A Cluster Model of Temperament as an Indicator of Antidepressant Response and Symptom Severity in Major Depression

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Objective   Not enough is known about which patients suffering from major depressive disorder benefit from antidepressant drug treatment. Individual temperament is relatively stable over a person's lifespan and is thought to be largely biologically predefined. We assessed how temperament profiles are related to depression and predict the efficacy of antidepressant treatment.

Methods   We recruited one hundred Finnish outpatients (aged 19 to 72) suffering from major depressive disorder, of whom 86 completed the 6-week study. We assessed their temperament features with the Temperament and Character Inventory and used cluster analysis to determine the patient's temperament profile. We also categorized the patients according to the vegetative symptoms of major depressive disorder.

Results   There was an association between skewed temperament profile and severity of major depressive disorder, but the temperament profiles alone did not predict antidepressant treatment response. Those with higher baseline vegetative symptoms score had modest treatment response. Our model with baseline Montgomery Åsberg Depression Rating Scale (MADRS) vegetative symptoms, age and temperament clusters as explanatory variables explained 20% of the variance in the endpoint MADRS scores.

Conclusion   The temperament clusters were associated both with severity of depression and antidepressive treatment response of depression. The effect of the temperament profile alone was modest but, combined with vegetative symptoms of depression, their explanatory power was more marked suggesting that there could be an association of these two in the biological basis of MDD.

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Key Words   Depressive disorder, Temperament, TCI, Antidepressive agents, Treatment response.

INTRODUCTION

According to the psychobiological model of temperament and character[1] the human temperament can be divided into four different independent dimensions and character into three different dimensions. The temperamental features are: 1) the behavior in relation to new or pleasure-producing stimuli (novelty seeking, NS), 2) behavioral inhibition in relation to issues which may lead to negative consequences (harm avoidance, HA), 3) continuing of behavior that has earlier been successful in the hope of reward (reward dependence, RD), and the tendency to maintain certain behavior despite frustration (persistence, P).[1] These temperament dimensions are suggested to be connected with central neurotransmitter circuits in the central nervous system: dopamine (novelty seeking), serotonin (harm avoidance) and norepinephrine (reward dependence).[2] The three dimensions of character mature in adulthood and influence personal and social effectiveness by insight learning about self-concepts. Self-concepts vary according to the extent to which a person identifies the self as 1) an autonomous individual (self-directedness, SD), 2) an integral part of humanity (cooperativeness, C), and 3) an integral part of the universe as a whole (self-transcendence, ST).[1]

The Temperament and Character Inventory (TCI) has been

used in general population studies and in studies including patients with major depressive disorder (MDD) to assess how different temperament dimensions are associated with this disorder.[1] HA has reportedly been higher in MDD patients than in general population[3-9] and has been state dependent in MDD.[5,6] HA has also been associated with depressive symptoms in general population.[10-12] HA, RD and NS have been found to have trait-like characteristics that are related to the familial occurrence of depression.[4] High HA has been reported to predict poor treatment outcome.[8,13-15]

HA also seems to have a trait-like characteristic, reflecting genetic susceptibility in depression prone subjects.[4,16] It seems that HA is both a state- and trait-dependent variable in MDD.[17] However, one study using the Hospital Anxiety and Depression Scale (HAD), which excludes somatic symptoms, found no association between HA and MDD.[18] This finding may suggest that HA is connected specifically to the somatic component of MDD. The contribution of other temperament dimensions in MDD is somewhat controversial or limited. Low RD may be associated with MDD and depressive symptoms in general population,[4] but the results are unequivocal.[10,19] NS seems to be state dependent in MDD and altogether lower in MDD patients.[4,11] However, high NS has been associated with history of suicide attempts in general population.[20] In one study P was a state marker in depression.[17]

In a study by Grucza et al.[20] different combinations of temperament dimensions were associated with different depressive symptoms. It has been proposed that the symptoms of MDD consist of clusters, which are linked to distinct genetic mechanisms which when combined in one individual, can lead to a diagnosable psychopathology.[21] Suzuki et al.[22] proposed a three-factor model of the MADRS to differentiate the vegetative symptoms (somatic symptoms) observed in a patient group. This three-factor model has been used in some studies with MDD patient samples.[23-25] It has been proposed that the vegetative symptoms are connected to enhanced expression of 5HT2A receptors.[25] We found no studies addressing the association of temperament and vegetative symptoms of MDD. The present study analyzes if temperament profiles in association with vegetative symptoms explain the antidepressant treatment response in MDD patients and if the severity of depression is associated with current temperament clusters.

METHODS

A hundred Finnish outpatients were recruited from secondary outpatient services, primary health care and by newspaper advertisements during the years 2002−2006 in the area of Tampere in southern Finland. The study was approved by the local Human Subjects Review Committee and subjects participated having given informed, voluntary, written consent. The recruitment resulted in 41 female and 59 male outpatients, aged 19−72 yrs (mean 40.7 years, SD±14.0). Patients met the criteria for major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). All patients were diagnosed by a psychiatrist and the severity of their depression was evaluated with the Montgomery-Åsberg Depression Rating Scale (MADRS). Those patients who scored 20 or higher at baseline MADRS were included in the study. Patients with severe somatic illness or medication affecting their mood, other significant psychiatric disorders (bipolar illness, psychosis or severe personality disorders) or patients with alcohol or substance abuse were excluded from the study. Eighty-six patients completed the entire study according to the protocol and were included in the final analysis.[26] Study data was collected on three occasions. At the first visit basic sociodemographic data was collected: gender, age, marital status, education, workplace before the sick leave, somatic illnesses and their medications, other psychiatric disorders, and possible use of psychotrophic medications. The baseline MADRS form was scored and the patients completed the temperament section of the TCI questionnaire to assess the temperament profile.[1] All patients were prescribed either citalopram, fluoxetine or paroxetine. Anxiolytics and sedative hypnotics as adjuvant treatment and other medication for concomitant general medical conditions were allowed. At the second visit, three weeks after initiation of treatment, patients' adherence to treatment and the dosage of the medications were checked. Compliance was evaluated by a medication diary kept by the patient. Treatment compliance was deemed sufficient if the patient had taken the medication on at least 80% of the days in the study period. At the third visit, six weeks after the initiation, patients' adherence was monitored again and the MADRS and TCI forms were completed again (endpoint data). In the case of possible dropouts the necessary patient information on the reasons for dropout was also collected. The temperament profiles were determined from the baseline TCI data. The vegetative symptoms were assessed as the sum of questions three to five in the MADRS.[22] These are impaired sleep, impaired appetite, and inner tension.

Statistical methods

A two-step cluster analysis was used for the definition of the patient's temperament profile. In our cluster model, we decided to use three temperament dimensions, NS, HA and RD with their baseline scores. In the statistical analysis the patients were divided into three clusters.

The differences in continuous variables (MADRS total score,

MADRS factor scores and age) between the clusters were calculated with ANOVA. The difference in MADRS change between low and high vegetative symptom groups was analyzed with t-test. Differences between grouping variables were calculated with χ^2-statistics. Non-parametric tests were used in comparisons in ordinal variables between different clusters (used medications, patient compliance). Pearson's correlation coefficients were calculated between MADRS total score and vegetative symptom score, both at baseline and endpoint.

In the multivariate analysis all variables included in the study and likely to have an impact on either depression severity or treatment response were used in the models. The effect of background variables on clusters was analyzed with a multinominal logistic regression model. Gender, age, severity of depression, antidepressant taken and dose, subjective adherence to treatment, and earlier depression episode were used as explanatory variables. A linear regression model (ANCOVA) was used for testing the effects of temperament clusters and other variables on MADRS endpoint scores. The first model included temperament clusters and age, and the second model temperament clusters, age and the MADRS vegetative symptoms (questions 3−5) at baseline as explanatory variables. All analyses were performed with SPSS for Windows software (version 17.0).

RESULTS

The cluster analysis resulted in the following clusters: LNS/HHA/LRD, INS/HHA/HRD and HNS/LHA/(HRD) with H indicating high level, L low level and I intermediate level on the temperament dimensions. In the third cluster RD did not reach statistical significance in the clustering model. In the first cluster we discovered the most robust slope in the NS and HA at baseline. In the second cluster there were elevated points in HA. The results of the cluster analysis and MADRS scores in each cluster are presented in Table 1.

There were no differences in the distributions of gender between the clusters (p=0.23, chi-square test). The patients in cluster 1 were older than in other clusters (age mean±SD, cluster 1=45.9±11.4, cluster 2=37.4±14.4, cluster 3=38.2±15.3; p=0.03, ANOVA). There was no difference between the clusters in the dosages of the medications taken in weeks one to three (p=0.48, Kruskal Wallis test), nor in compliance to treatment (p=0.69). Gender, severity of depression, antidepressant taken and dose, adherence to treatment, and earlier depression episode had no effect on the clusters in the multinominal regression model. Age of the patients had a marginal effect on clusters (p=0.051) in the multinominal regression model.

The correlations between MADRS vegetative symptom score with MADRS total score were at baseline 0.73, (p<0.001) and at endpoint 0.76, (p<0.001). The MADRS vegetative symptom score at baseline had a moderate correlation with MADRS endpoint scores (r=0.38, p<0.001), and a non-significant correlation with MADRS score change (r=0.13, p=0.26). We also analyzed the MADRS score change between patients with low (1−7, n=50) and high (8 or more, n=48) vegetative symptoms. The difference was close to significant [MADRS

Table 1. Results of the cluster analysis. All scores except response percentages are indicated as mean±SD

Cluster	LNS/HHA/LRD, N=33	INS/HHA/HRD, N=35	HNS/LHA/(HRD), N=30
TCI baseline score			
NS	13.9±5.2	19.6±7.1	25.7±4.9
HA	26.8±6.1	27.2±3.6	16.0±4.2
RD	11.8±2.2	18.2±2.5	16.6±3.6
Baseline MADRS*	28.3±6.1	27.3±5.7	25.0±4.4
Factor 1 (dysphoria)	8.5±2.6	7.8±2.2	7.4±1.4
Factor 2 (retardation)	11.7±2.2	12.1±2.7	11.0±2.9
Factor 3 (vegetative symptoms)	7.8±3.1	7.4±2.8	6.4±2.7
Endpoint MADRS**	14.1±9.1	13.5±8.3	8.3±5.5
Factor 1 (dysphoria)	3.7±3.2	3.9±2.7	2.5±1.9
Factor 2 (retardation)*****	6.3±4.5	6.0±3.7	3.4±3.0
Factor 3 (vegetative symptoms)	3.5±2.3	3.7±2.9	2.4±1.9
MADRS score change***	14.2±7.4	14.3±8.0	16.7±6.0
Response (percentage decline in MADRS)****	51.6%	51.9%	66.7%

*p=0.05 between groups (ANOVA), **p=0.01 between groups (ANOVA), ***p=0.36 between groups (ANOVA), ****p=0.04 between groups (ANOVA), *****p=0.01 between groups (ANOVA). TCI: Temperament and Character Inventory, MADRS: Montgomery-Åsberg Depression Rating Scale, NS: novelty seeking, HA: harm avoidance, RD: reward dependence, with H indicating high level, L low level and I intermediate level on the temperament dimensions

change, mean (±SD), low symptoms=13.5 (±5.5), high symptoms=16.6 (±8.5), p=0.052, t-test]. There were no differences in the MADRS vegetative symptom score at baseline or at endpoint between the different clusters (p=0.17, baseline; p=0.14, endpoint, ANOVA). There was a non-significant correlation between baseline MADRS dysphoria symptoms and MADRS score change (r=0.17, p=0.11). MADRS endpoint scores were used as the outcome variable in two linear regression models. In the first model age and temperament clusters were used as explaining variables. This model explained 10% of the variance in the MADRS endpoint scores (p=0.04; power 0.69). The clusters explained 9% (p=0.02), and age explained 1% (p=0.36). In the second model, baseline MADRS vegetative symptoms, age and temperament clusters were used as explanatory variables. This model explained 20% of the variance in the MADRS endpoint scores (p=0.001; power 0.96 for the complete model). In this model the baseline vegetative symptoms explained 12% (p=0.001), age 0.2% (p=0.70) and temperament clusters 5% (p=0.12). Using the delta scores of MADRS as an outcome variable, and age and temperament clusters as explanatory variables (first model), and vegetative symptoms, age and temperament clusters as explanatory variables (second model) resulted in non-significant models (first model: ηp^2=0.085, p=0.061, power=0.61; second model: ηp^2= 0.096, p=0.087, power=0.60).

DISCUSSION

Our main hypothesis was that temperament clusters in patients with MDD explain the treatment response. In practice this means that different temperament profiles could function as a classifying factor and that MDD patients could be divided into different groups with different outcomes for antidepressant treatment. In our study we used primarily the MADRS endpoint scores as an outcome variable in the multivariate analyses. Using the delta scores of MADRS as an outcome variable resulted in non-significant models although there was a trend towards a better response in patients with high vegetative symptoms. The present results suggest that the combined effect of vegetative symptoms and temperament clusters is important in relation to the depression treatment outcome when measured as post-treatment symptoms. However, these factors showed a non-significant effect when predicting the change in depression scores during treatment. This finding may be due to both the temperament clusters and pre-treatment vegetative symptoms representing depressive traits less connected with the magnitude of symptom alleviation during treatment.

The approach of using TCI temperament clusters for predicting the response to antidepressant treatment in MDD pa-

tients is novel. In several studies individual dimensions of temperament have been used as precursors. Two earlier studies with general population samples have used combinations of high or low temperament traits for predicting different clinical features, but in these studies no cluster analysis method was used in classifying the temperament traits.[18,20] This study did not include the character dimensions of the TCI (SD, C, ST) in the explanatory model. Adding the character traits to the predictors in the statistical model might have increased its predictive value regarding antidepressant response, since many studies have demonstrated that SD exhibits a state/trait marker in depression.[9,27,28]

There were some limitations concerning our patient sample and study setting. In contrast to some earlier studies, our patient sample comprised solely outpatients. This may have resulted in lower intensity of symptoms as reflected by the MADRS scores. Temperament profiles could have had more explanatory power if the patient sample had included inpatients with more severe depression. The patients were deemed compliant with medication if they took the prescribed medication at least 80% of the time, which can be regarded as a moderate level of treatment compliance, and the data were collected from patient reports, which in some cases may produce unreliable results. Nor did the patients receive any specific psychological treatment during the study, but were treated in a standard secondary outpatient setting.

As the relationship between temperament and vegetative symptoms of depression has not previously been studied, a post-hoc analysis with vegetative symptoms was performed in this study. This was done by separating the vegetative symptoms from the other symptoms of depression (dysphoria and retardation) which was based on the study by Suzuki et al.[22] It has been proposed that the vegetative symptoms are connected to enhanced expression of 5-HT2A receptors.[25]

To assess patients' temperament profiles we used Cloninger's TCI, which has been widely used, validated and shown to be reliable in studies on general population and MDD patients.[1] Temperament profiles were determined by clustering the distributions in the three temperament dimensions. Due to the limited sample size, the number of clusters was determined as three in the analysis to yield groups of reasonable size. The clustering method was able to differentiate between the three combinations of temperament traits, although in the third cluster the difference on the dimension RD did not reach statistical significance. It has been suggested that high RD correlates negatively with depressive symptoms, but the evidence is contradictory.[3,4,9,10] The clusters differed on the dimension NS as it was low in cluster one, intermediate in cluster two and high in cluster three. The third cluster (HNS/LHA/HRD) probably reflects more impulsive depression, and diverges substan-

tially from the typical temperament profile of an MDD patient, and in this study from the other two temperament clusters. This may explain why this subgroup of patients recovered better from the retardation symptoms than did the other patients. In addition, this group showed a higher percentage of MADRS changes. This difference in response could be due to the predictive effect of HA on MDD remission shown in our earlier report.[29] In the first cluster we discovered the most distinct sloping in the distribution of the NS and HA dimensions at baseline. According to earlier reports the subgroup in this cluster has an increased risk for MDD and their depression is more disease-like.[4-6,9] NS has been negatively associated with depressive mood state and tends to be at a low level in MDD patients.[4] The clusters might thus reflect an underlying factor explaining clinically different symptoms profiles and course of depression.

In our study the temperament clusters were associated with both baseline and endpoint depressive symptoms and with the treatment response. The findings suggested that depression was most severe and difficult to treat in cluster one patients. In clusters one and two, in which HA scores were high, the response in percentage decline of MADRS scores was lower than in cluster three. These findings concur with those of earlier studies on the association between HA and depression.[4,5,7-9,15,30]

Although the depression vegetative symptom score is only a subscale of MADRS, it may be considered a separate dimension in depression symptomatology.[22] MADRS total scores and vegetative symptoms showed a strong correlation at both baseline and endpoint. However, the correlation between MADRS endpoint total score and baseline vegetative symptom score was much lower, suggesting that the vegetative symptoms are a separate entity within depressive symptomatology.[22] Therefore we considered it justified to study the impact of baseline vegetative symptoms on total symptoms at endpoint.

In the linear regression models our aim was to predict the treatment response in MDD patients. The first model was designed to reveal the impact of temperament clusters on treatment outcome. When patient's age was also taken into account as an explanatory variable, the temperament clusters had only modest explanatory power. Age as such did not function as an explaining variable in this model at a significant level. In the second model we wanted to ascertain if there was an interaction with temperament clusters and vegetative symptoms of MDD. Therefore we added the vegetative symptom scores to the model as an explanatory variable. In this model, the vegetative symptoms explained about twice as much as the clusters of the variance of endpoint MADRS scores. However, the whole model explained as much as one fifth of the variance in response to SSRI treatment. The role

of the interaction between temperament clusters and vegetative symptoms on treatment result has to be interpreted cautiously, as the impact of clusters on treatment response in the final model was marginal. It seems that the vegetative symptoms of depression, in addition to a certain temperament profile, is a marked predictor for antidepressive treatment outcome. It is, however, possible that the vegetative symptoms alone have a more marked impact in both severity and response of depression compared to temperament. Even though the differences between the clusters in depression severity were marginal, our findings suggest an association between skewed temperament profile and severity of MDD. It is possible that the temperament profile can function as a predisposing factor to depression or have an impact on the clinical profile and course of depression.

In conclusion our study showed that MDD patients could be divided into different temperament clusters with different severity and outcomes of antidepressant treatment. The vegetative symptoms of depression combined with temperament profiles and age predicted antidepressant treatment response. The effect of the temperament profile alone was modest but, combined with vegetative symptoms of depression their explanatory power was more marked, suggesting that there could be an association between these two in the biological basis of MDD.

Acknowledgments

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