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# Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation

**Carmine M. Pariante**

*Stress, Psychiatry and Immunology Laboratory (SPI-Lab), Stress, Psychiatry and Immunology Lab & Perinatal Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, G.32.01, The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London SE5 9RT, United Kingdom*

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**Abstract**
Studies over the last 20 years have demonstrated that increased inflammation and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis are two of the most consistent biological findings in major depression and are often associated: but the molecular and clinical mechanisms underlying these abnormalities are still unclear. These findings are particularly enigmatic, especially considering the accepted notion that high levels of cortisol have an anti-inflammatory action, and therefore the coexistence of inflammation and hypercortisolemia in the same diagnostic group appears counter-intuitive. To celebrate the 2015 Anna-Monika Foundation Award to our laboratory, this review will discuss our own 20 years of research on the clinical and molecular evidence underlying the increased inflammation in depression, especially in the context of a hyperactive HPA axis, and discuss its implications for the pathogenesis and treatment of this disorder.


## 1. Introduction

Winning the prestigious Anna-Monika Foundation Award has been an ideal opportunity for me to reflect on the research that has been coming out of our laboratory over the last 20 years, especially since this long period of time has seen a very important theoretical advance in psychiatry: the transformation of *psychoneuroimmunology* (or, as it has been more recently called, *immunopsychiatry*) from a niche area of biological psychiatry and psychosomatics to an established mainstream research and translational area in mental health and clinical neuroscience (Pariante, 2015). Because of the focus of this review on our scientific production within the larger immunopsychiatry framework, the narrative and the citations are self-referential. However, this scientific production would not exist

*E-mail address:* Carmine.Pariante@kcl.ac.uk

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if we had not been supported by a number of friends, colleagues and collaborators who have shaped psychoneuroimmunology over the years.

## 2. Inflammation and the glucocorticoid receptor: love at first sight

Although my first publication on depression and immune system dates back to 1991 (Bartoloni et al., 1991), what really defined my future as researcher in this field was my encounter with the glucocorticoid receptor (GR) in the laboratory of Andrew H Miller at Emory University in Atlanta, in the years 1995–1997. At that time, it was well known that a hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis can be consistently identified in at least a subgroup of depressed patients. The prevailing model at that time – which is pretty much still unchanged today – was based on the notion of "glucocorticoid resistance". In a nutshell, the glucocorticoid receptor (one of the two receptors for the human glucocorticoid hormone, cortisol) physiologically mediates the HPA axis negative feedback, that is, the ability of cortisol to inhibit its own secretion, especially during an increased production due to stress; in contrast, in depression, a dysfunction of the GR leads to an impaired HPA axis negative feedback (a phenomenon called glucocorticoid resistance), which in turn leads to the HPA axis hyperactivity (Pariante and Lightman, 2008; Pariante and Miller, 2001). While this theoretical model was already established at that time, very little was known on the molecular mechanisms that could underpin these presumed GR abnormalities. To address this question, we started using a scientific approach that has continued to deliver many interesting findings over the years: we exploited *in vitro* models utilising fibroblasts, human blood cells, and neurons.

In the first paper on this topic, we found that incubating L929 mouse fibroblasts cells with the pro-inflammatory cytokine interleukin (IL)-1 leads to glucocorticoid resistance, *i.e.*, to an impairment of GR activation and translocation from the cytoplasm to the nucleus, resulting in reduced expression of GR-stimulated genes (Pariante et al., 1999). Interestingly, at the same time we also demonstrated that antidepressants *in vitro increase* GR activation and function, that is, reverse glucocorticoid resistance, thus confirming the crucial role of the GR as a target of both depressogenic (inflammation) and therapeutic (antidepressants) stimuli (Pariante et al., 1997). Two subsequent papers demonstrated similar findings in human peripheral blood mononuclear cells (Carvalho et al., 2008, 2010).

An interesting side-story following these initial findings was a series of subsequent studies (conducted in London) in which we demonstrated that the effects of antidepressants potentiating GR translocation and function is not only directly mediated through steroid-independent activation of the GR, but also indirectly by inhibition of the p-glycoprotein transporter that expels cortisol from cells (and, *in vivo*, from the brain). We found that, *in vitro*, these effects are common to all tested antidepressants and are present not only in mouse fibroblasts but also in rat neurons (Pariante et al., 2001, 2003a. 2003b, 2004b). In subsequent animal studies, we were able to demonstrate that p-glycoprotein regulates the effects of antidepressants on GR expression (Yau et al., 2007) but not, however, that p-glycoprotein or indeed antidepressants regulate cortisol levels in the brain (Mason et al., 2008, 2011).

## 3. From cells to humans

After moved to London in 1997, I expanded my research portfolio to include clinical studies. In 2008 we described increased plasma cortisol levels and increased inflammation (plasma IL-6) in the same depressed individuals, a group of severely depressed inpatients with treatment-resistant depression (Carvalho et al., 2008); moreover, these same subjects have glucocorticoid resistance, as shown by a reduced *in vitro* ability of their peripheral blood mononuclear cells to respond to dexamethasone and cortisol during an immune stimulus (Carvalho et al., 2009). Patients with the highest IL-6 levels are also the least likely to respond to antidepressants (Carvalho et al., 2013). These findings confirmed the notion that glucocorticoid resistance, cortisol hypersecretion and increased inflammation are indeed coexistent and related biological abnormalities. In two studies in healthy volunteers, we were also able to confirm that antidepressants reverse GR resistance, that is, increase GR function as measured by the HPA axis negative feedback (Pariante et al., 2004a) and the effects of cortisol on the EEG (Pariante et al., 2012). But these studies, while confirming that these biological changes are operating in man, did not help elucidate the potential molecular mechanisms underlying GR resistance in depression, nor its reversal by antidepressants.

To try to understand such molecular mechanisms, we measured the expression of candidate genes in the peripheral blood mRNA of patients with major depression (and healthy controls) from the GENDEP sample, a large European study funded by the European Commission. In this study, we found two noticeable results: first, we replicated the increased inflammation in depression as shown by increased mRNA expression of proinflammatory cytokines (IL-1, IL-6, TNF-alpha and macrophage inhibiting factor, MIF) together with a reduced expression of the anti-inflammatory cytokines, IL-4; and, second, we showed that these same patients also have molecular evidence of GR resistance as shown by a reduced expression of GR mRNA together with an increased expression of the GR chaperone protein, FKBP5 (Cattaneo et al., 2013). Both these findings indicate the possible molecular signature underlying GR resistance and increased inflammation in depression: a reduced GR expression (that is, less receptor available) together with a decreased GR responsivity (as FKBP5 binds to the GR and maintains it in an unresponsive state).

We subsequently tested the same hypotheses in an independent study, in which we measured HPA axis activity and inflammation in a group of older depressed patients with coronary heart disease. We were particularly interested in this group, as coronary heart disease is characterised by higher levels of chronic inflammation, and hence we hypothesised that depression in this context would have shown clear abnormalities of the immune system. And, indeed, this is exactly what we found: depressed patients with coronary heart disease have higher inflammation (higher IL-6 mRNA and higher levels of c-reactive protein (CRP), an acute phase response protein produced by the liver in response to IL-6) together with a reduced expression

of GR mRNA; that is, the same results that we had found in the GENDEP sample (Nikkheslat et al., 2015). Interestingly however, these findings were not associated with HPA axis hyperactivity but rather with hypoactivity. This biological picture, perhaps due to the advanced age of the subjects in questions and thus to the long chronicity of their depression, introduces a different type of GR resistance: an ineffective GR together with lower levels of cortisol (Nikkheslat et al., 2015).

## 4. And from humans to cells

While pursuing these clinical studies, we continued to use *in vitro* models in order to dissect the molecular mechanisms underlying these GR- and inflammation-related abnormalities, and their reversal by antidepressants. In particular, in the last few years we have used models of 'depression in a dish' where human neurones or neuronal hippocampal progenitor cells (able to differentiate into neurons) are treated with depressogenic stimuli (such as cortisol and IL-1), or with antidepressants and antidepressants-like compounds (such as anti-inflammatories and omega-3 fatty acids). Using these *in vitro* models, we have extended our research questions to include the understanding of whether inflammation exert a depressogenic effects by decreasing neurogenesis or by increasing neurotoxicity, and of whether the GR is involved in the rescue effects of antidepressants on neurogenesis.

With regard to the first question, we found that two pro-inflammatory cytokines, IL-1 and interferon-alpha, reduce human neurogenesis and human neuronal survival, an effect that is mediated by an increased production of neurotoxic tryptophan metabolites as well as an increased oxidative stress (Alboni et al., 2013; Horowitz et al., 2014; Zunszain et al., 2012). We also showed that the detrimental effects of these inflammatory stimuli can be reversed by antidepressant treatments as diverse as inhibitors of the kynurenine pathways, antioxidants and mitochondrial modulators, and omega-3 polyunsaturated fatty acids (Alboni et al., 2013; Horowitz et al., 2014; Zunszain et al., 2012).

With regard to the second question, we indeed demonstrated that antidepressants not only increase neurogenesis, but do so by activating a downstream cascade of second messenger mechanisms that requires the GR (Anacker et al., 2011). In fact, our most interesting finding in this field was the evidence that both antidepressants and cortisol require the GR to exert their effects on neurogenesis: but with antidepressants activating the GR in order to *increase* neurogenesis, while cortisol activating the GR in order to *decrease* neurogenesis. This apparent contradiction is due to the fact that different activators of the GR induce different patterns of GR phosphorylation and activation, eventually leading to different sets of downstream GR-stimulated genes. Specifically, antidepressants *increase* neurogenesis *via* a GR-dependent mechanism that requires protein kinase A (PKA) signalling and upregulation of genes such as p11 and the cyclin-dependent kinase-2 (CDK2) inhibitors, p27and p57 (Anacker et al., 2011), while cortisol *decreases* neurogenesis *via* activation and upregulation of the GR-stimulated gene, serum- and glucocorticoid-inducible kinase 1 (SGK1), leading to inhibition of TGFβ- SMAD2/3- and Hedgehog signalling (Anacker et al., 2013a, 2013b). Of note, although all of these results were initially from *in vitro* experiments, we were able to replicate both the antidepressant-induced upregulation of p11 and the cortisol-induced upregulation of SGK1 in the blood (mRNA) of depressed patients, and the cortisol-induced downregulation of TGFβ-SMAD2/3 and Hedgehog signalling in the hippocampus of adult rats exposed to prenatal stress (Anacker et al., 2013a, 2013b).

## 5. Why are some depressed patients inflamed?

Not all depressed patients have increased inflammation: so, who are these patients that present with this biological phenotype? What is their corresponding clinical phenotype? In 2007, working with Avshalom Caspi and Terrie Moffitt on the Dunedin study, we were the first to demonstrate that young adults with a history of childhood trauma show increased inflammation, as demonstrated by increased CRP, increased white blood cell counts and increased fibrinogen levels (Danese et al., 2007). In subsequent reports, we showed that this increased inflammation is present not only in subjects who are depressed and have a history of childhood maltreatment but also in those who have experienced maltreatment but are not depressed (Danese et al., 2008); moreover, the increased inflammation clusters with metabolic risk biomarkers such as being overweight or presenting with high blood pressure, high total cholesterol and high glycated hemoglobin (Danese et al., 2009). Together, these findings indicate that the increased inflammation is a 'biological scar' of the early exposure to high levels of stress, which originates in childhood and is characterised by abnormalities in both mental and physical health (Baumeister et al., 2016).

More recently, we have been able to replicate the association between early life trauma and increased inflammation also in 12-year-old children (Danese et al., 2011), and, most interestingly, in young adults who have been exposed to stress not in childhood but even earlier: *in utero* (Plant et al., 2016). For this latter study, we have followed-up the offspring of the South London Child Development Cohort, a longitudinal sample of depressed women who were recruited and assessed during pregnancy in 1986 (together with control pregnant women), and subsequently assessed with their offspring during childhood and adolescence. Over the years, this cohort has demonstrated that exposure to maternal depression during pregnancy (but not in the postpartum period) doubles the risk of the offspring developing themselves depression and other mental disorders in adolescence (Pawlby et al., 2011), and association that is mediated, at least in part, by an increased risk of the offspring being exposed to maltreatment and other stressful events in childhood (Plant et al., 2013, 2015). We have recently published that these same offspring exposed to maternal depression *in utero*, now young adults, have increased inflammation as shown by raised CRP levels (Plant et al., 2016). Moreover, we have find some preliminary evidence that exposure to medically-related inflammation in childhood (for example through infections and autoimmune disorders) also increase the risk of depression in adulthood (Du Preez et al., 2016). Taken together, all these lines of evidence indicate that increased inflammation is present in a subgroup of depressed patients who have a neurodevelopmentally-based form of depression, originating from exposure to stress (or possibly directly to inflammation) early in childhood or even *in utero*.

However, the neurodevelopmental origin may not be the only path to increased inflammation in depression. There is consistent evidence from candidate gene studies that genetic variants that increase immune responses are more frequent in patients with depression, or characterise a group of individuals who are at risk of developing a depressive phenotype in the context of an immune challenge (Barnes et al., 2017). For example, a few years ago we published that the functional G-174C polymorphism (rs1800795) in the promoter region of the IL-6 gene predicts depressive symptoms in patients taking interferon-alpha for chronic viral hepatitis (Bull et al., 2009). In a different study in a similar population, we have also found that two polymorphisms in genes regulating prostaglandin synthesis, the BanI polymorphism of the cytosolic phospholipase A2 (cPLA2) and the COX2 rs4648308 polymorphism in the cyclooxygenase 2 (COX-2) genes, also regulate the risk of developing interferon-alpha induced depression (Su et al., 2010). Interestingly, this latter study also offered us an opportunity for investigating the molecular mechanisms underlying this genetic predisposition: indeed, carriers of the two 'at risk' PLA2 and COX2 genotypes also have lower levels of the omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), before and during IFN-$\alpha$ treatment (Su et al., 2010). Considering the putative antidepressants and anti-inflammatory action of these omega-3 fatty acids, we speculated that genetically-driven low levels of these endogenous anti-inflammatory compounds increase the risk of interferon-alpha induced depression. Indeed, in a subsequent clinical trial we have recently demonstrated that prophylactic treatment with EPA and DHA prevents or delays the onset of interferon-alpha-induced depression (Su et al., 2014). This latter study truly shows the full translational potential of this area of research.

## 6. Are these findings clinically relevant?

Perhaps our most clinically-relevant contribution to the field of depression and inflammation comes from our studies using immune biomarkers to predict response to antidepressants. In the first such study based on the GENDEP sample, mentioned above (Cattaneo et al., 2013), we measured mRNA expression of genes belonging to inflammation, before and after eight weeks of treatment with antidepressants. We found that depressed patients who do not go on to respond to the prescribed antidepressants (escitalopram or desipramine) have higher baseline mRNA levels of IL-1, MIF and TNF-alpha. Together, the levels of these three cytokines predict approximately half of the variance in antidepressant response, although IL-1 and MIF explain most of the variance. We then replicated these findings in a second independent cohort of depressed patients, and using a novel "absolute mRNA values" measurement approach that allows easier comparability in-between laboratories. In this second cohort, we have confirmed and extended the predictive ability of IL-1 and MIF, and have identified cut-off values for the absolute mRNA measures that accurately predict response probability at an individual level, with positive predictive values and specificity for non-responders of 100% (Cattaneo et al., 2016). These latter findings were reported by a number of news outlets, leading to a Altimetric score of 1040 (top 1% for impact).

These series of studies not only have provided consistent evidence that increased inflammation characterizes a subgroup of depressed patients that is less likely to respond to conventional antidepressants, but also have established the measurement of blood mRNA immune genes as a reliable and clinically significant biomarker in the context of psychoneuroimmunology, to complement (and at times surpass) the routine measurement of serum/plasma cytokines (Hepgul et al., 2013). Indeed, in a recent paper we have examined the mRNA transcriptomics profile of patients taking interferon-alpha, and shown that patients who develop depression during this immune challenge present a hyperactive immune response that is evident by measuring mRNA but not plasma cytokines (Hepgul et al., 2016).

Finally, although this review focuses on our work in depression, it is important also to mention our contribution to the increasing evidence that an activated inflammatory system is also relevant for patients with psychotic disorders, such as schizophrenia, by affecting physical health, brain structure, clinical outcome and the action of antipsychotics (Di Nicola et al., 2013; Handley et al., 2016; Hepgul et al., 2012; Mondelli et al., 2011, 2015; Russell et al., 2015).

## 7. Conclusions

A rapid 20-year helicopter view on our scientific production has allowed us to identify successful answers but also outstanding questions in this research area. The field has burgeoned in the last few years, and we have now clear translational opportunities for psychoneuroimmunology and immunopsychiatry to help patients, delivering both predictive biomarkers to implement precision psychiatry and novel pharmacological agents that improves depression through an anti-inflammatory action. But questions still exist. What are the epigenetic mechanisms by which early life events – as early as *in utero* – create a long-term trajectory of increased inflammation? How do anti-inflammatories help depression, and are there differences between different anti-inflammatories in their antidepressant effects? How can we successfully reverse glucocorticoid resistance, and is normalising GR function helpful for depressed patients? Some of these answers maybe behind the corner, some may take 20 more years – but one thing is for sure: depression, and mental health problems in general, can no longer be seen only as disorders of the mind, or indeed only as disorders of the brain. The strong impact of the immune system on emotions and behaviour demonstrates that mental health is the health of the whole body.

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## Conflict of Interest

Author has no conflict to declare.

## Disclosure

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