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Association of depressive phenotype with affective family history is mediated by affective temperaments

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Abstract

Increasing data support an association of cyclothymic temperament with bipolarity, but our knowledge about the relationship of affective temperaments (ATs) to depressive symptoms based on inheritance in a non-clinical population is limited. The aim of this article was to demonstrate how ATs and affective family history relate to the depressive symptoms in a general population. Subjects comprised 501 Hungarian adults who completed a background questionnaire, the TEMPS-A, the Zung Self-Rating Depression Scale (ZSDS) and the depression subscale of the Brief Symptom Inventory (BSI-D). Stepwise linear regression was performed to analyse the role of ATs and affective family history (AFH_0 and AFH_1) in the variance of ZSDS and BSI-D scores. Cyclothymic, depressive and anxious temperaments have a significant role in the explained variance of depression scores, and they are all significantly related to AFH_1. Significant differences were found between AFH_1 and AFH_0 groups in ZSDS and BSI-D scores, and these effects were eliminated if ATs were entered as covariates. The probability of having any dominant temperament was more than two-fold in group AFH_1 compared with AFH_0 (OR=2.33). Our results suggest that a crucial part of inherited factors of depression is mediated by affective temperaments.

Keywords: TEMPS-A; Affective spectrum; Subclinical depression; General population; Dominant temperament; Depressive endophenotype; Family history

1. Introduction

It has been shown in several studies that both inherited and environmental factors play a significant role in affective disorders (Dunner et al., 1976; Levinson, 2006; Sullivan et al., 2000). However, we still do not have sufficient knowledge concerning the inherited background of these disorders and how these influence the manifestation of the illness through interaction with environmental factors. There are data available from case–control studies describing differences between healthy and clinical populations with depression. Although previous studies have proposed that affective disorders need to be interpreted as part of an affective spectrum also involving premorbid, subclinical, atypical or vulnerable subpopulations, research in this field has paid relatively little attention to these so far (Judd and Akiskal, 2000).

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Affective temperaments (ATs) are hypothesized to be associated with the genetic basis and the phenotypic expression of affective disorders (Whittle et al., 2006) and their relevance to endophenotype studies is also proposed (Gonda et al., 2006). ATs may be a genetically determined part of personality, remaining relatively stable during a lifetime, and being a potential nucleus for affective disorders (Akiskal and Akiskal, 2005). Affective temperaments, as defined by Akiskal, are regarded as subaffective manifestations of affective disorders (Akiskal et al., 2003). To date, the majority of results based on family history reports suggest that cyclothymic and hyperthymic ATs could play a significant role in the emergence of bipolarity (Cassano et al., 1992; Chiaroni et al., 2005; Evans et al., 2005; Kelsoe, 2003), and this supports the spectrum concept of bipolarity where the cyclothymic temperament is considered a mild version of a pathological state (Kesebir et al., 2005). Although several authors hypothesized associations between ATs and affective disorders (Akiskal, 1995; Kesebir et al., 2005; Rottig et al., 2007), to our knowledge, there are no studies available concerning the association of family history, ATs and depressive symptoms in a general population representing the affective spectrum.

The aim of our study was to demonstrate how affective temperaments (TEMPS-A) and affective family history relate to the emergence of depressive symptoms (as measured by the Zung Self-Rating Depression Scale (ZSDS) and the Brief Symptom Inventory (BSI)) in a general population.

2. Methods

2.1. Subjects

The study group comprised 501 unrelated Hungarian volunteers (350 women and 151 men). Participants were recruited from the practices of general practitioners, adult students participating in a long-distance learning program and a community-based population. The inclusion of subjects was random and independent of any positive psychiatric anamnesis. The mean age of participants was 33±3.2 years. All subjects were Hungarian and of Caucasian origin, and they gave written informed consent before entering the study. The study was approved by the Central Ethics Committee. The descriptive data of the study population are shown in Table 1.

Table 1
Parameters of the study population.

	n_{males}	$n_{females}$	$\sum n$	$\sum\%$
Gender	151	350	501	100
Education				
No qualification	2	7	9	1.7
GSCEs/O levels	29	33	62	12.3
A levels	98	256	354	70.6
Degree	22	46	68	13.5
Prevalence of depression				
Lifetime prevalence for depression	31	87	118	23.6
One-year prevalence for depression	8	33	41	8.2
Psychiatric family history				
Depression in family history	14	66	80	15.9
Suicide in family history	8	28	36	7.1
Bipolarity in family history	2	8	10	1.9
Total AFH	16	80	96	19.2

2.2. Measures

Detailed background information was obtained from all participants with the background questionnaire developed by our team. This well-structured self-rating questionnaire consists of 22 items and collects detailed information about medical history including psychiatric history and medications, family psychiatric history and socio-economic background. In the family medical history section, subjects had to indicate if depression, bipolar disorder/manic episode/manic depression or suicide was present in their families. We coded this information as a combined binary variable indicating whether any of the above indicators of affective-related positive family history was present or not (AFH_1 and AFH_0). Suicide was included because of the strong evidence on the relationship between depression and suicide and because it has been described previously that relatives of persons with mood disorder who attempt suicide are at a significantly greater risk for mood disorder (Mann et al., 2005).

All subjects completed three self-rated psychological questionnaires: the TEMPS-A, the Zung Self-Rating Depression Scale (ZSDS), and the depression subscale of the Brief Symptom Inventory (BSI-D).

The TEMPS-A questionnaire (Temperament Evaluation of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire) measures affective temperaments. It is a 110-item (109 for males) self-report psychological instrument with subscales representing five affective temperament dimensions: depressive, cyclothymic, hyperthymic, irritable and anxious (Akiskal et al., 2005). Average values were calculated and dominant temperaments (DTs) based on a z-score (mean±2S.D.) were also determined (Kesebir et al., 2005; Vahip et al., 2005; Vazquez et al., 2007). Persons carrying and not carrying any dominant affective temperament based on any subscale score were grouped separately (DT_1 or DT_0).

The Zung Self-Rating Depression Scale (ZSDS) is a well-validated and frequently used instrument consisting of 20 items and measuring symptoms of depression.

The Brief Symptom Inventory is a 26-item self-report symptom inventory developed from its longer parent instrument, the Symptom Checklist-90-Revised, which was designed to reflect the psychological symptom patterns of psychiatric and medical patients and non-patients. The brief 26-item version of the inventory reports profiles of obsessive–compulsive, interpersonal sensitivity, depression, anxiety and additional items (Derogatis and Melisaratos, 1983). Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (extremely). In this analysis we used only the depressive subscale (BSI-D) consisting of six items.

2.3. Statistical analysis

Descriptive statistics of the study population were evaluated with chi-square tests and Mann–Whitney *U* tests. To assess the effect of independent variables and explained variance of depressive symptoms, TEMPS-A score, family history, age and gender were entered into a linear regression model equation with a stepwise method, with the ZSDS and the BSI depressive subscale as continuous dependent variables. Pearson's test was performed to establish correlations between the variables. Regression residuals, representing covariate-adjusted ZSDS and BSI values, were computed and used in subsequent analyses. We performed Mann–Whitney *U* tests to compare the scores of groups on the different scales with and without positive affective family history (AFH_0 and AFH_1, respectively) as well as to investigate the effect of ATs and AFH on the depression scores. The effect of affective family history (AFH) on groups with and without dominant temperaments (DT_0 and DT_1, respectively) was investigated with logistic regression with an enter method.

In non-parametric tests empirical global *P* values were calculated after Monte-Carlo permutation procedures (10,000 permutations). The accepted level of significance was $P<0.05$. Results are presented as means ± standard deviation (S.D.). All statistical analyses were carried out using SPSS 15.0 for Windows.

Table 2
Mean scores of TEMPS-A subscales and prevalence of dominant temperaments.

	Mean±S.D.	Subjects with dominant temperaments					
		Males		Females		∑	
		n	%	*n*	%	*n*	%
TEMPS depressive	0.33±0.150	7	4.63	12	3.42	19	3.8
TEMPS cyclothymic	0.28±0.205	12	7.94	16	4.57	28	5.6
TEMPS hyperthymic	0.46±0.191	6	3.97	5	1.42	11	2.2
TEMPS irritable	0.24±0.190	11 *	7.28	8 *	2.28	19	3.8
TEMPS anxious	0.27±0.206	4	2.65	15	4.28	19	3.8
Any dominant temperament (DT_1)	–	29 *	19.2	42 *	12.0	71	14.7

* Significant difference in the ratio between males and females, $P<0.05$.

3. Results

3.1. Descriptive statistics and gender differences (Zung total, BSI depressive subscale scores, TEMPS-A subscale scores and prevalence of dominant temperaments in the sample)

There was a significant difference in ZSDS score ($mean_{female}=38.92\pm5.445$, $mean_{male}=37.99\pm5.606$; $P=0.010$) between the two gender groups but not in BSI-D subscale ($mean_{female}=3.16\pm4.167$; $mean_{male}=3.60\pm4.723$; $P=0.421$). Men scored significantly higher on the hyperthymic ($mean_{male}=0.495\pm0.203$, $mean_{female}=0.452\pm0.185$; $P=0.028$) and irritable ($mean_{male}=0.285\pm0.199$, $mean_{female}=0.222\pm0.183$; $P=0.003$) subscale of TEMPS-A and significantly lower on the anxious temperament subscale ($mean_{male}=0.236\pm0.204$, $mean_{female}=0.297\pm0.204$; $P=0.001$) compared with women. There were no significant differences between the two gender groups in cyclothymic ($mean_{male}=0.292\pm0.221$, $mean_{female}=0.282\pm0.198$; $P=0.993$) and depressive temperaments ($mean_{male}=0.320\pm0.165$, $mean_{female}=0.346\pm0.143$; $P=0.055$). Frequency of any dominant temperament was significantly higher in men compared with women ($\chi^2=4.416$, $P=0.036$). Frequency of dominant irritable temperament was significantly higher in men compared with women ($\chi^2=7.161$, $P=0.007$) (Table 2).

3.2. Correlation of affective temperaments and depressive symptoms (Zung total and BSI depressive subscale scores) in a linear regression model

Anxious, cyclothymic and depressive temperaments showed relatively strong correlations ($r=0.542$, 0.508 and 0.542, respectively, all $P<0.001$) while irritable temperament correlated moderately ($r=0.360$; $P<0.001$) and hyperthymic correlated negatively ($r=-0.361$; $P<0.001$) with the ZSDS total score. Affective temperaments and

Table 3A
Correlation of affective temperaments of TEMPS-A (depressive, cyclothymic, anxious) and depression scores: Zung Self-Rating Depression Scale (ZSDS); depression subscale of Brief Symptom Inventory (BSI-D).

	Significant variables				Total model	
	Anxious	Cyclothymic	Depressive	AFH		
	Beta, *t*-test (*P*)	Beta, *t*-test (*P*)	Beta, *t*-test (*P*)	Beta, *t*-test (*P*)	Adj. R^2	*F* (*P*)
ZSDS	0.291 (<0.001)	0.265 (<0.001)	0.177 (<0.001)	0.042 (<0.001)	0.387	78.5 (<0.001)
BSI-D	0.161 (<0.001)	0.368 (<0.001)	0.212 (<0.001)	–	0.385	103.82 (<0.001)

AFH were entered in a stepwise linear regression model, where the explained variance of the Zung total score was 38.7% (adjusted $R^2=0.387$). This effect was significant in the whole sample ($F_{4,497}=78.5$, $P<0.001$). The standardized regression coefficients of the entered variables were significant in the stepwise model ($beta_{anxious}=0.291$, $P<0.001$; $beta_{cyclothymic}=0.265$, $P<0.001$; $beta_{depressive}=0.177$, $P<0.001$; $beta_{AFH}=0.073$, $P<0.005$) while irritable and hyperthymic temperaments were not entered in the model. *T*-tests indicated a significant single effect for the anxious, cyclothymic and depressive affective temperaments on the variance of ZSDS total score ($P<0.001$ in all cases).

Cyclothymic, depressive and anxious temperaments showed correlations with the BSI depressive subscale at the same level but in a different order than with the ZSDS ($r=0.557$; $r=0.503$; $r=0.500$, respectively, all $P<0.005$). The irritable subscale correlated with BSI-D at a lower level ($r=0.406$; $P<0.001$), and the hyperthymic subscale showed a negative correlation ($r=-0.236$; $P<0.001$). Results of stepwise regression were similar to the model where depressive phenotype was measured by the ZSDS (adjusted $R^2=0.385$), but AFH was not entered into the statistical process in the stepwise model in this case, because it has no additional significant effect on the dependent variable. The effects of ATs were significant according to the *F*-test ($F_{3,498}=103.821$; $P<0.001$). *T*-tests indicated significant single effects of these variables on the BSI depressive subscale ($beta_{cyclothymic}=0.368$, $P<0.001$; $beta_{depresive}=0.212$, $P<0.001$; $beta_{anxious}=0.161$, $P=0.001$). Gender and age have no significant effect on the variance of ZSDS and BSI-D scores. The results are shown in Tables 3A and B.

Table 3B
Correlation between anxious, cyclothymic, depressive, irritable and hyperthymic subscales of TEMPS-A and depression questionnaires: Zung Self-Rating Depression Scale (ZSDS) and depression subscale of Brief Symptom Inventory (BSI-D) as demonstrated by Pearson's correlation tests.

	ZSDS		BSI-D	
	r	*P*	*r*	*P*
Anxious	0.543	<0.001	0.480	<0.001
Cyclothymic	0.508	<0.001	0.557	<0.001
Depressive	0.506	<0.001	0.502	<0.001
Irritable	0.360	<0.001	0.406	<0.001
Hyperthymic	−0.361	<0.001	−0.236	<0.001

3.3. Association of affective family history with affective temperaments

We compared the affective subscale scores between the two family history subgroups (AFH_0, AFH_1) using Mann–Whitney *U* tests. There was a significant difference between the two groups in the case of the anxious affective temperament score ($mean_{AFH0}=0.269\pm0.204$, $mean_{AFH1}=0.319\pm0.208$; $P=0.028$), the cyclothymic affective temperament score ($mean_{AFH0}=0.275\pm0.202$, $mean_{AFH1}=0.331\pm0.213$; $P=0.020$) and depressive affective temperament score ($mean_{AFH0}=0.331\pm0.143$, $mean_{AFH1}=0.370\pm0.176$; $P=0.037$). Family history was not related to the two other affective temperaments ($P_{irritable}=0.156$; $P_{hyperthymic}=0.191$). The results are presented in Table 4.

3.4. Association of family history and depressive symptoms

There was a significant difference in the age- and gender-adjusted ZSDS score between groups with positive (AFH_1) and negative affective family history (AFH_0) ($mean_{AFH0}=38.25\pm0.5.416$; $mean_{AFH1}=40.27\pm5.629$; $P=0.011$) which disappeared when the ZSDS score was

Table 4
Significant differences in depressive, cyclothymic and anxious subscales of TEMPS−A between negative (AFH_0) and positive (AFH_1) affective family history groups.

	AFH_0	AFH_1	*P*
	Mean±S.D.	Mean±S.D.	
Depressive	0.331±0.143	0.370±0.176	0.037
Cyclothymic	0.275±0.202	0.331±0.213	0.020
Anxious	0.269±0.204	0.319±0.208	0.028

Table 5
Differences in depressive symptom scores between two affective family history groups (AFH_0 and AFH_1).

	AFH_0	AFH_1	P	P_{adj} *
	Mean±S.D.	Mean±S.D.		
ZSDS	38.25±5.416	40.27±5.629	0.011	0.179
BSI-D	3.05±4.215	4.34±4.732	0.005	0.197

* Significant differences were eliminated when the model was adjusted by the TEMPS-A subscales (P_{adj}=0.179 and 0.197).

adjusted by ATs (P_{adj}=0.179). Similarly, there was a significant difference in depressive scores of the BSI between the two AFH groups ($mean_{AFH0}$=3.05±4.215; $mean_{AFH1}$=4.34±4.732; P=0.005), which was also eliminated when the ATs were entered in the model as covariates (P_{adj}=0.197). The results are shown in Table 5.

3.5. Dominant temperaments (DT), depressive symptoms and affective family history (AFH)

A significant difference was observed between the two groups (carrying and not carrying dominant temperaments, DT_1 and DT_0, respectively) in ZSDS score ($mean_{DT0}$=38.04±5.081, $mean_{DT1}$=42.43±6.447; P<0.001) and BSI depressive subscale score ($mean_{DT0}$=2.64±3.474, $mean_{DT1}$=7.49±6.351; P<0.001). The significant effect of AFH was determined based on the presence of DTs in a logistic regression with the enter method (χ^2=8.092; P=0.004). Wald's test indicated a significant power for this effect (Wald=8.675; P=0.003). In the case of positive family history (AFH_1), the chance of having a dominant affective temperament was more than two-fold compared to AFH_0 (OR=2.33). Gender and age had no significant effect on the model.

4. Discussion

Our results demonstrated that cyclothymic, depressive and anxious temperaments play a significant role in the explained variance (adjusted R^2) of depressive scores (ZSDS, BSI-D) in a general population. They are also significantly related to affective family history (AFH). The theory of the relationship between ATs and the clinical manifestations of mood disorders was outlined by Akiskal (1995), but temperaments so far have not been investigated with regard to the depressive scores as continuous variables in a general population representing the affective spectrum. When the ZSDS score was assessed in relation to TEMPS-A scores, three affective temperaments (anxious, cyclothymic and depressive) had a strong significant effect. Affective family history (AFH) entered in the model resulted in only a slight additional explained variance ($beta_{AFH}$=0.073, P=0.042). This indicates that the depressive score was almost completely explained by the temperaments on their own when ATs were also present, and AFH explained only a minor portion of the depressive scores. The same result appeared in the case of the BSI depressive subscale, where the three ATs explained most of the BSI depressive subscale score. In this case, AFH did not add any significant additional power to the regression analysis. These results are in harmony with our results in the case of Mann–Whitney U tests where the significant effect of AFH on depression scores (ZSDS, BSI) disappeared when ZSDS and BSI scores were adjusted to TEMPS-A subscales. Elimination of the significant association between AFH and depressive scores by the presence of ATs proves that heritability plays a crucial role in the pathomechanism of mood disorders through the ATs (Hamet and Tremblay, 2005). It is likely that a certain genetic inclination is represented in the emergence of ATs which mediate the inherited component related to affective family history and the manifestation of depressive symptoms.

The results of a few previous studies have also indicated that depressive symptoms and ATs might share a common genetic background based on molecular genetic methodology. Results of Gonda et al. (2006) show that carriers of the s allele of the 5HTTLPR polymorphism of the serotonin transporter gene score significantly higher on subscales measuring ATs with a depressive component (i.e. depressive, cyclothymic, irritable, and anxious) (Gonda et al., 2006). In this investigation irritable temperament was also significantly associated with the s allele, but in our study irritable temperament failed to show this association with AFH. A possible explanation for this difference is that males are represented in our population but Gonda et al.'s consisted of females only. The same polymorphism in the serotonin transporter gene was also found to be associated with subthreshold depression (Gonda et al., 2005), but in the case of major depression the results are less consistent (Collier et al., 1996; Levinson, 2006; Lotrich and Pollock, 2004). The heterogeneity in genetic studies of depression could be explained by acquired or environmental factors playing a crucial role in the pathomechanisms of mood disorders (Caspi et al., 2003). Our data propose that measuring affective temperaments provides an opportunity to compare the phenotype to the genotype providing the background of mood disorders in a large-scale population using a more exact method. Further studies are needed to find other

genetic markers associated with affective temperaments (Akiskal and Akiskal, 2005; Chiaroni et al., 2005).

Gender had no significant effect on depressive scores in our linear regression model. The literature is inconsistent about the effect of gender on the association of ATs with depression. Cassano et al. (1992) have reported that depressive temperament was more prevalent in women and correlated with earlier onset and higher frequency and greater severity of the depressive episode. Other data have not shown any effect of gender on the association of depression with ATs (Erfurth et al., 2005; Mendlowicz et al., 2005). We propose that no major difference could be observed between men and women in a population representing the affective spectrum. The different characteristics of the two gender groups might become significant when ATs reach the clinical level.

There are only a few results concerning dominant temperaments obtained from the TEMPS-A score in the literature. Kesebir et al. (2005) reported that a significantly higher frequency was observed for at least one DT of the proband group and the relative group than in controls. Furthermore, dominant hyperthymic temperament is more common in patients with bipolar disorders and relatives of bipolar patients than in controls. In our study subjects carrying any of the DTs scored significantly higher on both depression scales, which is in accordance with the theoretical supposition that they are premorbid, subclinical or vulnerable subjects of affective disorders (Akiskal et al., 2005). The significant association of dominant affective temperaments with positive affective family history underlies their heritability and gives further validation to the affective temperament model.

The parameters of our sample correspond with previous results concerning the prevalence of affective disorders and affective temperaments in the general population. Our analysis indicated that our study sample matched that of the general Hungarian population concerning lifetime and 1-year prevalence of affective disorders (Rozsa et al., 2006; Szadoczky et al., 1998). Similarly, our data showing that men scored significantly higher on the hyperthymic and significantly lower on the anxious subscale of the TEMPS-A are in accordance with the results of previous Hungarian and international studies (Pompili et al., 2008; Rozsa et al., 2006; Rozsa et al., 2008; Vazquez et al., 2007). The significantly higher frequency of dominant irritable temperament observed in men has been also reported by Rozsa et al. (2008) in the Hungarian population.

Our finding that anxious temperament showed the strongest correlation with the ZSDS score is in accordance with previous results (Rozsa et al., 2006). A possible explanation of this finding may be that subclinical depression in the general population is characterized by pronounced anxiety and the most common comorbidity of depression is anxiety (Rihmer et al., 2001). In previous studies, the presence of the s allele of the 5HTTLPR polymorphism was significantly associated with a higher anxiety score (Gonda et al., 2007). These findings, in addition to earlier results concerning the association of the s allele and depression, can indicate a strong relationship between anxiety and depressive symptoms insofar as their genetic background is concerned. In the case of the BSI depression subscale, cyclothymic temperament showed the strongest correlation with the depression score. This can be explained by the fact that the depressive symptoms measured by the BSI depressive subscale and the ZSDS do not correspond completely and cover different parts of the spectrum of depressive symptoms.

Hyperthymic temperament showed negative correlation with both the ZSDS and the BSI-D in Pearson's tests. These results support the affective spectrum model of mood where the two endpoints can be depressive and hyperthymic temperaments. Factor analyses of the TEMPS-A (Pompilli et al., 2008) found a factor containing depressive, cyclothymic and anxious temperaments, and hyperthymic temperaments correlated with this factor negatively, a finding that is also in accordance with our results. On the other hand, AFH was not correlated with hyperthymic and irritable temperaments. A possible explanation of this result is that these two temperaments are related to bipolarity (Kesebir et al., 2005), which is represented only in a small number of participants ($n=10$; 1.9%) in our sample.

A limitation of our study is that almost all the variables explored are self-rated. Self-evaluation might be prone to a selective memory bias influenced by temperamental characteristics both for depressive symptoms and reported family history.

Our results suggest that a significant part of the inherited component of depression is represented by the ATs in the general population. TEMPS-A scores are valuable measures for affective phenotypes in large-scale genetic studies representing the whole affective spectrum. A positive affective family history predicts the occurrence of DT, which was significantly associated with depression scores. The significant relationship between affective temperaments and affective family history allows us to propose DT as a clinical tool to establish vulnerability to affective disorders, especially because exploration of family history is often difficult or impossible.

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