Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways

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Abstract

There is now evidence that depression, as characterized by melancholic symptoms, anxiety, and fatigue and somatic (F&S) symptoms, is the clinical expression of peripheral cell-mediated activation, inflammation and induction of oxidative and nitrosative stress (IO&NS) pathways and of central microglial activation, decreased neurogenesis and increased apoptosis. This review gives an explanation for the multiple "co-morbidities" between depression and a large variety of a) brain disorders related to neurodegeneration, e.g. Alzheimer's, Parkinson's and Huntington's disease, multiple sclerosis and stroke; b) medical disorders, such as cardiovascular disorder, chronic fatigue syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel disease, irritable bowel syndrome, leaky gut, diabetes type 1 and 2, obesity and the metabolic syndrome, and HIV infection; and c) conditions, such as hemodialysis, interferon-α-based immunotherapy, the postnatal period and psychosocial stressors. The common denominator of all those disorders/conditions is the presence of microglial activation and/or activation of peripheral IO&NS pathways. There is evidence that shared peripheral and / or central IO&NS pathways underpin the pathophysiology of depression and the previously mentioned disorders and that activation of these IO&NS pathways contributes to shared risk. The IO&NS pathways function as a smoke sensor that detect threats in the peripheral and central parts of the body and signal these threats as melancholic, anxiety, and fatigue and somatic (F&S) symptoms. The presence of concomitant depression is strongly associated with a lower quality of life and increased morbidity and mortality in medical disorders. This may be explained since depression contributes to increased (neuro)inflammatory burden and may therefore drive the inflammatory and degenerative progression. It is concluded that the activation of peripheral and / or central IO&NS pathways may explain the co-occurrence of depression with the above disorders. This shows that depression belongs to the spectrum of inflammatory and degenerative disorders.

REVIEW

1. INTRODUCTION

Recently, we have reviewed in a special issue of Progress in Neuropsychopharmacology and Biological Psychiatry that depression is characterized by activation of peripheral and central immune-inflammatory pathways. Activation of peripheral cell-mediated immune, inflammatory and oxidative and nitrosative stress (IO&NS) pathways is indicated by increased levels of proinflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNFα) and interferon-γ (IFNγ) (Maes, 2010a); activation of indoleamine 2,3-dioxygenase (IDO) with lowered levels of plasma tryptophan and increased production of detrimental tryptophan catabolites (TRYCATs), such as kynurenine (Maes et al. 2010b); an acute phase response and lowered serum zinc (Maes, 2010a; Szewczyk et al. 2010); increased glucocorticoid secretion (Zunszain et al. 2010); mitochondrial dysfunctions (Gardner and Boles, 2010); and signs of O&NS with increased reactive oxygen species (ROS), damage to lipids, proteins and DNA (Maes et al. 2010a). As reviewed in this special issue, animal models of depression are characterized by microglial activation, as indicated by increased production of cytokines, TRYCATs and ROS, decreased neurogenesis and neurotrophic factors; induction of neuronal apoptotis pathways; and increased signs of neurodegeneration (Kubera et al. 2010; Maes et al. 2010b; Song and Wang, 2010). In that special issue we have reviewed how these pathways may be associated with the development of depression, including melancholic, anxiety, and fatigue and somatic (F&S) symptoms (Maes et al. 2010a; 2010b; Kubera et al. 2010; Szewczyk et al. 2010).

Activation of the abovementioned peripheral and central IO&NS pathways may explain why external (psychosocial) and internal (other medical disorders) stressors play a role in the onset of depression. For example, injection of lipopolysaccharide (LPS; an internal stressor) and induction of chronic mild stress or learned helplessness (external stressors) in the rodent, cause similar depressive-like behaviors including anhedonia, anxiety, psychomotor retardation, anorexia, fatigue, etc. that are associated to (neuro)inflammation, reduced neurogenesis, apoptosis, etc. (Song and Wang, 2010; Kubera et al. 2010). In humans, internal stressors, e.g. interferon-α (IFNα)-based immunotherapy and the postnatal period, and external stressors, e.g. negative life events, are accompanied by an increased prevalence of depression (Maes et al. 2010b). Moreover, depression shows a strong "comorbidity" with chronic medical disorders (Maes et al. 2010c). For example, depression frequently occurs in patients who suffer from cardiovascular disorder (CVD), while depressed patients have an increased cardiac morbidity and mortality (Maes et al. 2010c). Depression frequently occurs during the course of Myalgic Encephalomyelitis / chronic fatigue syndrome (ME/CFS) (Skapinakis et al. 2003; 2004), while fatigue is one of the key symptoms of depression (Maes et al. 1990). Even more, characteristic symptoms of ME/CFS, e.g. aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, irritable bowel, headache, and a flu-like malaise, are key symptoms of depression and in particular of melancholia and predict the severity and chronicity of depression (Maes, 2009).

The term "comorbidity" indicates that a medical disorder exists together but independently with another disorder. Another definition is that a specific medical disorder in a patient causes or is caused by another medical disorder (First, 2005; Valderas et al. 2009). The term "comorbidity" was first introduced by Feinstein et al. (1970) to denote those patients in which a distinct clinical disorder occurs during the course of another disorder. The term "psychiatric comorbidity" is used to describe the "comorbidity" between a psychiatric and a medical disorder (Maj, 2005). For example, a depression that develops after a myocard infarction is considered to be "comorbid depression". Indeed, one of the definitions of comorbidity is that a specific medical disorder, e.g. heart infarction, causes another disorder, e.g. depression, in the same patient (First, 2005; Valderas et al. 2009). According to the above definitions, both depression and ME/CFS are considered to be "comorbid" disorders.

There are different methods to estimate how comorbidity may predict morbidity or mortality (de Groot et al. 2003). One of the most commonly used methods is the Charlson comorbidity index (Charlson et al. 1987). The latter computes severity scores that predict the one-year mortality for patients suffering from different comorbid disorders. As such the Charlson comorbidity index predicts long-term survival for a particular patient. Another method is the Cumulative Illness Rating Scale (CIRS), a valid and reliable interview to screen the clinical burden of various medical problems in all relevant body systems in a same patient (Linn et al. 1968; Hudon et al. 2005). The CIRS can be used in psychiatrically disordered patients or in patients with comorbid psychiatric and medical disorder and shows a good inter-rater reliability and face validity (Miller et al. 1992). Another instrument is the index of Coexisting Disease (ICED), which measures two factors, a first is the index of physical impairment and a second, the severity of 19 medical disorders (Miskulin et al. 2001).

The postnatal period and IFNα-based immunotherapy and CVD and ME/CFS are only a few examples of the many disorders/conditions that are accompanied by "comorbid" depression. Probably, depression is the disorder which shows the greatest "multi-morbidity" with multiple other disorders. In fact, depression is not only a "multi-comorbid" disorder but comorbidity may be regarded as a characteristic of depression. Thus, in routine clinical care, depressed patients have a significantly greater medical and psychiatric co-morbidity than non depressed patients, including stroke, congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD), and dementia (Chen et al. 2007). In 31 studies involving 16,922 patients with chronic medi-

cal illnesses, such as diabetes, coronary artery disease (CAD), congestive heart failure, asthma, COPD, and rheumatoid arthritis (RA), the somatic symptoms were at least as strongly associated with depression comorbidity as were objective physiologic measures (Katon et al. 2007). Moreover, those patients with chronic medical illnesses and comorbid depression or anxiety reported significantly higher numbers of medical symptoms when controlling for severity of medical disorder compared to those with chronic medical illness alone (Katon et al. 2007). Likewise, treatment studies showed that improvement in depression is associated with decreased somatic symptom burden without improvement in physiologic measures. There are, however, many other disorders that frequently co-occur with depression, such as neurodegenerative brain disorders, e.g. Alzheimer's (AD) and Parkinson's disorder (PD); gastro-intestinal disorders, including inflammatory bowel disorder (IBD), irritable bowel syndrome (IBS) and leaky gut; autoimmune disorders, such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), and psoriasis; infectious disorders, such as HIV infection, etc. The question is then what shared mechanisms could explain the co-occurrence of depression with so many different brain and systemic disorders.

The purpose of this paper is to review a) the medical disorders that show a high comorbidity with depression and those conditions that cause depression; b) the shared pathways that may explain the increased prevalence of depression in those disorders/conditions; c) that concomitant depression may worsen the course or increase the risk for these disorders; and d) that the term "comorbidity" is not suited to reflect the true nature of the co-occurrence of depression

2. DEPRESSION'S COMORBIDITIES

2.1. Depression's comorbidity with brain disorders

The comorbidity between depression and brain disorders associated with neurodegenerative processes is now well established. According to Kanner (2005) depression is a common comorbid disorder with an incidence of 20–50% in brain disorders, such as stroke, MS, PD and dementia. Nearly 40–50% of patients with PD also suffer from depression (Menza et al. 1993; 2006; Poewe and Luginger, 1999). Concomitant depression in PD affects the quality of life; is predictive of distress even more than the motor disabilities (Menza et al. 1993; 2006); is associated with greater medical co-morbidity and greater healthcare utilization, including medical hospitalizations (Chen et al. 2007). A considerable number of AD patients suffer from depression, which should be regarded as the most frequent psychiatric comorbidity of AD (Amore et al. 2007). Depression may be a prodromal symptom for AD and may occur before and after the onset of dementia; depression may persist during AD and become more common as AD progresses (Amore et al. 2007). Depression is known to decrease the quality of life in AD patients and to reduce the duration of survival. Depression is highly prevalent in mild cognitive impairment (MCI), which may be a prelude to AD (Potter and Steffens, 2007). The comorbidity between depression and MCI causes a greater functional decline and an increased institutionalization rate (Potter and Steffens, 2007). Also, in patients with Huntington's disorder (HD) there is evidence for a higher-than-average prevalence of depression (De Marchi et al. 2000). Depression occurs in 20–80% of stroke victims with higher prevalence rates in women then in men (Tharwani et. al., 2007; Poynter et al. 2009). In a quarter of these patients depression may persist during two years (Huff et al. 2003). Depression in stroke patients is associated with greater disability, such as a greater impact on motor recovery, a lower quality of life and reduced daily life activities, a poorer prognosis in terms of increased morbidity and mortality (Poynter et al. 2009). In another brain disorder, associated with neurodegeneration, i.e. MS, the incidence of depression may be even greater than in other neurological diseases (Wilken and Sullivan, 2007). In Asian patients, it was shown that patients with MS have a higher risk of multiple medical comorbidities, including depression, compared to a matched control group (Kang et al. 2010). Also, in MS, concomitant depression is associated with a poor functional status and quality of life (Chwastiak and Ehde, 2007). Overall, concomitant depression negatively affects the course of the brain disorders and the recovery from the neurological defects and predicts poor quality of life in those patients.

2.2. Depression's comorbidity with systemic disorders

There is now abundant evidence of a high comorbidity of depression and COPD. In patients with severe COPD, the prevalence of depression was 25.0%, while in patients with mild COPD it was 19.6% and in controls 17.5% (van Manen et al. 2002). Other studies indicate that the prevalence of depression and anxiety may be as high as 50% (Mikkelsen et al. 2004). In older patients with COPD the prevalence of depression is estimated to be 40% (Yohannes, 2005). Ng et al. (2009) reported that depressive symptoms are associated with COPD independently from the known risk factors, including smoking behavior. In another study, depressed patients who had suffered from depression prior to the first diagnosis of COPD were excluded (van den Bemt et al. 2009). These authors found that the hazard ratios for a first episode of depression in COPD as compared to diabetes and controls were 1.80 (95% confidence interval [CI], 1.16 to 2.81) and 1.68 (95% CI, 1.20 to 2.35), respectively. Concomitant depression in COPD may lead to worse health, more objective impairment in functional status, impaired quality of life and increased morbidity (Ng et al. 2009; Norwood and Balkissoon, 2005; Mikkelsen et al. 2004).

On average, a patient with RA, a chronic autoimmune and inflammatory disorder that primarily affects

the joints, suffers from two or more comorbid conditions, including CVD, infections and depression (Michaud and Wolfe, 2007). Depression is highly comorbid with RA: up to 42% of RA patients may suffer from depression (Bruce, 2008). In patients with chronic rheumatological disorders, including RA (57%), SLE (17%) and systemic sclerosis (9%) the incidence of anxiety and depression was 65.8% (Waheed et al. 2006). Depression and anxiety were significantly related to permanent joint deformity, active inflammation and time elapsed since diagnosis (Waheed et al. 2006). RA and depression together contribute to decreased quality of life, disability and mortality and, thus, to increased health care costs (Bruce, 2008).

Overall, there is an increased prevalence of depression in dermatological patients, i.e. around 30% compared to 22% in general practice (Filakovic et al. 2008). Depression and anxiety have a higher prevalence in patients with psoriasis that in controls (Hayes and Koo, 2010). In 3,147 patients with psoriasis individually matched for age and gender with controls without psoriasis showed that there is an association between psoriasis and depression and that this appears to be related to the severity of psoriasis (Schmitt and Ford, 2010). In patients with psoriasis multiple associated comorbidities occur, not only depression, but also psoriatic arthritis, IBD, obesity, diabetes, cardiovascular disease, multiple sclerosis and metabolic syndrome (Naldi and Mercuri, 2010; Guenther and Gulliver, 2009).

In SLE, there is a high degree of comorbidity with hypertension, cataract, fractures, CVD, neurologic, lung, gall bladder and endocrine disorders and depression (Wolfe et al. 2010). Depression is present in around 34–39% of patients with SLE and is strongly associated with a lower quality of life (Wolfe et al. 2010). In 326 women with SLE up to 47% received a diagnosis of depression and 6% of bipolar-1, which are both significantly higher than in a control group (Bachen et al. 2009). In a review of 21 studies on the prevalence and type of psychiatric symptoms in SLE it was found that depression is by far the most frequent comorbid disorder reported during SLE (Wekking, 1993).

There is also a strong degree of comorbidity between inflammatory bowel disease (IBD) and depression. Depression is significantly more common in IBD and depressive and anxiety symptoms are more severe during active IBD (Graff et al. 2009). There is also evidence that the course of IBD is worse in depressed patients and that the quality of life is impaired in IBD patients with comorbid depression over and above the effects of IBD (Graff et al. 2009; Mikocka-Walus et al. 2007). Until now there is not enough information to support the thesis that in humans depression is a risk factor for IBD (Graff et al. 2009). Irritable bowel syndrome (IBS) symptoms frequently occur in depression and in melancholic depression (Maes, 2009), while depressive symptoms are increased in IBS patients and are even higher than in IBD (Kovacs and Kovacs, 2007). IBS is present in 54% of subjects in the general population who suffer from depressive symptoms as compared with 29% of nondepressed controls (Hillila et al. 2008). It has been shown that depressive symptoms contribute to a poor outcome in IBS (Creed et al. 2005). Another phenomenon that frequently occurs in IBD and IBS is increased translocation of gram negative bacteria or leaky gut. Leaky gut entails a weakening of the tight junctions, which stick the epithelial cells together that surround the gut wall. This loosening of the tight junctions barrier results in enlarged spaces between the epithelial cells (leaky gut) and an increased translocation of normally poorly invasive gram negative from the gut into the blood (Maes et al. 2008). It has been shown that depression is characterized by an increased bacterial translocation (Maes et al. 2008).

Leppävuori (2010) discussed that 11 to 31% of patients with diabetes suffer from depression and that depression is independently associated with weakening blood glucose homeostasis. Children and adolescents with diabetes have a two to three fold increased prevalence of depression (Grey et al. 2002). In a comprehensive review of the literature from 1966 to 2009 it was detected that comorbid depression in diabetes is associated with increased medical symptom burden, poor metabolic control, higher complication rates, such as increased risk of macrovascular and microvascular complications, decreased quality of life, increased disability and lost productivity, and increased mortality (Egede and Ellis, 2010). Patients with diabetes and depression have poorer glycemic control, more diabetes symptoms, and greater all-cause mortality (Fenton and Stover, 2006). In a prospective study of 759 primary-care patients with diabetes (n=2,759), the risk of major depression at 5-year follow-up among diabetes patients is increased by previous depression history, baseline diabetes symptoms, and having had cardiovascular procedures (Katon et al. 2009). A medline search for publications from 1950 through 2007 showed that depression is associated with a 60% increased risk of type 2 diabetes, whereas type 2 diabetes is associated with a modest increased risk of depression (Mezuk et al. 2008). In another review it was found that depression is more common in both type 1 and type 2 diabetes and negatively affects the course, morbidity and mortality of these disorders (Lustman and Clouse, 2005). Recently, a meta-analysis showed that obesity increases the risk of depression, while depression increases the risk for developing obesity (Luppino et al. 2010). Young obese women are at an increased risk for developing depression (van der Merwe, 2007). In an stratified random sample of 1,690 men and women aged 25–84 years, metabolic syndrome was associated with depression but not with psychological distress or anxiety (Dunbar et al. 2008). In men and women there is a significant association between long-term depressive illness and metabolic syndrome, suggesting that depression is a predisposing factor (Laudisio et al. 2009; Viinamaki et al. 2009; Vanhala et al. 2009).

There is also a link between infectious disorders and depression. Some previous studies reported that there is a comorbidity between Epstein Barr virus (EBV)

infections and depression (Allen and Tilkian, 1986), but probably these rare infections are rather the consequence of immune dysfunctions in depression. There is no evidence that other viral infections are involved in depression, except HIV infection. Many patients with HIV infection develop depressive symptoms and full-blown depression during the infection (Owe-Larsson et al. 2009).

Continuous ambulatory peritoneal dialysis (CAPD) is another condition that is accompanied by an increased prevalence of depression. Up to forty-three patients of the enrolled 81 stable CAPD patients showed depressive symptoms (Ko et al. 2010). Depression is very common in hemodialysis patients with an incidence of around 50% (Montinaro et al. 2010). Depression is associated with higher mortality rates in hemodialysis patients (Micozkadioglu et al. 2006).

Concomitant depression not only increases the morbidity and mortality in different chronic medical disorders, but also increases the healthcare costs in medially-ill patients (Unützer et al. 2009). These authors compared the 12-month healthcare costs in patients with diabetes mellitus or congestive heart failure (CHF) of whom 2,108 patients had depression and 1,081 possible depression (Unutzer et al. 2009). They found that depressed patients made markedly higher healthcare costs than those without depression in each quartile of increasing medical severity as measured using the Charlson Comorbidity Index.

3. SHARED IO&NS PATHWAYS UNDERPINNING DEPRESSION AND THE ABOVE DISORDERS/CONDITIONS

3.1. Shared IO&NS pathways underpinning depression and brain disorders

Common characteristics of the previously mentioned brain disorders are not only neurodegenerative processes and the high comorbidity with depression, but also neuroinflammation, which consists of activation of resident microglial cells and infiltrating T cells and monocytes (Glass et al. 2010). Microglia participate in the surveillance of the surrounding brain areas and microglial activation is a first line defense that aims to protect the CNS from injuries (Neumann, 2001; Kreutzberg, 1995). In response to perturbations of this local milieu, microglia cells undergo a phenotypic transformation to become potent effector cells and change their morphology, increase the expression of key cell surface molecules, secrete a plethora of effector molecules and can become motile and phagocytic (Neumann, 2001; Kreutzberg, 1995). Actually, microglia cells exist along a continuum of activation states between quiescent and fully activated. Upon activation, microglia upregulate the expression of detrimental factors, such as the production of pro-inflammatory cytokines, e.g. IL-1β, IL-6, IFNγ and TNFα, ROS / RNS; and the synthesis of TRYCATs, following activation of IDO by proinflammatory cytokines (Maes et al. 2010b). In fact, microglia show a Janus face with a "good" side, e.g. immune surveillance and release of neurotrophic factors and a "bad" side, e.g. increased production of pro-inflammatory cytokines, ROS/RNS and TRYCATs.

Neuroinflammation may induce neuronal pro-apoptotic pathways, with increased expression of cysteine-aspartic proteases (caspases) and lowered levels of anti-apoptotic and neurotrophic molecules, such as Bcl-2 and BAG-1 (Bcl-2 associated athanogene) (Kubera et al. 2010). Moreover, neuroinflammation is accompanied by suppression of neurogenesis and a reduced production of neurotrophic molecules, such as brain-derived neurotrophic factor (BDNF) (Huehnchen et al. 2010; Schnydrig et al. 2007). Neuroinfammation may cause neurodegeneration through the neurotoxic effects of cytokines and TRYCATs, damage by ROS and activation of the DNA damage response pathway; and pathologic apoptosis and necrosis of neurons (Kubera et al. 2010).

There is now evidence that microglial activation occurs in PD, HD, AD, MS and stroke (Sugama et al. 2009; Rogers et al. 2007; Kim and Joh, 2006). [11C](, R)-PK11195 positron emission tomography (PET) shows that microglial activation is present in brain disorders, such as AD, PD, MS and stroke (Gerhard et al. 2006; Cagnin et al. 2001; Vas et al. 2008; Thiel et al. 2010). Whether neuroinflammation is the primary cause in the initiation and/or progression of neurodegeneration is still a matter of debate. Nevertheless, even when microglial activation would be secondary to neurodegeneration and protein deposits, microglia contribute to neurodegeneration. For example, in PD and MS, the neuronal injuries are caused by a self-propagating cycle of neurotoxicity in which neuronally secreted misfolded proteins activate microglia that in turn cause neurodegenerative processes (Sugama et al. 2009; Pinteaux-Jones et al. 2008). In AD, activated microglia secrete high levels of detrimental proinflammatory compounds, e.g. IL-1, which activate microglia, resulting in a feed forward cycle promoting neuroinflammation and thus neurodegeneration (Vukic et al. 2009; Ramirez et al. 2008). There are two different pathways that may cause microglial activation in PD models. The first is administration of lipopolysaccharide (LPS), which directly activates microglia. The second is administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which first kills dopaminergic neurons and consequently leads to reactive microgliosis. However, in both the LPS and MPTP model microglial activation may be the driving force that causes dopaminergic neuron degeneration (Hunter et al. 2007; Hirsch, 2007; Hirsch et al. 2003). In MS, an autoreactive immune response leads to infiltration and reactivation of myelin-specific T cells in the CNS, which is followed by microglial activation, which contributes to lesion formation (Town et al. 2005; Dasgupta et al. 2005; Bhasin et al. 2007). There is now also evidence that the brain responds to ischemic injury with prolonged microglial activation in the infarct zone and that production of proinflammatory mediaters is

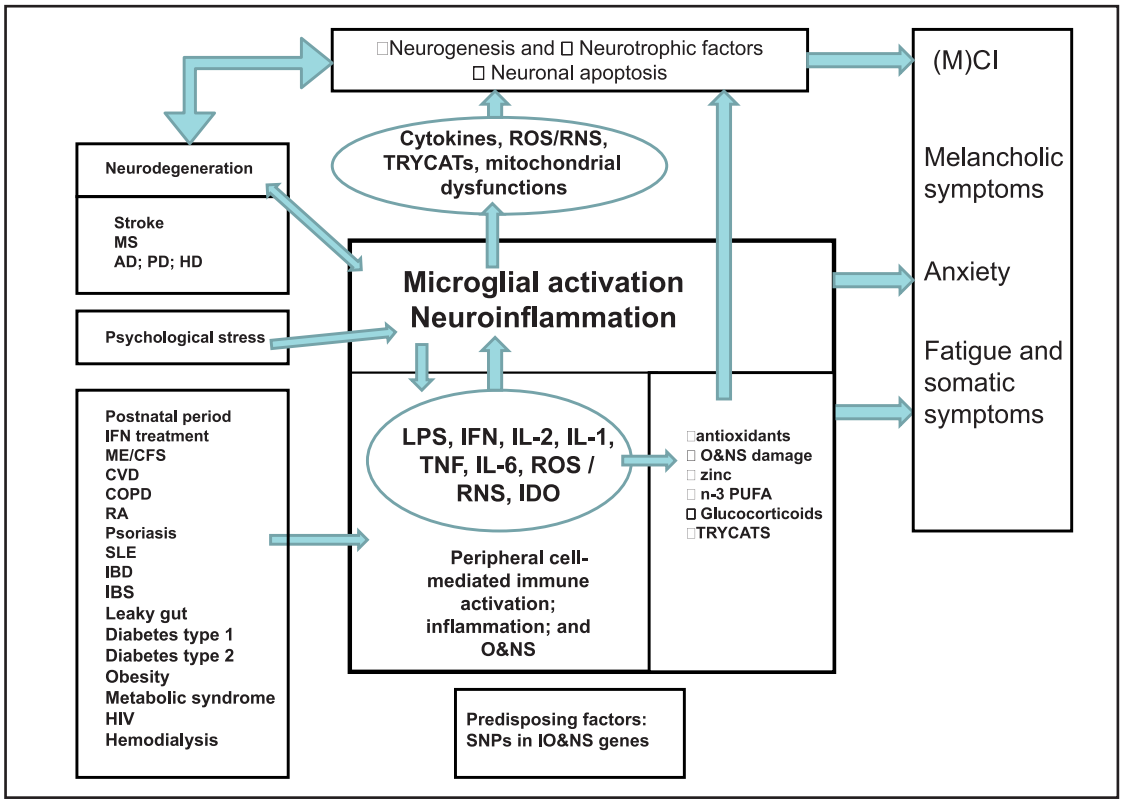

Figure 1. This Figure shows that microglial activation is induced by brain disorders such as Alzheimer's (AD), Huntington's (HD), and Parkinson's (PD) disorder; multiple sclerosis (MS) and stroke; and that peripheral cell-mediated immune activation and/or inflammation, and oxidative and nitrosative stress (O&NS) are induced by a) systemic disorders, such as myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS); cardiovascular disorder (CVD); chronic obstructive pulmonary disease (COPD); rheumatoid arthritis (RA); psoriasis; systemic lupus erythematosus (SLE); inflammatory bowel disease (IBD); irritable bowel syndrome (IBS); leaky gut; diabetes type 1 and 2; obesity and the metabolic syndrome, and HIV infection; and b) conditions, such as hemodialysis, interferon-α-based immunotherapy, and the postnatal period. Peripheral activation of IO&NS pathways is translated into microglial activation and both phenomena may cause depression in some predisposed persons (genetic vulnerability, etc). The pathways that may cause depression are increased levels of cytokines, such as interleukin-(IL-)1β, IL-2, IL-6, tumor necrosis factor-(TNF)α and interferon-(IFN)γ; lipopolysaccharides (LPS); activated reactive oxygen and nitrogen species (ROS/RNS); and activation of indoleamine 2,3-dioxygenase (IDO) with increased levels of tryptophan catabolites (TRYCATs); mitochondrial defects; lowered antioxidants, ω3 polyunsaturated fatty acids (PUFAs) and zinc; and increased glucocorticoids.

upregulated (Jin and Yang, 2010; Kriz, 2006). IL-1β and TNFα, which are known to induce depressive-like behaviors, are upregulated within hours in ischemic brain lesions and together with ROS may exert neurotoxic effects and contribute to infarct progression in the post-ischemic period (Stoll et al. 1998). There is also evidence that microglial activation is an early event in HD that occurs prior to the onset of symptoms and that there is pathogenic link between neuroinflammation and neuronal dysfunction (Tai et al. 2007).

Figure 1 shows that microglial activation with induced IO&NS pathways in AD, HD, PD, MS and stroke may explain the co-occurrence with depression. Phrased differently, the neuroinflammation that accompanies these brain disorders and is caused by neurodegeneration and protein misfolding explains the increased incidence of "comorbid" depression. It may be hypothesized that under these circumstances depression will develop in predisposed patients, e.g. those with specific single nucleotide polymorphisms in IO&NS genes (Maes et al. 2010a); and lowered peptidase, antioxidant, zinc and omega-3 polyunsaturated fatty acid (PUFAs) levels (Maes et al. 2009; 2010a, Song and Wang, 2010; Szewczyk et al. 2010).

As described above, microglia activation may have dual effects, i.e. a) neuroprotective effects by the production of neurotrophic compounds, anti-inflammatory cytokines, brain regeneration and modulation of synaptic plasticity (Kriz, 2006); and b) detrimental effects by the effects of neurotoxic cytokines, e.g. TNFα and IL-1β, TRYCATs and ROS (Maes et al. 2010a; 2010b; Kubera et al. 2010). **Figure 2** depicts the reciprocal relationships between microglial activation and neurodegeneration. Excessive and longstanding neuroinflammation and activation of microglia are implicated in the pathogenesis of neurodegeneration that may cause brain disorders, including AD, HD, PD, stroke, and MS; and in the onset of depression.

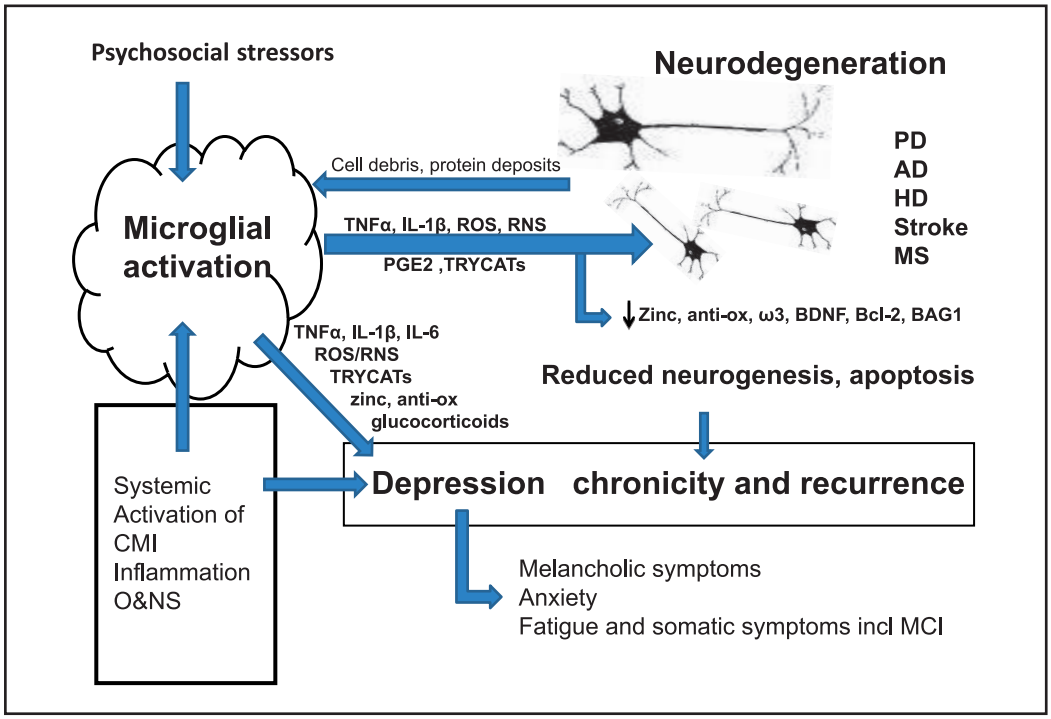

Figure 2. This Figure shows that brain disorders, including Alzheimer' s (AD), Huntington's (HD), and Parkinson's (PD) disorder, multiple sclerosis (MS) and stroke are characterized by reciprocal relationships between microglial activation and neurodegeneration, whereby the latter may cause microglial activation through neurodegeneration and protein misfolding, while microglial activation drives neurodegeneration through increased levels of neurotoxic cytokines, e.g. interleukin-(IL-)1β, and tumor necrosis factor-(TNF)α; activated reactive oxygen and nitrogen species (ROS/RNS); increased levels of tryptophan catabolites (TRYCATs); and prostagladins (PGs). Lowered zinc, antioxidants (anti-ox) and ω3 polyunsaturated fatty acids (ω3) are predisposing factors for neuroinflammation-induced reductions in neurogenesis and brain-derived neurotrophic factor (BDNF) levels, and apoptosis with reduced levels of Bcl-2 and BAG1 (Bcl-2 associated athanogene 1). Microglial activation following brain disorders (or psychosocial stressors) in conjunction with systemic cell-mediated immune (CMI) activation, inflammation and oxidative and nitrosative pathways may cause depression, including melancholic symptoms, anxiety and fatigue and somatic symptoms, including mild cognitive impairment (MCI). Reduced neurogenesis and apoptosis further determine the development and or chronicity or recurrence of depression. This Figure shows that the abovementioned brain disorders may cause depression primary through microglial activation and that other mechanisms, e.g. apoptosis and reduced neurogenesis may play a role as well.

3.2. Shared IO&NS pathways underpinning depression and systemic disorders/conditions

During the postnatal period there is a greatly increased inflammatory potential with increased levels of proinflammatory cytokines and detrimental TRYCATs, that are strongly related to the development of depression (Maes et al. 2000; 2002). During IFNα-based immunotherapy, the stimulated production of proinflammatory cytokines and detrimental TRYCATs is strongly correlated to the onset of IFNα-induced depression (Bonaccorso et al. 2001; 2002; Wichers et al. 2005). As we have discussed previously, shared IO&NS pathways contribute to endothelial microinflammation that leads to CVD and the monocyte-T lymphocyte and microglial activation that leads to depression (Maes et al. 2010c).

COPD is a pulmonary disorder characterized by an inflammatory response to inhaled substances such as cigarette smoking and air pollutants and by systemic manifestations such as osteoporosis, diabetes, CVD, skeletal muscle dysfunction, and hypertension (Stockley, 2009). The inflammatory pulmonary reactions result in an 'overspill' into the blood causing systemic inflammation (Stockley, 2009). Thus, inflammatory mediators may "translocate" from the lung surface to the blood. COPD patients show increased IO&NS biomarkers either in blood or in airways, e.g. CRP, IL-6, TNFα, and IL-4 and reactive oxygen metabolites (Foschino Barbaro et al. 2007). Patients with COPD have significantly increased plasma IL-8 as compared to smokers and non-smokers (Shaker et al. 2008). Importantly, the soluble TNF receptor-1 (sTNFR-1), a marker of cell-mediated immunity, is significantly related to depression in patients with COPD (Eagan et al. 2010). The systemic manifestations of COPD are mediated through increased plasma levels of pro-inflammatory mediators including cytokines (Kolsum et al. 2009). Increased IL-6, for example, may contribute towards pulmonary hypertension in COPD (Chaouat et al. 2009).

RA is characterized by similar systemic inflammatory pathways as can be found in CVD (Ku et al. 2009) and thus also in depression. Increases in proinflammatory cytokines, lowered antioxidant levels, increased ROS with damage to DNA and proteins are hallmarks of RA (Altindag et al. 2007; Kalpakcioglu and Senel, 2008; Al-Shukaili and Al-Jabri, 2006).

Previously, it has been documented that the comorbidity between psoriasis, an immune-mediated inflammatory skin disease, and depression may be explained by shared inflammatory pathways as both disorders are accompanied by increased levels of proinflammatory cytokines and acute phase proteins (Filakovićc et al. 2008). For example, Th1, Th17 and Th22 cells are significantly increased in patients with psoriasis (Kagami et al. 2010). Moreover, in psoriasis, O&NS pathways and increased ROS generation have been linked to skin inflammation (Rashmi et al. 2009). Serum hydroperoxide is significantly higher and total antioxidant capacity of the serum significantly lower is psoriatic patients than in controls (Coaccioli et al. 2009). Increases in systemic inflammatory and O&NS biomarkers are associated with a worsening of the clinical condition in psoriasis (Rocha-Pereira et al. 2004a; 2004b). Biomarkers of systemic activation of IO&NS pathways are detected in SLE, such as increased IL-1, IL-6, and TNFα, (Sabry et al. 2006; Alcocer-Varela et al. 1992); and increased levels of iNOS and nitrotyrosine, increased antibodies against malondialdehyde (MDA) and 4-hydroxynonenal, and lowered superoxide dismutase (SOD) activity (Wang et al. 2010). Widner et al. (1999; 2000) detected significantly decreased tryptophan, and increased kynurenin and neopterin concentrations in patients with SLE, showing that IDO is activated in association with immune activation.

In ulcerative colitis and Crohn's disease increased pro-inflammatory cytokines, such as TNFα and chemokines are observed in mucosal tissues and peripheral blood together with increased plasma LPS and abnormal microflora (Caradonna et al. 2000; Gardiner et al. 1995). Increased TNFα and systemic endotoxaemia are correlated with the clinical activity of ulcerative colitis (Gardiner et al. 1995). This shows that the systemic immune response in IBD is in part associated to an increased permeability of the intestinal mucosa. Moreover, patients with IBD show multiple signs of O&NS, such as increased MDA (Alzoghaibi et al. 2007), increased damage to DNA (Dincer et al. 2007) and lowered erythrocyte antioxidant defenses (Krzystek-Korpacka et al. 2010). Recently, it has been shown that IBS is characterized by microinflammation in the colonic mucosa (Spiller, 2009; Mearin et al. 2009). The latter authors review that the increase in inflammatory cells in the intestinal mucosa, such as mastocytes, CD3 and CD25 lymphocytes, contribute to the intestinal IBS symptoms (abdominal pain) and depressive symptoms as well. As reviewed elsewhere, leaky gut allows the translocation of gram-negative bacteria from the gut into the blood and an IgM-mediated immune response against the increased LPS load in the blood (Maes et al. 2008).

Type 1 diabetes is an autoimmune disorder in which inflammatory mediators cause apoptosis in pancreatic beta-cells which in turn causes insulin deficiency (Tsui et al. 2007). O&NS is one of the mechanisms that initiate diabetes. Thus, in streptozotocin (STZ) diabetes (type I) rats, STZ causes the synthesis of a NO-toxin, which damages DNA and activates necrosis and triggers inflammation (Van Dyke et al. 2010). Urate, an important blood-antioxidant, is significantly lowered in patients with diabetes type I and shows that this disorder is accompanied by ongoing O&NS (Van Dyke et al. 2010). Activation of inflammatory pathways is a key factor in diabetic arteriopathy, nephropathy and neuropathy (Huysman and Mathieu, 2009). Imbalances in cytokines and O&NS pathways are implicated in the development of type 2 diabetes. Thus, chronic hyperglycemia and subclinical inflammation augment ROS, which deteriorates pancreatic beta-cell function and increase insulin resistance (Kaneto et al. 2010). Low grade inflammation and in particular increased IL-6 concentrations predict incident type 2 diabetes (Duncan et al. 2003). Inflammatory markers, including IL-6, CRP and fibrinogen, correlate significantly with insulin resistance indices (Syrenicz et al. 2006). Both microinflammation and ROS are involved in the atherosclerotic development that frequently accompanies type 2 diabetes (Kaneto et al. 2010). Obesity in another risk factor for type 2 diabetes that shows a high comorbidity with depression. Recently, it has been shown that fatty tissue contain high concentrations of macrophages that are stimulated by fat cells to activate the 12/15-lipoxygenase gene leading to an increased expression of cytokines, such as IL-6 and TNFα (Chakrabarti et al. 2009). The key features of the metabolic syndrome are abdominal obesity, hypertension, insulin resistance, and dyslipidemia and chronic inflammation (Esposito and Giugliano, 2004). Inflammation is not only a triggering factor of the metabolic syndrome but also a consequence: inflammatory cytokines are produced by the fat cells and the resistance to the anti-inflammatory effects of insulin may cause increased cytokine levels (Esposito and Giugliano, 2004). Metabolic syndrome is accompanied by increased oxidized LDL (Holvoet, 2008).

CAPD patients with depressive symptoms show significantly higher levels of inflammatory markers and lower levels of albumin and IL-10 than CAPD patients without depressive symptoms (Ko et al. 2010). In hemodialysis patients, IL-1β, IL-6, TNFα and IL-10 are significantly higher than in controls, while increased IL-6 is related to psychological discomfort (Montinaro et al. 2010). In chronic hemodialysis patients depressive symptoms are significantly related to malnutrition and inflammation (Ibrahim and El Salamony, 2008), while patients with depression have greater inflammatory responses as measured by lower albumin and increased ferritin (Huang and Lee, 2007). Kalender et al. (2006) reported that hemodialysis patients with depression have lower hemoglobin, hematocrit

and serum albumin levels and higher CRP and ferritin levels than patients without depression.

Finally, patients with HIV infection are at risk to develop depression (Owe-Larsson et al. 2009). AIDS patients with depression have significantly more inflammatory and immune responses than AIDS patients without depression, suggesting that inflammatory pathways occurring in AIDS may determine the increased incidence of depression (Huang et al. 2006).

Figure 1 shows that systemic cell-mediated immune activation, inflammation and O&NS pathways occur in the abovementioned medical disorders and therefore may cause depressive symptoms in some predisposed subjects, i.e. those in which the peripheral IO&NS pathways are translated into neuroinflammation in the brain. As discussed somewhere else, lowered peptidase, antioxidant, and ω3 PUFA levels and specific single nucleotide polymorphisms in IO&NS genes may aggravate the activation of the IO&NS pathways and thus play a role in the development of neuroinflammation (Maes et al. 2009; 2010a; 2010b, Song and Wang, 2010; Szewczyk et al. 2010). In the next section, we discuss the pathways that may convey the peripheral immune and inflammatory signals to the brain.

3.3. Pathways signaling physiological or "bottom up" challenges

A critical function of the brain is to coordinate responses to behavioral and physiological challenges ("stressors"). "Stressors" are typically conceptualized as belonging to either of two categories (Dayas et al. 2001; Sawchenko et al. 2000). Viscerosensory / interoceptive pathways signaling physiological or "bottom up" challenges to internal bodily functions, like infection, inflammation, and pain. Psychological, "top down" stressors involve situations in the external or mental environment, and can range from social or cognitive challenges to fear of future consequences.

As we have discussed (Kubera et al. 2010), systemic inflammation with increased levels of cytokines, such as IL-1β, TNFα and IL-6, may provoke longstanding neuroinflammation in the CNS. This is because those cytokines can diffuse through blood-brain-barrier (BBB) deficient areas or be actively transported into the CNS by endothelial cell transporters and activate BBB endothelial cells to produce various factors, which activate microglia. Last but not least, inflammatory signals can proceed from the periphery to the brain via the afferent vagus nerve, which signals brain areas of the presence of systemic inflammation (Goehler et al. 2000; Banks, 2005; Turrin and Rivest, 2004; Pavlov and Tracey, 2005). Systemic inflammation, for example induced by LPS administration, induces central neuroinflammation and microglial activation, resulting in activated central IO&NS pathways, including increased TNFα levels that may remain elevated during months (Qin et al. 2007).

Moreover, immune and inflammatory challenges engage multiple ascending neural pathways, "the neuraxes" conveying information about the body's internal state to different brain regions (Gaykema et al. 2009). Studies in humans and rodents have shown that mood or behavioral symptoms may be "viscerosensorily" mediated ("bottom-up") and are caused by cytokines and other inflammatory products, that are induced by infection or inflammation (Anisman and Merali, 2002; Dantzer, 2004). Those viscerosensory systems may signal metabolic, gastrointestinal, and cardiovascular status, and infection and inflammation and, therefore, can drive symptoms of depression and anxiety (Lyte et al. 2006; Goehler et al. 2007). Peripheral viscerosensory signals including those related to inflammation are detected in the dorsal vagal complex (DVC) and ventrolateral medulla (VLM) of the caudal medulla. The VLM is driven by input from the dorsal vagal complex and spinal lamina 1, and modulates pulmonary and cardiovascular functions. Neurons in both the DVC and the VLM also project to more rostral brain regions, and contribute to immune and other visceral challenges (Gaykema et al. 2007; Dayas et al. 2001; Sawchenko et al. 2000).

Current evidence supports a pivotal role for brain systems responsible for coping with stressors and the induction of recuperative behaviors in the etiology of dysphoric symptoms concomitant with medical illness. Tracing studies in animals and functional neuroimaging studies have indicated that representation of viscerosensory information occurs in frontal and temporal brain regions that contribute to the regulation of affect (Drevets et al. 2001; 2008). Peripheral infections or inflammation have been shown to increase the drive on brain regions that process threat-related information (Castex et al. 1995; Lyte et al. 2006; Rossi-George et al. 2005). The insula in the temporal lobe and the anterior cingulate, medial and orbital prefrontal cortex process the information that is necessary for "interoceptive awareness" and the induction of appropriate autonomic and behavioral responses. Animal studies have indicated that these cortical areas are influenced during peripheral immune activation (Goehler et al. 2008, Konsman and Blomqvist, 2005). Infection-induced anxiety is associated with activation of peripheral viscerosensory nerves, based on expression in vagal sensory neurons of the activation marker protein c-Fos (Goehler et al. 2005; Lyte et al. 2006). The activation pattern in the brain is consistent with viscerosensory challenge, including responses in the DVC and VLM of the caudal brainstem, in the parabrachial nucleus and locus coeruleus in the pons, and in the hypothalmus, thalamus, amygdala, bed nucleus of the stria terminalis (BNST), and insula in the forebrain. When animals challenged with bacteria are exposed to an anxiogenic behavioral challenge, there is additional activation in brain regions involved in behavioral defense including the periaquaductal grey (PAG), as well as in the medial prefrontal cortex (mPFC). In particular, the immune challenge seemed to enhance responses in the hypotha-

lamic paraventrivular nucleus, amygdala, and mPFC. In addition, activity in the BNST seemed to contribute to the enhanced anxiety-like behavior (Goehler et al. 2008). Taken together, findings from infection or inflammation models provide strong evidence that viscerosensory pathways contribute to changes in mood, by influencing brain regions that coordinate defensive behavior and responses to stress. It is important to note that groups of neurons distributed throughout the brainstem, midbrain, hypothalamus and basal forebrain function as "arousal" systems directed toward coordinating sleep/wake cycles, de/synchronization of thalamocortical discharges, behavioral arousal, vigilance, and responses to exteroceptive challenges. All of these arousal systems receive direct viscerosensory projections from the DVC and VLM (Espana and Berridge, 2006; Gaykema et al. 2008; Hajszán and Zaborszky, 2002), and are influenced by peripheral inflammation or infection (Goehler et al. 2005, 2008; Gaykema et al. 2008).

All in all, there are different pathways through which peripheral immune and inflammatory responses, as occurring in the abovementioned disorders/conditions, may be translated into the brain: a) pathways leading to microglial activation; and b) the "neuraxes" that translate information about the body's internal state to neuronal activity in different brain areas, which coordinate anxiety, dysphoria, arousal, vigilance, appetite, coping with stressors, etc. Thus, activation of peripheral IO&NS pathways may induce a cascade of neuroinflammatory and neuronal changes in the brain which together may cause depression-like behaviors. This also explains why the inflammation of chronic medical illness may cause "concomitant" depression.

4. PSYCHOLOGICAL "TOP DOWN" STRESSORS

Psychosocial stressors predispose towards depression and may even trigger depression in particular in genetically predisposed persons. There is now evidence that negative early life experiences increase the inappropriate responses to external stressors and therefore increase the vulnerability to develop depression. Negative life events are well established as precipitating factors that are associated to the onset of depression (Maes, 1999; 2001). In humans and animals, psychosocial stressors activate IO&NS pathways and therefore may trigger the onset of depressive symptoms (Maes, 1995; Maes et al. 1995; 2009; Anisman, 2009). Maes et al. (1999) were the first to show that psychosocial stress in humans increases the production of proinflammatory cytokines, including IFNγ and TNFα (Maes et al. 1998a; 1998b). Since then there were more reports that those and other cytokines, such as IL-1β and IL-6, are increased following psychosocial stressors in humans (review: Maes, 1999, 2001). Also, in experimental animals, psychological stressors, including immobilization stress, inescapable shock, physical restraint, open field stress or conditioned, aversive stimuli and chronic mild stress, increase the production of IL-1 and IL-6 and the expression of IL-1 and IL-6 mRNA in the brain (Maes, 1999; 2001; Kubera et al. 2010; Minami et al. 1991; Shintani et al. 1995a; 1995b; Nguyen et al. 1998; Shizuya et al. 1997; Takaki et al. 1994; LeMay et al. 1990). Psychological stressors cause increased ROS and lipid peroxidation; oxidative damage to DNA; and a significantly decreased plasma antioxidant activity (Aleksandrovskii et al. 1988; Pertsov et al. 1995; Sosnovskii and Kozlov, 1992; Sivonova et al. 2004; Irie et al. 2001). Since depression may act as an additional psychosocial stressor, it may potentiate IO&NS pathways in the brain and the periphery. This increased drive could exacerbate ongoing inflammation and O&NS in the brain, the gastrointestinal tract, the cardiovascular system, the skin, the lungs, the fat cells or other peripheral tissues and sustain a feed-forward loop exacerbating both peripheral and central inflammation. Moreover, the disabilities caused by each of the above medical disorders may act as additional psychosocial stressors that could further aggravate the IO&NS pathways.

5. CONCOMITANT DEPRESSION MAY WORSEN THE COURSE OF CHRONIC MEDICAL DISORDERS

As discussed above, concomitant depression not only lowers the quality of life in patients with AD, PD, MS and stroke, but also negatively influences the recovery from their neurological defects thus predicting a higher morbidity and mortality. One explanation is that the activated microglia, which occur in PD, AD, MS and stroke, trigger depression which further activates microglia, resulting in a feed forward cycle promoting neuroinflammation and thus neurodegeneration. There are many depression-related factors that contribute to neurodegeneration, e.g. increased levels of pro-inflammatory cytokines, increased detrimental TRYCATs, increased O&NS, lowered antioxidant levels including zinc, lowered omega-3 PUFAs, and increased glucocorticoid levels (Maes, 2010a; Maes et al. 2010a; 2010b; Kubera et al. 2010; Song and Wang, 2010; Zunszain et al. 2010; Szewczyk et al. 2010).

As discussed (Maes et al. 2010b) depression is a common antecedent of neurodegenerative disorders, such as AD. In this respect, it has been shown that patients with depression and MCI have a more than doubled risk to become demented (Steffens et al. 1997). Depression may be an early manifestation of dementia before the neurocognitive symptoms appear (Geerlings et al. , 2000; Visser et al. 2000). This higher risk to develop AD is increased in patients who suffered from depression within 2 years of the diagnosis of the dementia (Modrego and Fernandez, 2004). In particular, a meta-analysis on the relation of AD and depression shows that depression is an independent risk factor for later AD; and that the time lag between diagnosis of depression and AD is positively correlated

to the increased risk of developing AD (Ownby et al. 2006). All the above indicates that depression-associated microglial activation may be a prelude to neurodegeneration in later life. Indeed, all factors that may contribute to increased neuroinflammatory burden may drive neurodegenerative progression, e.g. increased neurotoxic cytokines, O&NS, lowered antioxidants, glucocorticoid–induced reductions in neurotrophic factors, inflammation-induced apoptosis, the reduction in the neuroprotective TRYCAT, kynurenic acid, and an increased synthesis in the neurotoxic TRYCATS (Leonard and Myint, 2006; 2009; Maes et al. 2010b).

Depression also contributes to a decreased quality of life, and higher disability and mortality in "peripheral" medical disorders, such as CVD, COPD, RA, psoriasis, SLE, IBD, IBS and type 1 and type 2 diabetes. One explanation is that all factors that sustain systemic inflammation may aggravate the course of the above "inflammatory" disorders. Phased differently, the activated IO&NS pathways in depression may aggravate the pathophysiology and thus the condition of the above medical disorders and thus may confer an increased risk towards these disorders. As an example, we refer to our review on the co-occurrence between depression and CVD (Maes et al. 2010c) in which it was shown that the interplay between multiple IO&NS pathways in depression results in pro-atherogenic effects which confer increased risk to develop CVD. Recent findings suggest that depression has a possible causal effect on symptom-based exacerbations (worsening of at least one key symptom), event-based exacerbations (worsening of at least one symptom and change in regular medications) and hospitalizations in COPD (Xu et al. 2008). Jennings et al. (2009) also found that COPD patients with depressive symptoms have a significantly higher risk for exacerbations (Jennings et al. 2009). In their retrospective cohort study these authors followed COPD patients for 1 year after discharge. Patients with depression had significantly more exacerbations of COPD in the following year and suffered earlier from an exacerbation than nondepressed COPD patients. SLE women are more likely to have coronary artery calcification (CAC) as compared with controls, while depression in SLE women is associated with greater than 2-fold odds of having any CAC (Greco et al. 2009). Since this association is partly mediated by adiposity both depression and adiposity may contribute to the inflammatory burden in SLE and all together may cause an increased cardiovascular risk. Although little is known of the role of depression as a risk factor for IBD there is a recent report that in animal IBD models depression reactivates dormant chronic colitis (Ghia et al. 2009). Thus, in C57BL/6 mice with induced colitis, induction of depression – by olfactory bulbectomy or chronic intracerebroventricular injection of reserpine – reactivated inflammation and increased the production of monocytic cytokines. The development of post-infectious IBS is associated to polymorphism of pro- or anti-inflammatory cytokine genes and the presence of depression and anxiety at the time of acute infection (Mearin et al. 2009).

The above shows that the effects of depression may be harmful to the brain and the body. As explained in section 3.3 and in another review (Maes, 2010b), cytokines, like IL-1β and TNFα, produced by peripheral monocytes/macrophages, may cause depression-like and anxiety-like behaviors by transmitting "bottom-up" signals from the periphery to the brain thereby inducing microglial activation and neuronal activity in brain areas that provoke stress-related behaviors (Qin et al. 2007; Kubera et al. 2010; Gaykema et al. 2009; Goehler et al. 2008). Some authors regard these depression-like behavioral changes, called sickness behavior, as well-organized responses of the body to preserve homeostasis, cope with the primary infections, and enhance recovery, suggesting that depressive-like behaviors may have a protective function (Dantzer, 2004). The findings that depression may worsen the course of chronic medical illness and increase the risk to develop chronic illness and that depression is accompanied by increased O&NS damage, reduced neurogenesis, enhanced neuronal apoptosis and neurodegeneration shows that clinical depression has no protective function at all. This further underscores that sickness behavior and depression are different entities; the former being a protective, behavioral response by the brain to infection, the latter consisting of activation of many detrimental IO&NS pathways that are caused by a great variety in internal and external stressors.

It may be argued that depression – and in particular the first episodes – tends to be self-limiting, suggesting that depression does not have detrimental effects. We (Maes, 1995; Maes et al. 2010b) have explained previously that activation of the counter anti-inflammatory response system (CARS) may be involved. The presence of CARS in depression is demonstrated by, for example, ex vivo T cell exhaustion and T cell unresponsiveness, increased IL-1 receptor antagonists levels, lowered tryptophan and higher TRYCAT levels, increased levels of acute phase reactants, such as haptoglobin, etc., which all exert a negative feedback on the primary immune-inflammatory response in depression (Maes, 1995; Maes, et al. 2010; 2010b). Thus, the CARS that is activated in depression may dampen the primary activation of the IO&NS pathways and thus may attenuate the associated depressive symptoms. This mechanism could explain the self-limiting nature of depression, at least in the first stage of illness. This CARS may thus have protective effects. However, during the life-time course of depressed patients when episodes tend to re-occur and when depression, in particular when concomitant with chronic medical disease, becomes more chronic the (neuro)inflammatory and degenerative processes prevail.

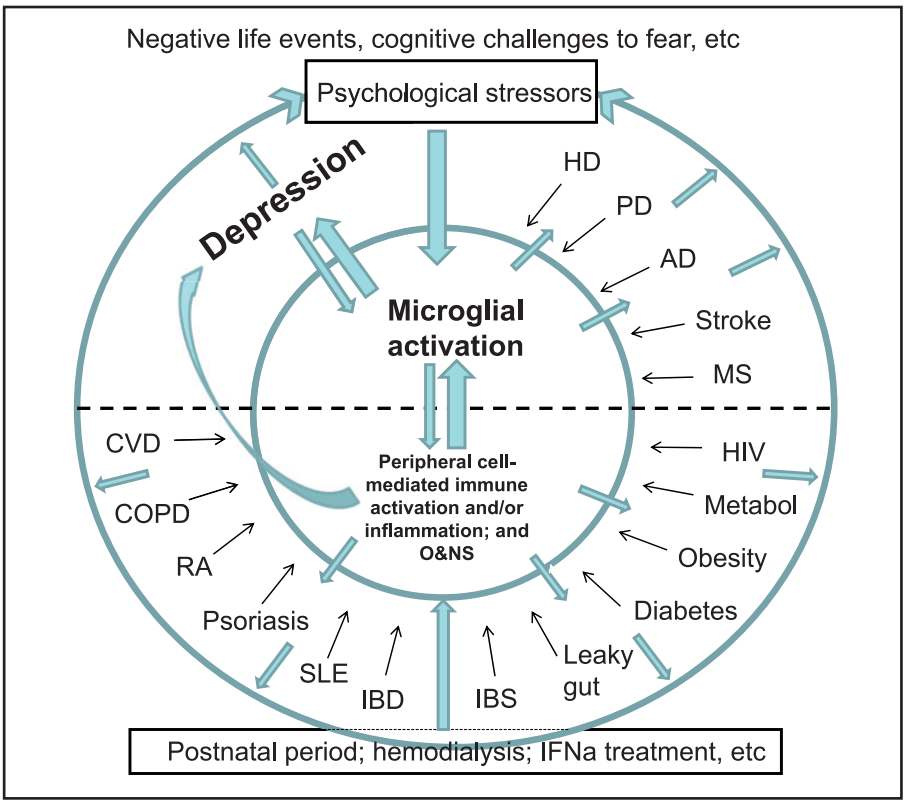

Figure 3. This Figure shows that depression is the clinical expression of activated immune, inflammatory and oxidative and nitrosative stress (IO&NS) pathways in the periphery and in the brain (microglial activation) caused by a) a number brain disorders, such as Alzheimer' s (AD), Huntington's (HD), and Parkinson's (PD) disorder; multiple sclerosis (MS) and stroke; and b) a number of systemic disorders, e.g. cardiovascular disorder (CVD); chronic obstructive pulmonary disease (COPD); rheumatoid arthritis (RA); psoriasis; systemic lupus erythematosus (SLE); inflammatory bowel disease (IBD); irritable bowel syndrome (IBS); leaky gut; diabetes type 1 and 2; obesity and the metabolic syndrome (metabol), and HIV infection. Activation of peripheral IO&NS pathways may cause microglial activation and neuronal changes in brain regions that coordinate mood and stress-related behaviors. Conditions, such as hemodialysis, interferon-α-based immunotherapy, and the postnatal period activate peripheral IO&NS pathways and are therefore other causes for depression. Psychosocial stressors activate IO&NS pathways in the brain and the periphery and may therefore cause depression. Depression itself may act as a modifiable condition that causes hyperactivation of central/peripheral IO&NS pathways and, therefore, may deteriorate the course of brain and systemic disorders. The psychosocial stress caused by suffering from depression and medical disorders may further aggravate the central and peripheral IO&NS pathways.

6. FROM "COMORBID" TO "PATH-SHARED" DISORDERS

As explained previously (Maes, 2010b; Maes et al. 2010c) the term "comorbidity" may not be the best to delineate the association between depression and the abovementioned disorders. In the Introduction, we described the various definitions of comorbidity, i.e. that a disorder a) exists together but independently with another disorder; or b) is caused or causes another medical disorder (First, 2005; Valderas et al. 2009; Feinstein et al. 1970). This review clearly shows that the co-occurrence of depression with other medical disorders is based on shared pathways and is not "independent". There is a clear dependency: shared IO&NS pathways underpin their pathophysiology. At first sight, a depression that occurs after stroke could be considered to be a "comorbid depression". However, depression may modify the course and outcome of stroke and depression may even act as a risk factor for future CVD, including stroke. In the case of AD, depression may be a first sign of AD or may even increase the risk for AD. When depression occurs during the course of PD and COPD, depression may act as a potentially modifiable condition that worsens the shared IO&NS pathways thereby modifying the course of these medical disorders and increasing mortality and morbidity. Thus, not one of the "comorbidity" definitions can be applied in the case of the co-occurrence between depression and the medical disorders listed here.

Another major drawback of the term "comorbidity" is that it denotes a co-occurrence at the clinical-phenotypic level only, while in fact their co-occurrence is based on the considerable overlap in the IO&NS pathways that underpin their pathophysiology. In this regard "path-shared disorders" would be a better term than "comorbid disorders" because it stresses that the co-occurrence of these disorders is the consequence of common pathways.

Figure 1 shows that depression is the clinical expression of activated IO&NS pathways that may be induced by a number of disorders and conditions. However, Figure 1 does not account for the fact that depression may worsen the IO&NS pathways and thus the course of these disorders, that depression may be a risk factor for some of these disorders, and that the psychological stress associated with depression and the medical disorders may further endanger the IO&NS pathways. Therefore, the circular model displayed in **Figure 3** is more appropriate to display the relevant pathways and interactions. All in all, the (neuro)inflammatory, O&NS, and (neuro)degenerative pathways that characterize depression, and the strong comorbidity between depression and some (neuro)inflammatory and (neuro) degenerative disorders show that depression belongs to the spectrum of inflammatory / degenerative disorders.

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