*Psychiatria Danubina, 2018; Vol. 30, Suppl. 7, pp 475-478* *Conference paper*


# CORRELATIONS BETWEEN EVENT-RELATED POTENTIALS AND NK CELLS, B AND T LYMPHOCYTES

**Camille Demont, Nicolas Zdanowicz, Christine Reynaert, Jacques Denis & Thomas Dubois**

*Université Catholique de Louvain, Psychosomatics Unit, Mont-Godinne University Hospital, Yvoir, Belgium*

## *SUMMARY*

***Background:*** *The links between psychiatry and immune dysfunctions are well known. By contrast, there are few studies that evaluate the link between neuroelectrophysiology and immune system disturbances.*

***Subjects and methods:*** *We retrospectively included 31 patients hospitalized between 2011 and 2012. They completed a socio-demographic questionnaire and were assessed using DSM IV TR on Axis 1. Event-related potentials were performed. Lymphocyte subtypes were quantified using flow cytometry.*

***Results:*** *In terms of P300 latency, there are correlations with the absolute value of leukocytes: for P3a component, we find a correlation in frontal derivation Fz (r=0.405*), in central derivation Cz (r=0.438*), in parietal derivation Pz (r=0.403*) and for P3b component, there is a correlation in Fz (r=0.414*), in Cz (r=0.402*) and in Pz (r=0.425*). In terms of P300 amplitude, for P3b component, there are correlations with CD3 lymphocytes percentage in all derivations (Fz (r=-0.621**); Cz (r=-0.567**); Pz (r=-0.499**)) and with CD19 lymphocytes percentage in all derivations (Fz (r=0.469*); Cz (r=0.466*); Pz (r=0.430*)). For P3a, it is correlated with CD3 percentage (in Fz (r=-0.539**); Cz (r=-0.406*)) and with CD19 percentage (Fz (r=0.364*); Pz (r=0.357*)). With respect to the relationship between mismatch negativity (MMN) amplitude and natural killer (NK) cells percentage, there are correlations in left temporal derivation T3 (r=-0.426*), in Cz (r=-0.401*) and in right temporal derivation T4 (r=-0.427*). A correlation is found between the contingent negative variation (CNV) amplitude and the lymphocytes percentage in Fz (r=-0.471**).*

***Conclusions:*** *There is a link between lymphocyte-related immunity and electrophysiological disturbances in psychiatric patients. Further studies would be needed to evaluate this relationship more specifically, particularly prospectively and by pathology.*

***Key words:*** *immunity - event-related potentials - lymphocytes*

* * * * *

## INTRODUCTION

### Event-related potentiels and psychiatry

Event-related potentials (ERP) are electroencephalographic tracings obtained following various types of stimulations (auditory, visual, etc.). They allow the processes underlying cognition and attention to be explored. The interpretation of these plots is based on two paradigms: one electrophysiological and the other neurocognitive. These ERP are useful in the exploration of psychiatric disorders.

They reveal an interest in three preferential domains:

- the field of description, understanding of cognitive disorders and especially attention disorders;
- that of the therapeutic relationship;
- that of the prescription of medicines (Timsit-Berthier & Gerono 1997, Timsit-Berthier 2003).

In this review, different types of waves are studied, including:

- The mismatch negativity (MMN), a negative depolarization wave obtained during a preattentive automatic discrimination task. To make it appear, rare stimuli are randomly issued, among frequent and repetitive stimuli, without active detection of the subject (Faugere et al. 2013, Sur & Sinha 2009). This wave is correlated with an extraction function of relevant information from irrelevant information flow (Hermens et al. 2018). In its auditory modality, it constitutes a preattentive auditory memory, an automatic alerting system (Langosh et al. 2008). It occurs between 100 and 250 ms (Faugere et al. 2013).

  It is a non-invasive way of exploring N-methyl-D-aspartate glutamatergic perturbations. It is moderately disturbed in bipolar disorder and more severely in schizophrenia (Hermens et al. 2018) and in Alzheimer's dementia. In schizophrenia, we find a decrease in amplitude and a latency delay (Faugere et al. 2013).
- The P300 wave corresponds to a positive hyperpolarization wave occurring in an auditory modality around 300 ms. It is obtained in a stimulation paradigm similar to that used for the MMN, this time with active detection from the subject who must, for example, perform a motor reaction to each target sound. There are two components: the P3a which intervenes in the orientation reactions of the attention to a stimulus. This wave is of frontal origin and dependent on dopamine and the P3b which corresponds to the update of the working memory with respect to this new stimulus. The latter is of temporo-parietal origin and is dependent on norepinephrine (Faugere et al. 2013, Somani & Shukla 2014).

  The P300 wave is modified in almost all cerebral pathologies (Sur & Sinha 2009). In schizophrenia, the amplitude is reduced and it corresponds to the distractibility phenomenons observed in clinical practice (Micoulaud Franchi et al. 2012).

- The contingent negative variation (CNV) is a depolarization wave obtained in the following paradigm: a warning stimulus is followed by an imperative stimulus to which the patient must quickly respond with a motor response. It involves processes of learning, by association, processes of sustained attention and motor preparation. It allows, in clinical practice, the reactivity of serotonergic and catecholaminergic receptors to be examined according to its amplitude (Timsit-Berthier & Gerono 1997) and to guide the treatment.

### Inflammation and Psychiatry

Associations between inflammation and psychiatric disorders are common. For example, the study by Zdanowciz et al. (2017) showed the existence of a link between severity of depression, adaptive immunity and external events (relationships, family dynamics, life events) and how these external events are managed (coping mechanisms and intrinsic determinants such as gender) and influence this depression-immunity pairing.

Many hypotheses have emerged about the mechanisms underlying this link between mental illness and immune system disruption. Thus, the article by Pitychoukis & Padadopoulou (2010) summarizes how inflammation and stress can influence each other and also reminds us of the importance of gender as a moderating factor.

On one hand, chronic stress influences the reactivity of the immune system, both in the sense of immunoactivation - as an example, we observe a migration to the nervous central system of myeloid cells in the rat subjected to a repeated social distress (Ménard et al. 2017) - and also in the sense of an increase in the secretion of interferon (IFN) by T cells, in depression. This latter process is underpinned by a modification of the glucorticoid receptor present on these cells, corisol can no longer ensuring its anti-inflammatory function (Eyre et al. 2014, Dantzer et al. 2008, Ménard et al. 2017). This influence of stress also leads to immunosupression, as it has been demonstrated in depression, via a decrease in the cytotoxic activity of natural killer cells, among others (Pitychoukis & Padadopoulou 2010).

On the other hand, inflammation causes stress. A first argument for this effect is the finding that deregulation of T lymphocytes may be an important precursor of depressive disorder (Eyre et al. 2014). A second argument is that excessive brain inflammation creates an imbalance among the two CD4 population subtypes (helper or auxilliary T lymphocytes), namely TH1 and TH2:

- In depression, the increase in TH1 activity induces the production of indoleamine 2,3-dioxygenase (IDO), an enzyme that degrades serotonin and increases the production of quinolinic acid from tryptophan in the brain. Quinolinic acid causes an excess of glutamate release, neurotoxic, which is noted for its role in depression (Najjar et al. 2013, Dantzer et al. 2008). Another mechanism in depression is a decrease in the enzyme tetrahydrobiopterin (BH4) activity by cytokines. The latter is normally involved in the dopamine synthesis. This mechanism would be responsible for amotivational syndrome and anhedonia related to inflammation (Capuron et al. 2011).
- In schizophrenia, an excess of TH2 activity directs the degradation of tryptophan towards the formation of kynuretic acid, antagonist of the glutamate receptor, which eventually causes a hypoglutamatergy at the brain level (Najjar et al. 2013).

### Neuroelectrophysiology and inflammation

These links can be observed in the literature as those existing between interleukin 2 (IL-2) and P300. The injection of IL-2, an inflammatory mediator secreted in particular by CD4, is one of the only substances causing a direct alteration of P300 with phencyclidine; interestingly, it has hallucinogenic properties like the latter (Smith & Maes 1995). Another article (Davidson et al. 1999) highlights the link between neuroelectrophysiology and inflammation and shows that "individual differences in prefrontal activation asymmetry predict natural killer cell activity at rest and in response to challenge". In his study, Davidson uses an electroencephalographic measurement for this purpose and explains that people with a negative basic affective tone have notably a greater depletion of natural killer (NK) cells activity when they are under stress.

To the best of our knowledge, there has been no study that has investigated the link between immunity factors like CD3, CD19, NK cells and ERP.

## SUBJECTS AND METHODS

We explored the correlations between immunity and:

- P300 latency;
- P300 amplitude;
- MMN alteration;
- CNV amplitude.

After retrospectively including 31 patients who were hospitalized during the 2011-2012 year, we used sociodemographic data such as age, sex and ethnicity. All patients were hospitalized for adjustment disorder, major depressive disorder (unipolar or bipolar), pain disorder, psychotic disorder, generalized anxiety, panic disorder, substance use disorder (including alcohol, sedative or opioide medication and cannabis), and were evaluated according to the DSM 4 TR on axis 1. All patients admitted to the department underwent an event-related potential.

In routine practice, we performed ERP for all our inpatients and blood analysis including white cells typology. Analysis by flow cytometry measured the various lymphocyte populations identified by the antigenic properties of the membrane markers. They included:

- CD3, present on all T cells. There are two subpopulations: helper/suppressor and cytotoxic T cells;
- 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. There are two CD4 subtypes: TH1, responsible for macrophage activation and TH2, which induces B cells to produce antibodies;
- CD8 which are cytotoxic markers. These cells are capable of targeted cells destruction once they have been activated;
- The CD4/CD8 ratio evaluates the health of the immune system, for example in the progress of AIDS;
- CD16 and 56 which are surface markers of NK cells. NK cells are part of the innated immune system and they are capable of destroying their target in the absence of major histocompatibility complex (MHC). NK cells are non-T cells (CD3);
- CD19 which are B cell surface proteins. These cells produce immunoglobulin. As the overall lymphocyte analysis of patients is normal, and for ease of presentation, we only present relative results (Zdanowicz et al. 2017).

All statistical tests were performed using SPSS 23.0 parametric methods; types 1 and 2 errors were taken into account. No post-hoc tests were performed. Correlations were performed using Pearson's correlation test. Selected significance levels were $p>0.95$ and $p<0.05$.

## RESULTS

We present our initial findings, the others will be the subject of other publications.

### Sociodemographic parameters

***Age***

The sample of patients is aged between 29 and 69 years, with a mean of 49 years (SD: 12).

***Gender***

There were 19 Women and 12 men.

***Ethnicity***

All patients were Caucasians.

### Correlation with the P300 latency

The P300 latency is correlated with the absolute value of leukocytes: for P3a component: in frontal derivation Fz (r=0.405*), in central derivation Cz (r=0.438*), in parietal derivation Pz (r=0.403*). For P3b component: in Fz (r=0.414*) in Cz (r=0.402*) in Pz (r=0.425*).

### Correlation with the P300 amplitude

For the P3a component: it is correlated with the CD16 & CD56 percentage in Fz (r=0.367*) and with the CD19 percentage (Fz: r=0.364*; Pz: r=0.357*). It is correlated with the CD3 percentage (Fz: r=-0.539**; Cz: r=-0.406*). The P3b amplitude is correlated with the absolute value of leukocytes in Pz (r=-0.389*) and with the CD3 percentage in all derivations (Fz: r=-0.621**; Cz: r=-0.567**; Pz: r=-0.499**). It is correlated with the CD16 & 56 percentage in frontal derivation (Fz: r=0.383*) and with the CD19 percentage in all derivations (Fz: r=0.469*; Cz: r=0.466*; Pz: r=0.430*).

### Correlation with the MMN

Regarding the amplitude: it is correlated with the lymphocytes percentage, in right temporal derivation T4: r=-0.430* and with the CD 16 & 56 percentage, in left temporal derivation T3: r=-0.426*; in Cz: r=-0.0401*; in right temporal derivation T4: r=-0.427*.

For latency, we find only one result with the absolute value of leukocytes (Cz: r=0.367*).

### Correlation with the CNV amplitude:

The CNV amplitude is correlated with the lymphocyte percentage (Fz: r=-0.471**).

So there seems to be a correlation between lymphocyte immunity and ERP in our patients.

Note: *P<0.05; **P<0.01; ***P<0.001.

## DISCUSSION

There are many biases in our study, whether from the point of view of the limited number of subjects or the retrospective nature of our study. Nevertheless, we can note different points:

First, these results seem consistent with previous studies examining the impact of IL-2 on the P300 amplitude since IL-2 is produced in particular by CD4 T cells. In addition, as stated in the introduction, it is known that CD4 lymphocytes may intervene in certain mechanisms underlying mental pathology.

Secondly, as event-related potential is a measure of cognitive and attentional processes, it could be argued that there is a link between cognitive function and lymphocyte immunity in patients. Preattentive automatic discrimination functions (MMN) appear to be linked to the NK cells rate. Orientation attention functions (P3a) and work memory update (P3b) seem to be related to the CD3 and CD19 rate, with a different type of correlation if it is the CD3 or CD19 population. Finally, this study asks the following questions: is there a transnosographic link between cognitive function and immune factors? Can this "cognitive function and immunity" pairing be found in the general population or is the link only present in persons with a disturbed mode of information processing?

## CONCLUSION

This study shows only a correlation between lymphocyte-related immunity and event-related potentials, providing information on attentional and cognitive functions. Further studies are needed to clarify the nature of this link.

## Acknowledgements:

**Financial support:**
This research received no specific grant from any funding agency, commercial or not-for-profit sectors

***Conflict of interest:*** None to declare.

## Contribution of individual authors:

Camille Demont is the first author, he conduct the study and write the manuscript.

*Nicolas Zdanowicz* made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

*Camille Demont, Christine Reynaert, Denis Jacques & Thomas Dubois* participated in the proofreading of the article.

## References

1. *Capuron L, Schroecksnadel S, Féart C, Aubert A, Higueret D, Barberger-Gateau P et al.: Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. Biol Psychiatr 2011; 70:175-182*
2. *Dantzer R, O'Connor JC, Freund GG, Johnson RW & Kelley KW: From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008; 9:46*
3. *Davidson RJ, Coe CC, Dolski I & Donzella B: Individual differences in prefrontal activation asymmetry predict natural killer cell activity at rest and in response to challenge. Brain Beha Immu 1999; 13:93-108*
4. *Eyre HA, Stuart MJ & Baune BT: A phase-specific neuroimmune model of clinical depression. Prog Neuropsychopharmacol Biol Psychiatry 2014; 54:265-274*
5. *Faugere M, Cermolacce M, Balzani C, Micoulaud Franchi JA & Vion Dury J: Potentiels évoqués cognitifs en psychiatrie. Dans Annales Médico-psychologiques, revue psychiatrique; 171:342-349. Elsevier Masson 2013*
6. *Hermens DF, Chitty KM & Kaur M: Mismatch negativity in bipolar disorder: A neurophysiological biomarker of intermediate effect? Schizophr Res 2018; 191:132-139*
7. *Langosh J, Rand S, Ghosh B, Sharma S, Tench C, Stratton et al.: A clinical electrophysiological study of emotional lability in patients with systemic lupus erythematosus. J Neuropsychiatry Clin Neurosci 2008; 20:201-209*
8. *Ménard C, Pfau ML, Hodes GE & Russo SJ: Immune and neuroendocrine mechanisms of stress vulnerability and resilience. Neuropsychopharmacology 2017; 42:62*
9. *Micoulaud Franchi JA, Vion Dury J & Cermolacce M: Endophénotypes neurophysiologiques et trouble schizophrénique: naissance et évolution d'un concept clinique. Encéphale 2012; 38:103-109*
10. *Najjar S, Pearlman DM, Alper K, Najjar A & Devinsky O: Neuroinflammation and psychiatric illness. J Neuroinfl 2013; 10:816*
11. *Pitychoukis PM & Padadopoulou-Daifoti Z: Of depression and immunity: does sex matter? Int J Neuropsychopharmacology 2010; 13:675-689*
12. *Smith RS & Maes M: The macrophage-T-lymphocyte theory of schizophrenia: additional evidence. Med Hypotheses 1995; 45:135-141*
13. *Somani S & Shukla J: The P300 wave of Event-Related Potential. RRJMHS Dec 2014; 3:33-42*
14. *Sur S & Sinha VK: Event-related potential: An overview. Ind Psychiatry J 2009; 18:70*
15. *Timsit-Berthier M & Gerono A: Manuel d'interprétation des potentiels évoqués endogènes (P300 et CNV). Mardaga Editions Bruxelles*
16. *Timsit-Berthier M: Intérêt de l'exploration neurophysiologique en psychiatrie clinique. Neurophysiol Clin 2003; 33:67-77*
17. *Zdanowciz N, Reynaert C, Jacques D & Dubois T: Depression and immunity: a psychosomatic unit. Psychiatr Danub 2017; 29:274-278*

*Correspondence:*
*Camille Demont, MD, MSc*
*Université Catholique de Louvain, Psychosomatics Unit, Mont-Godinne University Hospital*
*5530 Yvoir, Belgium*
*E-mail: camille.demont@student.uclouvain.be*