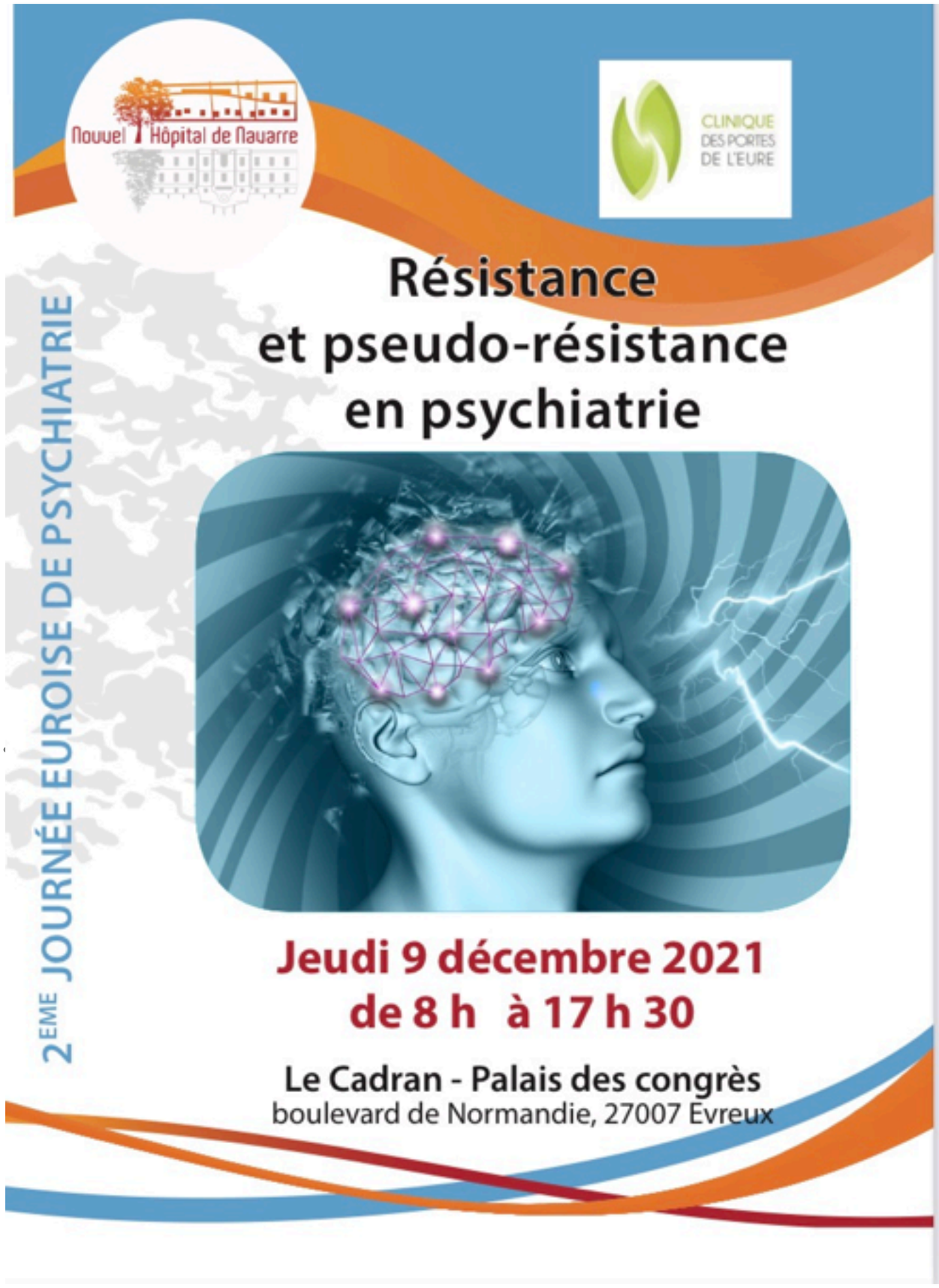
Immuno-inflammation et résistance aux traitements.

Nora HAMDANI

MD-PhD

Cabinet Cédiapsy

nora.hamdani@cediapsy.com



FACTEURS DE RESISTANCE AUX TRAITEMENTS DANS LA DEPRESSION ET LA SCHIZOPHRÉNIE

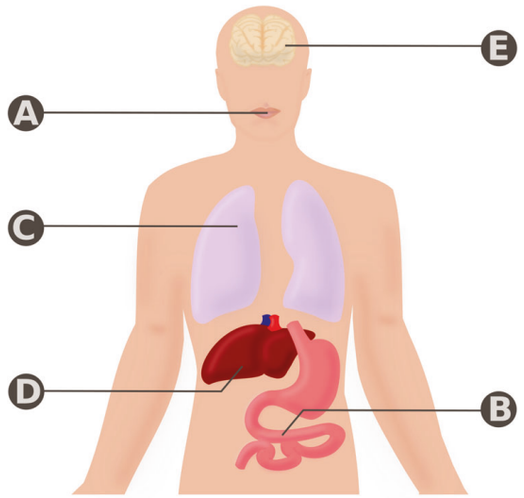


Fig. 3 Pseudo-resistance to treatment in psychiatry: treatment related factors. A Poor concordance with medication or forgetfulness may result in insufficient drug being taken to achieve a therapeutic response, **B** Polymorphisms in P-glycoproteins in the gut endothelia may result in poor absorption of drugs and insufficient drug exposure. **C** Smoking tobacco induces expression of CYP450 enzymes, particularly CYP1A2, in the liver (**D**) resulting in enhanced break down of psychiatric medication metabolised by these enzymes. Polymorphisms in CYP450 enzymes that enhance their activity or co-administration of other psychiatric/non-psychiatric medications that act as enzyme inducers will have a similar effect. **E** Poor brain accumulation of drug owing to poor blood brain barrier permeability and/or polymorphisms in P-glycoprotein may result in insufficient central nervous system drug levels to achieve a therapeutic response.

Table 2. Potential contributors to pseudo-resistance in schizophrenia and depression.

	Schizophrenia	Depression
Drug plasma levels and adherence	Over one third of patients identified as 'treatment resistant' show evidence of poor adherence [23]	A cross-sectional study observed that 15% of patients with MDD presenting with poor clinical response to tricyclic antidepressant therapy had 'unusually low plasma concentrations relative to dose' [119]. Poor adherence is reported in 10–60% of patients with depression [24]
Genetic variants affecting trans-membrane transporters	P-glycoprotein transporter polymorphisms influence antipsychotic response in schizophrenia [120]	P-glycoprotein transporter polymorphisms predict treatment response in depression [121]
Genetic variants affecting liver drug metabolism	Both first-generation and second-generation antipsychotics plasma levels and/or efficacy reduced by some CYP1A2, 2D6 and 3A4 polymorphisms [122]	Ultra-rapid metabolizer capacity recognised with polymorphisms of certain CYP450 enzymes (e.g., CYP2D6 and CYP2C19) result in reduced plasma levels for several antidepressants, including TCAs, SSRIs and SNRIs, and influence clinical response [123]
Liver drug metabolism: influence of co-prescribed psychiatric medication	Co-prescription of psychiatric medications that act as CYP450 inducers (e.g., lamotrigine and carbamazepine) can reduce plasma levels of some antipsychotics [124]	Co-prescription of psychiatric medications that act as CYP450 inducers (e.g., lamotrigine, carbamazepine) can reduce plasma levels of some antidepressants, including TCAs, SSRIs and bupropion [125]
Liver drug metabolism: influence of co-prescribed physical health medication	Co-prescription of medications that act as CYP450 inducers (e.g., omeprazole, phenytoin, St John's wort, rifampicin) can reduce plasma levels of some antipsychotics [122]	Co-prescription of medications that act as CYP450 inducers (e.g., St John's wort, phenytoin) may reduce plasma levels of some antidepressants [126]
Tobacco smoking	Smoking reduces plasma levels of those antipsychotics metabolised via CYP1A2 (e.g., olanzapine, clozapine) [127]	Smoking reduces plasma concentrations of various antidepressants [128]
Sex	Male gender predicts lower plasma levels of some antipsychotics [129]	Male gender predicts lower plasma levels of some antidepressants [130]
Alternative Diagnosis	Symptoms of other disorders, such as bipolar affective disorder, obsessive compulsive disorder or autism spectrum disorder, may be mistaken for schizophrenia [31, 32]	A minority of apparently resistant unipolar depression may in fact be depression associated with bipolar disorder [33, 34]

Further evidence is provided in eTable 1.
TCA tricyclic anti-depressant, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin and norepinephrine reuptake inhibitor.

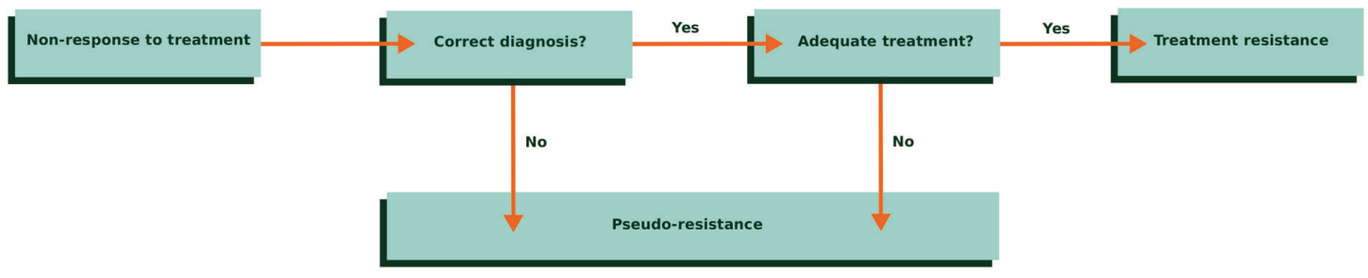


Fig. 4 Algorithm for approaching non-response to treatment in psychiatric illness. Persistent symptoms despite treatment could be due to treatment resistance or due to other factors that give the impression of treatment resistance when in fact adequate treatment has not been received (pseudo-resistance). Pseudo-resistance may be secondary to an incorrect primary diagnosis/psychiatric comorbidity/substance abuse, or be treatment related, including poor treatment adherence, malabsorption of drug, poor blood brain barrier penetrance of drug or fast metabolism of drug (see Table 2 and Fig. 3).

Les facteurs de risque environnementaux associés à BP/SZ

Prénatale/Périnatale:

- Grippe pendant la grossesse

(Parboosing et al., 2013)

- Stress Maternel

(Kleinhaus et al., 2013, Malaspina et al, 2008)

- Malnutrition Maternelle

(McGrath et al, 2011)

- Excès de naissances hiver/printemps

(Torrey et al., 1997)

Enfance:

- Stress très précoce pendant l'enfance

(Mortensen et al., 2003)

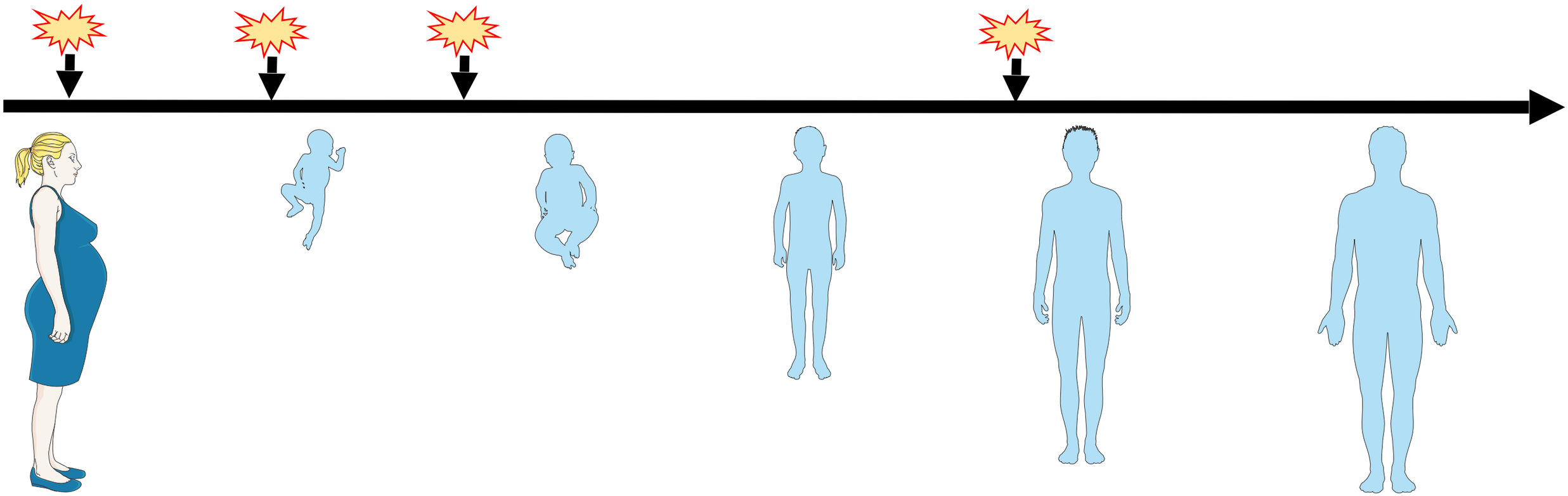
- Traumatisme pendant l'enfance (négligence et abus)

(Etain et al., 2013)

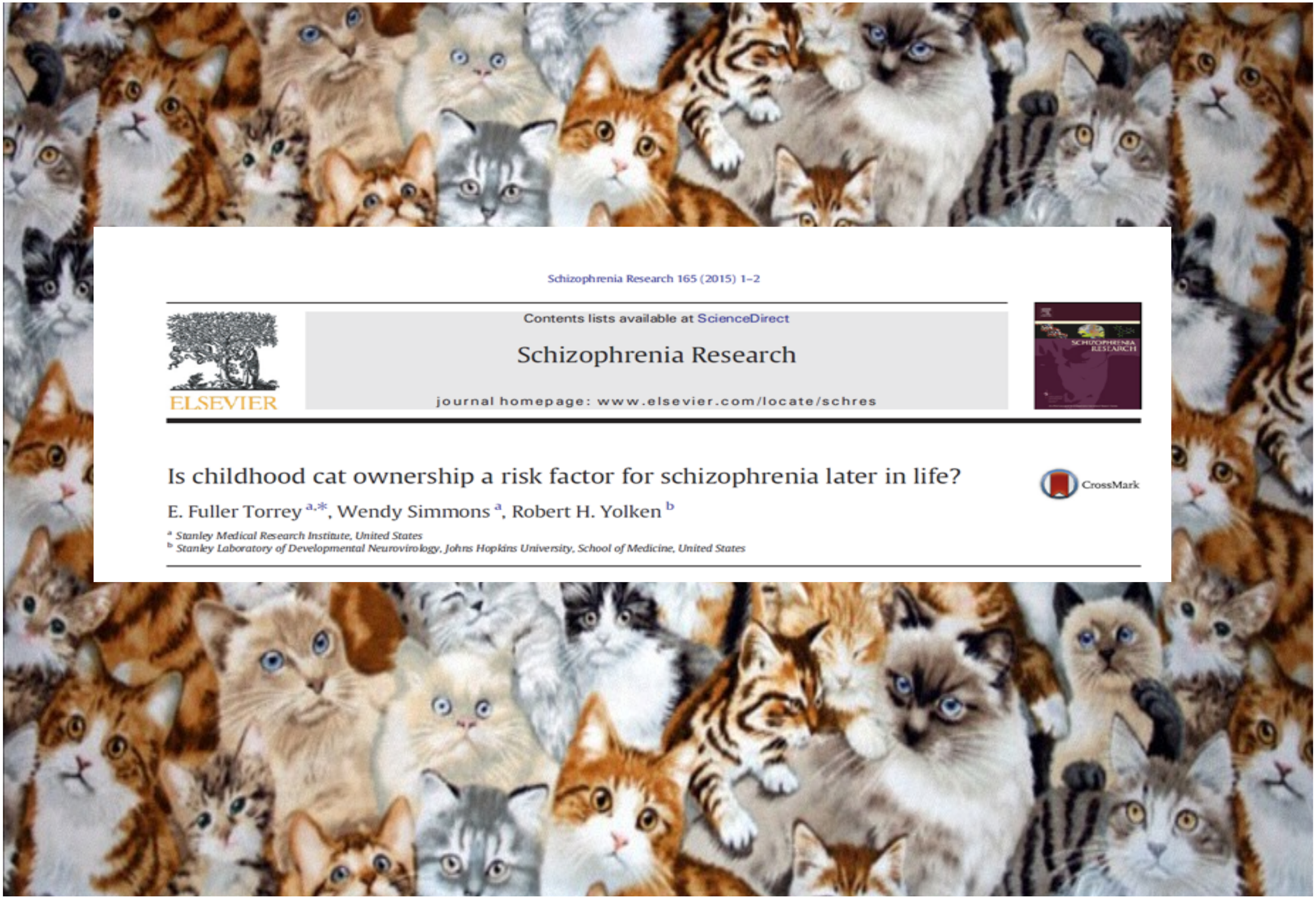
Jeunes adultes:

- Stress Psychosocial
- Manque de sommeil
- Alimentation
- Vitamine D basse

(Berk et al, 2013)



Toxoplasmose et schizophrénie



Schizophrenia Research 165 (2015) 1–2

Contents lists available at ScienceDirect

Schizophrenia Research

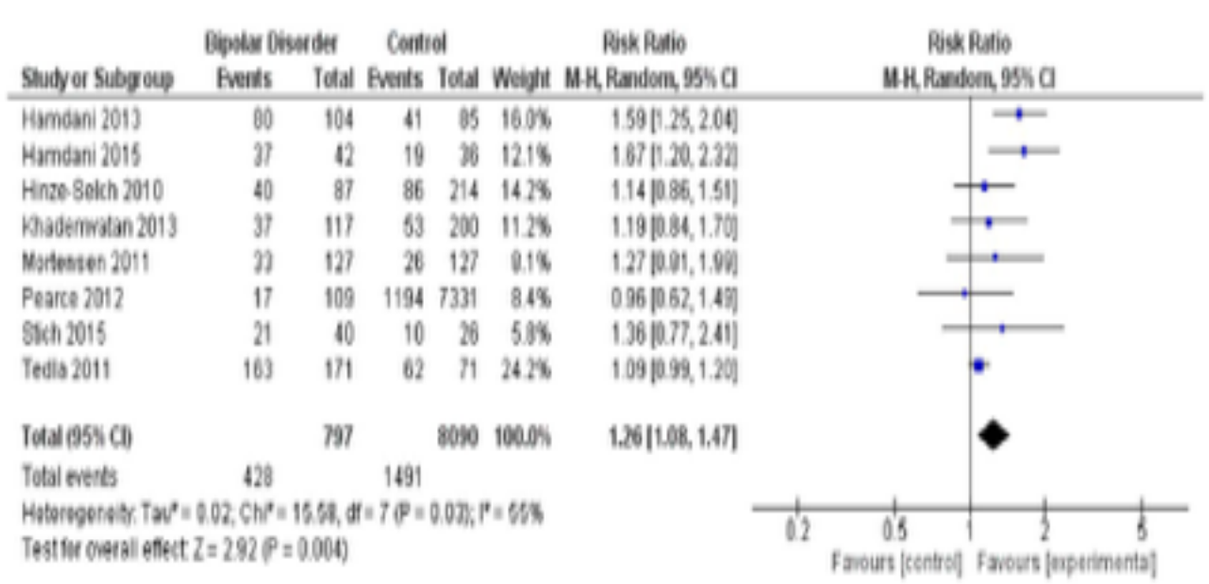
journal homepage: www.elsevier.com/locate/schres

Is childhood cat ownership a risk factor for schizophrenia later in life?

E. Fuller Torrey [a,*], Wendy Simmons [a], Robert H. Yolken [b]

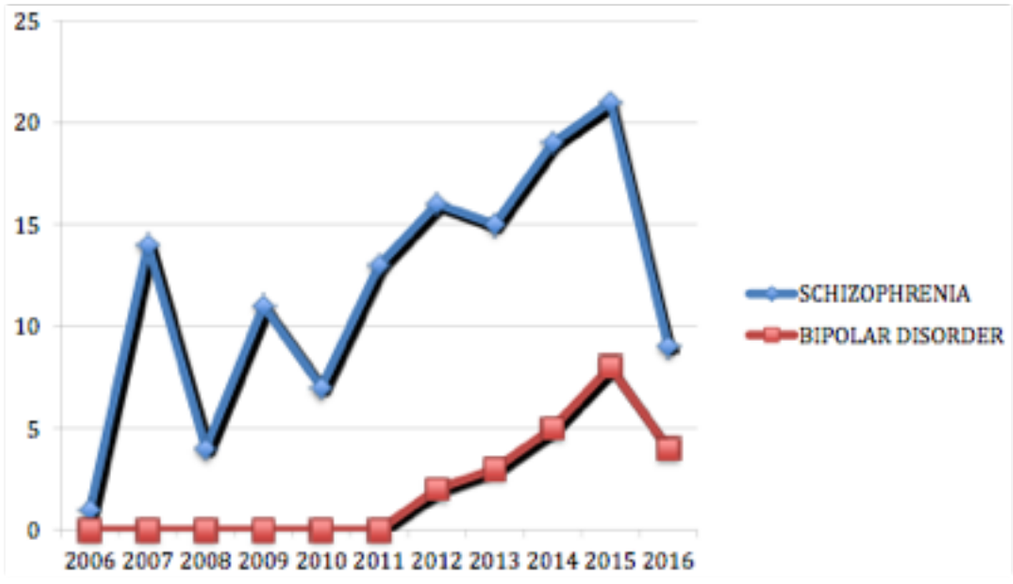
[a] Stanley Medical Research Institute, United States
[b] Stanley Laboratory of Developmental Neurovirology, Johns Hopkins University, School of Medicine, United States

ARE CATS RESPONSIBLE FOR BIPOLAR DISORDER?



OR = 1.52, p=0.02

Monteiro de Baros et al., 2017, *JAD*



Publications consacrées au trouble bipolaire et à la schizophrénie

Del Grande et al., 2017, *pathogens*

Toxoplasmose et trouble unipolaire

Flegr and Hodný *Parasites & Vectors* (2016) 9:8
DOI 10.1186/s13071-015-1290-7

Parasites & Vectors

RESEARCH Open Access

Cat scratches, not bites, are associated with unipolar depression - cross-sectional study

Jaroslav Flegr[1*] and Zdeněk Hodný[2]

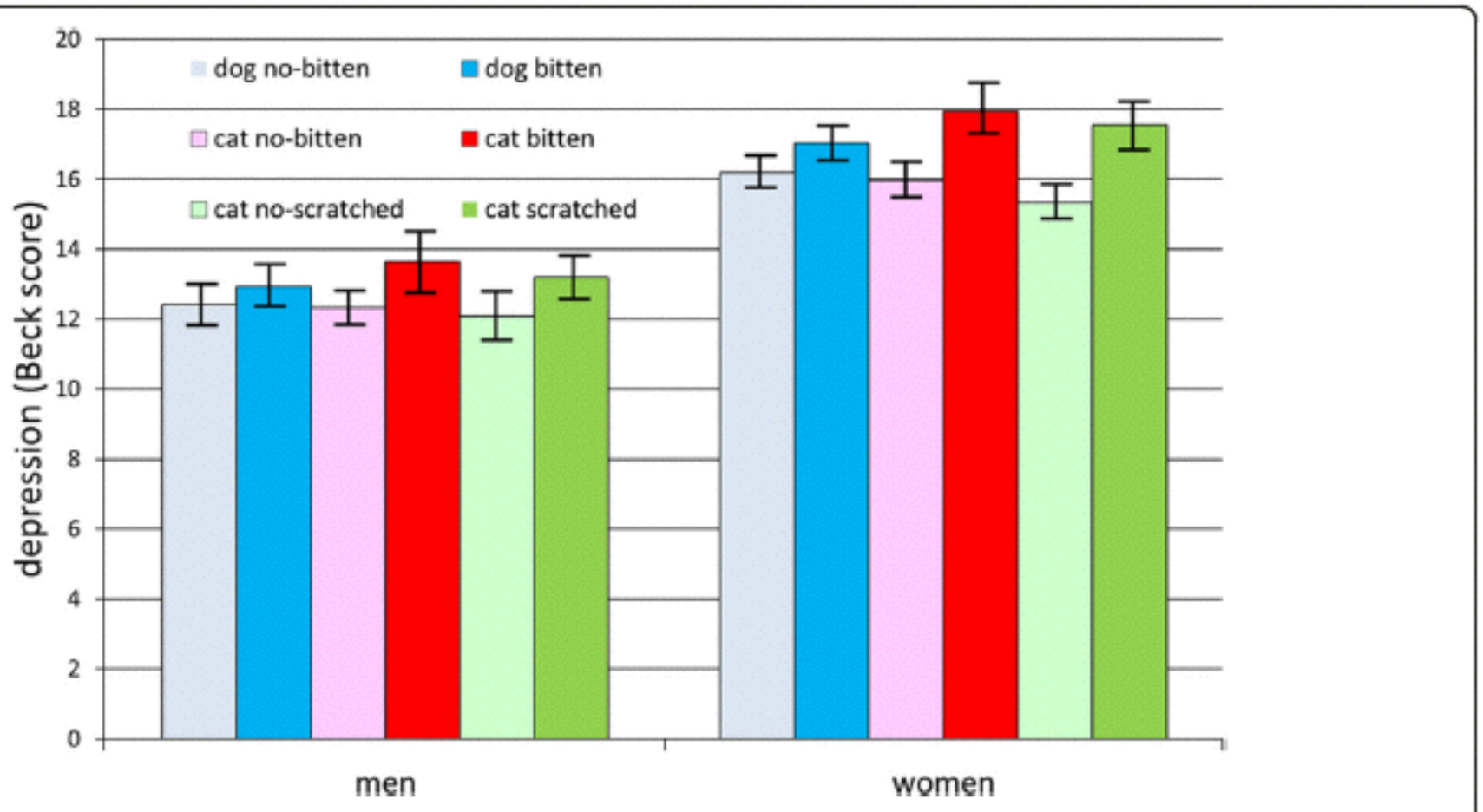
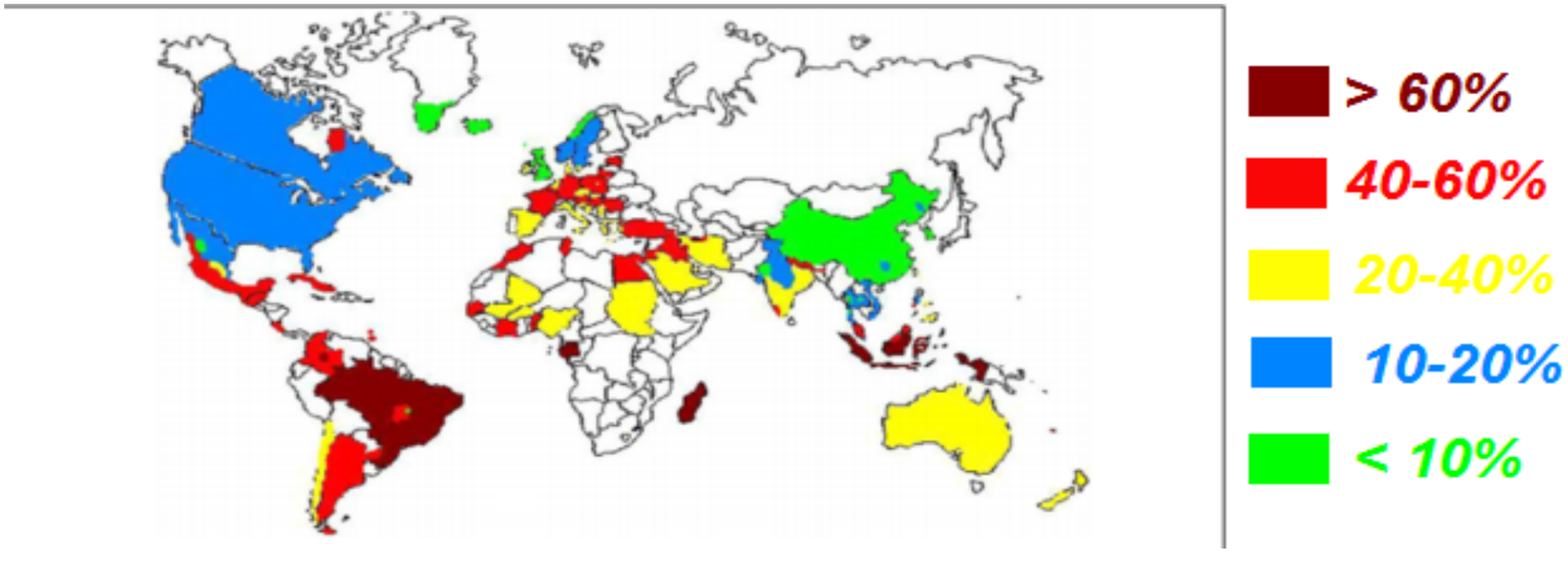
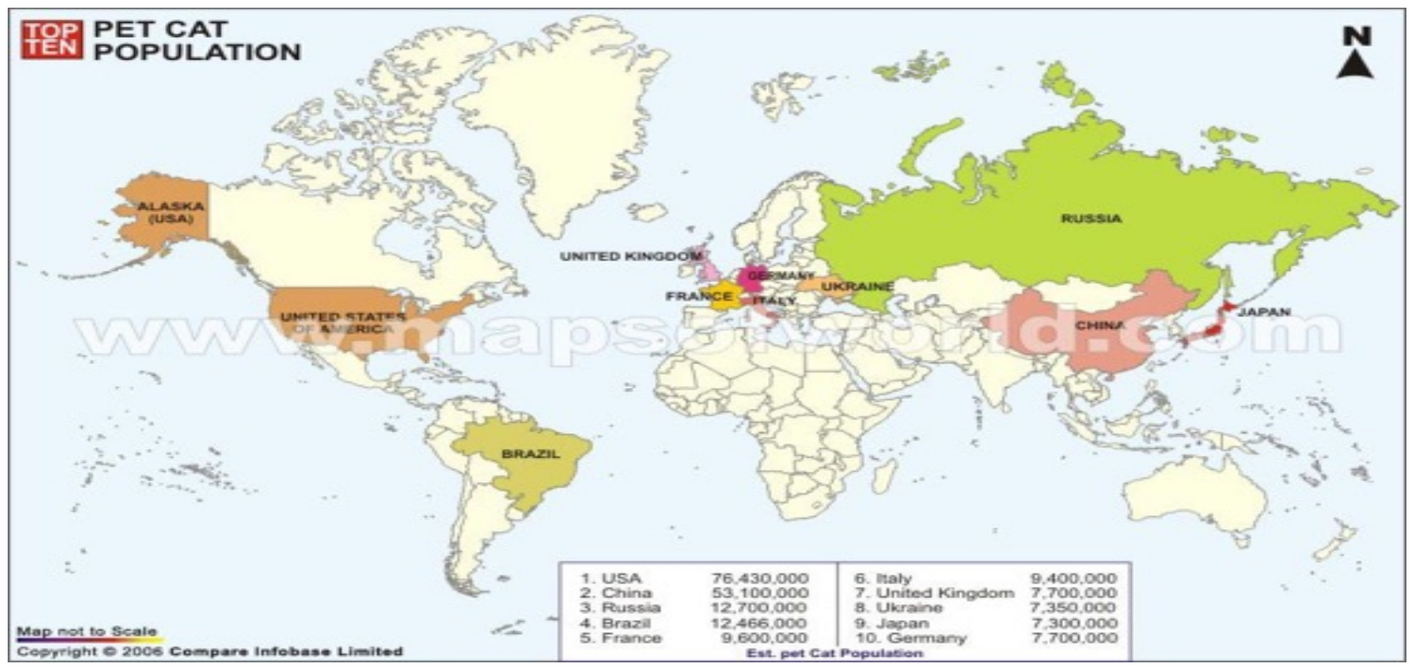


Fig. 1 Effects of a dog biting and a cat biting/scratching on Beck depression score. *Hights of columns shows awerage Back depression score in particular groups, the spreads show 95 % CI*

Epidémiologie de la toxoplasmose





Choisir un thymorégulateur ou un antipsychotique en fonction de ses propriétés anti-parasitaires

Journal of Psychiatric Research 63 (2015) 58–64

Contents lists available at ScienceDirect

Journal of Psychiatric Research

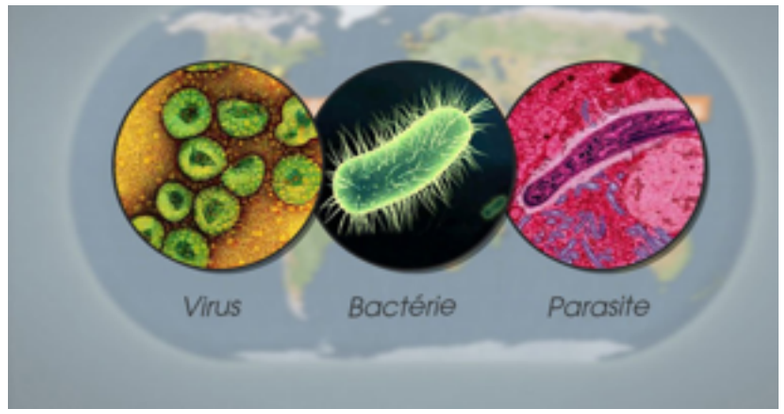
journal homepage: www.elsevier.com/locate/psychires

Treatment with anti-toxoplasmic activity (TATA) for toxoplasma positive patients with bipolar disorders or schizophrenia: A cross-sectional study

Guillaume Fond [a, b, *], Laurent Boyer [b, c], Alexandru Gaman [b], Hakim Laouamri [b], Dodji Attiba [b], Jean-Romain Richard [a, b], Marine Delavest [b, d], Josselin Houenou [a, b, e], Philippe Le Corvoisier [f], Dominique Charron [g], Rajagopal Krishnamoorthy [h], José Oliveira [b, f], Ryad Tamouza [f], Robert Yolken [i, j], Faith Dickerson [j], Marion Leboyer [a, b, f], Nora Hamdani [a, b, f]

*Lithium : diminue les infections bactériennes et virales notamment herpétiques (HSV1&2)

AP : activités anti-bactériennes et anti-toxo



Valproate et sels de valproate : activités anti-toxoplasma+++

Effects of the treatments in toxopositive patients with bipolar disorders: comparison of treatments with antitoxoplasmic activity (TATA+) versus those without (TATA-). Univariate and multivariate analyses. Significant associations ($p<0.05$) are in bold.

	Univariate analyses				Multivariate analyses	
	Whole sample n = 115	n = 59 TATA+	n = 56 TATA−	p value[a]	Adjusted OR [IC95]	p value[b]
Lifetime number of depressive episodes	**4 [0–35]**	**3 [0–27]**	**5 [1–35]**	**0.042**	**1.09 [1.01; 1.19]**	**0.048**

152 BP, 114 SZ

*R. Doukhan,… **N. Hamdani**. Hypothèses immuno-inflammatoires dans le trouble bipolaire. Ouvrage collectif « Troubles bipolaires ». Editions Lavoisier (Médecine-Sciences), Paris 2014, pages : 325-335.

Hamdani N et al., Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. Current Psy Reports, 2013, Sep;15(9):387

Hamdani N et al., Immuno-inflammatory markers of bipolar disorder: a review of evidence. Frontiers in Biosc, 2012, Jan 1;4:2170-8

Recherche d'une infection expliquant la résistance aux traitements

Hamdani *et al. BMC Psychiatry* 2013, **13**:81
http://www.biomedcentral.com/1471-244X/13/81

BMC Psychiatry

CASE REPORT Open Access

A bipolar disorder patient becoming asymptomatic after adjunctive anti-filiarasis treatment: a case report

Nora Hamdani[1,2,3,4*], Raphaël Doukhan[2], Aline Picard[2], Ryad TAmouza[5,6] and Marion Leboyer[1,2,3,4]

Accès maniaque résistant aux traitements avec isolement et contentions.

Intérêt de la NFS : hyperéosinophilie (Filariose).

Amélioration spectaculaire après adjonction d'antihelmintiques.

Les facteurs de risque environnementaux associés à BP/SZ sont également des facteurs pro- inflammatoires

Prénatale/Périnatale:

- Grippe pendant la grossesse

(Parboosing et al., 2013)

- stress Maternel

(Kleinhaus et al., 2013, Malaspina et al, 2008)

- Malnutrition Maternelle

(McGrath et al, 2011)

- Excès de naissances hiver/printemps

(Torrey et al., 1997)

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- Stress très précoce pendant l'enfance

(Mortensen et al., 2003)

- Traumatisme pendant l'enfance (négligence et abus)

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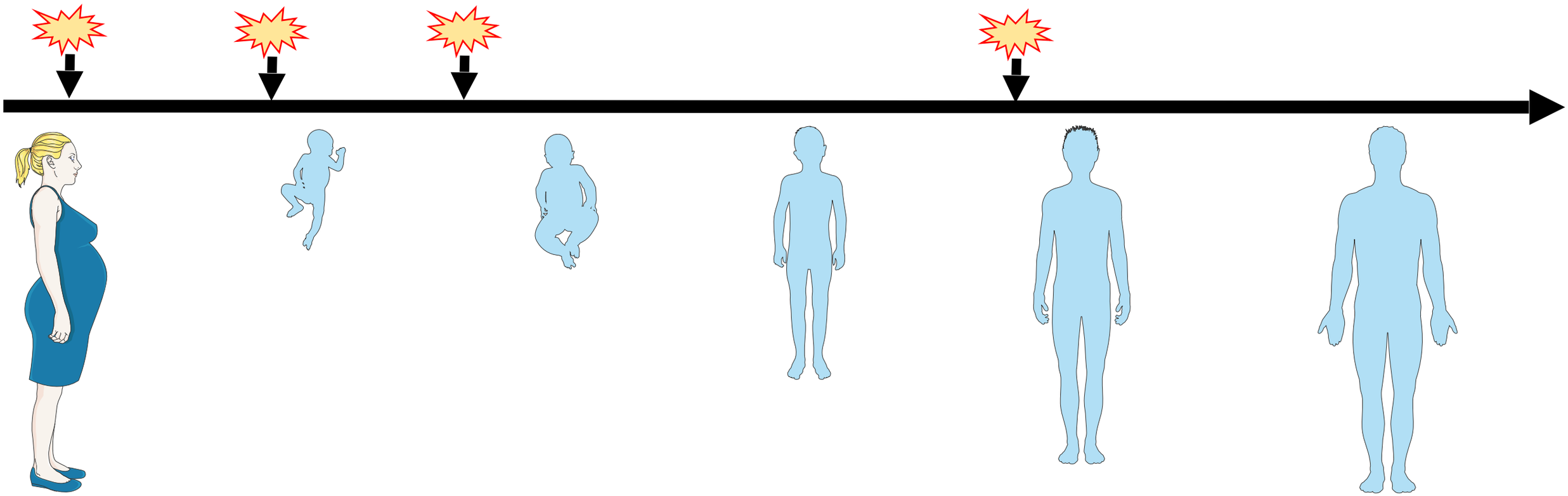
Jeunes adultes:

- Stress Psychosocial
- Manque de sommeil
- Alimentation
- Vitamine D basse

(Berk et al, 2013)



Les infections peuvent provoquer une inflammation : exemple du trouble bipolaire

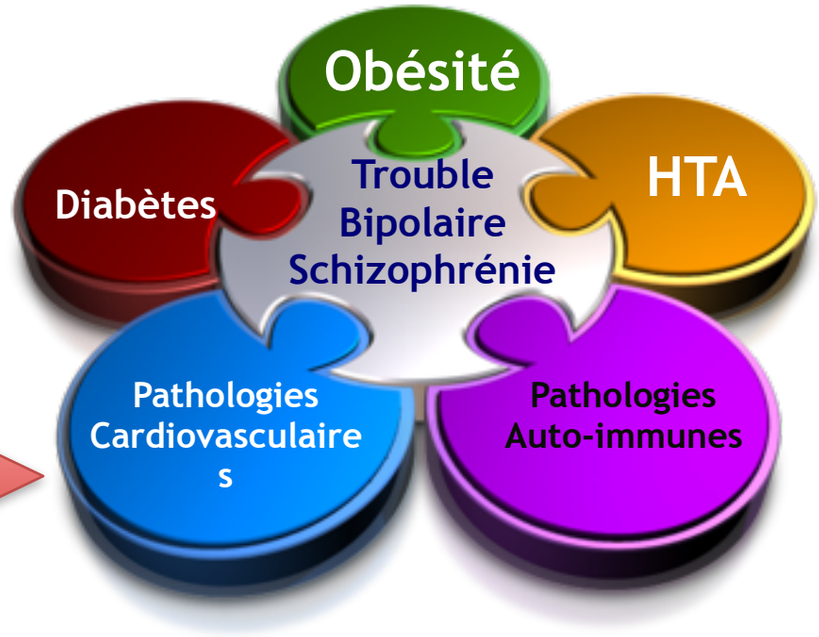
Cytokines
déséquilibre pro-inflammatoire

↗ TNF, IL-2, IL-4, **IL-6**
chemokines

(O'brien et al.,2006, Tsai et al., 1999; Knijff et al., 2007)

Immunité humorale

déficits IgG, A, M



Inflammation de bas grade

Immuno-génétique

HLA, TLR, NOD, CRP…

Oliveira et al., 2014, Clerici et al., 2009; Czerski et al., 2008)

↗ CRP
Phase aiguë et stable

(Wadee et al., 2002; Huang, 2007 DeBerardis et al., 2008; Tsai et al., 2012, Dickerson et al., 2007; Cunha et al.,2008)

Reviews

Hamdani N et al., Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. Current Psy Reports, 2013, Sep;15(9):387

Hamdani N et al., Immuno-inflammatory markers of bipolar disorder: a review of evidence. Frontiers in Biosc, 2012, Jan 1;4:2170-82

Marqueurs d'une inflammation de bas niveau dans le trouble bipolaire

Marqueurs d'une inflammation péripherique

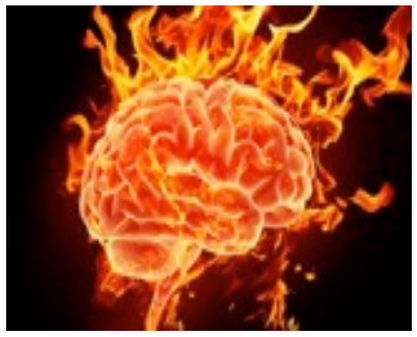
Modifications des taux de Cytokines (Modabbernia et al. *Biol Psychiatry*, 2013)

↑ IL-6, TNF-α , IL-10, IL-4, soluble IL-2 Receptor, sIL-6R, sTNFR1
Independent de la prise de traitement

↑ acute-phase proteins
C-reactive protein, haptoglobin, fibrinogen, α1-antitrypsin and hemopexin
(Dargél et al. *J Clin Psychiatry*, 2015; Maes et al. *Psychiatry Res*, 1997)

Activation pro-inflammatoire du système T-cell et macrophage-monocyte
(Breunis et al., 2003; Drexhage et al., 2011)

Marqueurs centraux d' inflammation



- ↑ IL-1β (liquide cérébro-spinal) (Söderlund et al. *J Psychiatry Neurosci*, 2011)
- ↑ taux de protéine et mRNA IL-1β, IL-1 recepteur, MyD88 and NF-κB (prefrontal cortex en post-mortem) (Rao et al. *Mol Psychiatry*, 2010)
- Activation microgliale (Stertz et al. *Curr Opin Psychiatry*, 2013

Reviews :
Hamdani N et al., Current Psy Reports, 2013
Hamdani N et al., Frontiers in Biosc, 2012

Impact cognitif de la toxoplasmose et/ou des virus de l'herpès sur la cognition dans le trouble bipolaire et la schizophrénie.

(Hamdani et al., J Clin Psy, 2017)

- **Agents infectieux**

- **T. gondii**

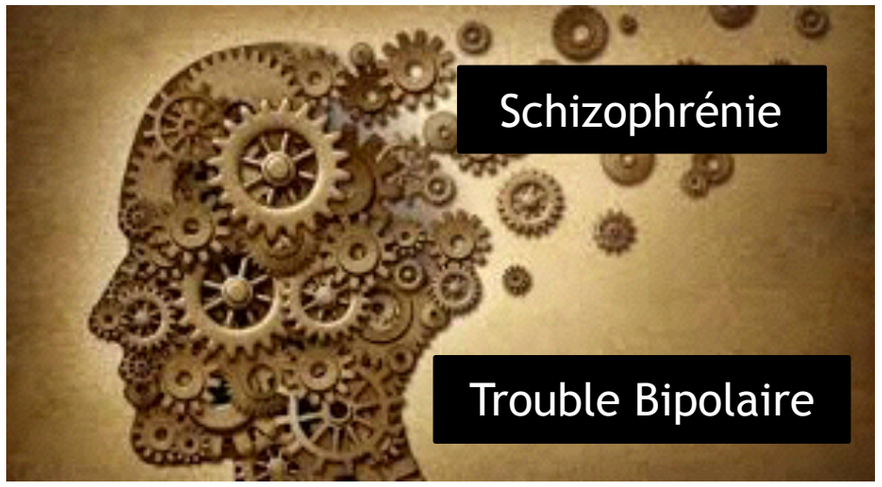
(baisse de QI, tr. mémoire et attention, Yolken et al., 2009; Flegr et al., 2017, 2014, 2013)

- **CMV**

(fcts exécutives, mémoire verbale, Shirts et al., 2008; Houenou et al., 2014)

- **HSV1**

(déclin cognitif, mémoire, attention, v de traitement, Atello et al., 2006, Dickerson et al., 2006, 2008, 2012)



- **Troubles cognitifs**

- Fréquents
- sévères
- avant la maladie et après stabilisation
- mémoire de travail, fcts executives, attention, cognition sociale, v de traitement…

(Keefe et al., Bourne et al., 2013; Hellvin et al., 2012)

Mesure de l'effet individuel de chaque agent infectieux (HSV1, HSV2, CMV, T. gondii) sur la cognition.
Mesure de l'effet combiné des agents infectieux sur la cognition
comparaison de 3 populations : bipolaires, schizophrènes et contrôles

T. gondii, trouble bipolaire et détérioration cognitive : rôle de l'IL-6

Journal of Affective Disorders 179 (2015) 161–166

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

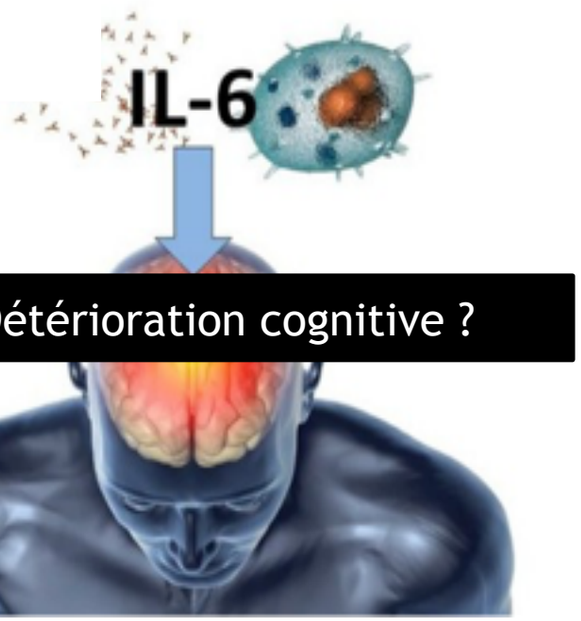
Cognitive deterioration among bipolar disorder patients infected by *Toxoplasma gondii* is correlated to interleukin 6 levels

Nora Hamdani [a,b,c,*], Claire Daban-Huard [a,b,c], Mohamed Lajnef [a,b,c], Rémi Gadel [a,b,c], Philippe Le Corvoisier [f], Marine Delavest [d,e], Soufiane Carde [a,b,c,d], Jean-Pierre Lépine [c,e], Stéphane Jamain [c,e], Josselin Houenou [a,b,c,d], Bijan Galeh [f], Jean-Romain Richard [a,c], Masayuki Aoki [c,g], Dominique Charron [c,g], Rajagopal Krishnamoorthy [h], Robert Yolken [i], Faith Dickerson [i], Ryad Tamouza [c,j,1], Marion Leboyer [a,b,c,1]

Détérioration cognitive

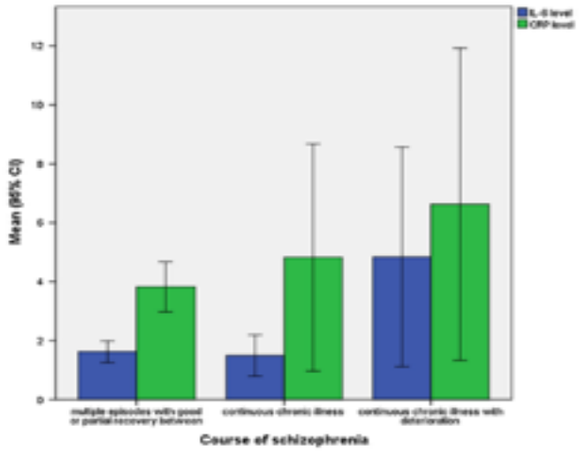
$$DI = \frac{\left|\frac{(\text{Information} + \text{Vocabulary})}{2} - \text{Digit Symbol}\right|}{\frac{|\text{Information} + \text{Vocabulary}|}{2}}$$

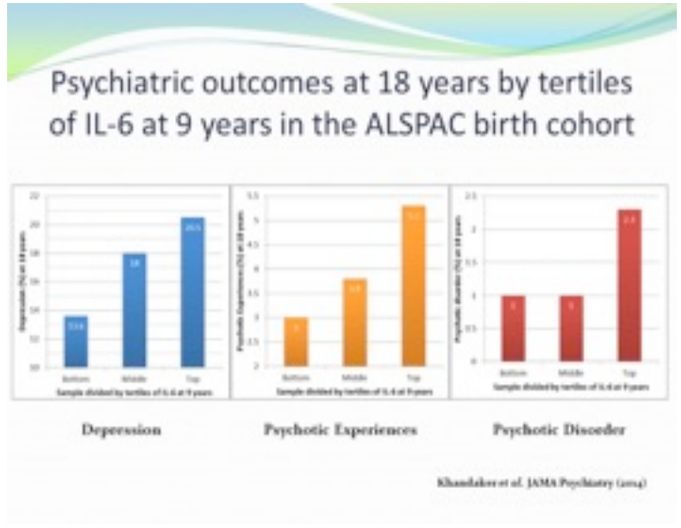
T. gondii



IL-6 : activation immédiate dans le cerveau
Voie Th2 stimulée avec production périphérique
Effets neurolotoxique microglie

Fig. 1 The comparison of hsCRP and IL-6 ($p > 0.05$ and $p = 0.01$, respectively) levels among patients with different course of schizophrenia (multiple episodes with good or partial recovery between episodes, continuous chronic illness, continuous chronic illness with deterioration)





Frydecka et al., Eur Arch Psy Clin Neurosc, 2014

INTÉRÊT DES ANTI-INFLAMMATOIRES DANS LA SCHIZOPHRÉNIE

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2014: 129: 163–179
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DOI: 10.1111/acps.12211

Review

Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review

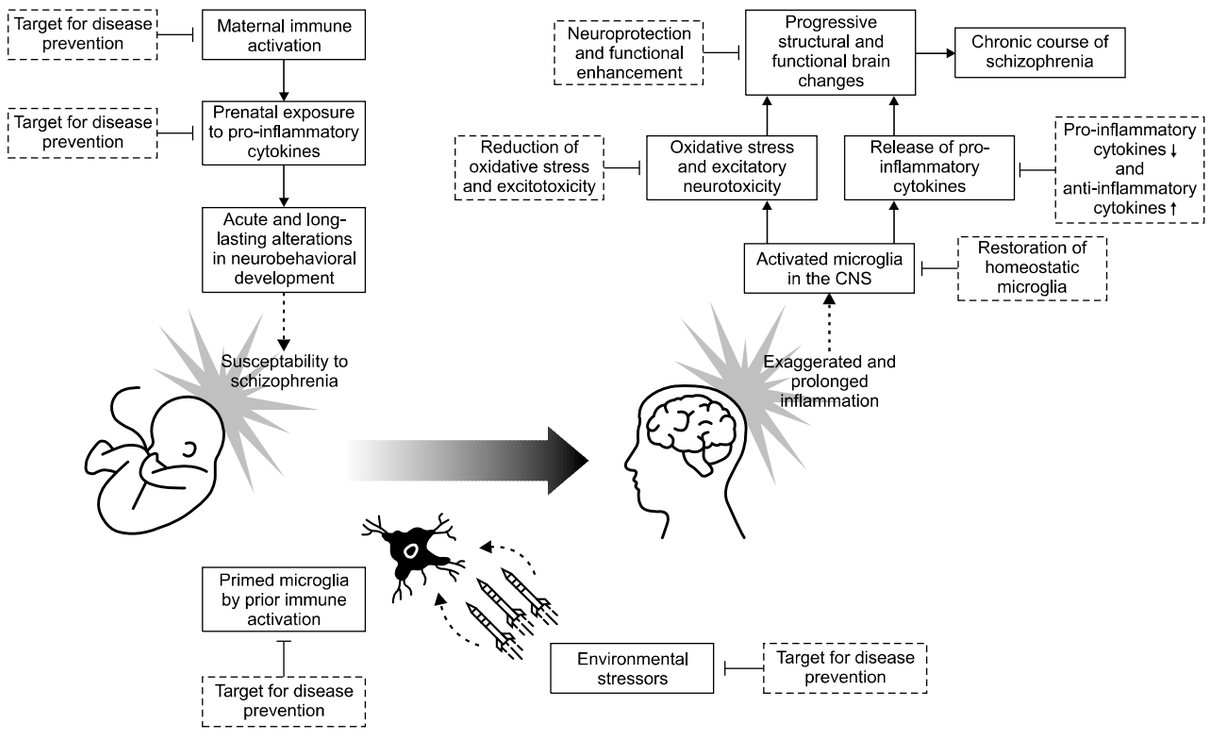
Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, Oliveira J, Le Guen E, Marlinge E, Tamouza R, Leboyer M.

G. Fond[1], N. Hamdani[1], F. Kapczinski[2], W. Boukouaci[3], N. Drancourt[1], A. Dargel[2,3], J. Oliveira[3], E. Le Guen[1], E. Marlinge[1], R. Tamouza[3,*], M. Leboyer[1,*]

Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review.

Objective: To provide a systematic review of the literature regarding the

Intérêt clinique en association,
si troubles cognitifs et début de la maladie.



The World Journal of Biological Psychiatry, 2015; Early Online: 1–8

ORIGINAL INVESTIGATION

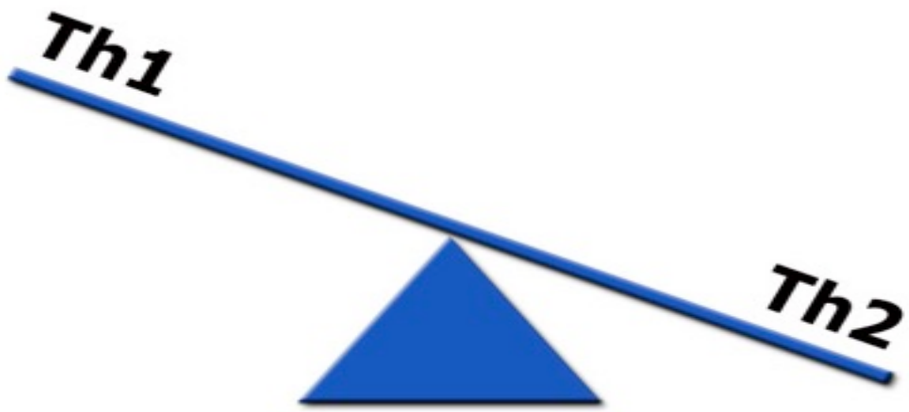
High predictive value of immune-inflammatory biomarkers for schizophrenia diagnosis and association with treatment resistance

CRISTIANO NOTO[1,2,3], MICHAEL MAES[4,5], VANESSA KIYOMI OTA[1], ANTÔNIO LÚCIO TEIXEIRA[6], RODRIGO AFFONSECA BRESSAN[1,3], ARY GADELHA[1,3] & ELISA BRIETZKE[1]

Table V. Differences in biomarkers in healthy controls (HC) and schizophrenia (SCZ) patients divided into those with or without treatment-resistance (TR).

Biomarker	HC[A]	SCZ-TR[B]	SCZ+TR[C]	*F*	df	*P*-value
sTNF-R1	791.1 (527,5)[B,C]	1081.4 (312.7)[A,C]	1384.7 (480.7)[A,B]	16.95	2/161	<0.001
sTNF-R2	5793.3 (1321.9)[C]	5894.3 (1225.5)[C]	7628.6 (2033.3)[A,B]	16.31	2/161	<0.001
MCP-1	334.1 (215.2)[C]	296.9 (144.9)[C]	454.0 (321.5)[A,B]	3.23	2/161	0.042

Schizophrénie résistante, équilibre cytokinique et anti-COX-2

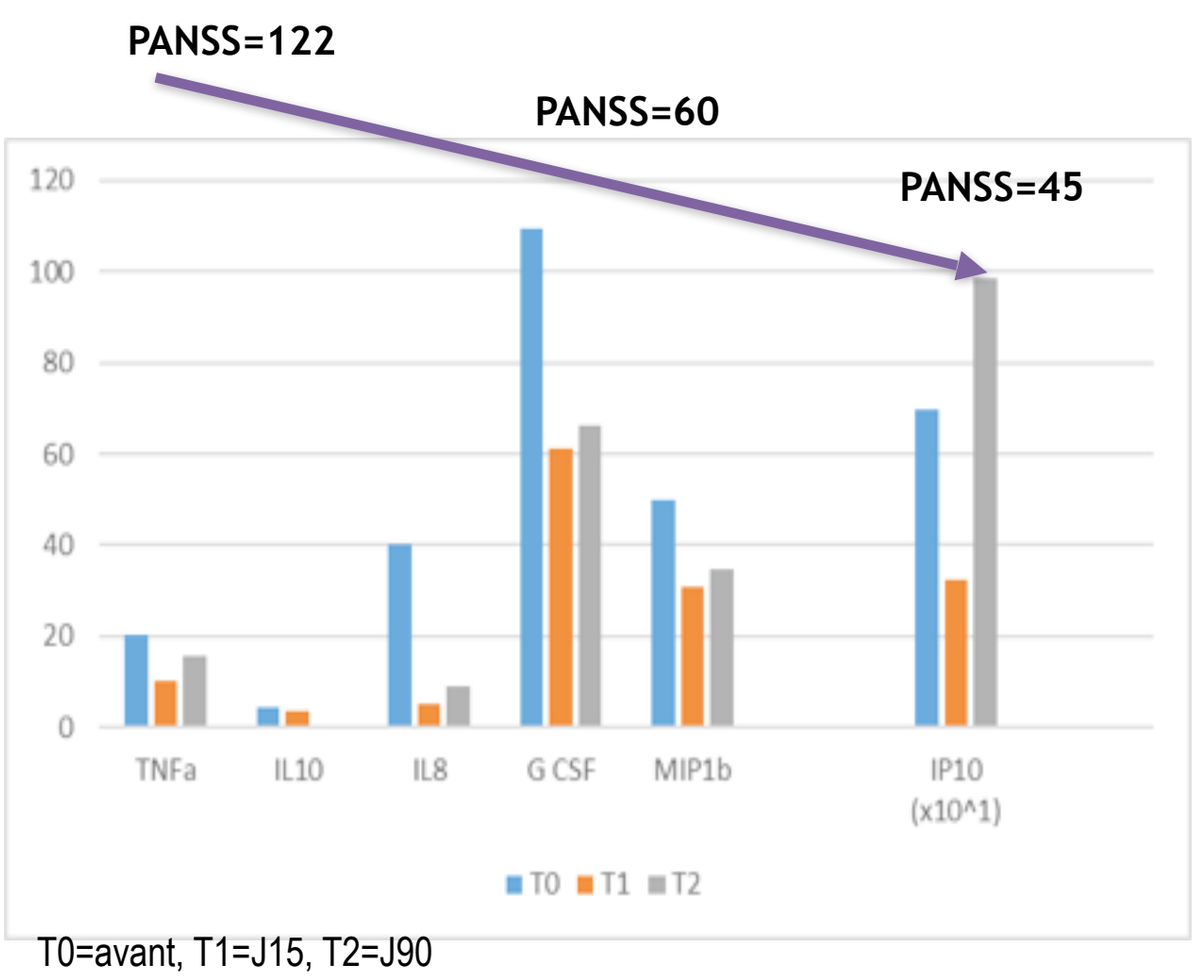


Avant traitement

Hyperpolarisation Th2

Après traitement

Baisse hyperpolarisation Th2
Repolarisation vers un profil Th1
Baisse de l'inflammation
Amélioration spectaculaire des symptômes :
Sortie de l'hôpital après 2 ans!



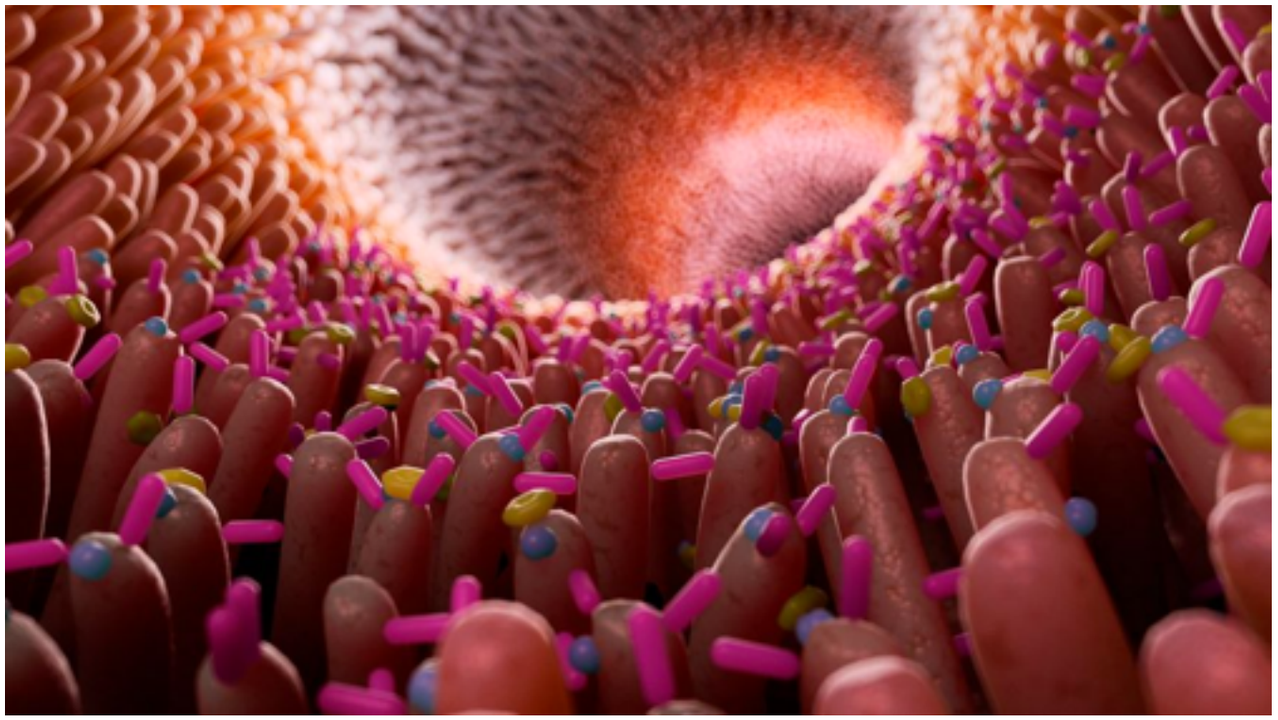
T0=avant, T1=J15, T2=J90

Hamdani et al., *in prep*

DÉPRESSION RESISTANTE ET ANTI-INFLAMMATOIRES

- Profil inflammatoire des déprimés :
- TNF, IL-6, CRP
- Non répondeurs : TNF, TNFR2, IL6, CRP
- Action sur recapture 5-HT, enzymes de dégradation des monoamines, métabolisme du glutamate.

MICROBIOTE INTESTINALE ET RESISTANCE AUX TRAITEMENTS DANS LA SCHIZOPHRÉNIE



500 espèces différentes de bactéries intestinales

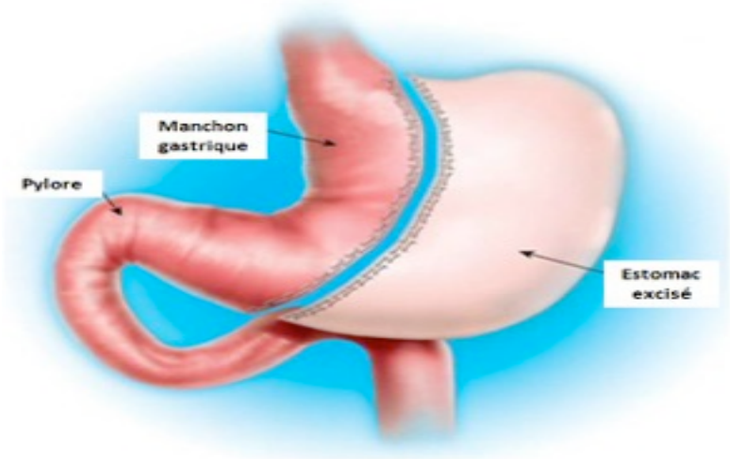
Absorption intestinale majeure gros intestin, reste dégradé dans le colon,

Action des enzymes bactériennes dans 70% de la dégradation des médicaments

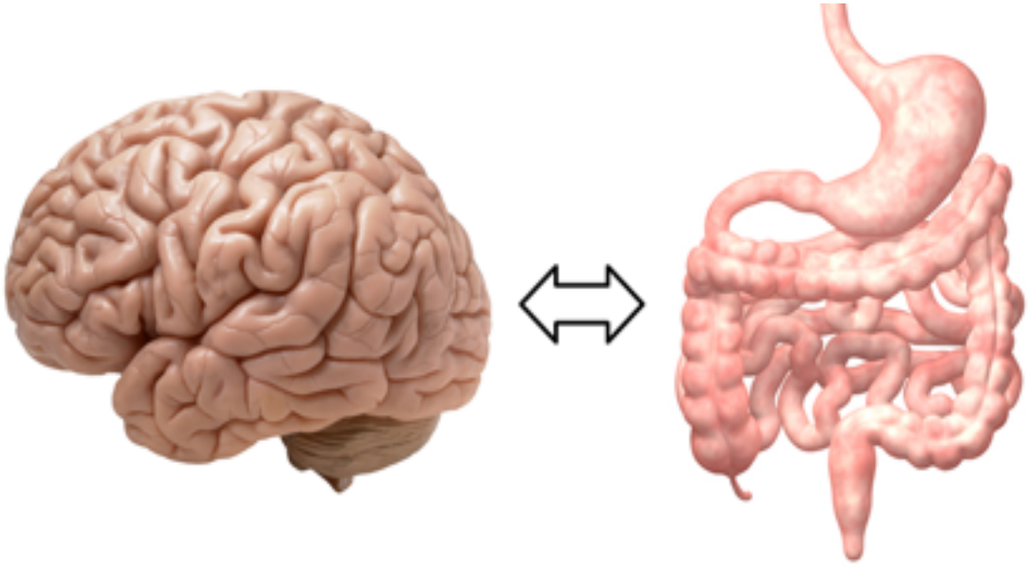
Métabolisation des antipsychotiques pour grande partie par la microbiote intestinale,

Place des traitements innovants : l'axe intestin-cerveau

Un accès maniaque traité avec succès par charbon actif



Une déferlante pro-inflammatoire d'origine digestive



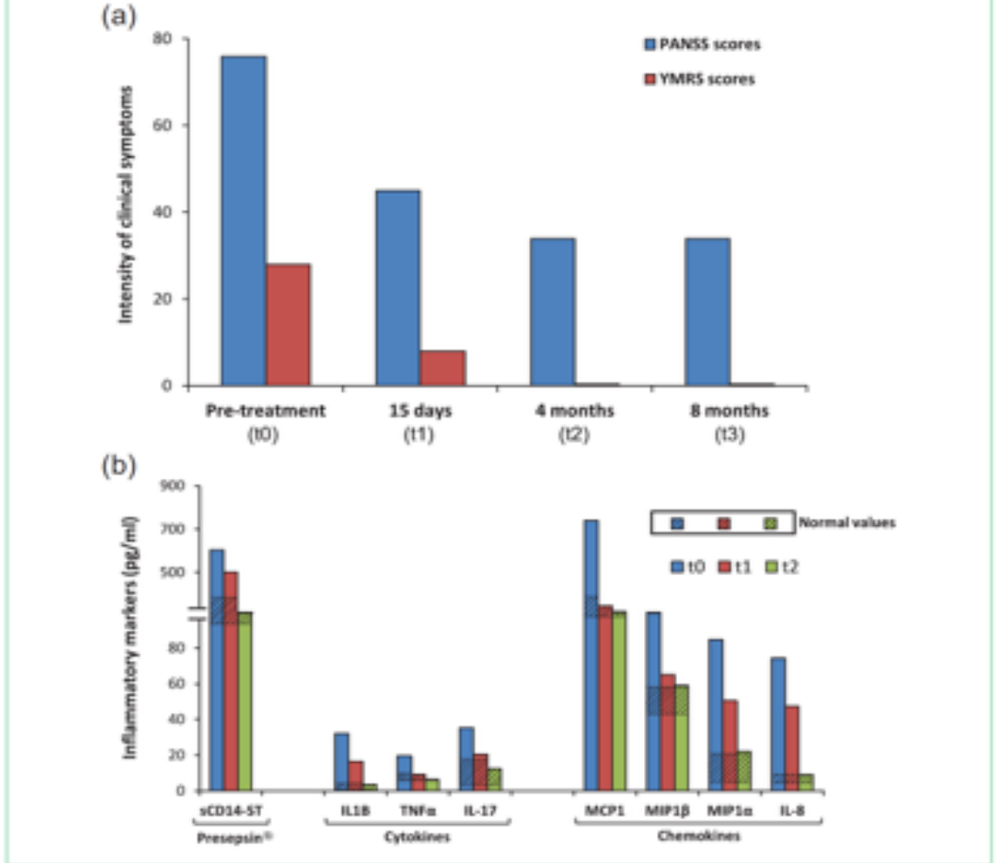
Charbon actif : 1g/j : adsorbant inflammation intestinale

Resolution of a manic episode treated with activated charcoal: Evidence for a brain–gut axis in bipolar disorder

Nora Hamdani[1,2,3], Wahid Boukouaci[3,4], Mohamed Reda Hallouche[1,2], Dominique Charron[3,4], Rajagopal Krishnamoorthy[4], Marion Leboyer[1,2,3] and Ryad Tamouza[3,4]

Baisse de l'inflammation parallèle à la résolution de l'épisode

Figure 1. Analyses of (a) manic (YMRS) and delusional symptoms (PANSS) and (b) immuno-inflammatory markers (soluble CD14; cytokines: TNF-α, IL-1, interferon γ and IL-17; chemokines: IL-8, MIP-α, MIP1-β and MCP-1), before treatment (T0) and 2 weeks (T1) and 4 months (T2) after the initiation of charcoal treatment. A fourth time point has been included, showing the clinical assessments at 8 months (T3).



Hamdani et al., Resolution of a, inaugural manic episode following a gastrectomy for obesity treated with activated charcoal: evidence for a brain-gut axis in bipolar disorder.***ANZJP, 2015***

ALLERGIES ALIMENTAIRES, RESISTANCE AUX TRAITEMENTS

Hypersensibilité dédiée par le système immunitaire : IL-4, IgE,

Allergies alimentaires associées moins bonne qualité de vie, dysphorie, IS, troubles mémoire et de la concentration,

Comorbidités psychiatriques,

ATCD d'allergies alimentaires augmente le risque de suicide

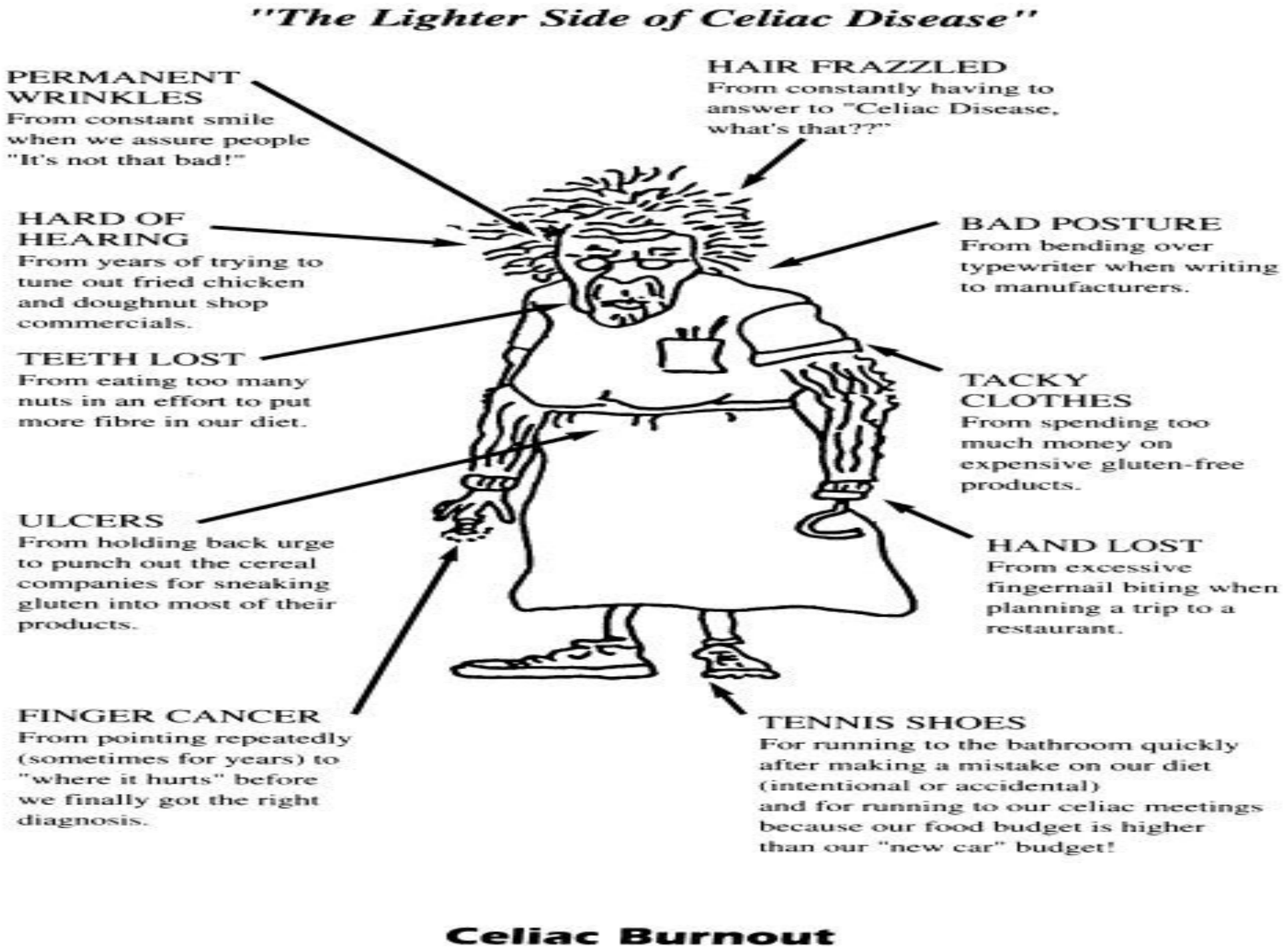
Maladies intestinales associées à d'autres pathologies auto-I

Certains aliments plus à risque de dépression.

BP avec cycles ultra-rapides,

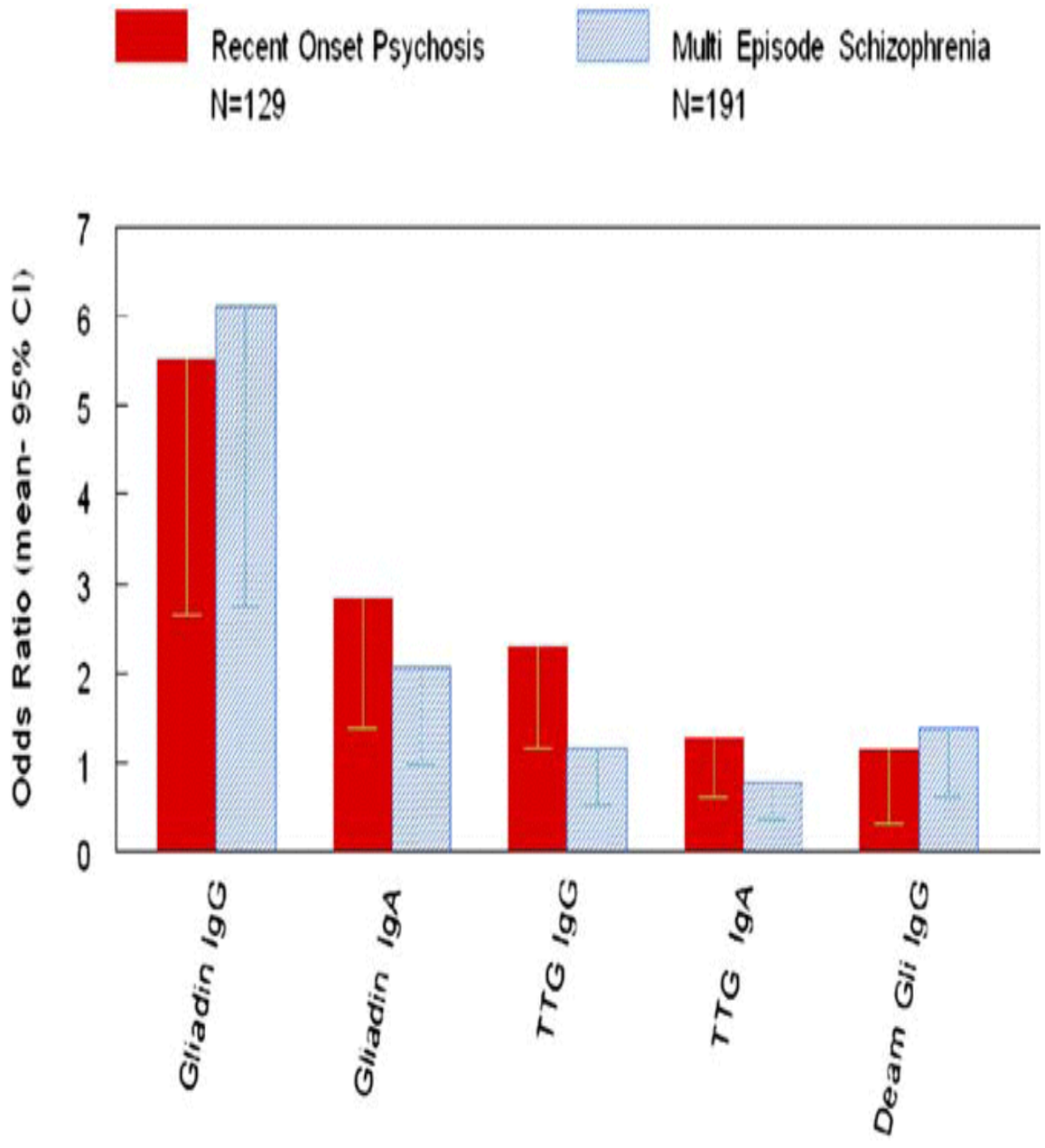
Asperger et comorbidité cycles ultra-rapides = régime alimentaire.

Maladie Coeliaque, troubles psychotiques

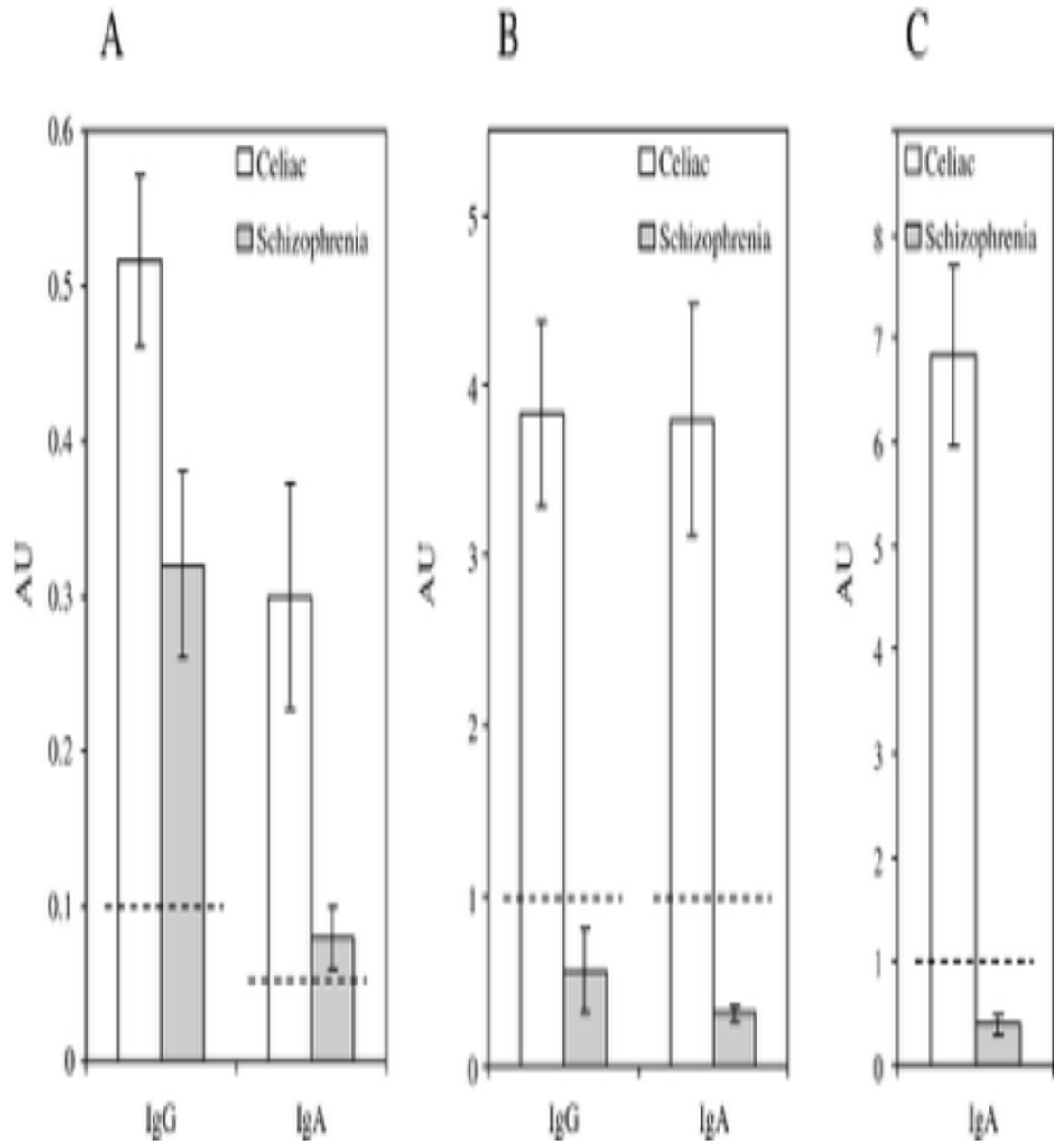


« La schizophrénie est rare si le grain est rare », Dohan, 1984

Marqueurs coeliaques, schizophrénie



Samaroo et al., 2009

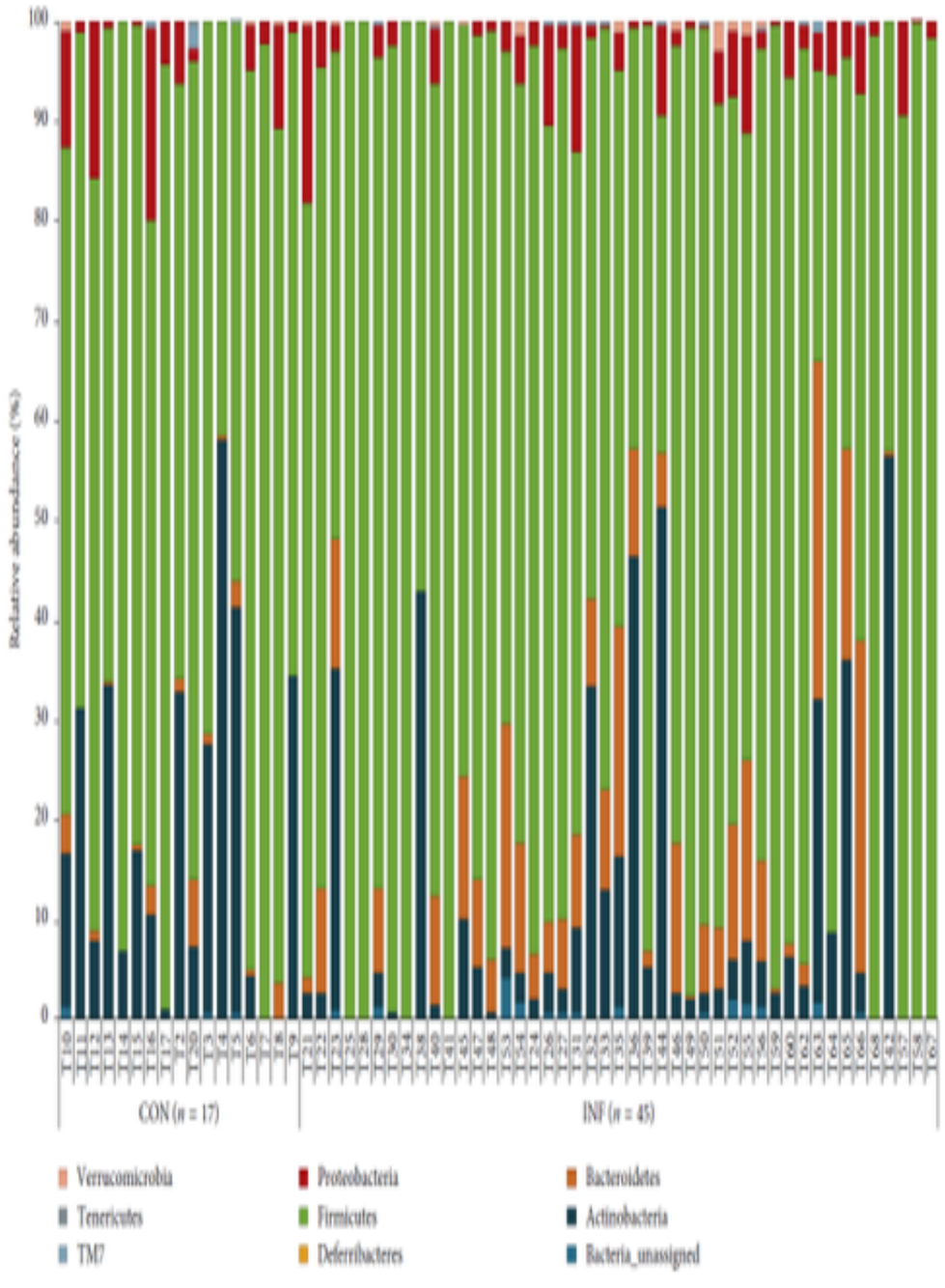


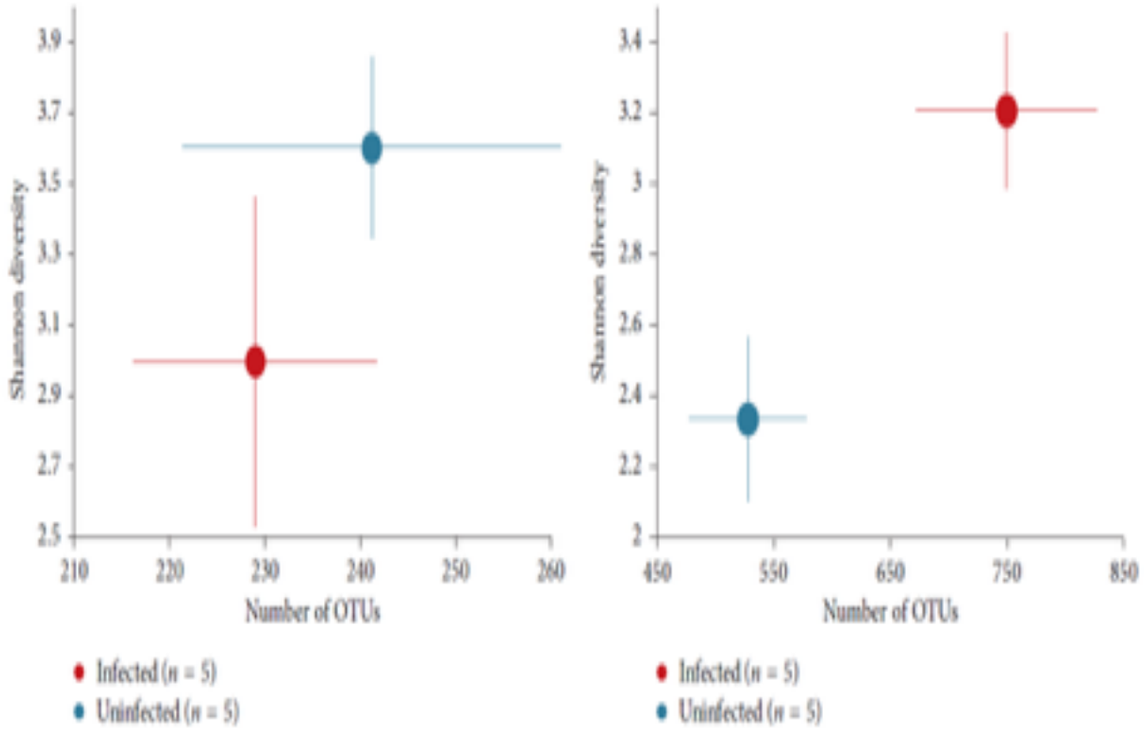
Dickerson et al., 2010

Hindawi
Scientifica
Volume 2018, Article ID 2308619, 11 pages
https://doi.org/10.1155/2018/2308619

Research Article

Toxoplasma gondii-Induced Long-Term Changes in the Upper Intestinal Microflora during the Chronic Stage of Infection





Stratégies thérapeutiques

Naissances hivernales
dépression associées
Luminothérapie

Inflammation digestive
Charbon
Régime

Infections virales : HSV, CMV
Valacyclovir

Résistance

Inflammation périphérique
Anti-Cox2
Aspirine
Omega 3

Patients Toxo+
choisir un AP anti-parasitaire

Inflammation centrale
D- cycloserine
Immunosuppresseurs

Épisode récent, symptômes négatifs
Minocycline

Faire un bilan inflammatoire et +/-infectieux si troubles cognitifs

Tester les antigènes alimentaires