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DEPRESSION, FAMILY AND CELLULAR IMMUNITY: INFLUENCE OF FAMILY RELATIONSHIPS AND CELLULAR IMMUNITY ON THE SEVERITY OF DEPRESSION

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SUMMARY

***Background**: Exposure to stress activates the hypothalamic-pituitary-adrenal axis through the release of catecholamines, which modify humoral and cellular immunity. On the one hand, this psycho-immunological theory makes it possible to forge links between immunity and depression. On the other hand, we know that family determinants are an important variable in the model of vulnerability to depression. Our study weighs the influence of cellular immunity and family relations on the severity of depression.*

***Subjects and method**: 498 inpatients with major depressive disorder were enrolled in an open-label trial. In addition to a socio-demographic questionnaire, they completed Olsen's FACES III and the Beck Depression Inventory (BDI). Flow cytometry was used to assess lymphocyte subsets.*

***Results**: In terms of immunity, there are correlations between the BDI and percentages of CD3 ($p=0.015$; $r=-0.112$), CD4 ($p<0.000$; $r=-0.175$), CD4/CD8 ($p=0.045$; $r=-0.093$) and CD16 and 56 ($p=0.014$; $r=0.113$). In terms of family relationships, there is a correlation between the BDI and family of origin, both for cohesion ($p=0.007$; $r=-0.169$) and adaptability ($p=0.035$; $r=-0.133$) measures. With respect to the relationship between family dynamics and immunity, there are correlations between adaptability in the family of origin and CD3 ($p=0.04$; $r=0.094$) and CD4 ($p=0.044$; $r=0.093$). A logistic regression model for family variables explained 11.4% of the BDI, compared to 12.7% for immune variables, while a model including the two explained 16%.*

***Conclusions:** While both the family and immunity can explain the BDI, it is surprising they have a greater effect in combination than individually. This suggests that the psycho-immunological theory should look at the relation between immunity and family life, notably in relation to the family of origin.*

***Key words:** immunity – family – Olson – depression*

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INTRODUCTION

Since the work of Selye (Selye 1956), we have known the stressful stimulus activates the hypothalamic-pituitary-adrenal axis through the release of catecholamines, which modify humoral and cellular immunity. This psycho-immunological theory makes it possible to forge links between immunity and depression. Two main lines of research have developed as a result. The first, and the oldest, takes stress as a starting point to explain immune depression. Reynaert (Reynaert 1995, 2010) highlighted lower levels of Natural Killer (NK) cell activity in patients with major depressive disorder as a function of their health locus of control, which can be reversed with antidepressants. Using the same logic, but at a humoral level, Seidel (Seidel 1999) note an increase in pro-inflammatory cytokines in melancholic depression. Subsequently, Steiner (2011) highlight monocytosis, increased blood levels of interleukin (IL-1, IL-6) and tumour necrosis factor (TNF α) in acute episodes of major depression.

The second line of research, which has received more attention in the past 10 years, takes as its starting point immune cell activation and the release of inflammatory cytokines (Blume 2011) or C-reactive protein (CRP) (Zorrilla 2001) as the cause of depression. Wium-Andersen (Wium-Andersen 2013) show that an increase in CRP is associated with a higher risk of developing an anxiety or mood disorder. These inflammatory responses have a neurotoxic effect leading to neuronal micro-damage, such as a reduction in dendritic length, splines, and branching in the hippocampus and prefrontal cortex. In parallel, the production of brain-derived neurotrophic factor (BDNF) is inhibited (Wager-Smith 2011), which delays neuronal regeneration. In a similar vein, Maes (Maes 2011) show an increase in the CD25 count, related to the CD4 percentage and the CD4/CD8 ratio. The authors also show a rise in class II MHC HLA-DR, monocytes and memory T cells.

Alongside psycho-immunological hypotheses, the old vulnerability model (Pardoen 1996) predicts the risk of depression based on life events and family structure. The importance of family dynamics has also been demonstrated by Zdanowicz (Zdanowicz 2011).

The aim of this study is to weigh the influence of family and immunological variables on the severity of depressive episodes. We test three hypotheses:

- *H1:* There is a correlation between immune variables and severity of depression.
- *H2:* There is a correlation between family dynamics and severity of depression.
- *H3:* There is no correlation between immune variables and family dynamics.

SUBECTS AND METHODS

Our study is an open-label trial carried out over 4 years and includes all 498 patients hospitalized for a major depressive episode in the Psychosomatic Department of the Cliniques Universitaires de Mont-Godinne, Belgium.

All patients admitted to the Department completed a socio-demographic questionnaire (gender, ethnicity, employment status, marital status), together with:

- A visual analogue scale of the severity of life events in the past year.
- The Beck Depression Inventory (BDI), consisting of 21 items.
- Olson's Family Adaptability and Cohesion Evaluation Scale (FACES III).

The BDI is a quantitative scale used to estimate the severity of depressive disorders; it has been validated for adults and adolescents aged at least 13 years and is the most widely-used scale in the adult population (Bouvard & Cottraux 2002).

FACES III consists of 20 questions that provide a quantitative estimate of the cohesion and adaptability of a system – whether it is the nuclear family, the family of origin, or the current or ideal family or couple.

Routine analysis by flow cytometry measured the various lymphocyte populations identified by the antigenic properties of membrane markers; they include:

- *CD3: present on all T cells.* There are two subpopulations: helper/suppressor and cytotoxic.
- *CD4: found on helper or auxiliary T cells.* These lymphocytes activate the immune response through the release of cytokines and in liaison with other immune cells. The CD4 cell count is a key measure in monitoring HIV infection; a reduction is an indicator of progression towards immunosuppression. Certain bacterial infections can also cause a long-term reduction in the number of CD4 lymphocytes. Conversely, CD4 lymphocytosis is often observed in autoimmune diseases.
- *CD8: is a cytotoxic marker.* These cells are capable of targeted cell destruction once they have been activated. An increase in CD8 is associated with the rapid progression towards immunosuppression. Levels of CD8 can be reduced in autoimmune diseases. Conversely, CD8 lymphocytosis is an indicator of the activation of the immune system. This increase has been observed in viral infections, graft rejection, chronic fatigue syndrome and certain neutropenia.
- *The CD4/CD8* ratio evaluates the health of the immune system, for example in the progress of AIDS.
- *CD16 and 56: are surface markers of NK cells.* NK cells are capable of destroying their target in the absence of major histocompatibility complex (MHC). NK cells are non-T cells (CD3). NK cell lymphocytosis is common and usually reflects a mild and transient condition.
- *CD19: a B cell surface protein.* These cells produce immunoglobulin.

As the overall lymphocyte analysis of patients is normal, and for ease of presentation, we only present relative results.

All statistical tests were performed using SPSS 21.0 parametric methods; Type 1 and 2 errors were taken into account. No post-hoc tests were performed. Correlations were performed using Pearson's R Correlation test. Comparisons of qualitative variables used the chi-square test. Means were compared using Student's t-test. Linear regression was used for quantitative variables, where necessary co-variables were classified in descending order of correlation coefficient. Selected significance levels were $p>0.95$ and $p<0.05$.

RESULTS

Influence of socio-demographic variables on the severity of depression

Age

The sample of depressed patients is aged between 18 and 90 years, with a mean of 48 years (SD=10). There is a statistically significant correlation between the severity of depression and age (p=0.000; r=-0.172).

Gender

The sample consists of 188 men and 310 women; a gender ratio of 0.6. Average BDI scores are 30 for women and 27 for men and the difference is significant (t=2.492; p=0.013).

Ethnicity

All subjects are Caucasian.

Domestic situation

The average BDI score for the 242 subjects who are in a relationship is 30 (SD 13). The average score for the 256 individuals who do not have a partner is of 27 (SD=13). Student's t-test (t=2.700, p=0.007) shows that these averages are statistically different.

Employment status

The average BDI score for the 243 subjects who are employed is 30, while for the 255 who are not in work, it is 28. The Student's t-test shows no significant difference (t=-1647, p=0.100).

Life events over the past year

There is a correlation between the severity of life events in the past year and the severity of depression ($p<0.000$; $r=0.248$).

Socio-demographic impact

Statistical analyses show that age, gender, domestic situation and life events influence the level of depression. Tests of hypotheses therefore control for these variables.

Hypothesis testing

Hypothesis 1: ***There is a correlation between immune variables and severity of depression***

Table 1 shows that all cell classes are correlated with the severity of depression, with the exception of CD19. Linear regression shows that the overall model explains 12.7% (adjusted R^2) of the variance ($p<0.000$). In particular, the CD4 count is significant ($p=0.018$), and explains 7.7% of the variance (beta coefficients).

T**able** 1. Correlation between lymphocyte subsets and severity of depression

		Beck
CD3	r	-0.112
	p	0.015
CD4	r	-0.175
	p	0.000
CD8	r	0.080
	p	0.060
Ratio CD4/CD8	r	-0.093
	p	0.045
CD19	r	0.044
	p	0.346
CD16&56	r	0.113
	p	0.014

Hypothesis 2: ***There is a correlation between family dynamics and severity of depression***

Table 2 shows that only cohesion and adaptability of the family of origin are correlated with the severity of depression. Linear regression of these two variables explains 11.4% of the variance (adjusted R^2) ($p<0.000$).

A comprehensive model including the variables identified in Hypotheses 1 and 2 explains 16% of the variance (adjusted R^2) of the severity of depression ($p<0.000$). CD4 is, once again, the most powerful factor with an explanation of 9% of the variance ($p=0.018$).

Table 2. Correlation between FACESIII and severity of depression

		Beck
Family of origin cohesion	r	-0.169
	p	0.007
Family of origin adaptability	r	-0.133
	p	0.035
Nuclear family cohesion	r	-0.001
	p	0.992
Nuclear family adaptability	r	-0.001
	p	0.991
Current couple cohesion	r	0.026
	p	0.685
Current couple adaptability	r	0.019
	p	0.765
Ideal family cohesion	r	0.021
	p	0.740
Ideal family adaptability	r	-0.041
	p	0.518
Ideal couple cohesion	r	0.036
	p	0.569
Ideal couple adaptability	r	0.023
	p	0.721

Hypothesis 3: ***There is no correlation between immune variables and family dynamics***

We wanted to rule out a potential influence of family dynamics (identified in Hypothesis 2) on the lymphocyte subset (identified in the Hypothesis 1). Contrary to our expectations, Table 3 shows that there are correlations between adaptability in the family of origin and CD3, CD4 and CD16-56 counts.

DISCUSSION

Overall results are shown in Figure 1.

Various elements emerge. First, although both immune and family variables are correlated with the severity of depression (each explain about 12% of the variance) the combination of the two is a little disappointing as it only explains 16% of the variance. On the other hand, this weak cumulative effect underlines the interaction between the two variables seen Hypothesis 3. The level of interaction between family and immunity is therefore impressive. However, on reflection, this is not a new discovery, as Gusta (1994) compared the effect of cohabitation and living alone on CD4 levels in monkeys.

Table 3. Correlation between FACESIII and percentage of lymphocyte subset

		CD3	CD4	CD8	Ratio CD4/CD8	CD16&56
Family of origin cohesion	r	0.001	-0.001	0.025	-0.062	0.108
	p	0.984	0.978	0.584	0.180	0.019
Family of origin adaptability	r	0.094	0.093	0.029	-0.003	0.000
	p	0.040	0.044	0.533	0.950	0.997

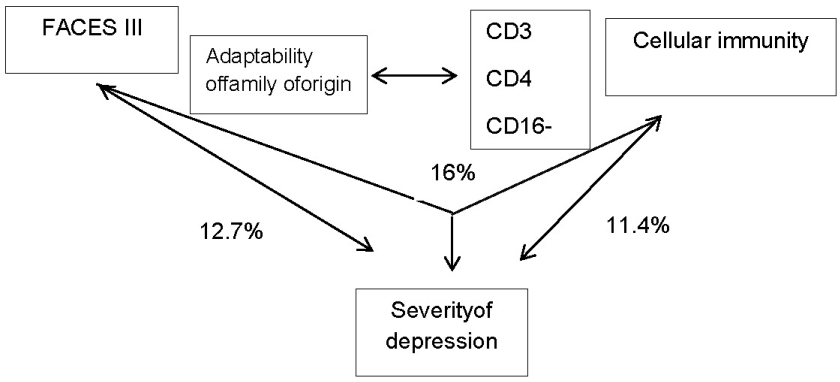

Figure 1. Interactions between immunity – family – depression

Nevertheless, this is the first demonstration of a three-way interaction between a 'mood disorder', family situation and CD4. CD4 appears to be the biological kingpin that goes beyond the concept of the 'support group' and touches upon an older idea, which is the dynamics of our family of origin.

CONCLUSION

Although the family and immunity can both explain the severity of depression, what is surprising is that they have a greater effect in combination than individually. This suggests that the psycho-immunological theory should look at the relation between immunity and family life, notably the family of origin.

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