IMMUNITY, COPING AND DEPRESSION

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SUMMARY

Background: 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 coping strategies are an important variable in the model of vulnerability to depression. Our study weighs the influence of cellular immunity and coping strategies 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 answered a Cousson's coping test and the Beck Depression Inventory (BDI).

Results: In terms of immunity, there are correlations between the BDI and percentages of CD8 (p=0.000; r=0.163), CD19 (p=0.046; r=0,090), CD16&56 (p=0.011; r=0.282), ratio CD4/CD8 (p=0.003; r=-0.135). A linear regression model for immune variables explained 25% of the BDI. In terms of coping, there is a correlation between severity of depression and ea (escape avoidance) (p=0.000; r=0.218), pr (positive reappraisal) (p=0.000; r=-0.265) and pps (planful problem solving) (p=0.000; r=-0.296). However, there is no correlation between the severity of depression and d (distancing). A linear model for coping strategies explained 12% of the BDI. Finally, there are correlations between distancing and CD8 (p=0.005; r=-0.119), CD19 (p=0.017; r=-0.102) and CD 16&56 (p=0.029; r=-0.227) but also CD3 (p=0.008; r=-0.114) and CD4 (p=0.027; r=-0.095) but not between those immune variables and the other coping strategies. In this case, a linear regression for distancing explained 10.3% of immune variables.

Conclusion: Every coping strategy has an impact on depression. But not in the same way. Ea, pps and pr strategies influence directly the risk of depression while distancing influences the immune variables themselves. Knowing that those variables impact the risk of depression, distancing has then an indirect effect on depression.

Key words: immunity – coping – depression - distancing

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INTRODUCTION

Since the work of 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 et al. (1995, 2010) highlight 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 et al. (1999) note an increase in pro-inflammatory cytokines in melancholic depression. Subsequently, Steiner et al. (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 et al. 2011) or C-reactive protein (CRP) (Zorrilla et al. 2001) as the cause of depression. Wium-Andersen et al. (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 et al. 2011), which delays neuronal regeneration. In a similar vein, Maes et al. (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.

On the other hand, studies focused on the link between coping mechanisms and the risk of depression (Kato 2014, 2015, Sugawara et al. 2012), showing that some strategies decreased the risk while others increased it. cc, ea, pr, had a stronger influence on depression than other strategy.

Other studies focused on the possible link between cancer and coping strategies (Bruchon-Schweitzer et al. 1994, Reynaert et al. 2000, Langevin et al. 2013) but without proving a direct link between cellular immunity or humoral immunity.

The aim of this study is to weigh the influence of coping and immunological variables on the severity of depressive episodes and to know the influence of coping strategies on the immune variables itself.

We test three hypotheses:

- *H1:* There is a correlation between immune variables and severity of depression;
- *H2:* There is a correlation between coping strategies and severity of depression;
- *H3:* There is a correlation between coping strategies and immune variables.

SUBJECTS 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;
- A Cousson's coping test: a 27 items French version based on the the original version created by Lazarius and Folkman coping test.

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).

Coping is defined as a process of "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person (Lazarus et al. 1984).

Lazarus et Folkman suggest two types of dimensions:

- Problem-focused coping used when we feel we have control over the situation, thus can manage the source of the problem. There are four steps to manage this stress:
  1. Define the problem;
  2. Generate alternative solutions;
  3. Learn new skills to dealing with stressors;
  4. Reappraise and find new standards of behavior.

- Emotion focused coping used when an individual feels as if they cannot manage the source of the problem. It involves gaining strategies for regulating stress:
  - Avoiding (I am not going to school);
  - Distancing (yourself from the stress, 'it doesn't matter');
  - Acceptance (I failed that exam, but I have 4 other subjects);
  - Seeking Medical Support;
  - Turning to alcohol.

The studies focusing on the adjustment strategies show us a third type of regulation: looking for social support (Cousson and al. 1996).

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: 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 22.0 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 CD3 and CD4. A linear regression shows that the overall model explains 25.0% (adjusted R2) of the variance (p<0.000).

Hypothesis 2: There is a correlation coping and severity of depression

Table 2 shows that only ea, pr and pss are correlated with the severity of depression. A linear regression with these variables explains 12% (adjusted R2) of the variance.

Hypothesis 3: There is a correlation between immune variables and coping

Table 3 shows that the immune variables are correlated with distancing but not with the others coping strategies. A linear regression with these variables explains 10.3% (adjusted R2) of the variance. Taken apart, we see that CD8 (1.4%) and CD16/56 (5%) have the strongest correlations.

Table 1. Correlation between lymphocyte subsets and severity of depression

		Beck
CD3	r	0.070
	p	0.119
CD4	r	0.008
	p	0.866
CD8	r	0.163
	p	0.000
Ratio CD4/CD8	r	-0.135
	p	0.003
CD19	r	0.090
	p	0.046
CD16 et 56	r	0.282
	p	0.011

Table 2. Correlation between coping strategies and severity of depression

		Beck
Confrontive coping (cc)	r	0.047
	p	0.295
Distancing (d)	r	-0.054
	p	0.234
Self control (sc)	r	0.023
	p	0.602
Seeking social support (sss)	r	0.072
	p	0.109
Accepting responsibility (ar)	r	0.087
	p	0.053
Escape avoidance (ea)	r	0.218
	p	0.000
Planful problem solving (pps)	r	-0.216
	p	0.000
Positive reappraisal (pr)	r	-0.265
	p	0.000

Table 3. Correlation between lymphocyte subsets and coping strategies

		cc	d	sc	sss	ar	ea	Pps	pr
CD3	r	0.004	-0.114	0.013	0.076	-0.032	0.066	0.027	0.017
	p	0.922	0.008	0.763	0.076	0.456	0.122	0.526	0.685
CD4	r	0.006	-0.095	0.006	0.047	-0.042	0.041	0.042	0.046
	p	0.883	0.027	0.890	0.270	0.325	0.338	0.324	0.287
CD8	r	0.000	-0.119	-0.052	0.099	0.011	0.075	-0.002	-0.034
	p	0.998	0.005	0.224	0.021	0.801	0.079	0.955	0.429
Ratio CD4/CD8	r	-0.034	0.007	0.032	-0.043	-0.026	0.002	0.061	0.053
	p	0.429	0.874	0.464	0.316	0.544	0.964	0.161	0.221
CD19	r	0.010	-0.102	-0.008	-0.024	0.012	0.042	0.052	0.011
	p	0.809	0.017	0.855	0.584	0.786	0.334	0.224	0.795
CD16/56	r	-0.085	-0.227	0.007	0.074	0.194	0.167	-0.037	-0.129
	p	0.415	0.029	0.945	0.478	0.063	0.110	0.724	0.216

DISCUSSION

Since a long time, hypothesis of links between psychological factors and cancer, have been established in our culture. So far, numerous researches have tempted to indicate stress, coping facing the disease, depression or "type C" personality as factors participating to the onset and/or the course of the cancer (Bruchon Schweitzer et al. 1994, Reynaert 2005). However, we find very few studies analyzing the circular relation between the immunological variables, depression and coping.

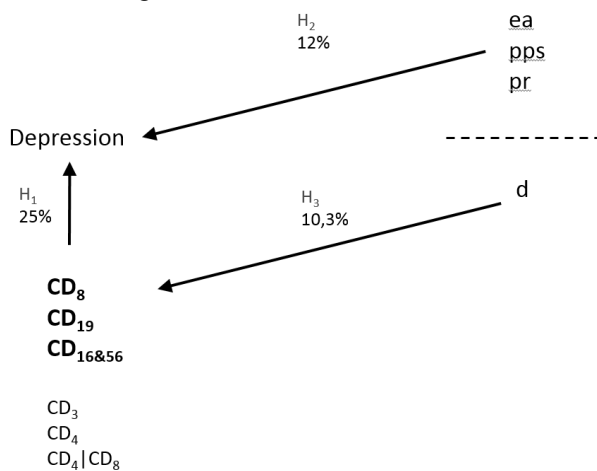Overall results are shown in figure 1. Various observations emerge.

Figure 1. Interactions between immunity-coping-depression

First

There is a correlation between coping, the immunological variables and depression.

Second

However, inside coping itself, we observe that ea, pps and pr are related to depression, while d is only linked to the immune variables (especially CD8, CD19 and CD16&56).

Third

But those same immune variables have an effect on depression.

On the one hand, we know that psy-immunological theories make it possible to forge links between immunity and depression (Wium-Andersen 2013, Zdanowicz et al. 2015). On the other hand, in our study it seems that addressing stressful events while taking some emotional step back (distancing) has a direct influence on immune variables. Distancing could then indirectly influence the risk of depression.

However, ea, pps and pr could also have a direct impact on depression, without influencing our immune system. How is that possible? It should be important to know. Some leads have already been investigated: neuro-endocrine factors, inflammatory factors, but rarely related to coping strategies.

CONCLUSION

Every coping strategy has an impact on depression. But not in the same way. Ea, pps and pr strategies influence directly the risk of depression while distancing influences the immune variables themselves. Knowing that those variables impact the risk of depression, distancing has then an indirect effect on depression.

The question regarding the mechanisms at play in this process is still open. It would be crucial to find the answer to this question considering the impact such a discovery could have in immunology, oncology.

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