found significant correlations between F&S symptoms, such as pain, muscular tension, fatigue, concentration difficulties, failing memory, irritable bowel, and headache, on the one hand, and signs of increased IO&NS, such as damage caused by O&NS; increased IgA responses against LPS of gram-negative enterobacteria, higher NFκB, COX-2 and iNOS production and lowered CoQ10 levels, on the other (Maes *et al.* 2007a; 2007b; 2007c; 2009a). Also, in depression, there are results that the F&S symptoms are related to disorders in the IO&NS pathways, e.g. inflammation, oxidative stress, lowered CoQ10 and an IgM-mediated immune responses against gram-negative enterobacteria (Maes *et al.* 1993; 2007c; 2008a; 2008b; 2009b; 2009c). These results show that the F&S dimension is an expression of underlying disturbances in IO&NS pathways. These findings constitute an external validation of the F&S dimension, which we have symptomatically delineated in the present study.

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