Lithium : rechargez les batteries de votre cerveau !

Docteur Franz HOZER

Praticien Hospitalier

Service de Psychiatrie de l'Adulte et du Sujet Âgé du Pr Limosin

Hôpital Corentin-Celton, AP-HP

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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PARIS DESCARTES

4e Congrès

SF3PA Société Francophone de Psychogériatrie et de Psychiatrie de la Personne Âgée

1ER et 2 juin 2023 - Limoges

Aucun conflit d'intérêts à signaler

Le trouble neuro-cognitif majeur

- **Enjeu majeur de santé publique**
  - Principale cause de dépendance/invalidité du SAG
  - Coût socio-économique majeur++ (818 milliards de $)
  - Vieillissement de la population => ↑ prévalence (47 millions de cas en 2015, 131 millions en 2050)
  - Pas de traitement curatif disponible (traitement symptomatique de certaines dimensions cliniques)

- **Plutôt prévenir que guérir ?**
  - Retard apparition TNCM (même modeste) : impact majeur en terme de réduction coûts (retard d'apparition de 5 ans d'un TNCM <=> ↓ impact économique de 40%)

Zissimopoulos et al, 2014 ; Livingston et al, 2017

Prévention générale du TNCM

www.thelancet.com Vol 396 August 8, 2020 The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

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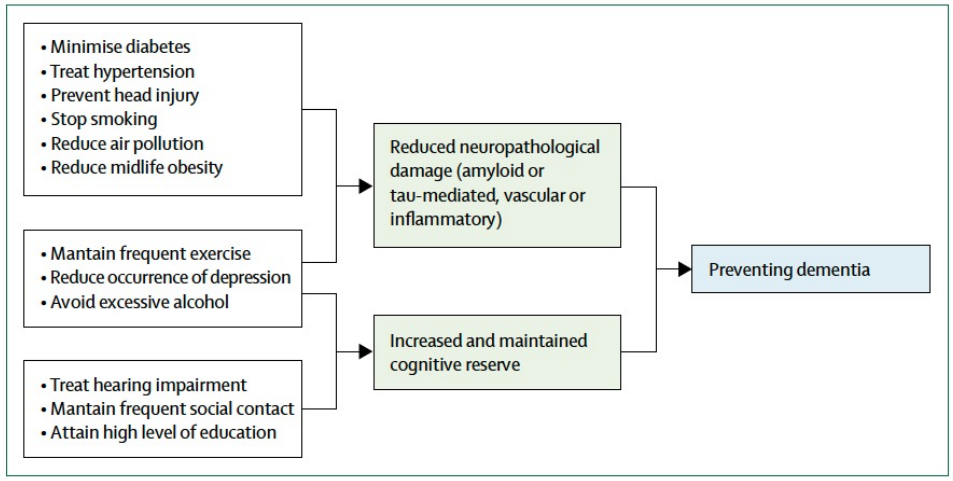

Figure 2: **Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia**

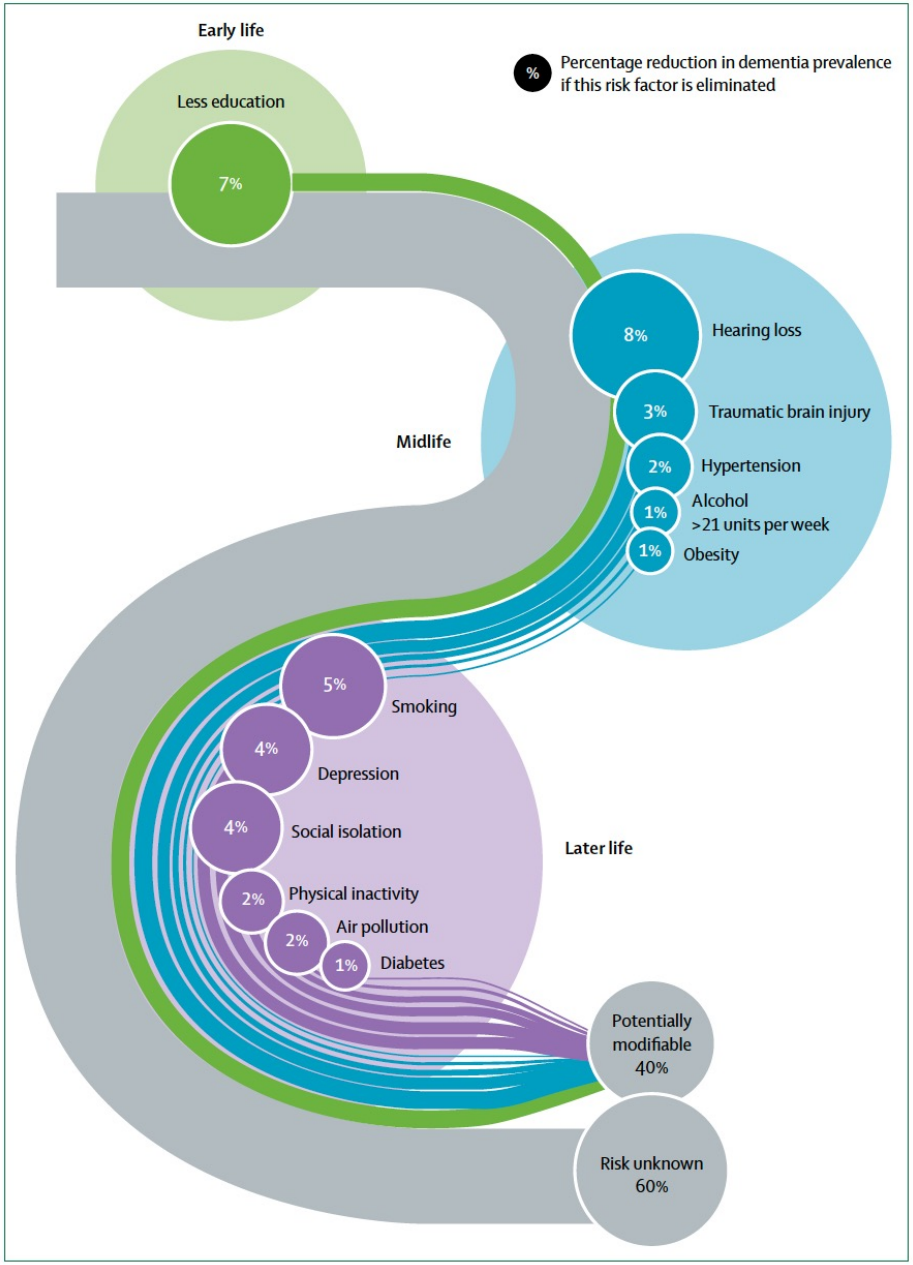

Figure 7: **Population attributable fraction of potentially modifiable risk factors for dementia**

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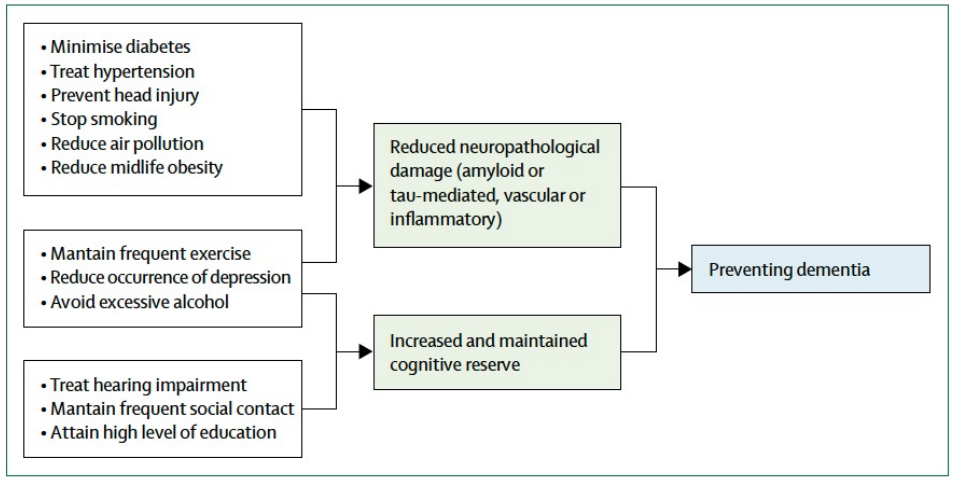

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Traitement préventif

Lithium ?

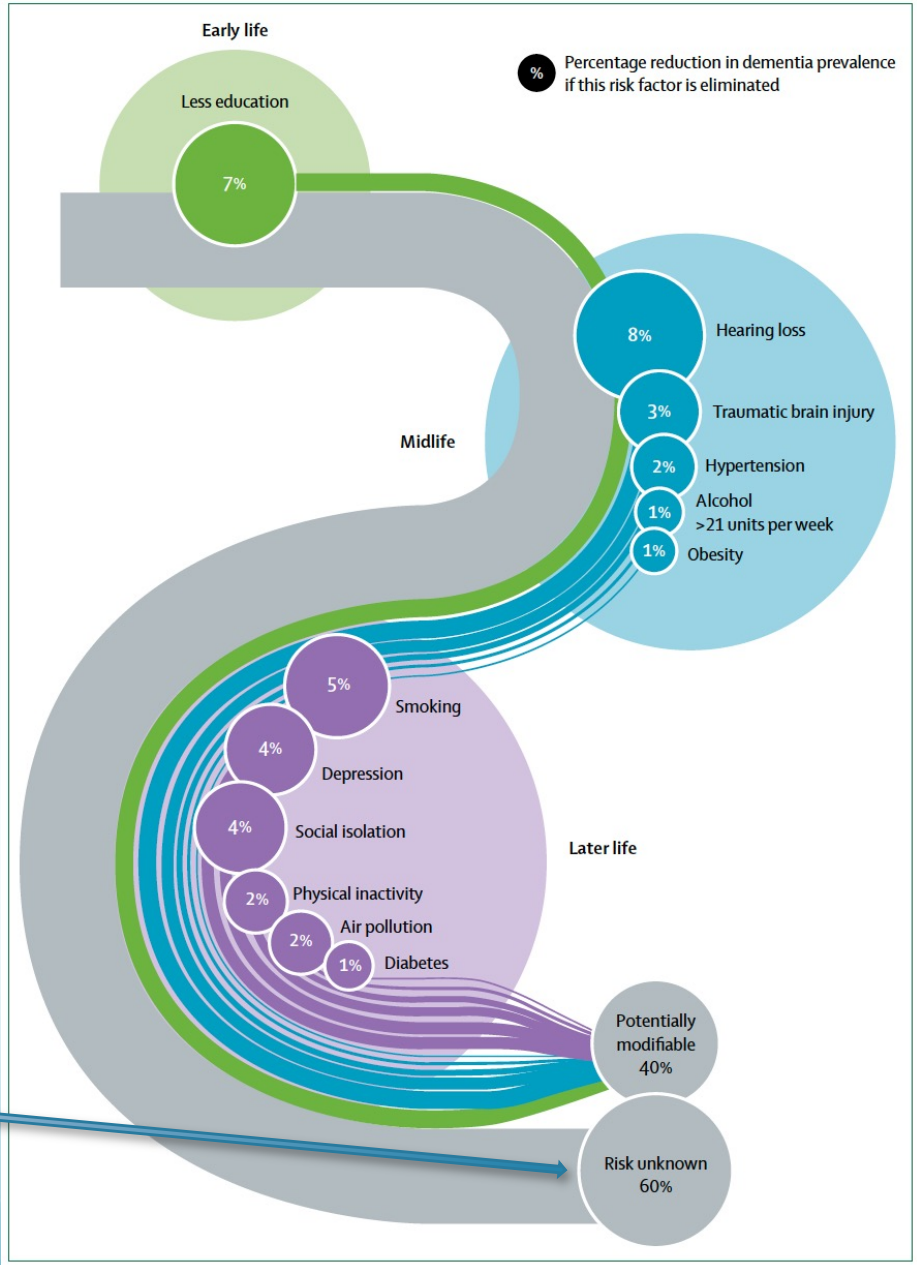
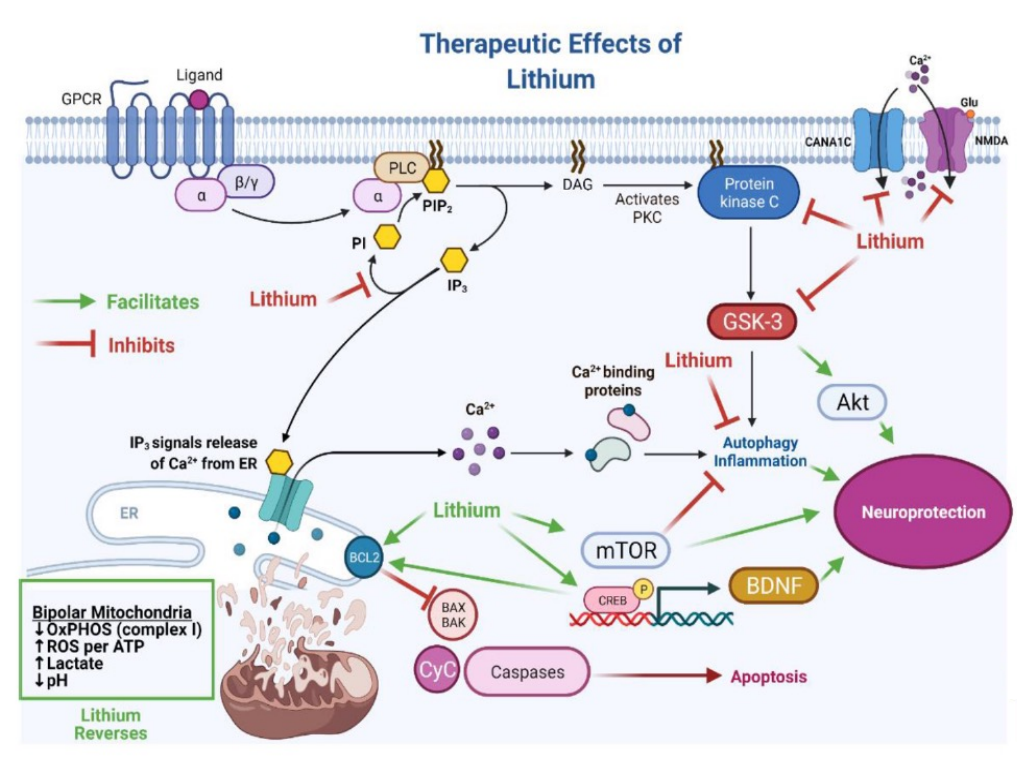


Figure 7: **Population attributable fraction of potentially modifiable risk factors for dementia**

Le Li protège les neurones

- Multiples mécanismes intra-cellulaires impliqués
  - Inhibition GSK-3β
  - ↑ synthèse BDNF
  - ↑ protéine BCL-2



Jones et al, 2022

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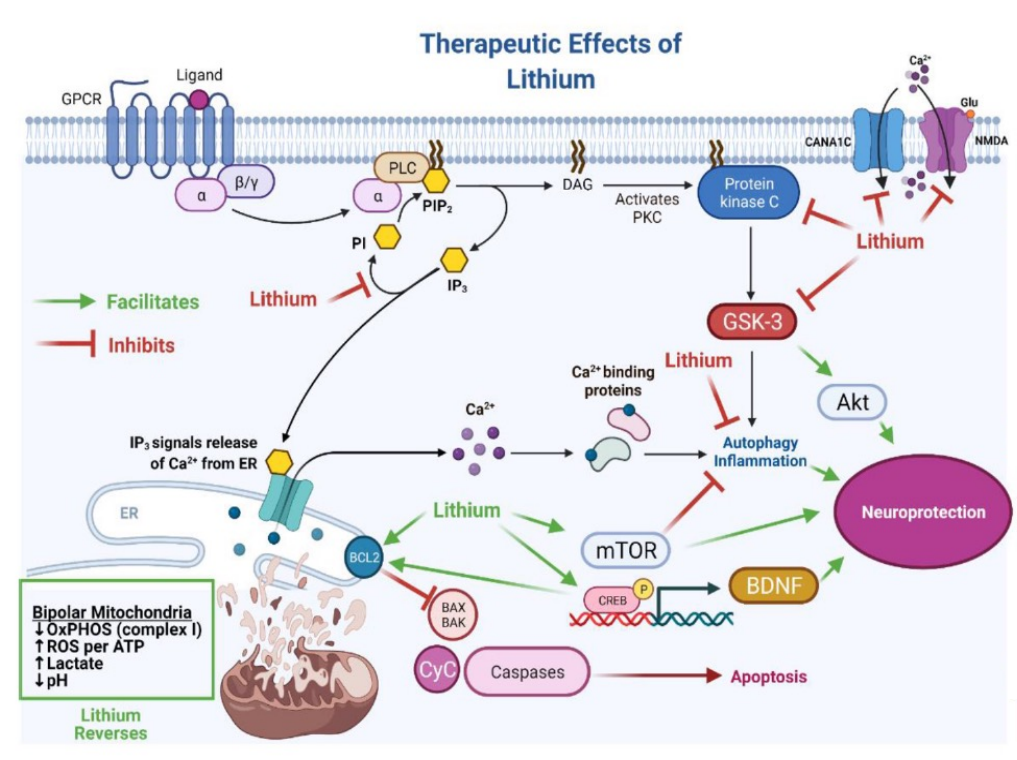

⇒ **Effets neuroprotecteurs** (via ↓ apoptose, ↓ stress oxydatif cellulaire, ↓ inflammation, régulation autophagie cellulaire, ↑ fonctionnement mitochondrial)…

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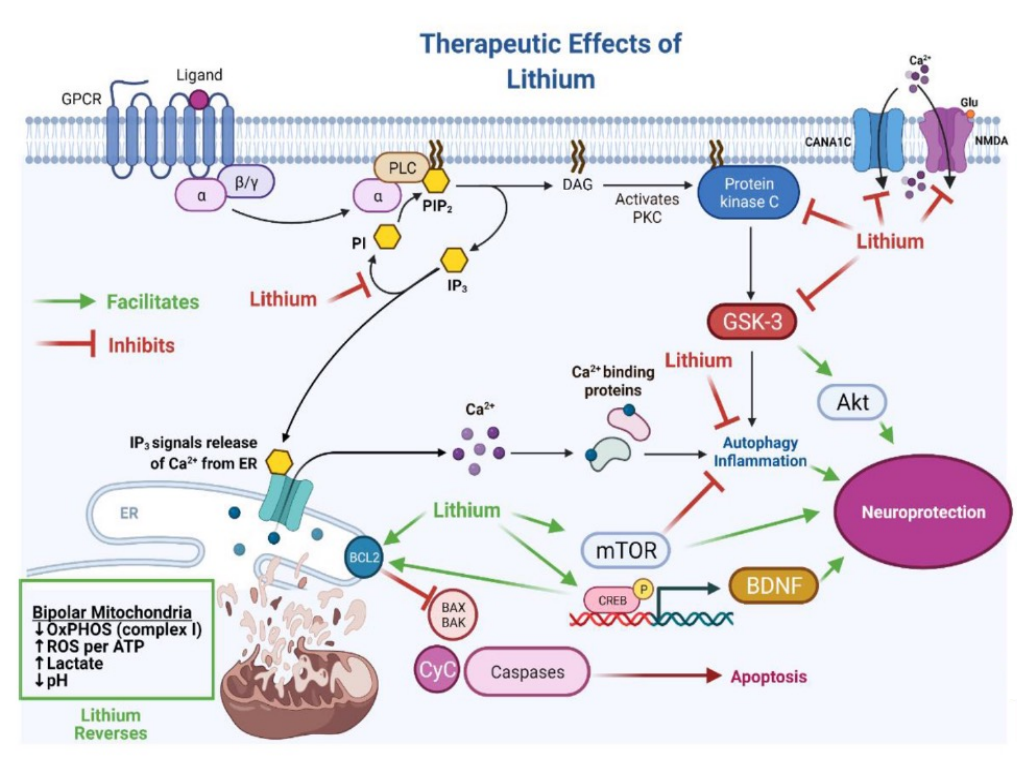

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⇒ … voire **neurotrophiques ?**

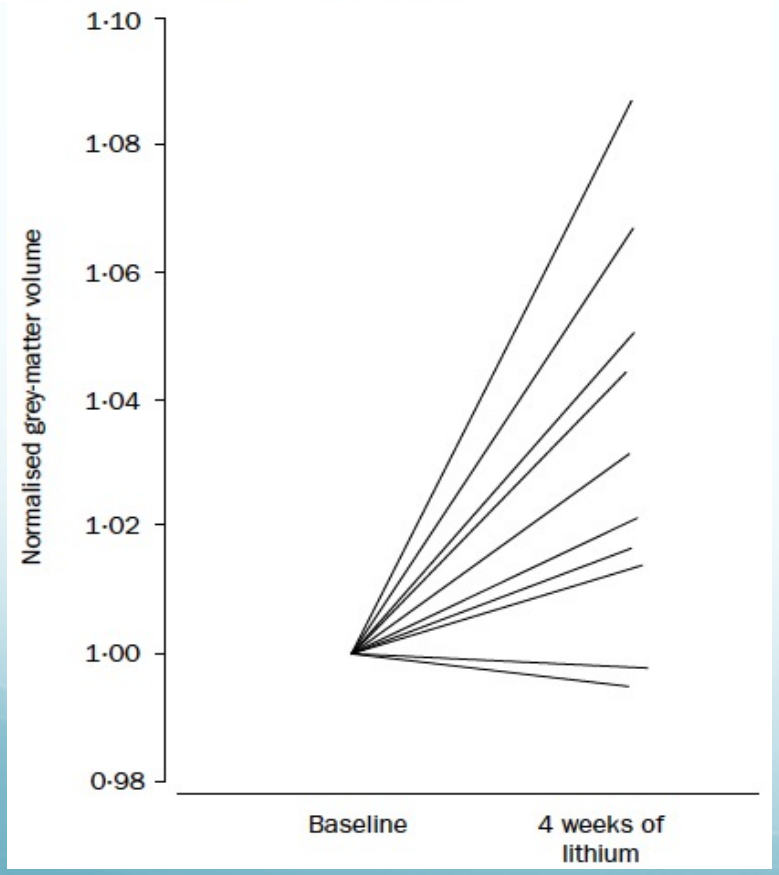
Jones et al, 2022

Li : des effets neurotrophiques ?

Lithium-induced increase in human brain grey matter

Gregory J Moore, Joseph M Bebchuk, Ian B Wilds, Guang Chen, Husseini K Menji

THE LANCET • Vol 356 • October 7, 2000



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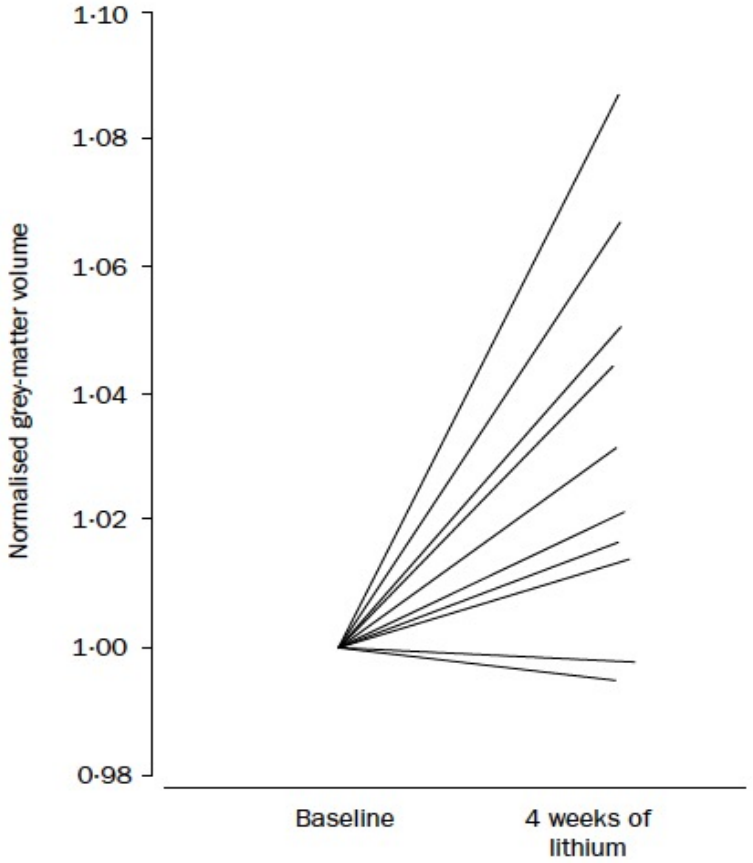
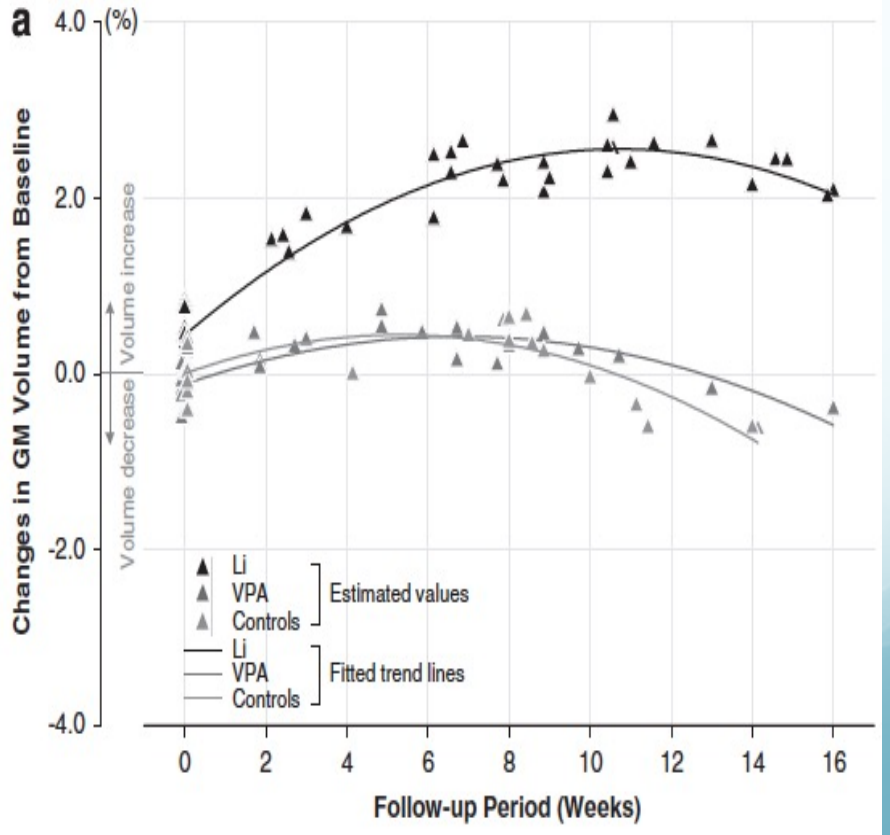


Lithium-Induced Gray Matter Volume Increase As a Neural Correlate of Treatment Response in Bipolar Disorder: A Longitudinal Brain Imaging Study

In Kyoon Lyoo*[1,2], Stephen R Dager[3,4], Jieun E Kim[1], Sujung J Yoon[5], Seth D Friedman[4], David L Dunner[6] and Perry F Renshaw[7,8,9]

Neuropsychopharmacology (2010) 35, 1743–1750



Li : des effets neurotrophiques ?

Translational Psychiatry

Lithium treatment and human hippocampal neurogenesis

Alish B. Palmos[1], Rodrigo R. R. Duarte[1,2], Demelza M. Smeeth[3], Erin C. Hedges[3], Douglas F. Nixon[2], Sandrine Thuret[3,4,5] and Timothy R. Powell[1,2,5]✉

2021

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2021

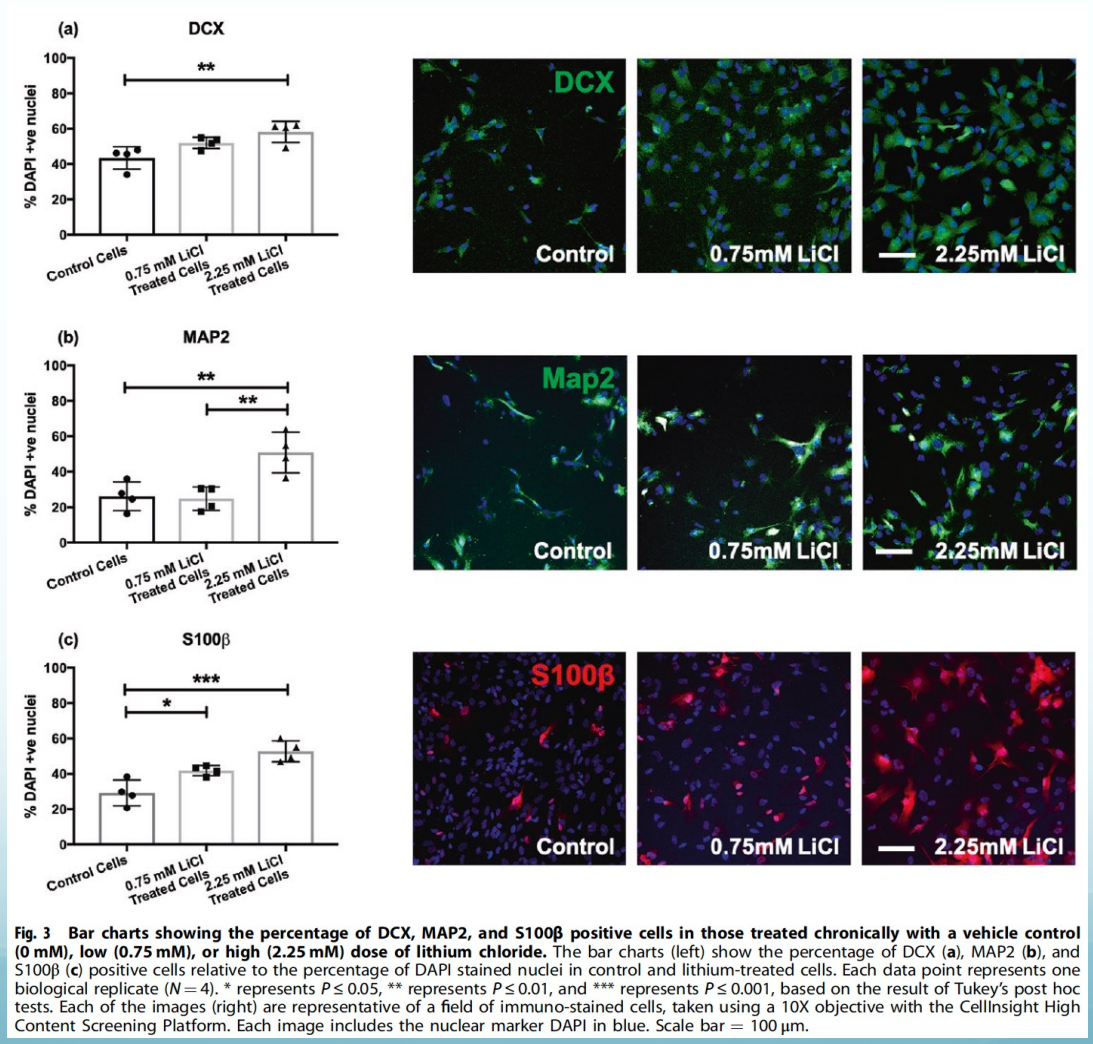

Fig. 3 Bar charts showing the percentage of DCX, MAP2, and S100β positive cells in those treated chronically with a vehicle control (0 mM), low (0.75 mM), or high (2.25 mM) dose of lithium chloride. The bar charts (left) show the percentage of DCX (**a**), MAP2 (**b**), and S100β (**c**) positive cells relative to the percentage of DAPI stained nuclei in control and lithium-treated cells. Each data point represents one biological replicate ($N = 4$). * represents $P \leq 0.05$, ** represents $P \leq 0.01$, and *** represents $P \leq 0.001$, based on the result of Tukey's post hoc tests. Each of the images (right) are representative of a field of immuno-stained cells, taken using a 10X objective with the CellInsight High Content Screening Platform. Each image includes the nuclear marker DAPI in blue. Scale bar = 100 µm.

Li : des effets neurotrophiques ?

Biological Psychiatry September 1, 2020; 88:426–433 www.sobp.org/journal

Biological Psychiatry

Archival Report

Accumulation of Lithium in the Hippocampus of Patients With Bipolar Disorder: A Lithium-7 Magnetic Resonance Imaging Study at 7 Tesla

Jacques Stout, Franz Hozer, Arthur Coste, Franck Mauconduit, Nouzha Djebrani-Oussedik, Samuel Sarrazin, Joel Poupon, Manon Meyrel, Sandro Romanzetti, Bruno Etain, Cécile Rabrait-Lerman, Josselin Houenou, Frank Bellivier, Edouard Duchesnay, and Fawzi Boumezbeur

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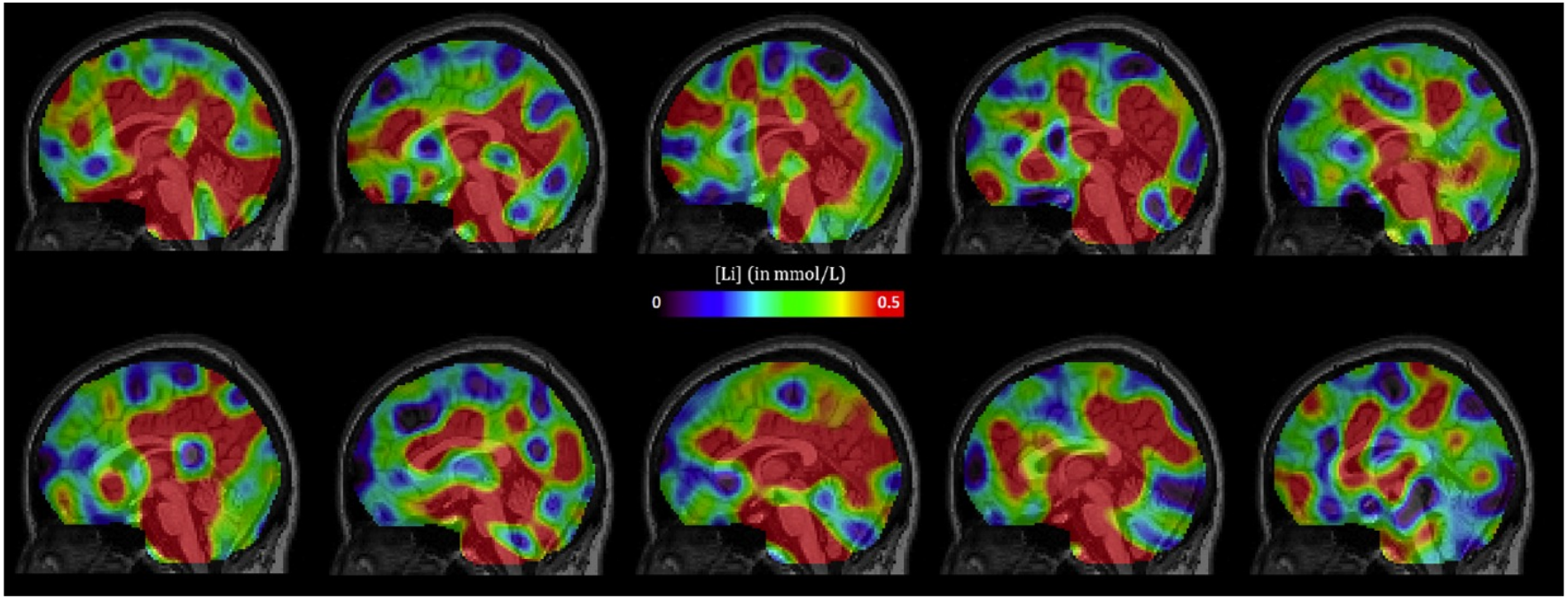

Figure 1. Gallery of lithium concentration ([Li]) maps acquired at 7T from 10 patients with bipolar disorder. Individual ^{7}Li images were interpolated at the resolution of their anatomical reference for transformation into the MNI152 template space.

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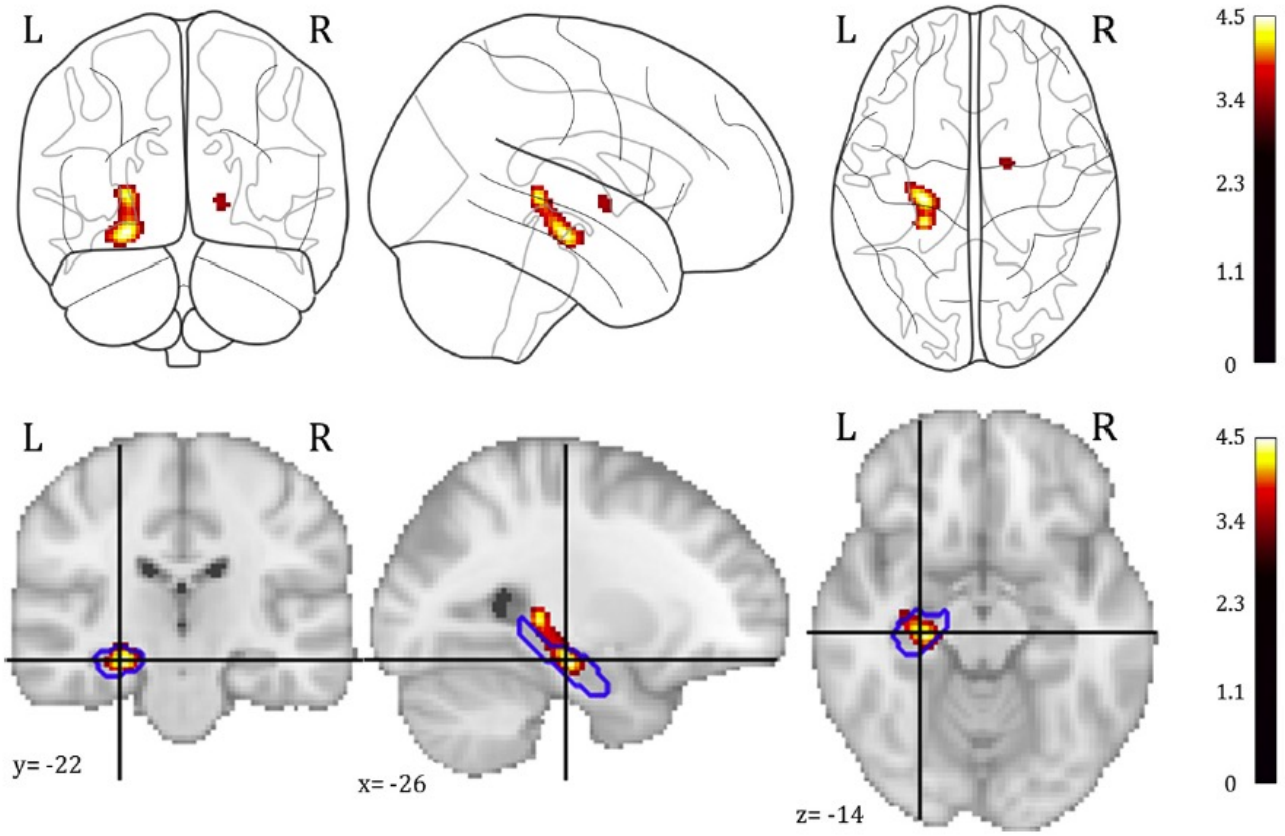

Figure 4. Voxel-based statistical map (Student's *t* test score) of increased lithium concentration over the individual mean, thresholded at $p < 10^{-3}$. Top: coronal, sagittal, and axial glass views highlight a large cluster in the left hippocampus and a small cluster in the right pallidum. Bottom: The hippocampus, as defined by the Harvard-Oxford atlas (blue contour), overlaps with our thresholded statistical map. L, left; R, right.

Li : quels effets sur le TNCM ?

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Effets préventifs dans le TBP ?

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Données imagerie
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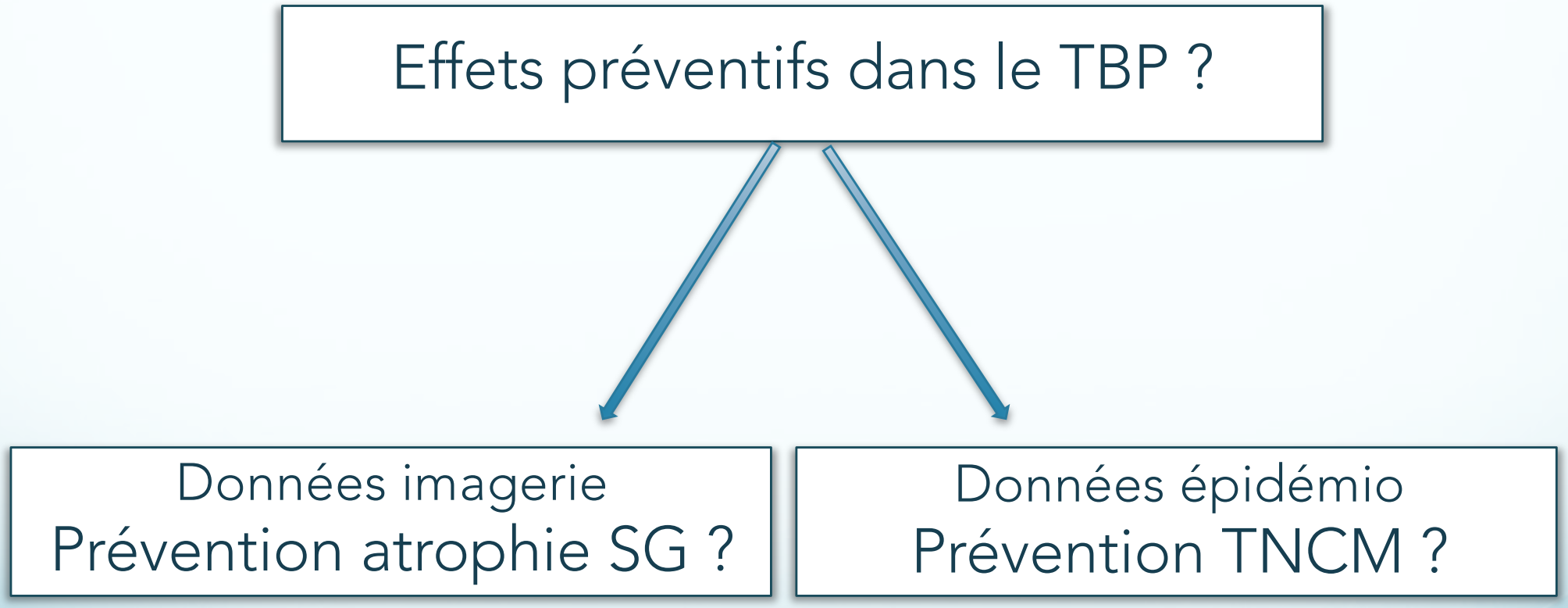
Li : quels effets sur le TNCM ?



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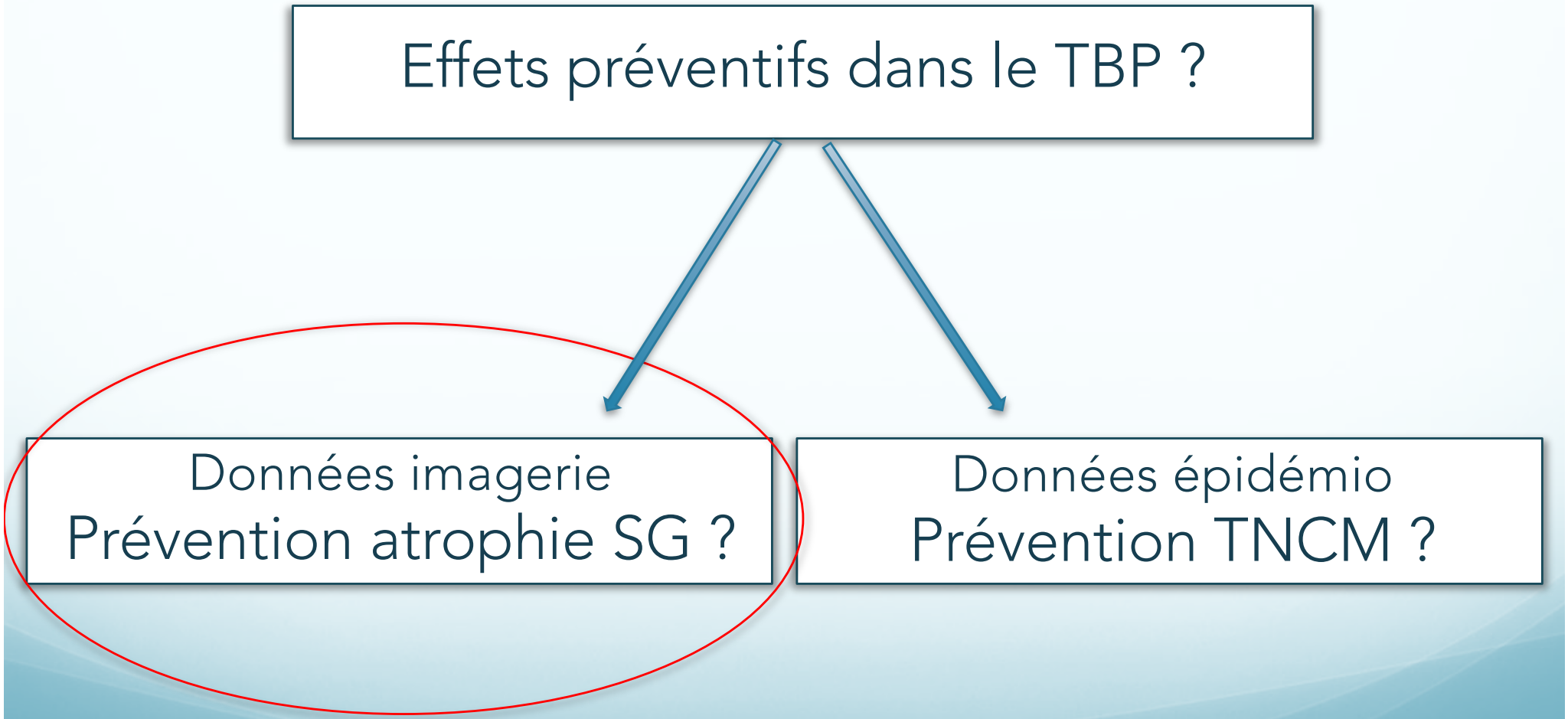

Li dans le TBP : données d'imagerie

Références	Design	Régions
Moore et al, 2000 Sassi et al, 2002 Beyer et al, 2004 Chen et al, 2007 Javadapour et al, 2007 Chen et al, 2007 Monkul et al 2007 Sherk et al, 2007 Yucel et al, 2007, 2008 Bearden et al, 2008 Foland et al, 2008 Kempton et al, 2008 Moore et al, 2009 Bora et al, 2010 Germana et al, 2010 Lyoo et al, 2010 Hallahan et al, 2011 Baykara et al, 2012 Hajek et al, 2012 Selek et al, 2012 Van Erp et al, 2012 Emsell et al, 2013 Wijterane et al, 2013 Hajek et al, 2014 Benedetti et al, 2015 Giakoumotos et al, 2015 Hartberg et al, 2015 Quigley et al, 2015 Abramovic et al, 2016 Hibar et al, 2016, 2017 Sun et al, 2018 Abé et al, 2020 Hozer el al, 2020 Jones et al, 2022	Études transversales++ Méta-analyses	SG totale++ SG corticale++ Hippocampe++ Amygdale++ CPF++ CCA++ COF++ Insula Cortex temporal Thalamus

Li dans le TBP : données d'imagerie

Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Hozer F *et al* (2020). Lithium prevents grey matter atrophy in patients with bipolar disorder: an international multicenter study. *Psychological Medicine* 1–10. https://doi.org/10.1017/S0033291719004112

Lithium prevents grey matter atrophy in patients with bipolar disorder: an international multicenter study

Franz Hozer[1,2,3,4], Samuel Sarrazin[3,4], Charles Laidi[3,4,5,6], Pauline Favre[3,4], Melissa Pauling[3,4,5,6], Dara Cannon[7], Colm McDonald[7], Louise Emsell[8,9], Jean-François Mangin[10], Edouard Duchesnay[10], Marcella Bellani[11], Paolo Brambilla[12], Michele Wessa[13], Julia Linke[13], Mircea Polosan[14], Amelia Versace[15], Mary L. Phillips[15], Marine Delavest[16,17], Frank Bellivier[16,17], Nora Hamdani[4,5,6], Marc-Antoine d'Albis[3,4,5,6], Marion Leboyer[4,5,6,18] and Josselin Houenou[3,4,5,6,18]

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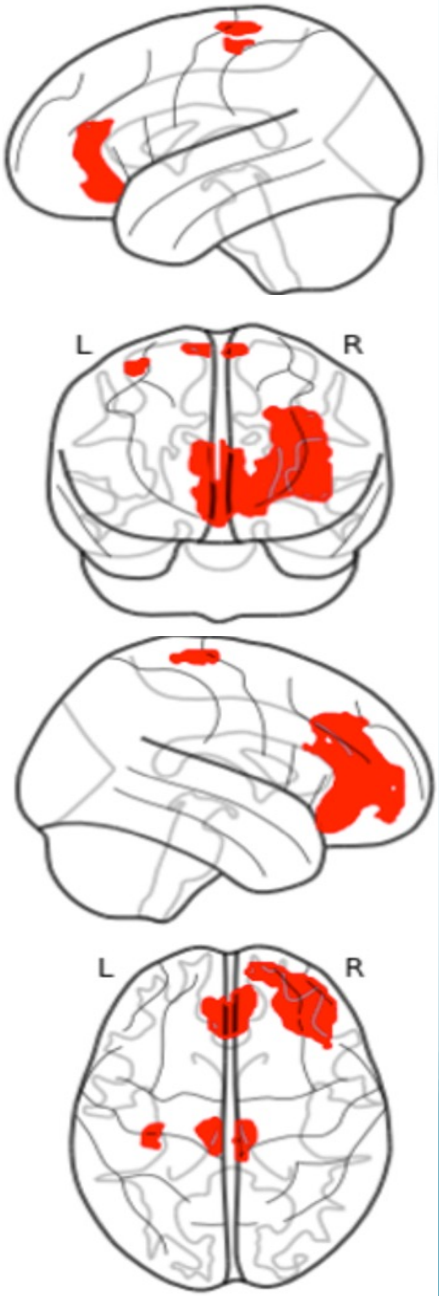
Table 2. Prediction of cortical grey matter volume among patients with bipolar disorder

	Cortical grey matter volume			
Variable	*B*[a]	S.E.[b]	*t*[c]	*p*
Use of Li (Y minus N)	10 253.9	4084.6	2.51	0.013
Sex (F minus M)	18 165.2	4132.5	4.40	<0.0005
History of OH misuse (Y minus N)	−14 042.5	6045.5	−2.32	0.021
Age	−2021.3	222.7	−9.08	<0.0005
Illness duration	12.9	261.5	0.05	0.961

F, female; Li, lithium; M, male; N, no; OH, alcohol; Y, yes.
[a]Unstandardized regression coefficient.
[b]Standard error of the coefficient.
[c]*t* value.



Li dans le TBP : données d'imagerie

Molecular Psychiatry (2018) 23, 932–942

ORIGINAL ARTICLE

www.nature.com/mp

Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group

DP Hibar[1,2], LT Westlye[3,4,5], NT Doan[3,4], N Jahanshad[1], JW Cheung[1], CRK Ching[1,6], A Versace[7], AC Bilderbeck[8], A Uhlmann[9,10], B Mwangi[11], B Krämer[12], B Overs[13], CB Hartberg[3], C Abé[14], D Dima[15,16], D Grotegerd[17], E Sprooten[18], E Bøen[19], E Jimenez[20], FM Howells[9], G Delvecchio[21], H Temmingh[9], J Starke[9], JRC Almeida[22], JM Goikolea[20], J Houenou[23,24], LM Beard[25], L Rauer[12], L Abramovic[26], M Bonnin[20], MF Ponteduro[16], M Keil[27], MM Rive[28], N Yao[29,30], N Yalin[31], P Najt[32], PG Rosa[33,34], R Redlich[17], S Trost[27], S Hagenaars[35], SC Fears[36,37], S Alonso-Lana[38,39], TGM van Erp[40], T Nickson[35], TM Chaim-Avancini[33,34], TB Meier[41,42], T Elvsåshagen[3,43], UK Haukvik[3,44], WH Lee[18], AH Schene[45,46], AJ Lloyd[47], AH Young[31], A Nugent[48], AM Dale[49,50], A Pfennig[51], AM McIntosh[35], B Lafer[33], BT Baune[52], CJ Ekman[14], CA Zarate[48], CE Bearden[53,54], C Henry[23,55], C Simhandl[56], C McDonald[32], C Bourne[8,57], DJ Stein[9,10], DH Wolf[25], DM Cannon[32], DC Glahn[29,30], DJ Veltman[58], E Pomarol-Clotet[38,39], E Vieta[20], EJ Canales-Rodriguez[38,39], FG Nery[33,59], FLS Duran[33,34], GF Busatto[33,34], G Roberts[60], GD Pearlson[29,30], GM Goodwin[8], H Kugel[61], HC Whalley[35], HG Ruhe[8,28,62], JC Soares[11], JM Fullerton[13,63], JK Rybakowski[64], J Savitz[42,65], KT Chaim[66,67], M Fatjó-Vilas[38,39], MG Soeiro-de-Souza[33], MP Boks[26], MV Zanetti[33,34], MCG Otaduy[66,67], MS Schaufelberger[33,34], M Alda[68], M Ingvar[14,69], ML Phillips[7], MJ Kempton[16], M Bauer[51], M Landén[14,70], NS Lawrence[71], NEM van Haren[26], NR Horn[9], NB Freimer[72], O Gruber[12], PR Schofield[13,63], PB Mitchell[60], RS Kahn[26], R Lenroot[13,73], R Machado-Vieira[33,74], RA Ophoff[26,72], S Sarró[38,39], S Frangou[18], TD Satterthwaite[25], T Hajek[68,75], U Dannlowski[17], UF Malt[76,77], V Arolt[17], WF Gattaz[33], WC Drevets[78], X Caseras[79], I Agartz[3,19], PM Thompson[1] and OA Andreassen[3,4] for the ENIGMA Bipolar Disorder Working Group

Li dans le TBP : données d'imagerie

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ORIGINAL ARTICLE www.nature.com/mp

Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group

DP Hibar[1,2], LT Westlye[3,4,5], NT Doan[3,4], N Jahanshad[1], JW Cheung[1], CRK Ching[1,6], A Versace[7], AC Bilderbeck[8], A Uhlmann[9,10], B Mwangi[11], B Krämer[12], B Overs[13], CB Hartberg[3], C Abé[14], D Dima[15,16], D Grotegerd[17], E Sprooten[18], E Bøen[19], E Jimenez[20], FM Howells[9], G Delvecchio[21], H Temmingh[9], J Starke[9], JRC Almeida[22], JM Goikolea[20], J Houenou[23,24], LM Beard[25], L Rauer[12], L Abramovic[26], M Bonnin[20], MF Ponteduro[16], M Keil[27], MM Rive[28], N Yao[29,30], N Yalin[31], P Najt[32], PG Rosa[33,34], R Redlich[17], S Trost[27], S Hagenaars[35], SC Fears[36,37], S Alonso-Lana[38,39], TGM van Erp[40], T Nickson[35], TM Chaim-Avancini[33,34], TB Meier[41,42], T Elvsåshagen[3,43], UK Haukvik[3,44], WH Lee[18], AH Schene[45,46], AJ Lloyd[47], AH Young[31], A Nugent[48], AM Dale[49,50], A Pfennig[51], AM McIntosh[35], B Lafer[33], BT Baune[52], CJ Ekman[14], CA Zarate[48], CE Bearden[53,54], C Henry[23,55], C Simhandl[56], C McDonald[32], C Bourne[8,57], DJ Stein[9,10], DH Wolf[25], DM Cannon[22], DC Glahn[29,30], DJ Veltman[58], E Pomarol-Clotet[38,39], E Vieta[20], EJ Canales-Rodríguez[38,39], FG Nery[33,59], FLS Duran[33,34], GF Busatto[33,34], G Roberts[60], GD Pearlson[29,30], GM Goodwin[8], H Kugel[61], HC Whalley[35], HG Ruhe[8,28,62], JC Soares[11], JM Fullerton[13,63], JK Rybakowski[64], J Savitz[42,65], KT Chaim[66,67], M Fatjó-Vilas[38,39], MG Soeiro-de-Souza[33], MP Boks[26], MV Zanetti[33,34], MCG Otaduy[66,67], MS Schaufelberger[33,34], M Alda[68], M Ingvar[14,69], ML Phillips[7], MJ Kempton[16], M Bauer[51], M Landén[14,70], NS Lawrence[71], NEM van Haren[26], NR Horn[9], NB Freimer[72], O Gruber[12], PR Schofield[13,63], PB Mitchell[60], RS Kahn[26], R Lenroot[13,73], R Machado-Vieira[33,74], RA Ophoff[26,72], S Sarró[38,39], S Frangou[18], TD Satterthwaite[25], T Hajek[68,75], U Dannlowski[17], UF Malt[76,77], V Arolt[17], WF Gattaz[33], WC Drevets[78], X Caseras[79], I Agartz[3,19], PM Thompson[1] and OA Andreassen[3,4] for the ENIGMA Bipolar Disorder Working Group

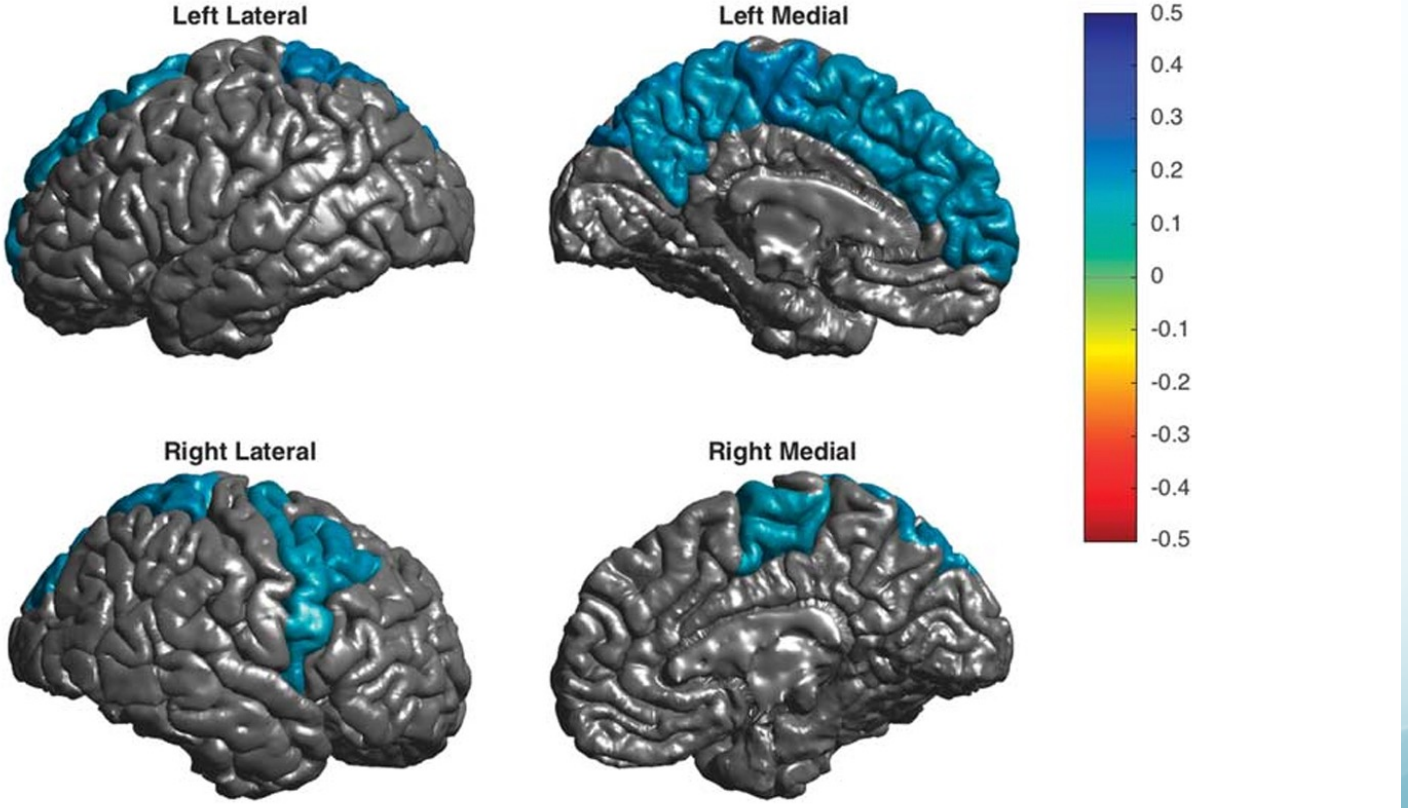
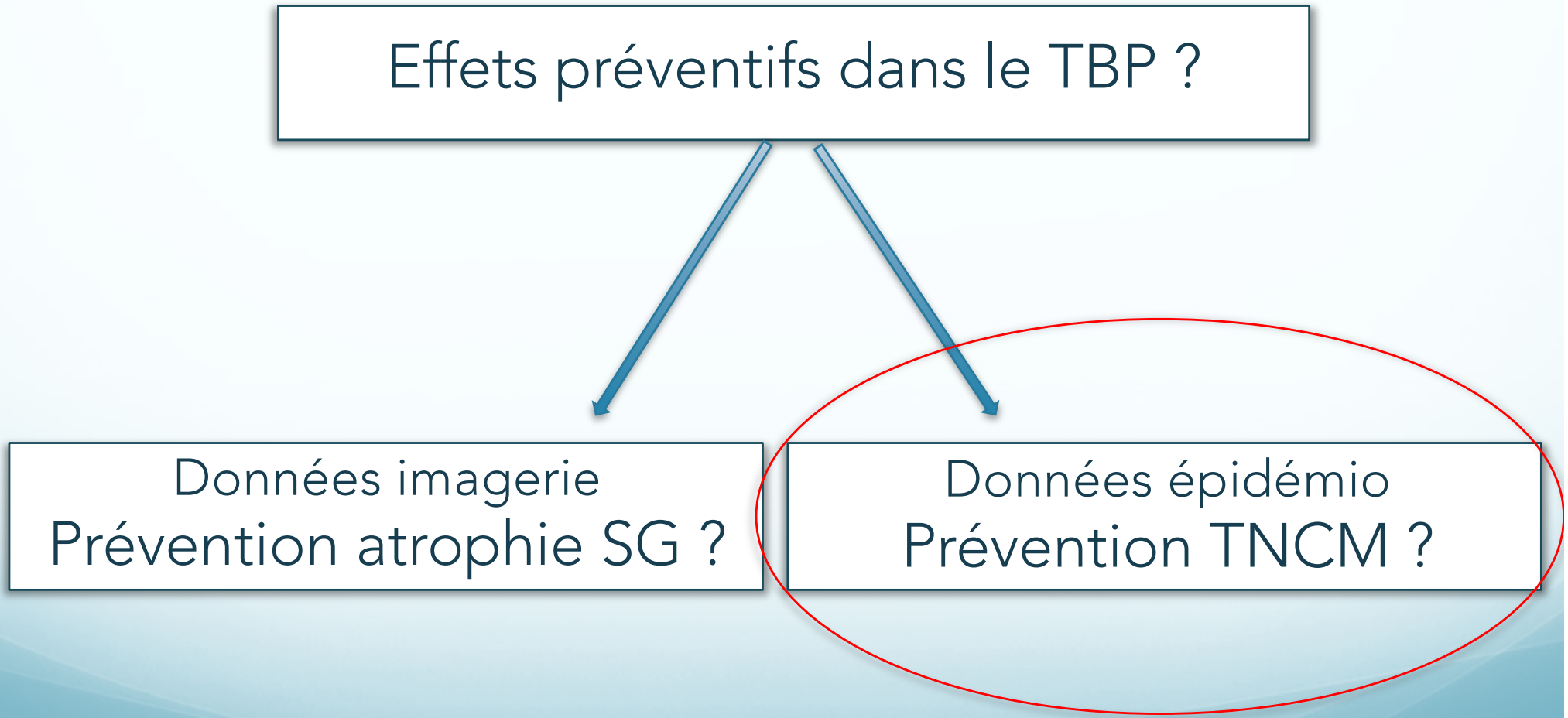


Figure 3. Cortical thickening in adult patients with bipolar disorder associated with lithium treatment. Cohen's *d* effect sizes are plotted for each region of interest on the cortical surface of a template image. Only significant regions are shown; non-significant regions are colored in gray.

Li : quels effets sur le TNCM ?



Li dans le TBP : données cliniques

Acta Psychiatr Scand 2020: 141: 510–521

Systematic Review Or Meta-Analysis

Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses

Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, de Azevedo Cardoso T.

Li dans le TBP : données cliniques

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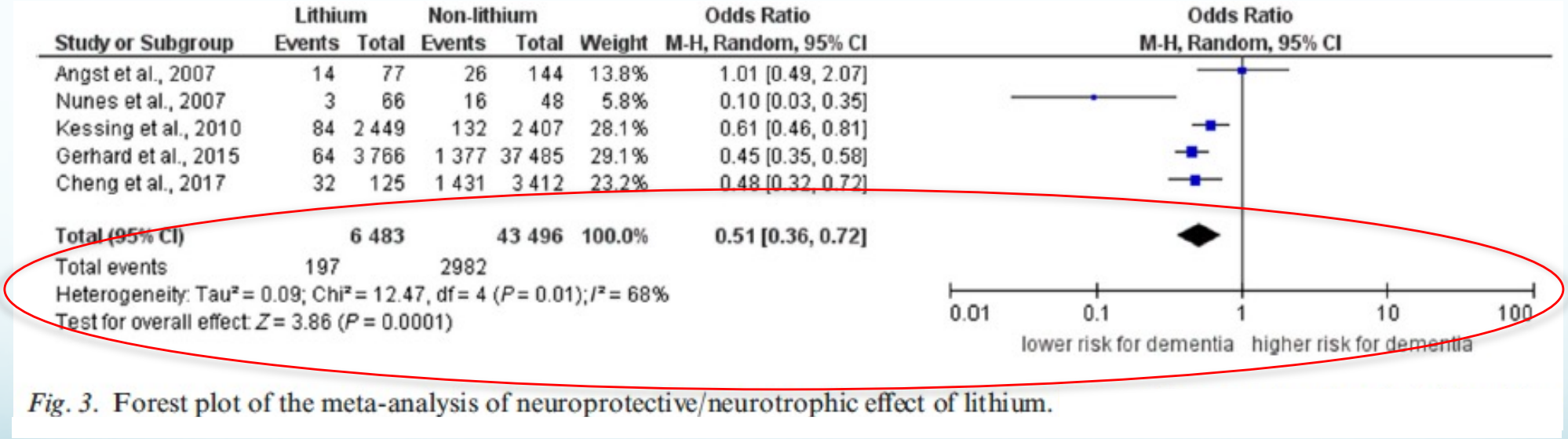

Fig. 3. Forest plot of the meta-analysis of neuroprotective/neurotrophic effect of lithium.

Li dans le TBP : données cliniques

Association between lithium use and the incidence of dementia and its subtypes: A retrospective cohort study

Shanquan Chen[1]*, Benjamin R. Underwood[1,2], Peter B. Jones[1,2,3], Jonathan R. Lewis[2], Rudolf N. Cardinal[1,2]

PLOS Medicine | https://doi.org/10.1371/journal.pmed.1003941 March 17, 2022

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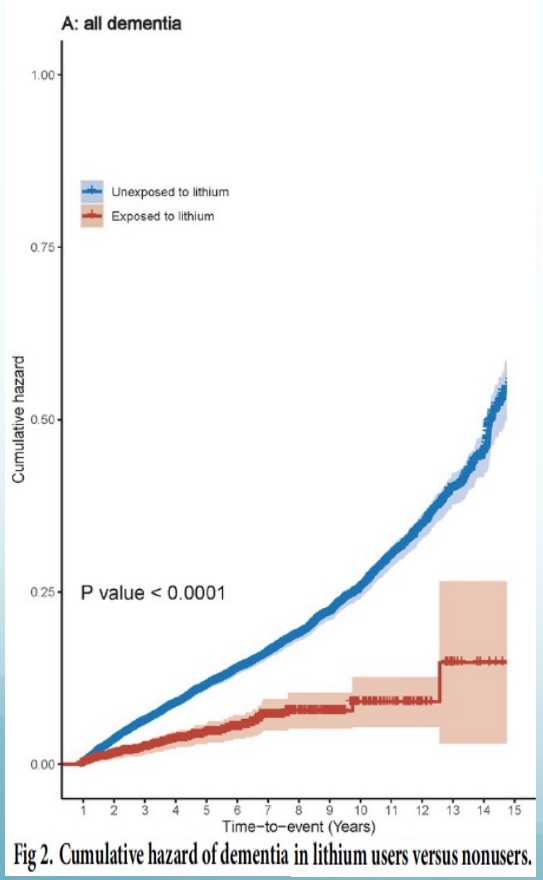

Fig 2. Cumulative hazard of dementia in lithium users versus nonusers.

Outcomes	HR (95% CI), P value	Adjusted HR (95% CI), P value
All dementia	0.58(0.42−0.81), 0.0012	0.56(0.4−0.78), 0.0006

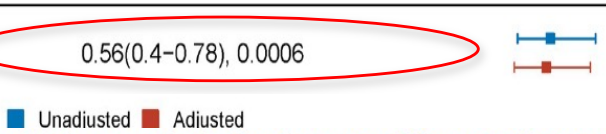

Fig 3. HRs, 95% CIs, and *p*-values for the association of lithium with the development of dementia by Cox proportional hazards models.

All dementia

Duration of lithium exposure	HR (95% CI), P value	Adjusted HR (95% CI), P value
Lithium non−exposure	Reference	Reference
>0, <= 1 years	0.64(0.43, 0.95), 0.0282	0.6(0.4, 0.9), 0.0122
>1, <= 2 years	0.5(0.11, 2.28), 0.3672	0.66(0.14, 3.09), 0.5934
>2, <= 3 years	1.1(0.41, 2.98), 0.8466	1.5(0.56, 3.99), 0.4158
>3, <= 4 years	0.55(0.13, 2.29), 0.4137	0.62(0.14, 2.71), 0.5259
>4, <= 5 years	0.42(0.08, 2.09), 0.2877	0.46(0.09, 2.45), 0.3612
>5 years	0.37(0.2, 0.7), 0.0023	0.36(0.19, 0.71), 0.0031

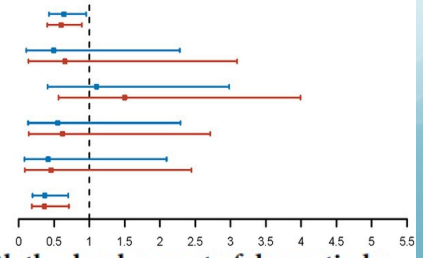

Fig 4. HRs, 95% CIs, and *p*-values for the association of duration of lithium exposure with the development of dementia by Cox proportional hazards models.

Li : quels effets sur le TNCM ?

Effets préventifs dans le TBP ?

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Effets préventifs dans le TBP ?

Ralentissement évolution TNCM ?

Li dans le TCNM

J Clin Psychiatry 70:0, Month 2009

FOCUS ON ALZHEIMER'S DISEASE AND RELATED DISORDERS

Lithium Trial in Alzheimer's Disease: A Randomized, Single-Blind, Placebo-Controlled, Multicenter 10-Week Study

Harald Hampel, MD, MsC; Michael Ewers, PhD; Katharina Bürger, MD; Peter Annas, PhD; Anette Mörtberg, MD; Anna Bogstedt, PhD; Lutz Frölich, MD, PhD; Johannes Schröder, MD; Peter Schönknecht, MD; Matthias W. Riepe, MD; Inga Kraft, PhD; Thomas Gasser, MD; Thomas Leyhe, MD; Hans-Jürgen Möller, MD; Alexander Kurz, MD; and Hans Basun, MD, PhD

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Table 3. Neuropsychological and Psychiatric Measures at Baseline and End of Treatment for Each Treatment Group[a]

Variable	Baseline	End of Treatment
MMSE score, mean (SD)		
Lithium	23.6 (1.6)	22.6 (3.5)
Placebo	23.6 (1.7)	23.2 (2.7)
ADAS-Cog score, mean (SD)		
Lithium	15.8 (4.2)	15.6 (4.4)
Placebo	15.4 (5)	16.6 (5.1)
NPI total score, mean (SD)		
Lithium	8.9 (10.6)	10.9 (11.0)
Placebo	11.2 (11.3)	12.5 (9.7)
NPI depression/dysphoria score (yes/no)[b]		
Lithium	13/19	11/18
Placebo	16/21	16/20

[a]None of the group differences in changes of each score were statistically significant ($P > .05$).

[b]Number of patients with presence (yes) or absence (no) of depressive or dysphoric symptoms.

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

Li : quels effets sur le TNCM ?

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Ralentissement évolution TNCM ?

Ralentissement évolution MCI ?

Li dans le MCI

BJPsych | The British Journal of Psychiatry (2019)
215, 668–674. doi: 10.1192/bjp.2019.76

Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial

Orestes V. Forlenza, Márcia Radanovic, Leda L. Talib and Wagner F. Gattaz

Li dans le MCI

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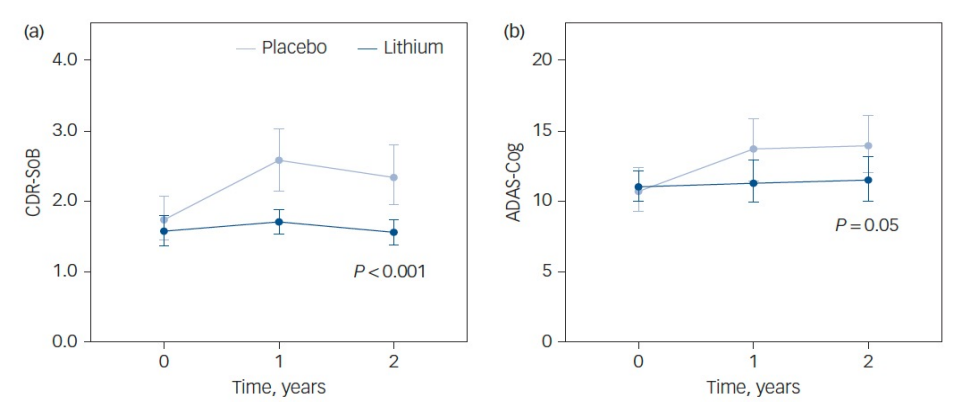

Fig. 1 Cognitive and functional changes according to group allocation (lithium versus placebo) in 2 years of follow-up.

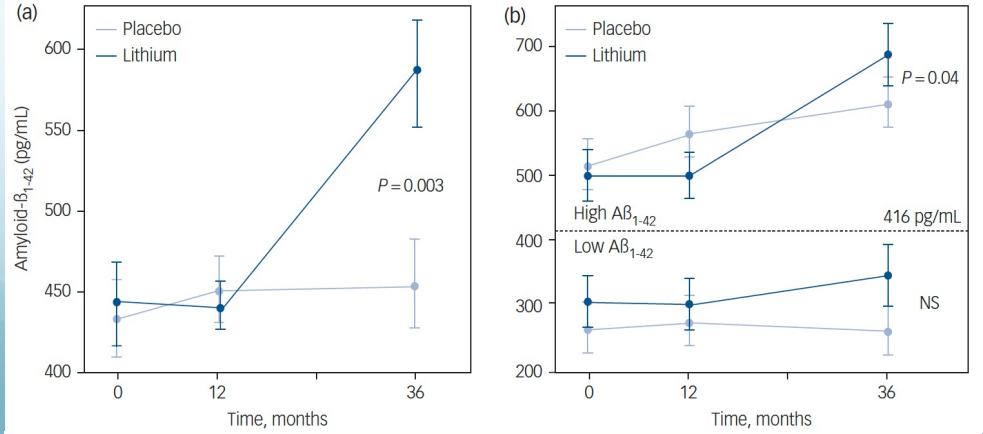

Fig. 3 Longitudinal changes in cerebrospinal fluid (CSF) concentrations of amyloid-β peptide ($A\beta_{1-42}$) in lithium-treated and control groups.

(a) Indicates a 30% increase in CSF $A\beta_{1-42}$ after 3 years in the lithium group ($F = 3.11$, $P = 0.003$). (b) Displays changes in CSF concentrations of $A\beta_{1-42}$ in lithium and placebo groups subdivided at baseline according to the magnitude of $A\beta_{1-42}$ burden, i.e., high- and low-CSF $A\beta_{1-42}$. NS, non-significant.

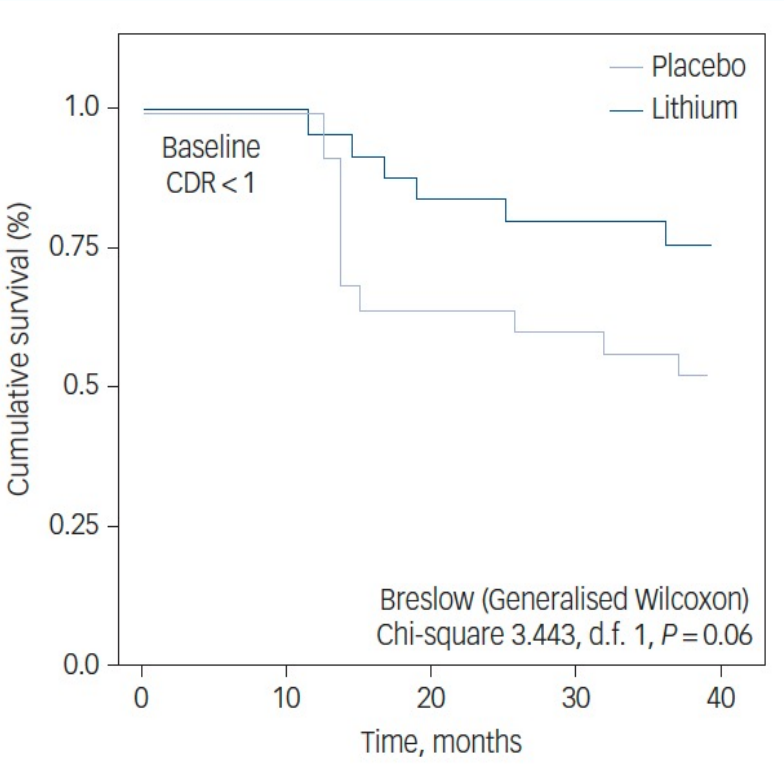

Fig. 2 Kaplan–Meier curves indicating the rate of conversion from mild cognitive impairment (MCI) to dementia, according to exposure or not to lithium treatment

Li dans le MCI

Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2023 Jan-Feb;45(1):46-49
doi:10.47626/1516-4446-2022-2767
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BRIEF COMMUNICATION

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Table 2 Associations between lithium use and neuropsychiatric/cognitive outcome measures

	Lithium				95%CI	
Outcome measures	No	Yes	p-value	Effect size	Lower	Upper
FAST†	4 (1-13)	4 (1-14)	0.92	0.02‡	-	-
MADRS Total†	6.5 (3-22)	5 (0-41)	0.50	0.18‡	-	-
CDR GS†	0.75 (0-3)	0.5 (0-3)	0.97	0.01‡	-	-
CDR SoB†	3.75 (0-18)	4.75 (0-18)	0.83	0.05‡	-	-
MMSE	**18.3 (10.9)**	**25.5 (5.3)**	**0.04**	**0.92§**	**0.02**	**1.80**
VFT (animals)	10 (8.2)	13.1 (4.5)	0.25	0.50§	-0.35	1.34
VFT (FAS)	**11.6 (10.1)**	**34.7 (14.4)**	**< 0.001**	**1.78§**	**0.71**	**2.82**
CDT	1.44 (1.3)	2.27 (1.1)	0.12	0.69§	-0.18	1.54
IQCODE	3.83 (0.7)	3.84 (0.7)	0.96	-0.01§	-0.69	0.65
Time to BADL decline (years)‖	7 (4.1)	10.8 (1.5)	0.05	-1.20§	-2.44	0.11
Time to IADL decline (years)‖	7.9 (4.9)	5.6 (4.6)	0.34	-0.47§	-1.43	0.50

Bold type denotes $p < 0.05$.
BADL = basic activities of daily living; CDR = Clinical Dementia Rating; CDT = Clock Drawing Test; FAS = phonemic Verbal Fluency Test (VFT); FAST = Functional Assessment Staging Tool; GS = Global Score; IADL = Instrumental activities of daily living; IQCODE = Informant Questionnaire on Cognitive Decline in Elderly; MADRS = Montgomery-Åsberg Depression Rating Scale; MMSE = Mini Mental State Examination; SoB = Sum of Boxes.
† Test score values shown as median/range (min-max) and statistics calculated with the Mann-Whitney *U* test or as means/SD calculated with Student's *t*-test.
‡ Rank biserial correlation.
§ Cohen's *d*.
‖ Time to decline in autonomy (estimated in years after participation in the trial).

Li : quels effets sur le TNCM ?

Effets préventifs dans le TBP ?

Ralentissement évolution TNCM ?

Ralentissement évolution MCI ?

Prévention TNCM en pop générale?

Li au long cours en pop générale ?

- Li : des effets **neuroprotecteurs d'autant plus marqués** que le ttt est initié **précocement**

=> intérêt d'une mise en place **précoce en population générale** ?

Li au long cours en pop générale ?

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- Problématique principale : **tolérance** au long cours

=> intérêt des faibles voire des **micro-doses** ?

Micro-doses de Li chez l'animal

Micro-doses de Li chez l'animal

Beneficial effects of low-dose lithium on cognitive ability and pathological alteration of Alzheimer's disease transgenic mice model

Meng Liu[a], Ting Qian[a], Wei Zhou[a], Xiaodon
Lei Zhao[b]

Current Alzheimer Research, 2018, *15*, 1220-1230

RESEARCH ARTICLE

Microdose Lithium NP03 Diminishes Pre-Plaque Oxidative Damage and Neuroinflammation in a Rat Model of Alzheimer's-Like Amyloidosis

ı Iulita[2], Hélène Hall[2], Grant L. Austin[3],
Adam R. Marks[2], D. Allan Butterfield[3,4], and

ORIGINAL ARTICLE

BACE1 inhibition by microdose lithium formulation NP03 rescues memory loss and early stage amyloid neuropathology

EN Wilson[1,4], S Do Carmo[2], MF Iulita[2], H Hall[2], A Ducatenzeiler[2], AR Marks[2], S Allard[2], DT Jia[2], J Windheim[2] and AC Cuello[1,2,3]

Journal of Alzheimer's Disease 73 (2020) 723–739

NP03, a Microdose Lithium Fo
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Joshua T. Emmerson[b], Adriana Ducatenzeiler[b] and A. Claudio Cuello

PLOS ONE | November 25, 2015

RESEARCH ARTICLE

Chronic Microdose Lithium Treatment Prevented Memory Loss and Neurohistopathological Changes in a Transgenic Mouse Model of Alzheimer's Disease

Marielza Andrade Nunes[1,4☯], Natalia Mendes Schöwe[2,4☯], Karla Cristina Monteiro-Silva[1], Ticiana Baraldi-Tornisielo[1,4], Suzzanna Ingryd Gonçalves Souza[1], Janaina Balthazar[2], Marilia Silva Albuquerque[1,4], Ariadiny Lima Caetano[1,4], Tania Araujo Viel[2,3,4], Hudson Sousa Buck[1,4]*

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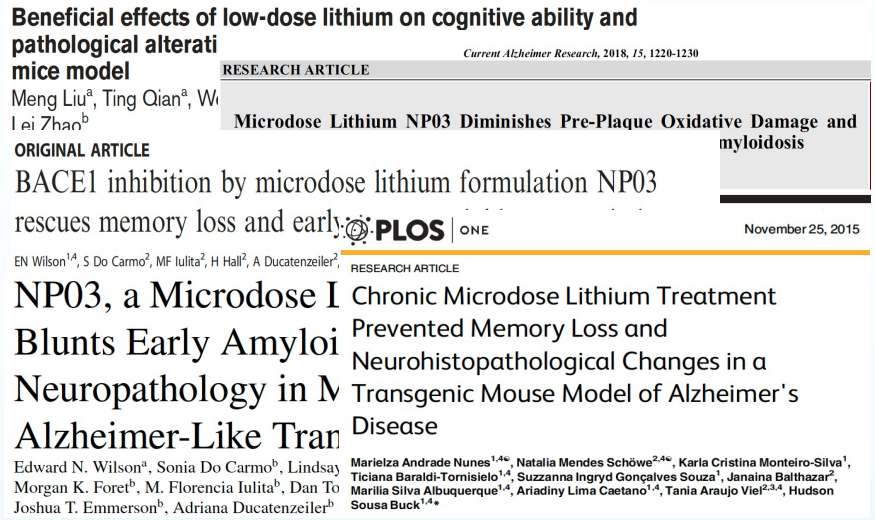

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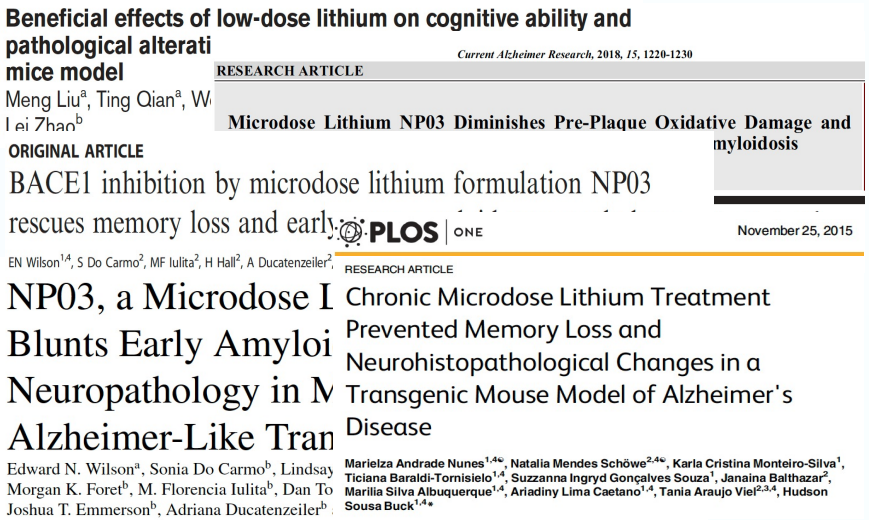

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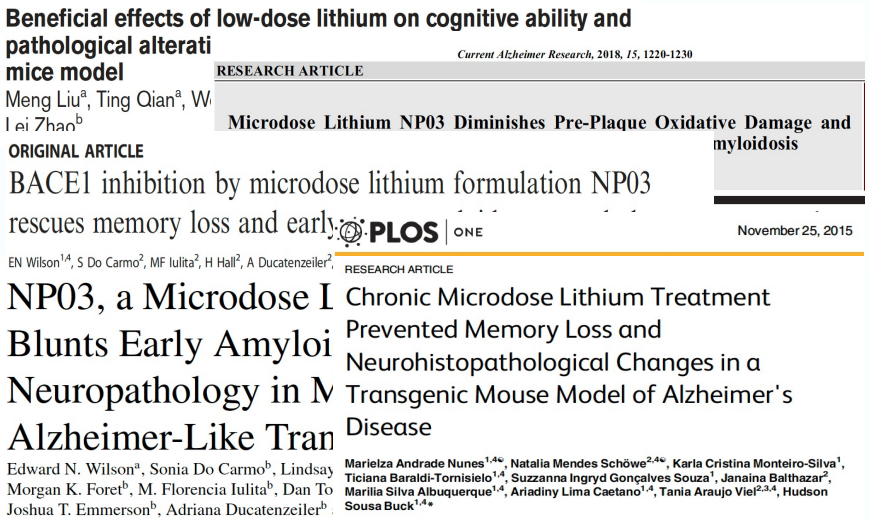
Micro-doses de Li

- 800
- 250
- 40

µg/kg/j

Micro-doses de Li chez l'animal



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Marielza Andrade Nunes[1,4☯], Natalia Mendes Schöwe[2,4☯], Karla Cristina Monteiro-Silva[1], Ticiana Baraldi-Tornisielo[1,4], Suzzanna Ingryd Gonçalves Souza[1], Janaina Balthazar[2], Marilia Silva Albuquerque[1,4], Ariadiny Lima Caetano[1,4], Tania Araujo Viel[2,3,4], Hudson Sousa Buck[1,4*]

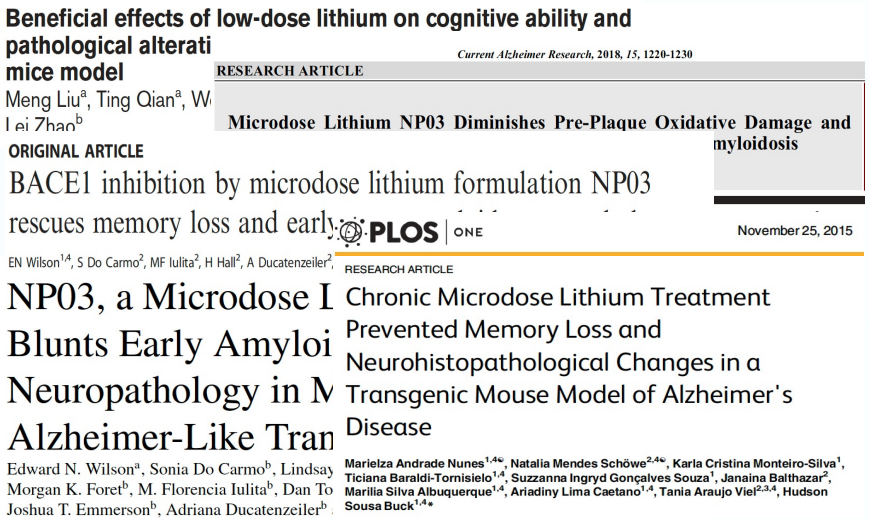
Micro-doses de Li

- 800
- 250
- 40

µg/kg/j

↑ performances cognitives

Micro-doses de Li chez l'animal



Beneficial effects of low-dose lithium on cognitive ability and pathological alterati
mice model
Meng Liu[a], Ting Qian[a], W
Lei Zhao[b]

Current Alzheimer Research, 2018, 15, 1220-1230

RESEARCH ARTICLE

Microdose Lithium NP03 Diminishes Pre-Plaque Oxidative Damage and
myloidosis

ORIGINAL ARTICLE

BACE1 inhibition by microdose lithium formulation NP03
rescues memory loss and early

PLOS ONE | November 25, 2015

EN Wilson[1,4], S Do Carmo[2], MF Iulita[2], H Hall[2], A Ducatenzeiler[2],

NP03, a Microdose I
Blunts Early Amyloi
Neuropathology in M
Alzheimer-Like Tran

Edward N. Wilson[a], Sonia Do Carmo[b], Lindsay
Morgan K. Foret[b], M. Florencia Iulita[b], Dan To
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↓ plaques β-amyloïdes

↓ protéine τ

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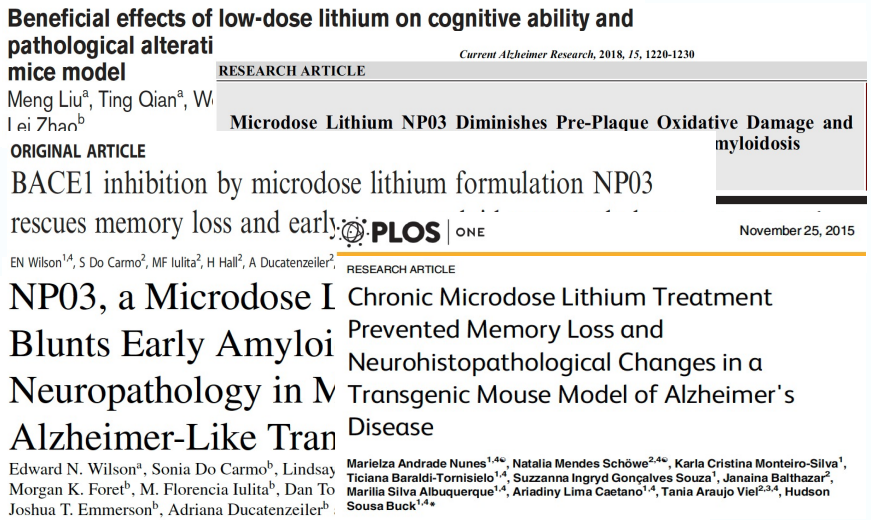

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- 800
- 250
- 40

µg/kg/j

↑ performances cognitives

↑ BDNF

↓ plaques β-amyloïdes

↓ marqueurs inflammation
↓ stress oxydatif

↓ protéine τ

Micro-doses de Li dans DTA

Current Alzheimer Research, 2013, *10*, 104-107

Microdose Lithium Treatment Stabilized Cognitive Impairment in Patients with Alzheimer's Disease

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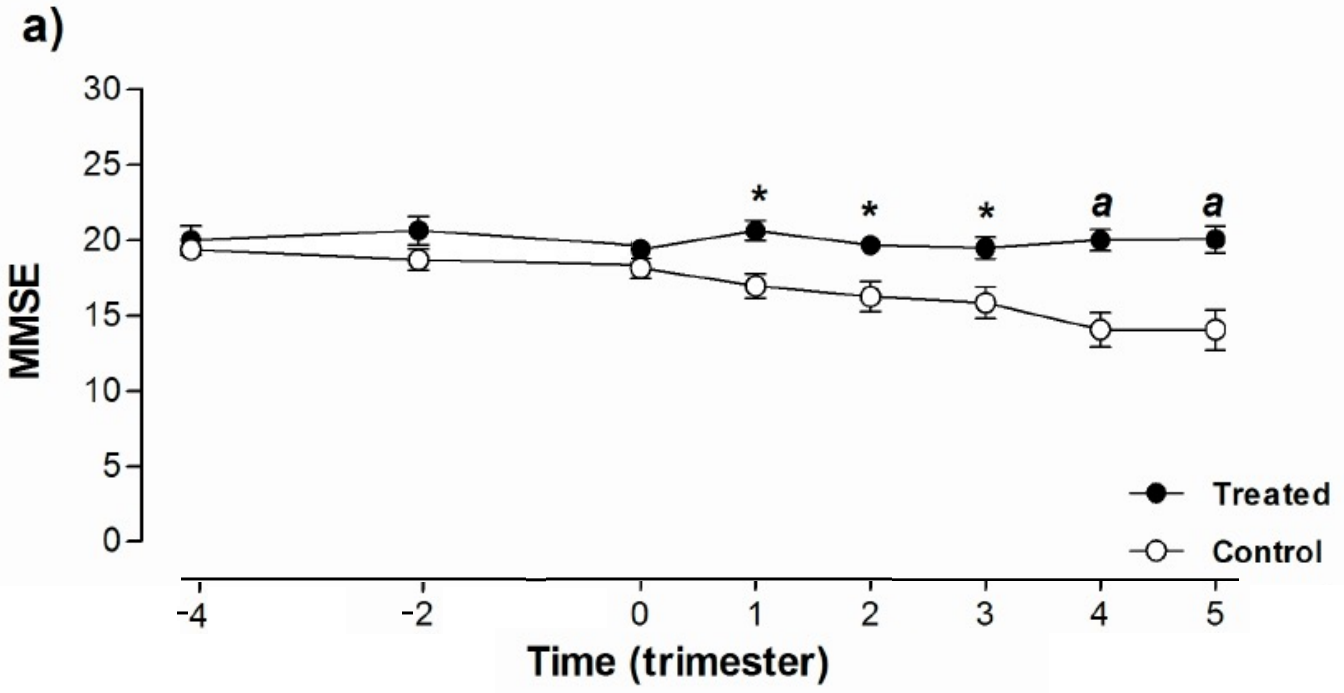


Fig. (1). Scores in the mini-mental state examination (MMSE) of subjects from control or treated groups before placebo or lithium therapy. Statistical differences are represented by * ($P < 0.01$) and ***a*** ($P<0.001$).

Micro-doses de Li en pop générale

JAMA Psychiatry | Original Investigation

October 2017 Volume 74, Number 10

Association of Lithium in Drinking Water With the Incidence of Dementia

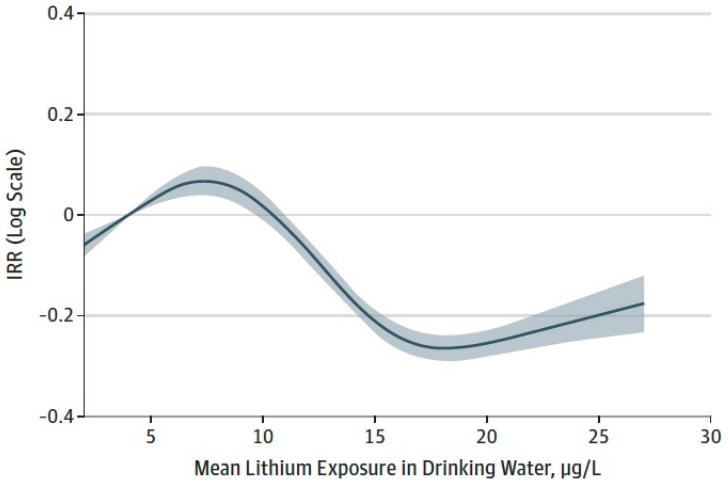
Lars Vedel Kessing, MD, DMSc; Thomas Alexander Gerds, MSc, PhD; Nikoline Nygård Knudsen, MSc; Lisbeth Flindt Jørgensen, MSc; Søren Munch Kristiansen, MSc, PhD; Denitza Voutchkova, MSc, PhD; Vibeke Ernstsen, MSc, PhD; Jörg Schullehner, MSc, PhD; Birgitte Hansen, MSc, PhD; Per Kragh Andersen, MSc, PhD, DMSc; Annette Kjær Ersbøll, MSc, PhD

Micro-doses de Li en pop générale

Table. Lithium Exposure and Rates of Dementia (Overall), Alzheimer Disease, and Vascular Dementia

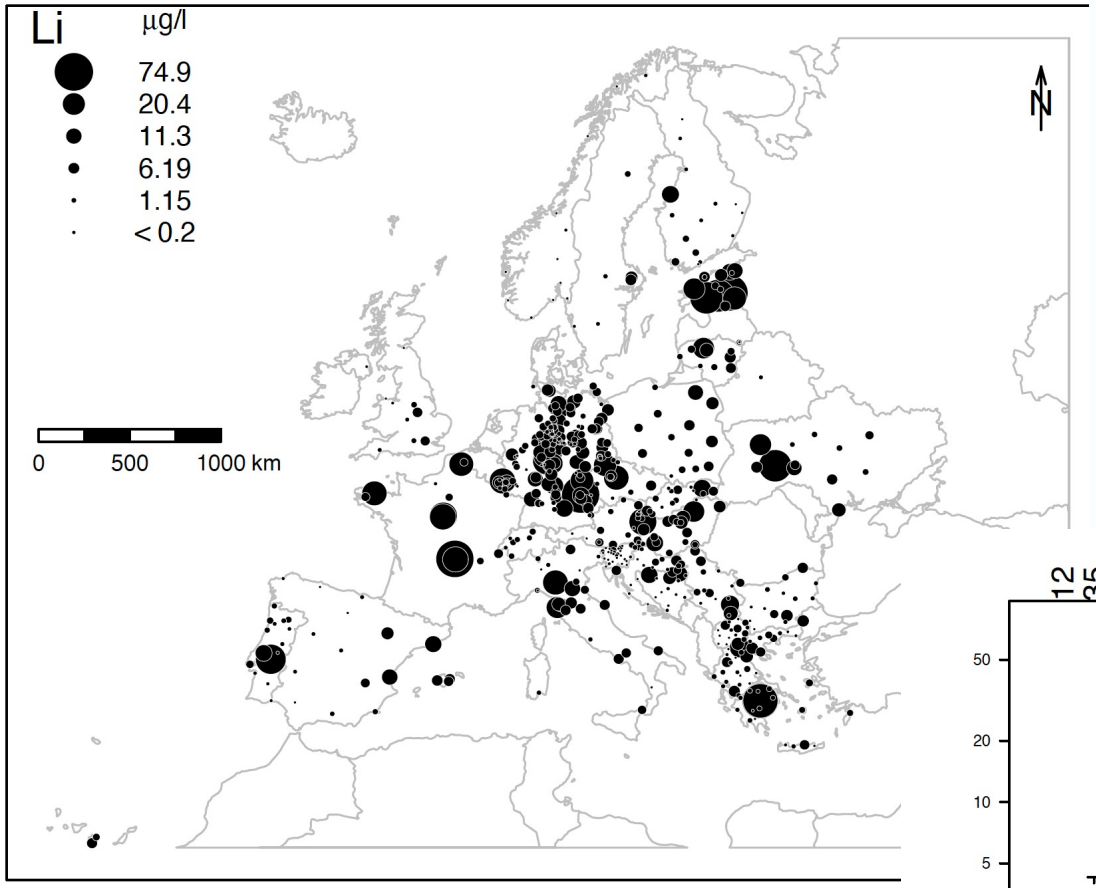
Mean Lithium Exposure, µg/L	No. (%) Patients	No. (%) Control Individuals	Incidence Rate Ratio (95% CI)	*P* Value
Dementia (Overall)				
2.0-5.0	9105 (12.4)	90 052 (12.4)	1 [Reference]	
5.1-10.0	19 694 (26.9)	158 627 (21.8)	1.22 (1.19-1.25)	<.001
10.1-15.0	26 471 (36.1)	264 647 (36.3)	0.98 (0.96-1.01)	.17
15.1-27.0	18 010 (24.6)	214 947 (29.5)	0.83 (0.81-0.85)	<.001

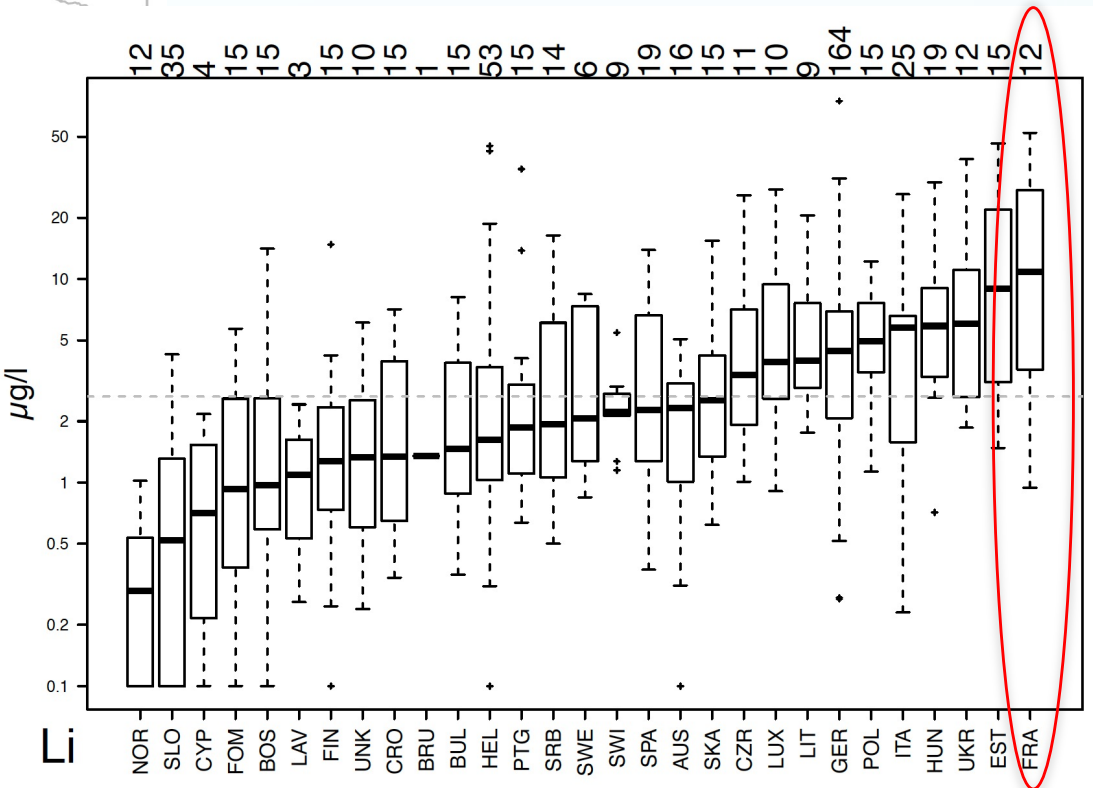
Figure. Association Between Mean Lithium Exposure in Drinking Water on a Continuous Scale and the Overall Dementia Rate



Data are the incidence rate ratios (IRRs) in relation to the mean (4 µg/L) of the lowest group on a logarithmic scale. Shaded area indicates 95% CIs.

Li et eau du robinet en France





Flem et al, Applied Geochemistry, 2015

Synthèse

- Li : propriétés **neuroprotectrices** voire **neurotrophiques…**
- … permettant la **prévention TNCM** ?
- Effets présents dès **micro-doses** (bien + faibles que les doses thérapeutiques)
- **Données robustes**++: modèles cellulaires in vitro, modèles animaux, études cliniques pop BP (prévention atrophie, prévention TNCM), études pop MCI (prévention aggravation TNCM), étude pop générale (prévention TCNM)
- Intérêt d'un **traitement micro-dosé préventif au long cours** passé l'âge de 40 ans ?


Lithium
Oligosol
Li
28


LIFE EXTENSION
Lithium
1000 mcg
Essential Mineral for Brain and Body Health*
100 VEGETARIAN CAPSULES | DIETARY SUPPLEMENT
HERB-OLOGY
NATURE'S TECHNOLOGY
VEGETARIAN LITHIUM OROTATE
HIGHLY BIOAVAILABLE ELEMENTAL LITHIUM
5 MG
œmine
LITHIUM
Prune
Stress - Anxiété
Oligosol
Lithium
Li
28
LITHIUM
5mg
elemental lithium per tablet, from lithium orotate
LINDENS
pure
encapsulations
Lithium
(orotate)
5 mg
hypo-allergenic dietary supplement
90 CAPSULES
Supplement Facts
PROGRESSIVE
PROFESSIONAL
LITHIUM
OROTATE
5 MG
MINERAL SUPPLEMENT
100 VEGETABLE CAPSULES
Supplement Facts
PiperRock
LITHIUM
OROTATE
5 MG
3
Li
Lithium
6.94
180 QUICK RELEASE CAPSULES
DIETARY SUPPLEMENT
LIFE EXTENSION
Memory Protect
Defends Against Memory Loss*
12 COLOSTRININ-LITHIUM (C-LI) VEGETARIAN CAPSULES
24 LITHIUM (LI) VEGETARIAN CAPSULES
36 DAY SUPPLY | DIETARY SUPPLEMENT


Merci pour votre attention