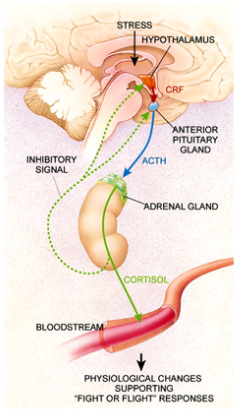
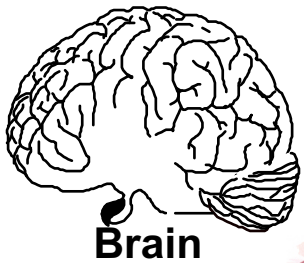
Section of
Perinatal Psychiatry

SPI LAB

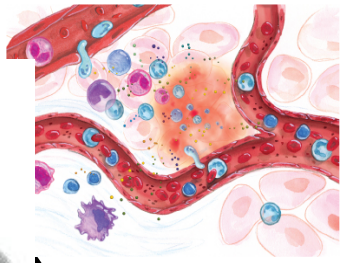
Carmine M. Pariante, MD, FRCPsych, PhD
@ParianteSPILab

Professor of Biological Psychiatry
Institute of Psychiatry, King's College London





Brain



Hormones ⟷ **Inflammation**

Brain under siege

The body's immune system is designed to make us hide away when we get sick. Could this also cause depression? Dara Mohammadi reports

MIKE had struggled with depression his whole life, but one day in 1995 it all got too much. "I completely fell apart," he says. "I backed out of life."

Mike tried to kill himself with an overdose of prescription painkillers. Medics saved him, but the next 15 years of treatment brought little respite. He cycled through dozens of types of antidepressants, with side effects including sickness, insomnia and anxiety. Nothing worked.

Then, in 2010, Mike received a call from his doctor, offering him the chance to take part in a clinical trial. Rather than targeting brain chemistry, as most standard antidepressants do, this was a trial of a drug normally reserved for Crohn's disease, an inflammatory bowel condition where the body's immune system attacks the gut. Desperate for a break, he signed up. And it worked. About a week after the first treatment, the fog of depression cleared. "I just sort of woke up," Mike says.

This trial is one of a growing number of studies probing the idea that the

These are the effects of inflammation, the first line of defence in the body's two-pronged response to infection or injury.

On detection of a harmful stimulus, macrophages, a type of white blood cell, release signalling molecules called cytokines. These signals of inflammation rally other immune cells to the scene to help fight infection or repair damage. They also make their way to the brain, which has a separate immune system to the rest of the body, divided by the blood-brain barrier.

The signals trigger neuro-inflammation, which is where microglial cells come into play. These are macrophage-like cells in

"If the immune signals keep coming, the brain keeps us feeling miserable"

The link between depression and inflammation is not in itself new. People who have diabetes, which Mike has, or rheumatoid arthritis, are known to have elevated baseline levels of inflammation and to also be at higher risk of depression. In the US, people with diabetes are twice as likely to have depression as the average person.

About a third of people with depression also have higher than normal levels of inflammatory cytokines in the blood, and most of these people don't respond to standard drugs.

Further evidence for the link between inflammation in the body and disease in the brain came last year with the first study to measure inflammation in children and see what happened when they grew up. By the time they were 18, those who had high levels of inflammatory markers in the blood when they were 9 years old were significantly more likely to have had bouts of depression, or a psychotic disorder like schizophrenia.

The obvious question, then, is whether

27 June 2015 | New Scientist

New blood test targets depression

By Michelle Roberts
Health editor, BBC News online

7 June 2016 | Health

UK scientists have developed a blood test to help doctors pick the best drug for patients with depression.

Neuropsychopharmacology (2008), 1–8

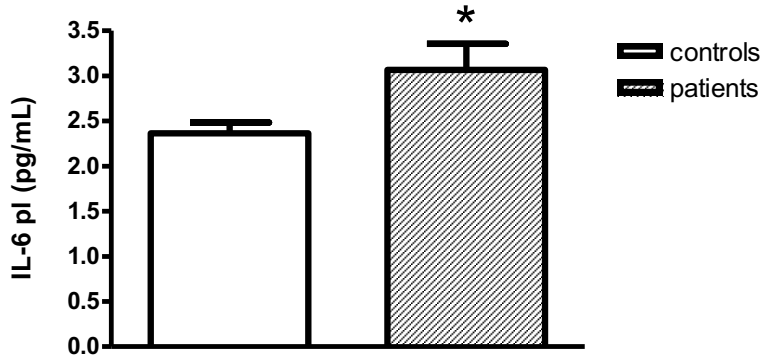
www.neuropsychopharmacology.org

Clomipramine *In Vitro* Reduces Glucocorticoid Receptor Function in Healthy Subjects but not in Patients with Major Depression

Livia A Carvalho*[1], Mario F Juruena[1,2,3], Andrew S Papadopoulos[2,3], Lucia Poon[2,3], Rob Kerwin[4], Anthony J Cleare[2,3] and Carmine M Pariante[1,4]

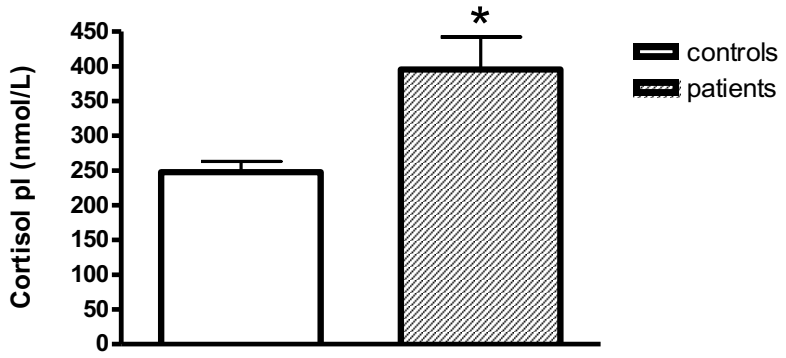
[1]King's College London, Section for the Laboratory of Stress, Psychiatry and Immunology, Institute of Psychiatry, London, UK; [2]Section of Neurobiology of Mood Disorders, Institute of Psychiatry, King's College London, London, UK; [3]Affective Disorders Laboratory, Affective Disorders Unit, Bethlem Royal Hospital, Kent, UK; [4]The Late Dr Kerwin formerly of Section of Clinical Neuropharmacology, Institute of Psychiatry, King's College London, London, UK.

Plasma IL-6 in Depressed Patients and Controls



Carvalho et al., 2008

Plasma Cortisol in Depressed Patients and Controls



Carvalho et al., 2008

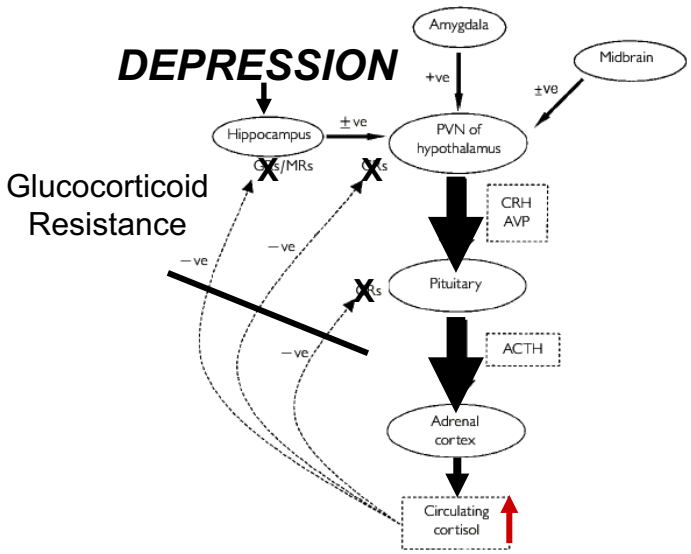
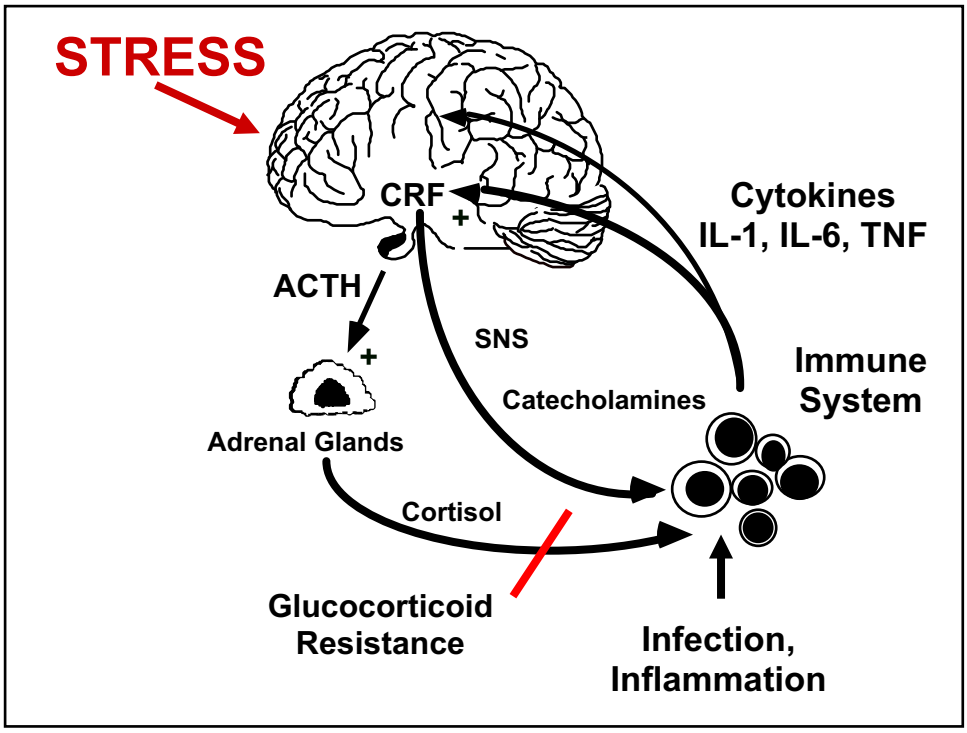
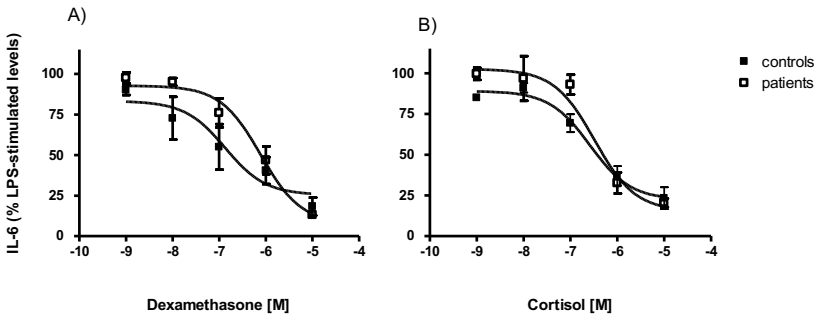


Fig. 1 Simplified schematic diagram of the hypothalamic–pituitary–adrenal (HPA) axis, describing regulation and negative feedback of cortisol via glucocorticoid receptors.



Mood disorder patients have reduced GR function



GR function – % Glucocorticoid inhibition of LPS-induced IL-6 levels

Carvalho et al., 2009

Neuropsychopharmacology (2012), 1–9

www.neuropsychopharmacology.org

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Candidate Genes Expression Profile Associated with Antidepressants Response in the GENDEP Study: Differentiating between Baseline 'Predictors' and Longitudinal 'Targets'

Annamaria Cattaneo[1], Massimo Gennarelli[1,2], Rudolf Uher[3], Gerome Breen[3], Anne Farmer[3], Katherine J Aitchison[3,4], Ian W Craig[3], Christoph Anacker[5], Patricia A Zunsztain[5], Peter McGuffin[3] and Carmine M Pariante*[,5]

[1]Department of Biomedical Sciences and Biotechnology, Genetic and Biology Section, University of Brescia, Brescia, Italy; [2]Genetic Unit, IRCCS San Giovanni di Dio, Fatebenefratelli Centre, Brescia, Italy; [3]Institute of Psychiatry, MRC Social, Genetic and Developmental Psychiatry, King's College London, London, UK; [4]Department of Psychiatry, University of Alberta, Edmonton, Canada; [5]Department of Psychological Medicine, Institute of Psychiatry, Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology (SPI-lab), King's College London, London, UK

Gene-expression of immune genes in the GENDEP sample and controls

IL-1α	0.3	+4
IL-1β	<0.0001	+48
IL-4	0.02	−9
IL-6	<0.0001	+24
IL-7	0.36	−4
IL-8	0.68	+1
IL-10	0.31	+2
TNF-α	<0.0001	+58
MIF	<0.0001	+32

Gene-expression of HPA axis genes in the GENDEP sample and controls

FKBP-4	0.70	−1
FKBP-5	<0.0001	+27
GR	<0.0001	−18

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Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

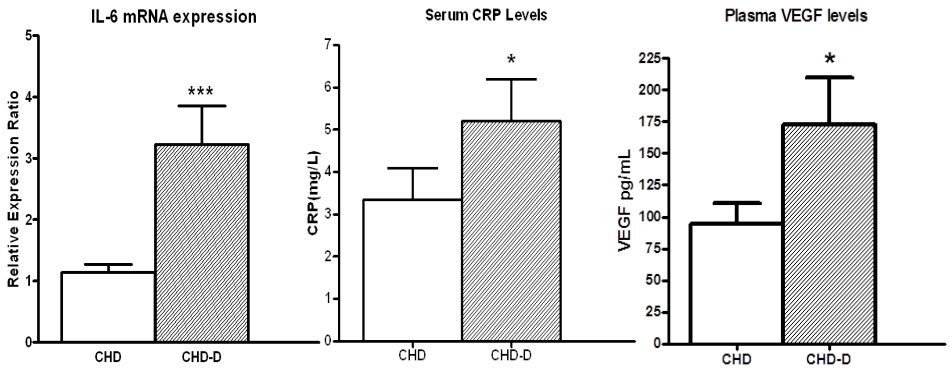
journal homepage: www.elsevier.com/locate/ybrbi

Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression

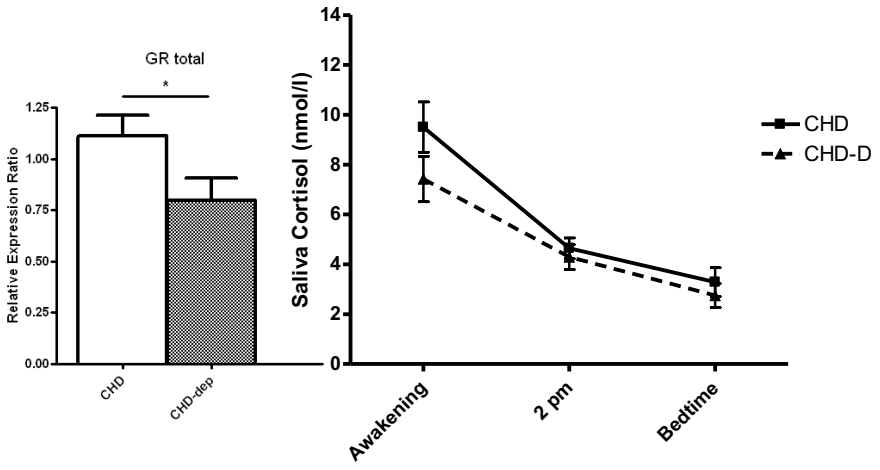
Naghmeh Nikkheslat [a,b], Patricia A. Zunszain [a], Mark A. Horowitz [a], Izabela G. Barbosa [a], Jennie A. Parker [b], Aye-Mu Myint [e], Markus J. Schwarz [e], Andre T. Tylee [d], Livia A. Carvalho [c], Carmine M. Pariante [a,*]

[a] Department of Psychological Medicine, Institute of Psychiatry, King's College London, UK
[b] Department of Life Sciences, University of Roehampton, London, UK
[c] Department of Epidemiology and Public Health, University College London, UK
[d] Health Service and Population Research Department, Institute of Psychiatry, King's College London, UK
[e] Faculty of Medicine, Ludwig-Maximilian University, Munich, Germany

CHD patients with depression show higher levels of inflammation



CHD patients with depression show reduce GR expression



OPEN

Molecular Psychiatry (2015), 1–8

www.nature.com/mp

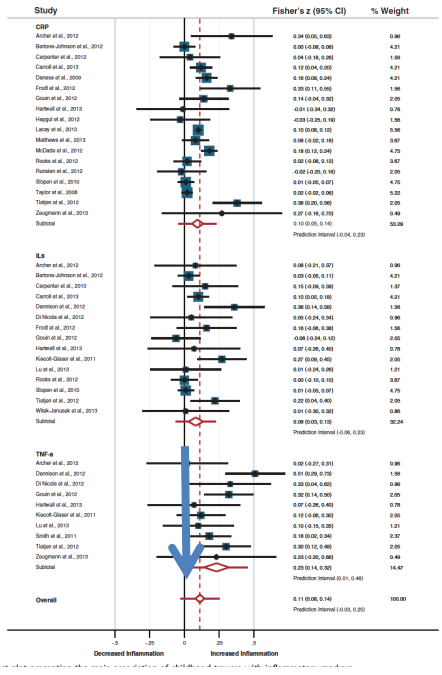
ORIGINAL ARTICLE

Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α

D Baumeister[1,2], R Akhtar[3], S Ciufolini[4,5], CM Pariante[1] and V Mondelli[1,5]

Childhood trauma confers higher risk of adulthood physical and mental illness; however, the biological mechanism mediating this association remains largely unknown. Recent research has suggested dysregulation of the immune system as a possible biological mediator. The present paper conducted a meta-analysis to establish whether early-life adversity contributes to potentially pathogenic pro-inflammatory phenotypes in adult individuals. A systematic search of Pubmed, PsycINFO, EMBASE, Scopus and Medline identified 25 articles for the meta-analysis, including 18 studies encompassing a sample of 16 870 individuals for C-reactive protein (CRP), 15 studies including 3751 individuals for interleukin-6 (IL-6) and 10 studies including 881 individuals for tumour necrosis factor-α (TNF-α). Random-effects meta-analysis showed that individuals exposed to childhood trauma had significantly elevated baseline peripheral levels of CRP (Fisher's $z = 0.10$, 95% confidence interval (CI) = 0.05–0.14), IL-6 ($z = 0.08$, 95% CI = 0.03–0.14) and TNF-α ($z = 0.23$, 95% CI = 0.14–0.32). Subgroup analyses for specific types of trauma (sexual, physical or emotional abuse) revealed that these impact differentially the single inflammatory markers. Moreover, meta-regression revealed greater effect sizes in clinical samples for the association between childhood trauma and CRP but not for IL-6 or TNF-α. Age, body mass index (BMI) and gender had no moderating effects. The analysis demonstrates that childhood trauma contributes to a pro-inflammatory state in adulthood, with specific inflammatory profiles depending on the specific type of trauma.

Molecular Psychiatry advance online publication, 2 June 2015; doi:10.1038/mp.2015.67



Neuropsychopharmacology (2012), 1–9

www.neuropsychopharmacology.org

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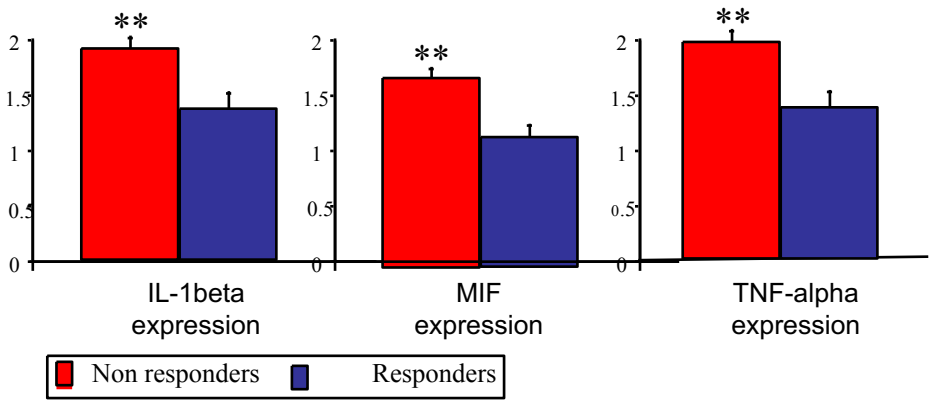
Candidate Genes Expression Profile Associated with Antidepressants Response in the GENDEP Study: Differentiating between Baseline 'Predictors' and Longitudinal 'Targets'

Annamaria Cattaneo[1], Massimo Gennarelli[1,2], Rudolf Uher[3], Gerome Breen[3], Anne Farmer[3], Katherine J Aitchison[3,4], Ian W Craig[3], Christoph Anacker[5], Patricia A Zunsztain[5], Peter McGuffin[3] and Carmine M Pariante*[,5]

[1]Department of Biomedical Sciences and Biotechnology, Genetic and Biology Section, University of Brescia, Brescia, Italy; [2]Genetic Unit, IRCCS San Giovanni di Dio, Fatebenefratelli Centre, Brescia, Italy; [3]Institute of Psychiatry, MRC Social, Genetic and Developmental Psychiatry, King's College London, London, UK; [4]Department of Psychiatry, University of Alberta, Edmonton, Canada; [5]Department of Psychological Medicine, Institute of Psychiatry, Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology (SPI-lab), King's College London, London, UK

IL-1β, MIF and TNF-α levels predict treatment outcome



IL-1β, MIF and TNF-α levels predict treatment outcome

Linear regression analyses to evaluate the contribution of each cytokine in predicting treatment outcome

	adjusted R2	pvalue
IL-1beta	31%	<0.001
MIF	37%	<0.001
TNF-alpha	19%	<0.001
IL1beta, MIF, TNF-alpha	46%	<0.001

International Journal of Neuropsychopharmacology Advance Access published June 6, 2016

OXFORD

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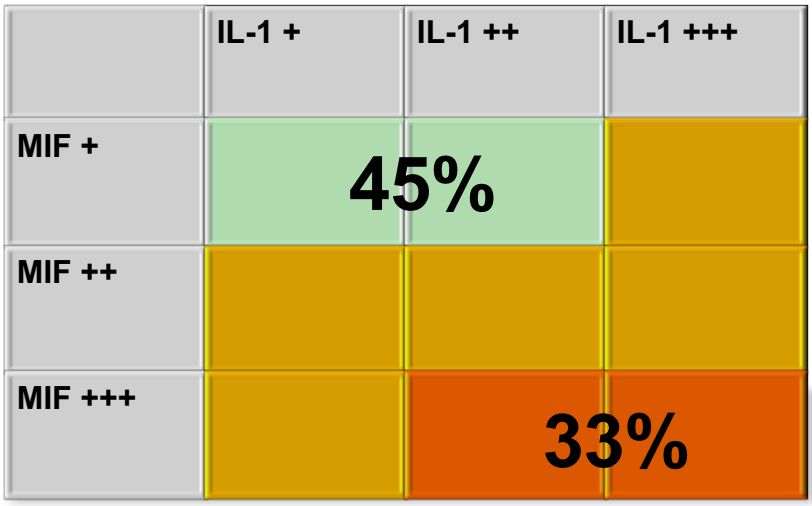
Research Article

RESEARCH ARTICLE

Absolute Measurements of Macrophage Migration Inhibitory Factor and Interleukin-1-β mRNA Levels Accurately Predict Treatment Response in Depressed Patients

Annamaria Cattaneo, PhD; Clarissa Ferrari, PhD; Rudolf Uher, MD; Luisella Bocchio-Chiavetto, PhD; Marco Andrea Riva, PhD; the MRC ImmunoPsychiatry Consortium, and Carmine M. Pariante, MD, FRCPsych, PhD

Probability of Treatment Response (Replicated in two independent samples)



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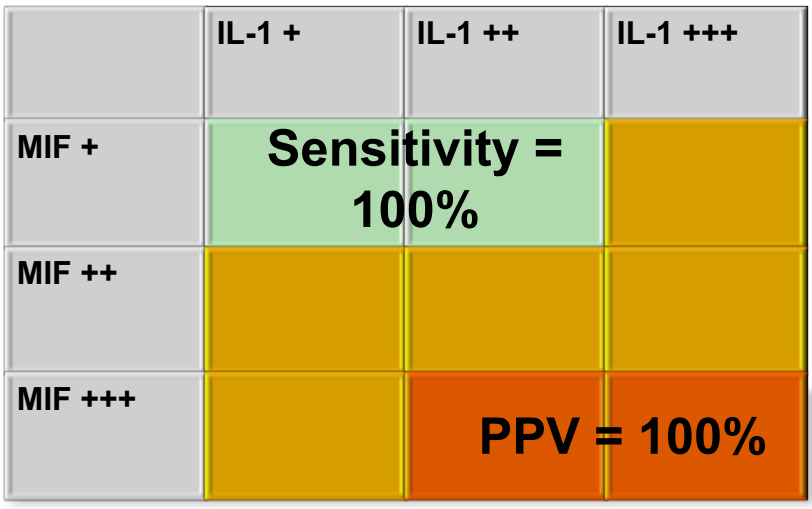

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Schizophrenia Bulletin
doi:10.1093/schbul/sbv028

Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis

Valeria Mondelli*[,1,2], Simone Ciufolini[2,3], Martino Belvederi Murri[1], Stefania Bonaccorso[3], Marta Di Forti[3], Annalisa Giordano[3], Tiago R. Marques[3], Patricia A. Zunszain[1,2], Craig Morgan[4], Robin M. Murray[2,3], Carmine M. Pariante[1,2], and Paola Dazzan[2,3]

[1]Department of Psychological Medicine, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK; [2]National Institute for Health Research Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, London, UK; [3]Department of Psychosis Studies, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK; [4]Department of Health Services and Population Research, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK

*To whom correspondence should be addressed; Sections of Perinatal Psychiatry & Stress, Psychiatry and Immunology (SPI-Lab), Centre for the Cellular Basis of Behaviour, The James Black Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 125 Coldharbour Lane, London SE5 9NU, UK; tel: 44-0-20-7848-0352, fax: 44-0-20-7848-0986, e-mail: valeria.mondelli@kcl.ac.uk

Baseline inflammation and treatment response in psychosis