IL CERVELLO CHE CAMBIA 9. Recenti avanzamenti e frontiere di ricerca in… 9 Novembre, 2019

«Valutazione e gestione dei disturbi psico-comportamentali: quali i recenti avanzamenti e frontiere di ricerca?»

Gianluca Serafini M.D., *Ph*.D.

Dipartimento di Neuroscienze,
Università di Genova
e.mail:
gianluca.serafini@unige.it

Aula Magna Clinica Neurologica, Genova

Outline presentation

- **Valutazione e gestione dei disturbi psico-comportamentali: i dati della Clinica Psichiatrica**

- **Quali i recenti avanzamenti e frontiere di ricerca in tema di trattamento?**

Il processo della valutazione dei disturbi psico-comportamentali è essenziale in qualsiasi setting clinico

Colloquio clinico

Strumenti standardizzati

La valutazione deve rispettare il principio della muldimensionalità/interprofessionalità:

- Funzioni cognitive
- Stato funzionale
- Sintomi non cognitivi
- Comorbidità somatica
- Stress dei caregivers

Clinica Psichiatrica: valutazione/approfondimento relazione tra disturbi psichiatrici e deterioramento cognitivo

Attività mirata alla **valutazione** dei **disturbi cognitivi nell'ambito** della **malattia di Alzheimer** e delle **demenze**

1. **Visita psichiatrica**
2. Eventuale **visita neurologica**

→ **Aspetti psicopatologici** della persona

3. Svolgimento di **test neurocognitivi** di valutazione **standardizzati**
4. **Esami strumentali**

→ **Capacità di autonomia** legata al vivere quotidiano

Finalizzati a **individuare** le **fasi precoci** del **deterioramento cognitivo** fino alla diagnosi di demenza

I nostri strumenti di valutazione: quali specificità? In primis, la comprensione del vissuto e il riuscire a restituire una traccia di senso

- **Colloquio psichiatrico**
- **Mini Mental State Examination** (Folstein et al., 1975)
- **Geriatric Depression Scale** (Yesavage et al., 1983)
- **ADL** (Katz et al, 1963) e **IADL** (Lawton et al, 1971)
- **FAB** (Dubois et al. 2000) **e Clock Drawing Test** (Sunderland et al., 1989)
- **Valutazione sistematica del rischio suicidario**

Quali peculiarità nella valutazione/approfondimento dei malati psichiatrici con compromissione cognitiva?

1. **Habitus personologico** caratterizzato da **notevole fragilità emotiva;**

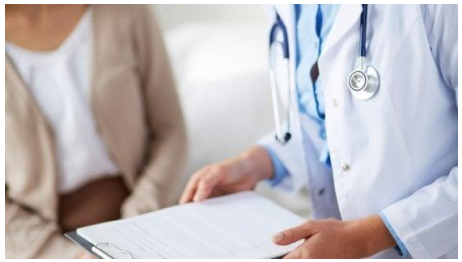
2. **Probabile** (anche se non dimostrata in maniera univoca) **maggior aggressività** e compromissione cognitiva **mediate da danno neurotossico accumulatosi** in seguito a episodi psicopatologici pregressi;

3. **Scarsa autostima e molteplici esperienze di fallimento** da parte del **paziente e dei suoi caregivers;**

4. **Maggiori comorbidità medico-internistiche legate a trascuratezza/ deprivazione sensoriale, stigma della malattia**

Le peculiarità nella modalità **di presentazione iniziale dei deficit** cognitivi **non si traducono in percorsi di gestione *ad hoc***

I pazienti psichiatrici con iniziale compromissione funzioni cognitive: motivi della diagnosi precoce

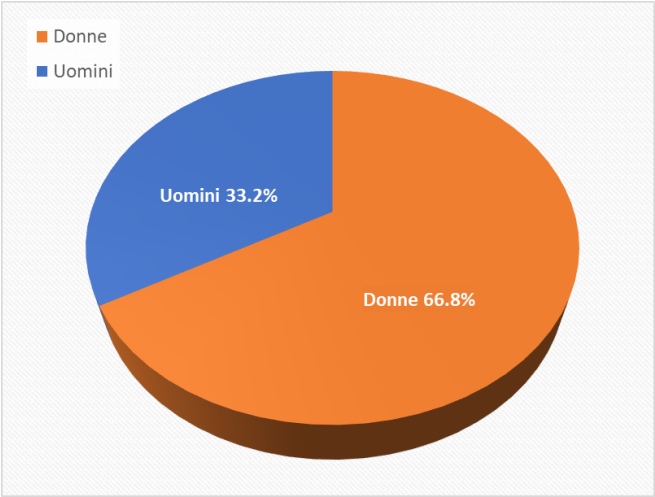


- **Peggiore/assente risposta** ai **trattamenti**
- **Sottotipi disturbi** psichiatrici **biologicamente più aggressivi**
- **Maggior aggressività terapeutica** legata a **disturbi comporta-mentali di più complessa gestione (e.g., politerapie)**
- **Aumentati tassi di riospedalizzazione** a breve termine

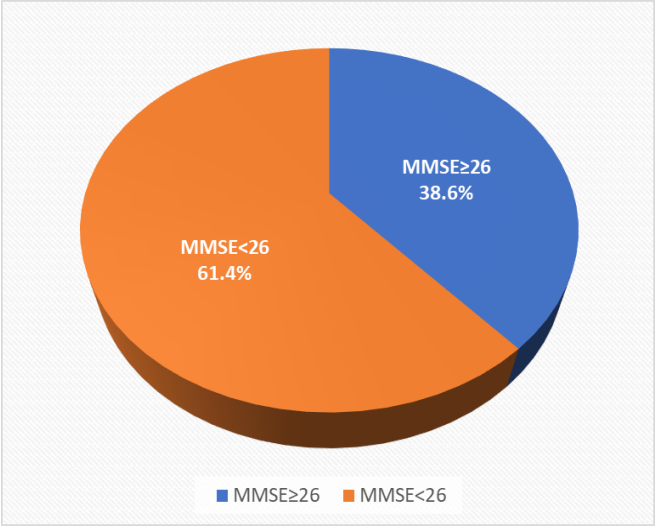
Outcome nettamente poco favorevole

La Clinica Psichiatrica: i nostri dati

- **349 pazienti** dell'**ambulatorio UVA** della Clinica Psichiatrica
- **Età** compresa fra 53 e 95 anni (**media 77±8**)
- **Donne 66.8%; uomini 33.2%**



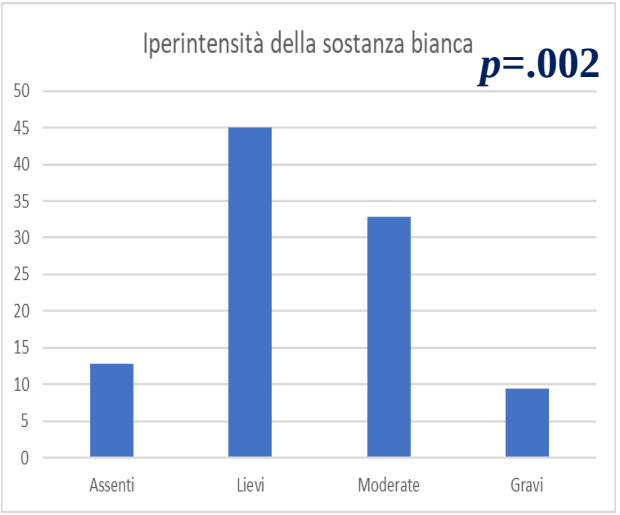
- Il **punteggio medio** al **MMSE**, **corretto per età** e **scolarità** è **22.99** ± 4.96
- Il **61.4%** aveva **MMSE <26**, il 38.6% aveva MMSE≥26

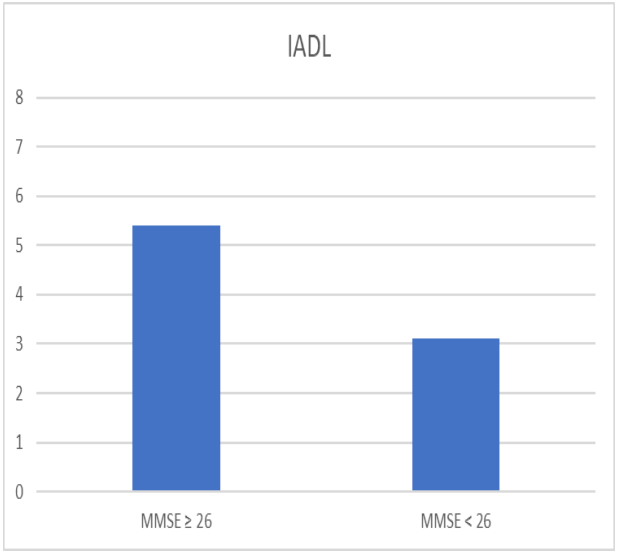


Serafini and Amore, unpublished data, 2019

Risultati: iperintensità della sostanza bianca e livelli di autonomia funzionale. Quali considerazioni cliniche?

- **L'87.2%** dei pazienti aveva **iperintensità** della **sostanza bianca.** Il **33.5%** aveva **iperintensità moderate o gravi** (gradi 2-3 della scala Fazekas)
- I **pazienti con iper-intensità moderate-gravi** avevano **più frequentemente diabete** rispetto a quelli senza iperintensità (28.8% *vs.* 10.8%, *p*=.006)
- I **pazienti con maggiore compromissione cognitiva** erano **autonomi in un numero minore di IADL** (3.1 vs 5.4, *p*=.002).
- **Risultati simili** si riscontravano **per le ADL, ma senza** raggiungere la **significatività** (*p*=.055).





Serafini and Amore, unpublished data, 2019

I livelli di autonomia funzionale quale unico predittore della compromissione cognitiva

- **Il punteggio alle IADL** è **emerso come unico predittore** di maggiore **compromissione cognitiva**

Variabili	B	SE	Wald χ^2	p	OR
Costante	-3.675	2.957	1.544	.214	.025
Età	.010	.035	.082	.775	1.010
Diabete tipo II	.613	.665	.850	.357	1.846
Fumo	.357	.930	.148	.701	1.429
M. di Alzheimer	.238	.664	.128	.720	1.268
ADL	-.284	.231	1.519	.218	.753
IADL	.484	.153	9.985	**.002**	**1.623**

Serafini and Amore, unpublished data, 2019

Dati preliminari relativi al progetto depressione resistente condiviso con i membri del DMT

N=63

	Casi (tot. 40)	Controlli (tot. 23)	*p*
Risposte totali, ±DS	50,2±25,4	73,8±11,6	P<0,001*
Omissioni totali, ±DS	31,2±21,7	15,6±10,7	P=0,005*
2DN risposte corrette, ±DS	20,7±9,2	27,1±3,6	P=0,005*
2DN errori di omissione, ±DS	6,4±6,5	2,9±3,6	P=0,032*
3DN risposte corrette, ±DS	16,7±9,5	25,3±4,7	P=0,001*
3DN errori di omissione, ±DS	10,4±8,5	4,8±4,7	P=0,009*
4DN risposte corrette, ±DS	12,7±7,8	21,2±4,7	P=0,000*
4DN errori di omissione, ±DS	14,4±8,1	8,9±4,7	P=0,008*

***CPT= disturbi dell'attenzione visiva sostenuta**

	Casi (tot. 40)	Controlli (tot. 23)	*p*
TMT, valori patologici, %:			
-A	31,6	0	P=0.233
-B	13,5	0	P=0,026*
Fluenza fonemica, %:			P=0,003*
-0 (patologico)	8	0	
-4 (normale)	40,5	87	
Fluenza semantica, %:			P=0,047*
-0	32,4	4,3	
-4	62,2	91,3	
Parole di Rey, %:			
-IR	20	0	P=0,001*
▪ **0**	17,5	68,2	P=0,026*
▪ **4**	10,3	5	
-DR	28,2	68,2	
▪ **0**			
▪ **4**			
Stroop, %:			
-W			P=0,002*
▪ **0**	6	0	
▪ **4**	42,4	95,7	
-C			P<0,001*
▪ **0**	16,2	0	
▪ **4**	32,4	95,7	
-CW			P<0,001*
▪ **0**	24,3	0	
▪ **4**	24,3	82,6	

***TMT A/B= disturbi della pianificazione spaziale;**
***Parole di Rey= disturbi della capacità di apprendimento verbale e memoria;**
***Fluenza verbale=disturbi nella capacità di accesso al lessico;**
***Stroop test=disturbi dell'attenzione visiva**

Serafini and Amore, in preparation, 2019

Possibili predittori di resistenza

Analisi di regressione logistica

N=63

Le variabili cliniche maggiormente correlate alla TRD sono:

- **STROOP-WI**
  Tempo di reazione a stimoli non ambigui

- **STROOP-CW**
  Capacità di controllo e soppressione delle interferenze

							95% C.I. per OR	
	B	SE	Wald	gi	Sign.	OR	Inf.	Sup.
STROOP-WI	2,10	1,04	4,08	1	0,044*	8,20	1,06	63,29
STROOP-CW	1,10	0,41	7,29	1	0,007*	3,01	1,35	6,68

$R^2 = 0,575$

Serafini and Amore, in preparation, 2019

Correlazioni preliminari tra variabili cliniche, psicometriche e dati neuroimaging nella TRD

N=11

	GMF	BPF	WMF	GM
Tensione (HARS item 2)	**r=-0.610 p=0.046**			**r=-0.643 p=0.033**
Sintomi intellettivi (HARS item 5)	**r=-0.754** p=0.007	**r=-0.730** p=0,011		—
Sintomi respiratori	**r=-0.644** p=0.03			
Sintomi gastrointestinali (HARS item 11)	r=-0.806 p=0.003	**r=-0.684** p=0.033		—
HARS total score	**r=-0.767** p=0.006	r=-0.730 p=0.011		**r=-0.681 p=0.021**
Uso di supporto sociale (COPE)	**r=-0.682** p=0.030	**r=-0.813** p=0.004		**r=-0.719 p=0.019**
Disengagement comportamentale (COPE)	**r=-0.704** p=0.023	**r=-0.635** p=0.048		—
Umorismo (COPE)			**r=-0.710** p=0.022	
Efficacy Index (CGI-3)		**r=-0.640** p=0.033		

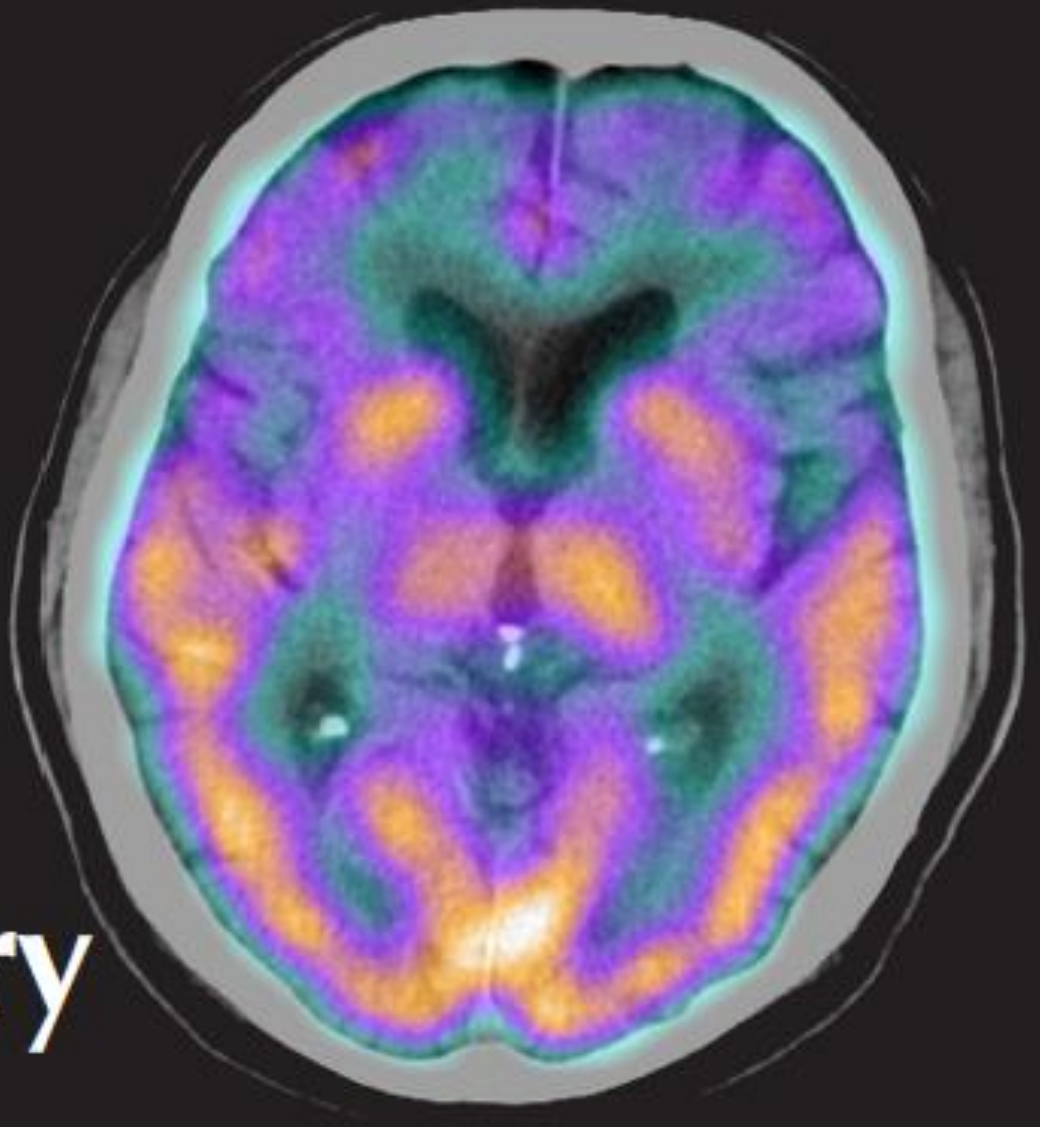
Serafini and Amore, preliminary data, 2019

Clinica Psichiatrica. Quale il profilo del soggetto a rischio?

Outline presentation

- **Valutazione e gestione dei disturbi psico-comportamentali: i dati della clinica psichiatrica**

- **Quali i recenti avanzamenti e frontiere di ricerca in tema di trattamento?**



Inflammatory illness:

Why the next wave of antidepressants may target the immune system

By Nicole Wetsman

Steven Needell/Science Source

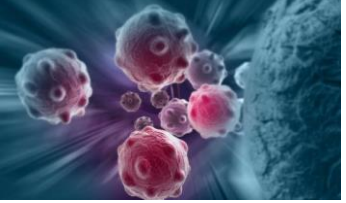
Julius Wagner-Jauregg was working in an Austrian asylum when he witnessed something curious…..

Julius Wagner-Jauregg who treated psychiatric illness with malaria

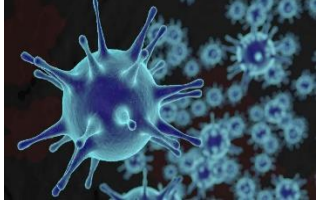
Julius Wagner-Jauregg and colleagues in Vienna in 1927

While making his rounds, **Wagner-Jauregg encountered a woman with psychotic delusions** who had caught **a skin infection**, which caused **a high fever**. But **once her temperature resolved**, she **became coherent**, and **her symptoms** of psychosis **disappeared**. **He** spent the next decades of his career **attempt**ing **to replicate that observation**. But he had relatively little success **until 1917**, when he **started injecting patients** who had developed psychosis as a result of late-stage syphilis **with blood from soldiers with malaria**. Upwards of ha**lf of patients returned to normal life after they received it**. The treatment, referred to as **malariotherapy** (for it **Wagner-Jauregg won the Nobel Prize in Physiology or Medicine in 1927**) for his development of the treatment.

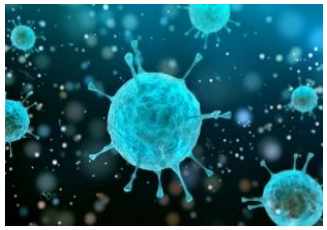
Wetsman, Nature Med, 2017



Miller's study laid the foundation for future work at the intersection of psychiatry and immunology



In the **late 1990s**, **patients with cancer** who were **treated with interferon-alpha** developed **anxiety** and had **depressed moods**. **Patients lacked motivation**, had **difficulty concentrating** and were **fatigued**



Miller and his team at Emory began giving (N=60) infusions of infliximab, used to reduce the levels of **TNF-a** and **treat Crohn's disease and rheumatoid arthritis**

A subset of patients who had the highest blood C-reactive protein levels did **experience a significant improvement**

The team at Emory deserves kudos," **says Roger McIntyre**, the head of the Mood Disorders Psychopharmacology Unit at the University Health Network in Toronto. **"They had the vision, they got this on the map and really got this going."**

Valentine et al. Sem. Oncol. 1998

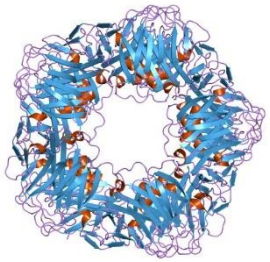
C-reactive protein (CRP) is a reliable marker of systemic inflammation and it is testable in medical laboratories

CRP level can **differentially predict who will respond better to two antidepressants** with distinct mechanisms of action

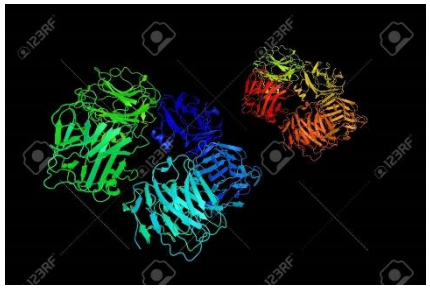
Subjects with low baseline CRP levels (< 1 mg/L) have been shown to respond better to escitalopram

CRP measures **can be perturbed by** recent **infections, injuries, BMI or inflammatory conditions**

Subjects with higher baseline CRP levels (> 1 mg/L) respond better to nortriptyline



CRP and its interaction with drug explained more than 10% of the individual-level variance in treatment outcome



(Uher et al., 2014; Jha et al., 2017)

The macrophage theory of depression

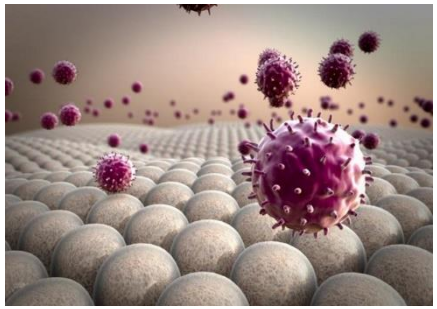
Pro-inflammatory cytokines:

IL-1

TNF-alpha

IL-6

IFN



were **associated with** the principal **symptoms of depression**

(Pariante and Miller, 2001)

Antiinflammatory cytokines:

IL-4

IL-10

IL-13

were reduced

This concept that has been substantiated with additional evidence showing that:

The activated prostenoid pathway (leading to an increase in prostaglandin **E2, PGE2)**

The activated nitric oxide sythase (resulting in an increase in nitric oxide)

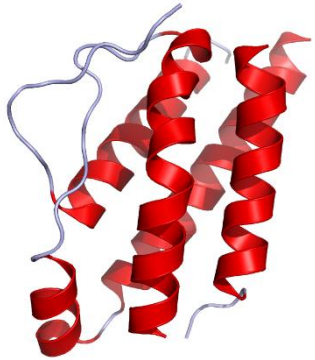
played **key roles in the damaging effects of** chronic **low grade inflammation**

Connor and Leonard, 1998; Kubera et al., 2001; Janelidze et al., 2011; Maes, 1999; Kim et al., 2002; Leonard, 2001

The levels of pre-treatment biomarkers can be useful predictors of treatment response

The depressed patients who were **SSRI non-responders had marked activation of p**ro-inflammatory **cytokines with higher levels of:**

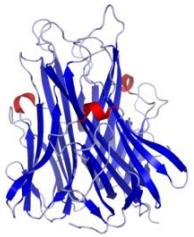
IL-6 **TNF-α**



Suppression of pro-inflammatory **cytokines may be necessary for** clinical **recovery** from depression **and reduction in inflammation might not happen in depressed patients who fail to respond to treatment**

Feltes et al., J Psychopharmacol, 2017

Exploring the Potential Antidepressant Mechanisms of TNFα Antagonists



*Kyle J. Brymer[1], Raquel Romay-Tallon[2], Josh Allen[2], Hector J. Caruncho[2] and Lisa E. Kalynchuk[2]**

[1] Department of Psychology, University of Saskatchewan, Saskatoon, SK, Canada, [2] Division of Medical Sciences, University of Victoria, Victoria, BC, Canada

Human and animal studies suggest an intriguing relationship between the immune system and the development of depression. Some peripherally produced cytokines, such as TNF-α, can cross the blood brain barrier and result in activation of brain microglia which produces additional TNF-α and fosters a cascade of events including decreases in markers of synaptic plasticity and increases in neurodegenerative events. This is exemplified by preclinical studies, which show that peripheral administration of pro-inflammatory cytokines can elicit depression-like behavior. Importantly, this depression-like behavior can be ameliorated by anti-cytokine therapies. Work in our laboratory suggests that TNF-α is particularly important for the development of a depressive phenotype and that TNF-α antagonists might have promise as novel antidepressant drugs. Future research should examine rates of inflammation at baseline in depressed patients and whether anti-inflammatory agents could be included as part of the treatment regimen for depressive disorders.

Front. Neurosci. 2019; 13:98

Drugs that reduce the neurotoxic challenge caused by cytokines, NO, prostaglandin E2 have potential antidepressant action

COX inhibitors (Celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, firocoxib)

↓

Antidepressant-like activity

Minocycline, an antibiotic with **antioxidant properties**, that **inhibits activated microglia** has also been shown to **restore hippocampal neurogenesis**

↓

Reduction in depressive-like behaviour

Nitric oxide synthase (NOS) inhibitors

↓

Antidepressant properties

(Ekdahl et al., 2003; Harkin et al., 1999, 2003; Joca and Guimaraes, 2006)

The inhibition of activated microglia may be important in the mode of action of some types of antidepressants

The activation of murine **microglia** in vitro **by IFN-gamma**, was **attenuated by 1) imipramine**, 2) **fluvoxamine** and 3) **reboxetine**

Hashioka et al. (2007)

Neither 1) buproprion nor 2) agomelatine, that do not have a SSRI antidepressant profile, **inhibit the release of cytokines from** activated **microglia**

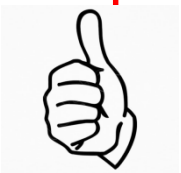
Horikawa et al. (2010)

1) **Atomoxetine** and 2) **desipramine do not inhibit** the **release** of **TNF-gamma** and **NO**

O'Sullivan et al. (2009)

The **atypical antipsychotic aripiprazole does inhibit the release of TNF-alpha from activated microglia**

(Kato et al., 2008)



Antidepressivi e neuroinfiammazione

➢ **Antidepressants**:

1

reduce peripheral/ central inflammatory pathways by **decreasing IL-1β**, **TNFα** and **IL-6** levels

2

stimulate neuronal differentiation, synaptic **plasticity**, axonal growth and **regeneration** through stimulatory effects **on neurotrophic factors** (e.g. trkB, the receptor for **BDNF**)

3

attenuate apoptotic pathways by **activating Bcl-2** and **Bcl-xl** proteins, and suppressing caspase-3

The clinical efficacy of antidepressants may be ascribed to their ability to reverse these different pathways. The final effect might be explained by the down-regulation of microglial activation.

M. Kubera et al. / Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 744–759

Summary of clinical studies that assessed the anti-inflammatory effect of antidepressants on cytokines in MDD

Author	Type of patients	Antidepressant(s)	Duration	Cytokines assessed	Outcome
Brunoni et al. [2014]	103 unipolar depressive patients	Sertraline (SSRI)	6 weeks	IL-2, IL-4, IL-6, IL-10, IL-17, INF-γ, TNF-α	↓IL-2, ↓IL-4,↓IL-6, ↓IL-10,↓IL-17,↓ IFN-γ
Basterzi et al. [2005]	23 MDD and 23 controls	Not specified (SSRI)	6 weeks	IL-6	↓IL-6
Eller et al. [2008]	100 MDD and 45 controls	Escitalopram (SSRI)	12 weeks	sIL-2R, IL-8, TNF-α	↓sIL-2R
Eller et al. [2009]	28 MDD and 45 controls	Escitalopram + bupropion (SSRI + atypical AD)	6 weeks	sIL-2R, IL-8, TNF-α	↑IL-8
Hernandez et al. [2008]	31 MDD and 22 controls	Fluoxetine, paroxetine, sertraline (SSRI)	52 weeks	IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-13	↑IFN-γ, ↑IL-1β, ↓IL-2, ↓IL-4, ↓IL-10, ↓IL-13
Lanquillon et al. [2000]	24 MDD and 15 controls	Amitriptyline (TCA)	6 weeks	IL-6, TNF-α	↓IL-6, ↓TNF-α
Piletz et al. [2009]	22 MDD and 17 controls	Venlafaxine (SNRI)	8 weeks	IL-1β, TNF-α	No significant change
Sluzewska et al. [1995]	22 MDD and 11 controls	Fluoxetine (SSRI)	8 weeks	IL-6	↓IL-6
Taraz et al. [2013]	50 MDD patients	Sertraline (SSRI)	12 weeks	IL-6, TNF-α, IL-10	↓IL-6, ↓TNF-α, ↑IL-10
Tousoulis et al. [2009]	250 with HF (154 with MDD)	Not specified (SSRI and SNRI/TCA)	6 months	IL-6, TNF-α	SNRI/TCA: ↓TNF-α
Tuglu et al. [2003]	26 MDD and 17 controls	Sertraline, fluoxetine, citalopram, fluvoxamine, paroxetine (SSRI)	6 weeks	TNF-α	↓TNF-α
Vogelzangs et al. [2012]	1132 current depression; 789 remitted depression; 494 controls	Not specified (SSRI, TCA and SNRI)	8 years	IL-6, TNF-α	SSRI: ↓IL-6
Yoshimura et al. [2009]	51 MDD and 30 controls	Paroxetine, sertraline, fluvoxamine (SSRI); milnacipran (SNRI)	8 weeks	IL-6, TNF-α	↓IL-6

Feltes et al., J Psychopharmacol 2017

The Role of Inflammation in Depression and Fatigue

*Chieh-Hsin Lee [1] and Fabrizio Giuliani [1,2]**

Efficacy prediction and immunomodulatory effect of therapies

	Efficacy prediction from immune markers	Immunomodulatory/treatment effect
IMMUNE TARGETING THERAPIES		
Minocycline		Animal: antidepressant effect with increase in IL-10, IL-15, and VEGF in the brain (120, 121)
Anti-TNF	Human: higher CRP, TNFα, and sTNFR linked to better efficacy (122)	Human: anti-fatigue effect in RA and sarcoidosis (76, 123) Human: antidepressant effect with significantly greater CRP decrease in responders (122, 124)
Anti-IL-6		Human: antidepressant effect (124)
Dexamethasone		Animal: immune suppression effective in sepsis model (99) Human: anti-fatigue effect with prophylactic treatment (125)
B cell depletion		Human: anti-fatigue effect in RA (126)

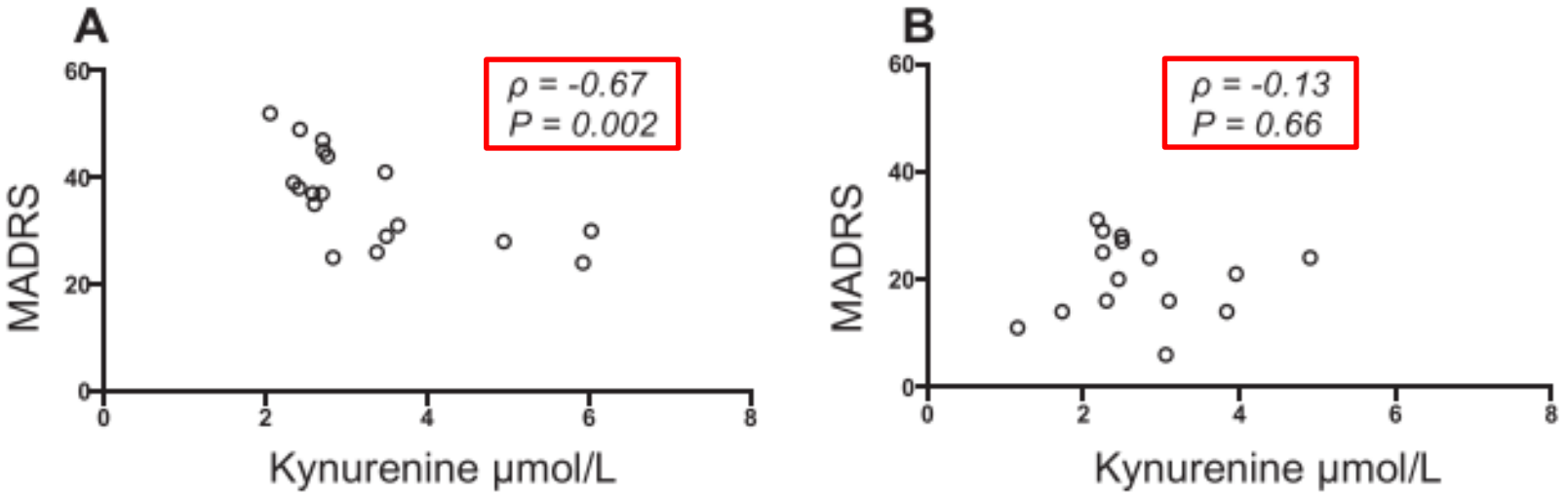
Summary of the interaction with the immune system of various antidepressant and anti-fatigue treatments, with the predictive efficacy of immune markers and their immunomodulatory effect listed. TNF, Tumor necrosis factor; sTNFR, Soluble tumor necrosis factor receptor; CRP, C-reactive protein; FGF, Fibroblast growth factor; IL, Interleukin; IP-10, Interferon gamma-induced protein 10; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; IFNγ, Interferon-γ; G-CSF, Granulocyte colony-stimulating factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; PBMC, Peripheral blood mononuclear cell; PDGF, Platelet-derived growth factor; VEGF, Vascular endothelial growth factor; RA, Rheumatoid arthritis

Lee and Giuliani, Front Immunol. 2019;10:1696

Electroconvulsive therapy suppresses the neurotoxic branch of the kynurenine pathway in treatment-resistant depressed patients

Journal of Neuroinflammation

Lilly Schwieler[1*], Martin Samuelsson[1,2], Mark A. Frye[3], Maria Bhat[4,5], Ina Schuppe-Koistinen[1,6], Oscar Jungholm[1], Anette G. Johansson[5], Mikael Landén[7,8], Carl M. Sellgren[1,9,10] and Sophie Erhardt[1]



Plasma kynurenine inversely correlates to MADRS score in MDD patients before treatment with ECT

This correlation was not observed after three ECT administrations

Schwieler et al., J Neuroinflammation, 2016

Personalizing care: an amazing journey but some caveats should be considered

Roger McIntyre

- In 2015, **McIntyre** and his team **in Toronto initiated** a clinical trial **using infliximab**, to treat depression.

- However, in this study, **one of the criteria for participation is a CRP level above the value that predicted a reduction in depression in response** to the antibody drug **in the 2013 trial (Miller's study)**.

- **Another ongoing** clinical **trial**, **is dosing patients who have depression with** an antibody called **sirukumab** (**originally developed to treat rheumatoid arthritis**), which acts **to neutralize** the inflammatory protein **IL-6**. This study is **focused on how this drug will work in participants** with **higher CRP levels**.

- Another antibody to IL-6, **tocilizumab** (currently **indicated to treat rheumatoid arthritis**), is **being used** in a clinical trial **by a team at Brigham and Women's Hospital to treat depression**.

Unfortunately, **getting approval to use an anti-inflammatory medications** (that may be even expensive) for these disorders **could take years**

McIntrye, 2015

Disturbi psicocomportamentali: quale gestione?

Sfide per il clinico

Diagnosi precoce

Disturbi psico-comportamentali

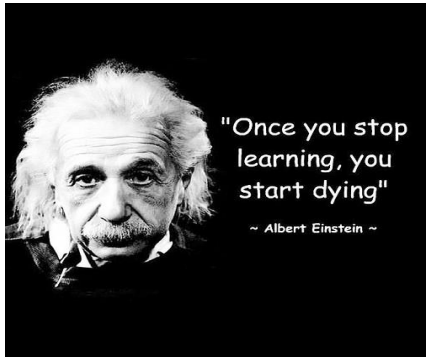
Gestione

Trattamento

Iperintensità della sostanza bianca; livelli di autono-mia funzionale

Possibili markers di progressione della malattia?

1) Affidabilità
2) Replicabilità



I farmaci psicoattivi (sia le molecole tradizionali che quelle più innovative) potranno essere composti ad attività immunomodulante