Seeking biomarkers for electroconvulsive therapy in depression

Miriam Zangani Jaer MD (Psychiatrist) PhD student Akershus University Hospital Norway NACT May 2024



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AHUS

ECT clinic located at the emergency psychiatric unit

ECT capacity: 25 patients a week.

n= 100 patients/year

Part of PRECISE-study. First patients enrolled.



ahus.no

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Consortium for Precision Treatment with ECT in Severe Depression: (PRECISE)

The goal of this project is to map central phenotypic and biological factors that predict long-term treatment response to electroconvulsive therapy (ECT), using a naturalistic approach to enable clinically transferable discovery in a large dataset

PRECISE

Inclusion criteria:

- Age \geq 18 years
- Diagnosis of unipolar major depressive episode
 - According to the Mini
 International Neuropsychiatric
 Interview (MINI), with or
 without psychotic symptoms
 - ICD-10 codes F32.2, F32.3,
 F33.2, F33.3
- Ability to
 - co-operate in testing

Exclusion criteria:

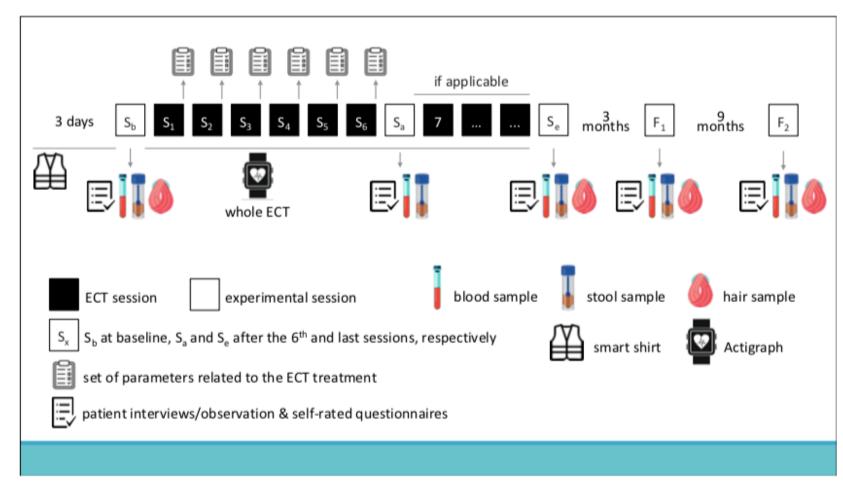
Pregnancy

AHUS study nurses



PRECISE

Summary of study procedures



Overview of the presentation

- What are biomarkers?
- Understanding the significance of biomarkers for ECT in depression
- Overview of widely studied circulating biomarkers
- Meta-analysis NSE and S100

Biomarkers

• "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention."

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools)2016

Biomarkers and ECT: Paving the way for tailored depression treatment?

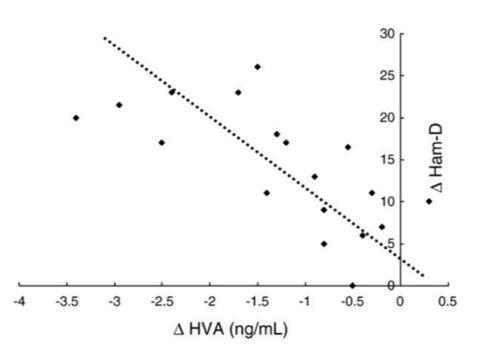
- Predict ECT response
- Differentiate between likely responders and non-responders
- Minimize trial and error in treating depression
- Objective measure beyond traditional symptom-based assessments

Biomarkers for ECT in depression

- Monoaminergic
- Endocrine
- Neurotrophic
- Inflammatory and immune biomarkers
- Genetic/Epigenetic biomarkers
- mRNA
- Neuroimaging
- Clinical predictors

Monoaminergic biomarkers

Monoamine metabolite: Homovanillic Acid (HVA) (Okamoto et al. 2008)



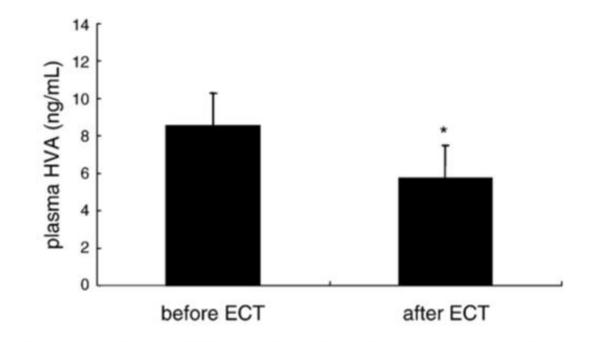
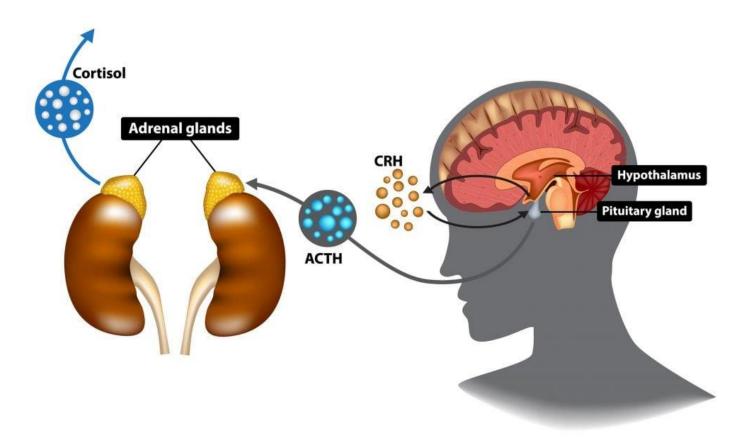


Fig. 2. Negative association between the changes in Ham-D and the changes in plasma HVA levels before and five weeks after start of ECT (n=18). rho=-0.620, p=0.0052.

Fig. 1. Changes in plasma HVA levels before and after (i.e., five weeks after starting) ECT treatment (n = 18). *p = 0.008, compared with before ECT.

Endocrine biomarkers

• HPA-axis



Endocrine biomarkers

Corticotropic axis: 22 studies included 6-62 patients

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Contents lists available at ScienceDirect

Brain Stimulation 11 (2018) 29-51

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review

Antoine Yrondi ^{a, b, *}, Marie Sporer ^a, Patrice Péran ^b, Laurent Schmitt ^a, Christophe Arbus ^{a, b}, Anne Sauvaget ^c

^a Psychiatric Department, CHU Toulouse-Purpan, 330 Avenue de Grande Bretagne, 31059 Toulouse, France

^b Toulouse NeuroImaging Center, ToNIC, University of Toulouse, Inserm, UPS, France

^c CHU Nantes, Addictology and Liaison Psychiatry Department, Neuromodulation Unit in Psychiatry, Nantes, France

Neurotrophic biomarkers

 Brain derived neurotrophic factor (BDNF)

- 28 studies n=778
- Mean age 50 (SD 12)

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY 2023, VOL. 24, NO. 1, 24–33 https://doi.org/10.1080/15622975.2022.2058083



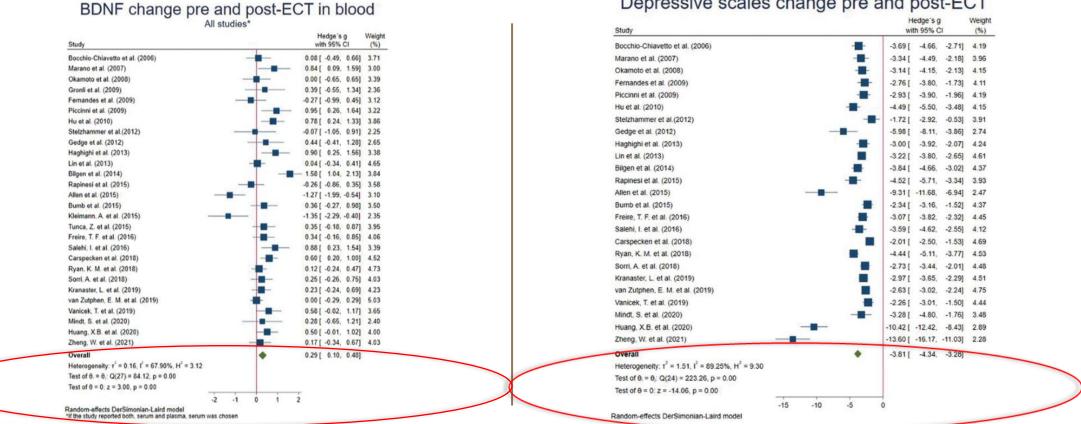
Check for update:

ORIGINAL INVESTIGATION

BDNF blood levels after electroconvulsive therapy in patients with mood disorders: An updated systematic review and meta-analysis

Rebeca Pelosof^a* (b), Leonardo A. dos Santos^a* (b), Luis C. Farhat^a (b), Wagner F. Gattaz^{a,b} (b), Leda Talib^{a,b} (b) and André R. Brunoni^{a,b,c} (b)

^aDepartment of Psychiatry, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil; ^bService of Interdisciplinary Neuromodulation, Department of Psychiatry, Laboratory of Neurosciences (LIM-27), Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil; ^cInterdisciplinary Center for Applied Neuromodulation University Hospital, Universidade de São Paulo, São Paulo, Brazil



Depressive scales change pre and post-ECT

Figure 2. Forest plot for the BDNF meta-analysis.

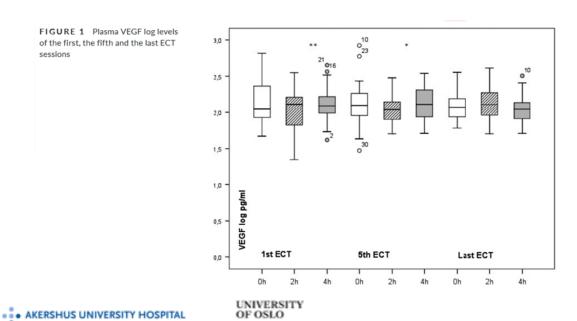
Figure 4. Forest plot for the depressive symptoms meta-analysis.

BDNF as a biomarker for predicting ECT treatment outcomes in depression



Neurotrophic biomarkers

• Vascular endothelial growth factor (VEGF) (Minelli et al. 2011, Minelli et al. 2014, Clark-Raymond et al. 2017, Ryan & McLoughlin 2018, Kranaster et al. 2019, Maffioletti et al. 2020, Sorri et al. 2020, Maffioletti et al. 2021(review)





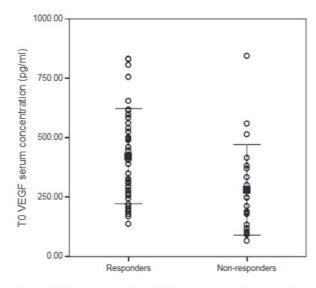
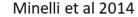


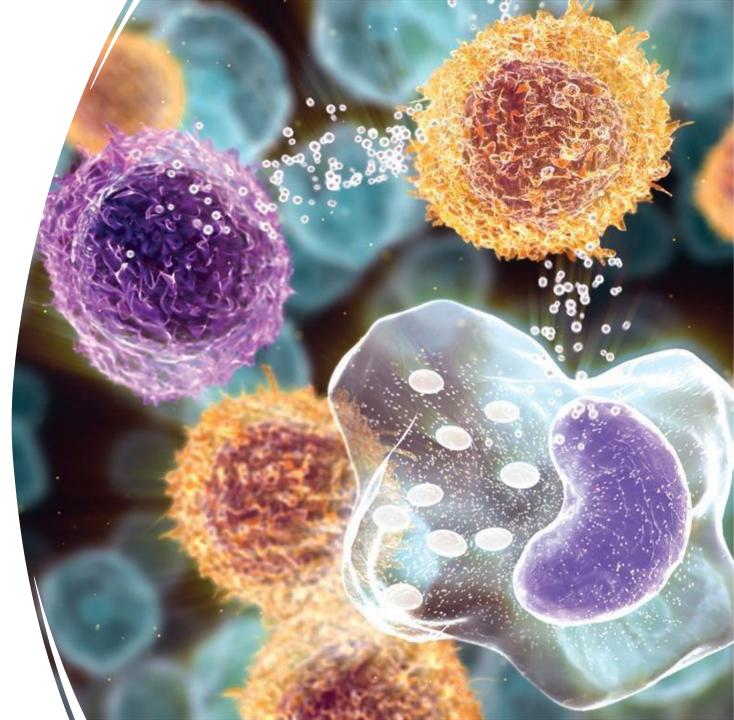
Fig. 1. Difference of the VEGF serum levels at baseline between patients that did or did not respond to ECT treatment by the time of follow-up. Error bars show mean ± 1.0 SD.



VEGF as a biomarker for predicting ECT treatment outcome in depression



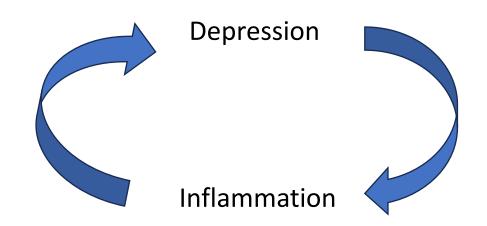
Inflammatory and Immune biomarkers



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Inflammatory and immune biomarkers



Kiecolt-Glaser et al Am J Psychiatry 2015

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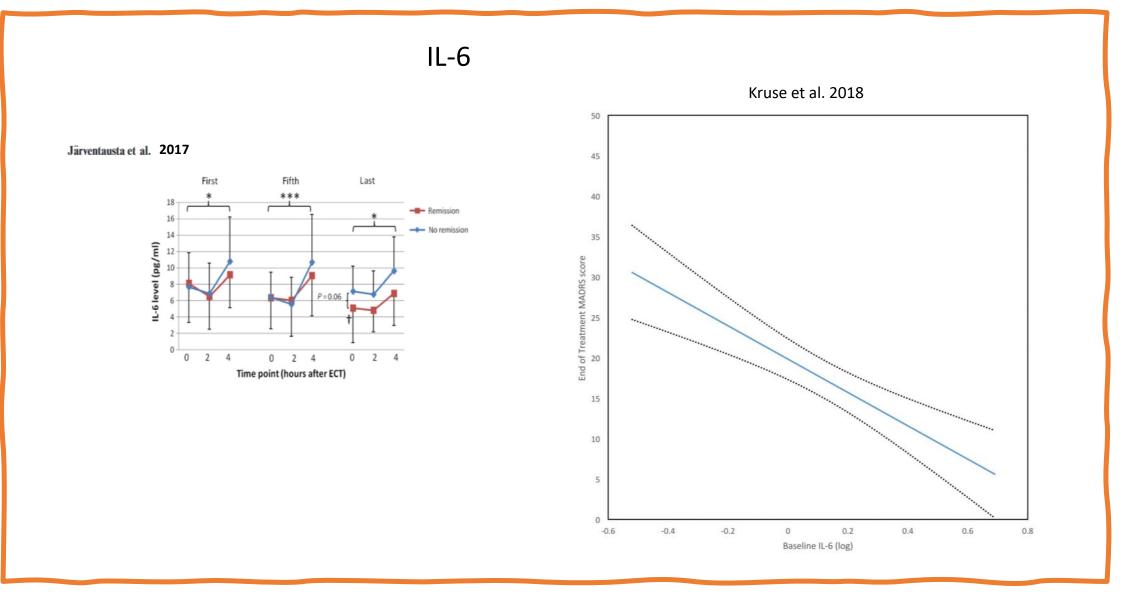
Inflammatory and immune biomarkers

 Cytokines ; Gay et al 2021 : Cytokines changes associated with electroconvulsive therapy in patients with treatment-resistant depression: a Meta-analysis

n= 198 patients

Mean age: 48,87 years [33-59 years]

	Bet	ore EC	т	Af	ter ECT			Std. Mean Difference	Std. Mean Difference
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
IL-6									
Belge et al.2020	0.74	0.84	62	0.65	0.9	62	32.3%	0.10 [-0.25, 0.46]	
Fluitman et al. 2011	1,785	568	12	1,184	1,284	8	4.7%	0.63 [-0.29, 1.55]	
Jarventusta et al. 2016	7.9	4.4	30	8.6	4.2	30	15.6%	-0.16 [-0.67, 0.35]	
Kranaster et al. 2017	3.18	3.06	12	2.6	1.8	12	6.2%	0.22 [-0.58, 1.03]	
Kruse et al. 2018	1.2	1.4	29	1.3	1.8	29	15.1%	-0.06 [-0.58, 0.45]	
Zincir et al. 2016 Subtotal (95% CI)	34.98	36.89	50 195	44.56	93.59	50 191	26.0% 100.0%	-0.13 [-0.53, 0.26] 0.01 [-0.19, 0.21]	
Heterogeneity: $Tau^2 = 0$.00; Chi ²	1 = 3.29), df =	5 (P = 0)	.65); I ²	= 0%			
Test for overall effect: Z									
TNF-a									
Belge et al.2020	2.22	0.72	62	2.13	0.78	62	28.1%	0.12 [-0.23, 0.47]	
Fluitman et al. 2011	131	73	12	100	39	8	7.3%	0.48 [-0.43, 1.39]	
Kruse et al. 2018	6.5	2.8	29	7.8	7.6	29	17.8%	-0.22 [-0.74, 0.29]	
Mindt et al. 2019	8.7	1.41	7	8.41	1.38	7	5.6%	0.19 [-0.86, 1.25]	
Sorri et al. 2018	1.65	0.56	30	1.39	0.43	25	16.7%	0.51 [-0.03, 1.05]	-
Zincir et al. 2016 Subtotal (95% CI)	86.49	17.06	50 190	78.28	11.48	50 181	24.5% 100.0%	0.56 [0.16, 0.96] 0.26 [-0.00, 0.52]	•
Heterogeneity: Tau ² = 0	.03; Chi	1 = 7.20), df =	5(P = 0	.21); 12	= 31%			
Test for overall effect: Z	= 1.95	(P = 0.0)	5)						
IL-4									
A Design of the second s					200	~	22.01/		
Fluitman et al. 2011	122	152	12	181	265	8	32.0%	-0.28 [-1.18, 0.62]	
Mindt et al. 2019		16.32		99.36		7	29.8%	-0.10 [-1.15, 0.95]	
Zincir et al. 2016 Subtotal (95% CI)	22.6	14.12	50 69	8.45	7.58	50	38.2% 100.0%	1.24 [0.81, 1.67] 0.35 [-0.76, 1.47]	
	an chi			2 (0	0.0031			0.33 [-0.70, 1.47]	
Heterogeneity: Tau ² = 0 Test for overall effect: Z				2 (P =	0.002);	1 = 84	170		
rest for overall effect: Z	= 0.62	(r = 0.5	3)						
IL-10									
Fluitman et al. 2011	54	38	12	43	31	8	30.1%	0.30 [-0.60, 1.20]	
Mindt et al. 2019	16.34			15.94		7	26.2%	0.33 [-0.73, 1.39]	
Zincir et al. 2016		24.84		32.39		50	43.8%	-0.71 [-1.11, -0.30]	
Subtotal (95% CI)	20.00		69		20.07		100.0%	-0.14 [-0.92, 0.65]	
Heterogeneity: $Tau^2 = 0$ Test for overall effect: Z				2 (P = 0	.04); I ²	= 68%			
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									0 1



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Inflammatory and immune biomarkers

 Cytokines ; Gay et al 2021 : Cytokines changes associated with electroconvulsive therapy in patients with treatment-resistant depression: a Meta-analysis

n= 198 patients

Mean age: 48,87 years [33-59 years]

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Zincir et al. 2016	34.98	36.89	50	44.56	93.59	50	26.0%	-0.13 [-0.53, 0.26]	
Subtotal (95% CI)			195			191	100.0%	0.01 [-0.19, 0.21]	◆
Heterogeneity: $Tau^2 = 0$	0.00; Chi	2 = 3.29	, df =	5 (P = 0)	.65); 12	= 0%			
Test for overall effect: Z	= 0.08	(P = 0.9)	4)						
TNF-a									
Belge et al.2020	2.22	0.72	62	2.13	0.78	62	28.1%	0.12 [-0.23, 0.47]	
Fluitman et al. 2011	131	73	12	100	39	8	7.3%	0.48 [-0.43, 1.39]	
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Zincir et al. 2016	86.49	17.06	50	78.28	11.48	50	24.5%	0.56 [0.16, 0.96]	
Subtotal (95% CI)			190			181	100.0%	0.26 [-0.00, 0.52]	•
Heterogeneity: Tau ² = 0).03; Chi	1 = 7.20), df =	5 (P = 0)	.21); 12	= 31%			
Test for overall effect: Z	= 1.95	(P = 0.0)	5)						
IL-4									
Fluitman et al. 2011	122	152	12	181	265	8	32.0%	-0.28 [-1.18, 0.62]	
Mindt et al. 2019	97.72	16.32	7	99.36	13.27	7	29.8%	-0.10 [-1.15, 0.95]	
Zincir et al. 2016	22.6	14.12	50	8.45	7.58	50	38.2%	1.24 [0.81, 1.67]	
Subtotal (95% CI)			69			65	100.0%	0.35 [-0.76, 1.47]	
Heterogeneity: Tau ² = 0				2 (P =	0.002);	$1^2 = 84$	196		
Test for overall effect: Z	= 0.62	(P = 0.5)	3)						
IL-10									
Fluitman et al. 2011	54	38	12	43	31	8	30.1%	0.30 [-0.60, 1.20]	
Mindt et al. 2019	16.34			15.94	0.73	7	26.2%	0.33 [-0.73, 1.39]	
Zincir et al. 2016 Subtotal (95% CI)	16.88	24.84	50 69	32.39	18.07	50 65	43.8% 100.0%	-0.71 [-1.11, -0.30] -0.14 [-0.92, 0.65]	
Heterogeneity: Tau ² = 0 Test for overall effect: Z				2 (P = 0	.04); I ²	= 68%			
Test for overall effect: Z	2 = 0.34	(P = 0.7	4)						-2 -1 0 1

$TNF-\alpha$

Hestad et al. 2003

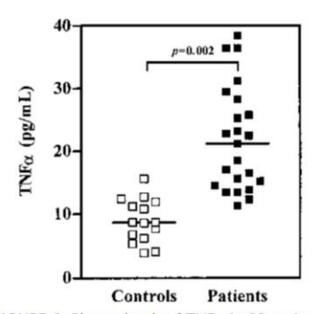
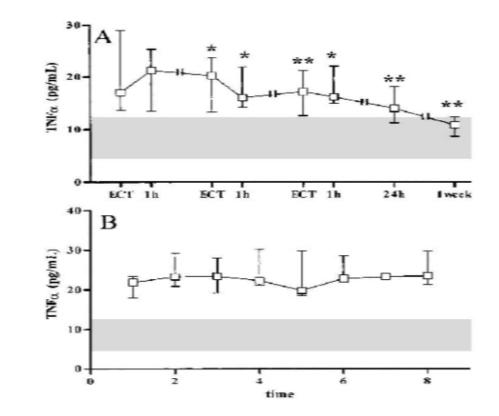


FIGURE 1. Plasma levels of $TNF\alpha$ in 23 patients with depression and 15 sex- and age-matched healthy controls. Horizontal lines represent median values.



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Inflammatory and immune biomarkers

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2016: 134: 469-484 All rights reserved DOI: 10.1111/acps.12656 © 2016 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd ACTA PSYCHIATRICA SCANDINAVICA

Meta-analysis

Interleukin-1 β-targeted treatment strategies in inflammatory depression: toward personalized care

Ellul P, Boyer L, Groc L, Leboyer M, Fond G. Interleukin-1 β-targeted treatment strategies in inflammatory depression: toward personalized care.



Inflammatory and Immune biomarkers

• C-reactive protein (CRP) Kruse et al. 2018, Carlier et al. 2019, Ryan&McLoughlin 2022

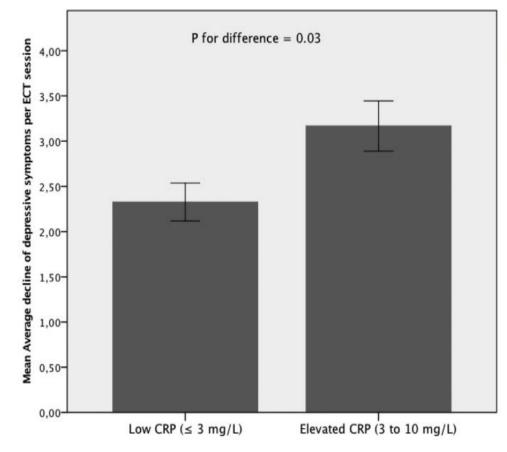


Fig. 1. Contribution of low and elevated CRP levels to the speed of decline in MADRS points, per ECT administration in depressed patients Using linear regression, we examined the association between elevated CRP and the speed of decline of depressive symptoms per ECT administration, adjusting for age, gender, and MADRS score at baseline. Can inflammatory and immune markers be used as biomarker(s) for predicting ECT treatment outcome in depression

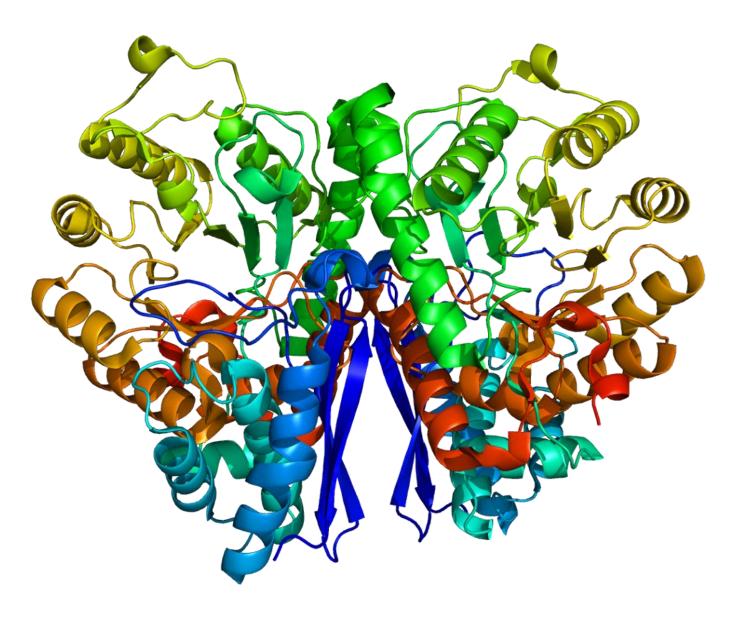


Meta-analysis NSE and S100 protein

 Systematic review and meta-analysis of the levels of neuron-specific enolase and S100, markers of cellular damage in brain tissue, before versus after electroconvulsive therapy in patients experiencing psychiatric illness.

NSE

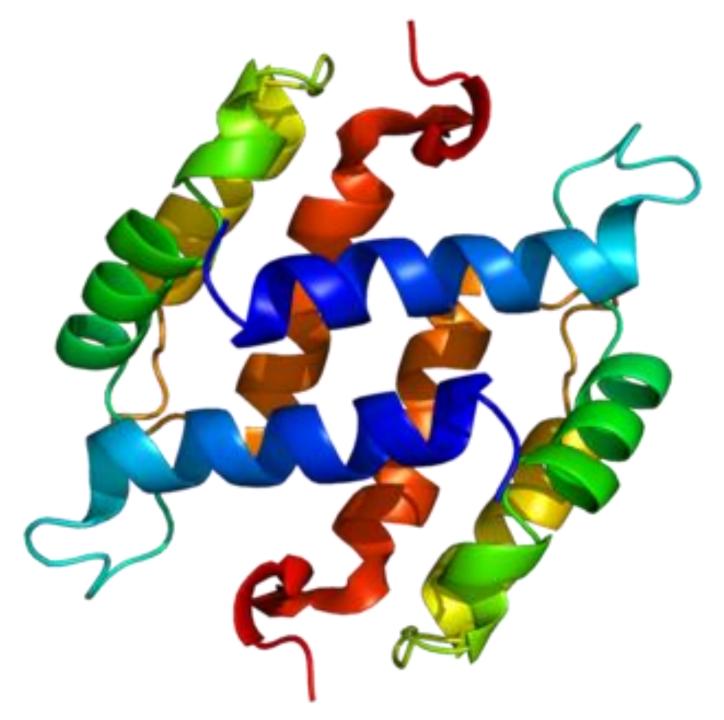
- Dimeric glycolytic enzyme
- Found in the cytosol of many cells in the CNS



S100 protein

• Protein family with 21 members

• S100B



The journey ahead



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THANKS FOR THE ATTENTION

MIRIAM.ZANGANI@GMAIL.COM