

# Aging, inflammation and depressive behavior: a review

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## Abstract

One of the most common co-morbidities of cerebrovascular disorders is neuroinflammation, a hallmark and decisive contributor to many central nervous system (CNS) diseases. Although neuropathological conditions differ in etiology and in the way in which the inflammatory response is mounted, cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment or after cerebral insult such as stroke. Moreover, a number of highly prevalent risk factors such as hypertension, diabetes and atherosclerosis are increasingly understood to act as "silent contributors" to neuroinflammation – not only establishing the condition as a central pathophysiological mechanism, but also constantly fuelling it. Mild, but continuous neuroinflammation can provide the ground for disorders such as cerebral small vessel disease (cSVD) and subsequent dementia. Acute neuroinflammation, often in the context of traumatic or ischemic CNS lesions, aggravates the acute damage and can lead to depression, post-stroke dementia and neurodegeneration. All of these sequelae impair recovery and provide the ground for further cerebrovascular events.

## Keywords

*Metabolic syndrome; Inflammation; Aging*

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## Introduction

Cerebrovascular diseases are among the most prevalent health care problems in Europe. Total European cost of brain disorders in 2010 was 798 billion € of which 64.1 billion € was related to stroke alone [1]. In many cases, the result of cerebrovascular disorders is a loss of independent living and secondary health problems affecting not only patients but also their families. The number of elderly people is increasing with a number of co-morbidities increasing the risk of cerebrovascular diseases [2]. Thus, strategies in guiding patient selection and novel preventive and neuroprotective therapies are urgently needed. Emerging evidence suggest that several diseases show overlapping pathology with neuroinflammation as one possible common mechanism leading to increased risk of cerebrovascular disorders.

In demographically developed countries, the average age at which stroke occurs is around 73 years reflecting the older age structure of these countries. The probability of a first stroke or first transitory ischemic attack is around 1.6 per 1,000 and 0.42 per 1,000, respectively. In less developed regions, the average age of stroke will be younger due to the different population age structure resulting from higher mortality rates and competing causes of death.

Stroke patients are at highest risk of death in the first weeks after the event, and between 20% to 50% die within the first month depending on type, severity, age, co- morbidity and effectiveness of treatment of complications. Patients who survive may be left with no disability or with mild, moderate or severe disability. Considerable spontaneous recovery occurs up to about six months [3]. However, patients with a history of stroke are at risk of a subsequent event of around 10% in the first year and 5% per year thereafter [4].

The negative consequences of stroke extend well beyond the victims themselves, ultimately including families, caregivers, social networks and employers. The proportion of patients achieving independence in self-care by one year after a stroke ranges from around 60% to 83%. This wide variation relates to whether the studies are community based or hospital based, which activities are considered in estimating independence, and the methods used to rate ability. In established marked economies (EMEs), depending on the organization of hospital services, between 10% and 15% of survivors are resident in an institution at one year [5].

Worldwide stroke it is increasing in parallel with modernization, changes in lifestyle, and the growing elderly population. In particular, rates in Eastern Europe have been increasing, such that currently the highest rates are found in countries such as Bulgaria, Romania, and Hungary. Among the women and men individuals with a low-risk lifestyle (smoking, exercising daily, consuming a prudent diet including moderate alcohol and having a healthy weight during mid-life) had a significantly lower risk of stroke than individuals without a low-risk lifestyle. Therefore the relatively high incidence of stroke may be due in part to the impact of numerous known risk factors in these populations [6]: arterial hypertension, diabetes, high cholesterol, smoking, alcoholism, obesity, stress, and a sedentary lifestyle.

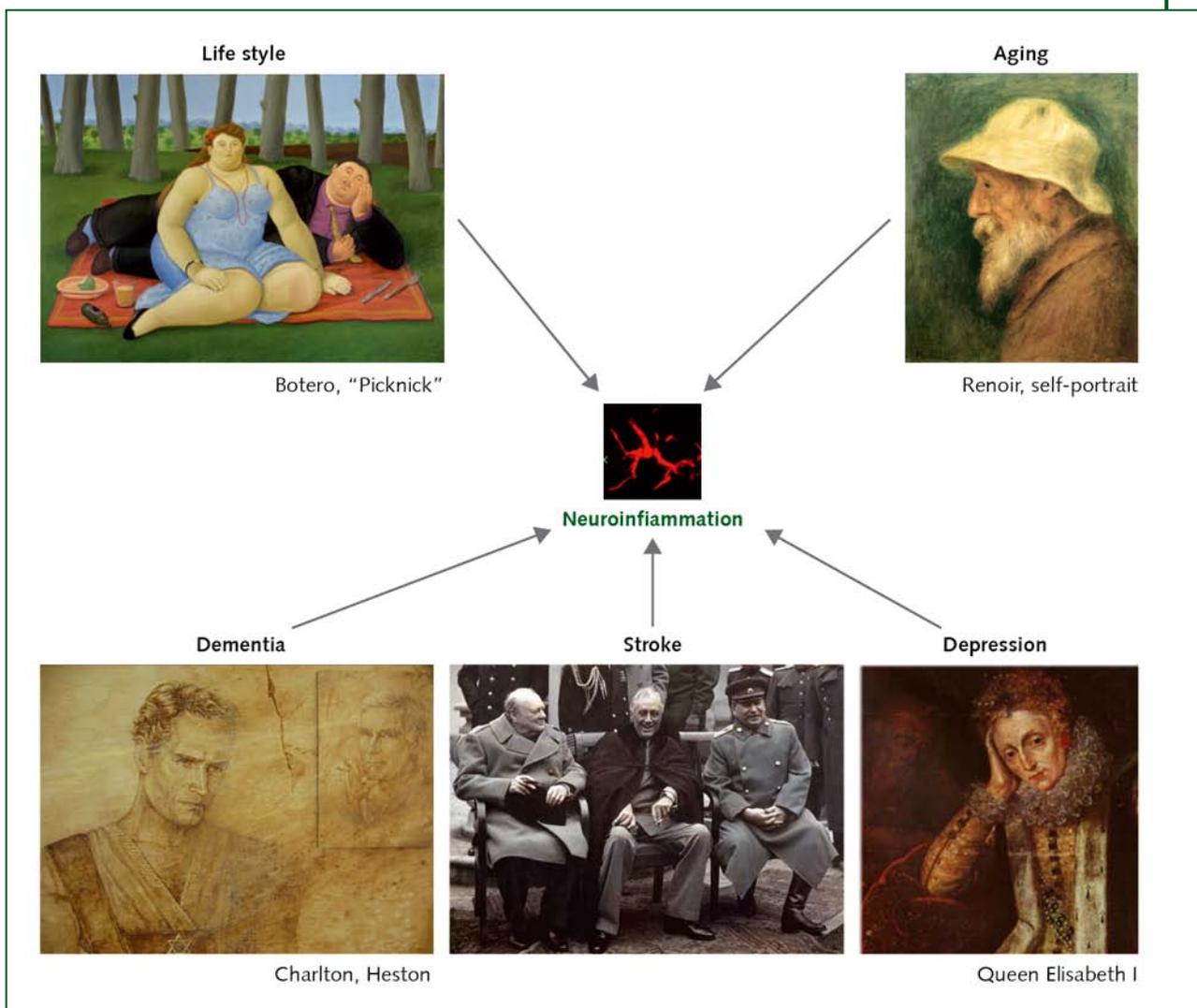
Virtually all drug interventions that have been successful pre-clinically in experimental stroke have failed to translate this success to the clinical setting. We and others propose that this is due to the failure of these pre-clinical studies to fully consider the aging and comorbidities for stroke present clinically [7-9]. It is quite possible that an intervention showing efficacy in a normal animal may not be effective when co-morbidity exists. We have shown that ischemic damage occurs very rapidly in the brain of aged rodents after experimental stroke and that infarct development in aged rats can be slowed down by hypothermia.

## Neuroinflammation in cerebrovascular comorbidities

Cerebrovascular disease co-morbidities share a similar pathophysiology particularly with respect to neuroinflammation, a hallmark and contributor to many central nervous system (CNS) diseases.

Although neuropathological conditions differ in aetiology and in the way in which the inflammatory response is mounted, cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment or after cerebral insult such as stroke [10]. Moreover, a number of highly prevalent risk factors such as hypertension, diabetes and atherosclerosis are increasingly understood to act as “silent contributors” to neuroinflammation – not only establishing the condition as a central pathophysiological mechanism, but also constantly fuelling it (Figure 1).

Subtle, but continuous neuroinflammation can provide the ground for disorders such as cerebral small vessel disease (cSVD) and subsequent dementia. Acute neuroinflammation, often in the context of traumatic or ischemic CNS lesions, aggravates the acute damage and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. All of those sequelae impair recovery and most of them provide the ground for further cerebrovascular events (Figure 1).



**Figure 1.** Life style, aging, hypoperfusion and neuroinflammation precipitate neuropsychiatric diseases

## Metabolic inflammation

It is becoming well established that lifestyle, especially dietary habits, greatly affect metabolic health. Bad nutritional habits can lead to metabolic disorders, triggered by a system-wide chronic inflammation, also called metaflammation, metabolic inflammation [11]. A metaflammation state can lead to a series of disorders and diseases, including hypertension, metabolic syndrome, CVD, stroke, insulin resistance and T2DM. It is postulated that lipid hormones including sphingolipids and eicosanoids in concert with cytokines and adipokines play an important role in this process by inducing adverse regulatory responses in target cells such as macrophages. The role of genetics in driving metabolic disease development is strongly indicated by the higher concordance rate of T2DM in monozygotic than in dizygotic twins. It has been estimated that 30% to 70% of T2DM risk can be attributed to genetics [12]. The investigation of gene-environment interactions through large collaborative efforts holds promise in furthering our understanding of the interplay between genetic and environmental factors [13].

### Obesity, inflammation and rehabilitation odds in Stroke Patients

The Obesity paradox has been reported in many articles as a inverse relationship between the body mass index (BMI) and mortality in stroke patients. The relationship between BMI and functional recovery in post stroke patients has not been well described [14-20].

A cohort study from the China National Stroke Registry analysed the relationship between the body mass index (BMI), mortality and post stroke functional recovery at 3 months after disease onset. The study enrolled and analysed 10,905 patients with eligible acute ischemic stroke. Favourable functional recovery was seen in 52,4% of underweight (BMI = 18,5 kg/m<sup>2</sup>), 55,0% of normal weight (BMI = 18,5-22,9 kg/m<sup>2</sup>), 61% of overweight (BMI = 23-27,4 kg/m<sup>2</sup>), 59,2% of obese (BMI = 27,5-32,4 kg/m<sup>2</sup>) and 60,3% of severe obese (BMI > 32,5 kg/m<sup>2</sup>) stroke survivors. The overweight AIS survivors had better 3-month functional recovery and moderate obesity showed a protective trend. However, severe obesity was associated with higher mortality and overweight/obesity was not a protective factor of survival at 3 months after stroke [21].

A study on the Effect of Body Mass Index on Stroke Rehabilitation including 819 patients reported that among patients admitted to an acute rehabilitation hospital, overweight patients had better functional progress than did patients in the other weight categories [22].

Still another study on the Obesity Paradox that included 510 TIA survivors, showed that an excess adiposity increased the risk of severe disability after ischemic stroke. Since BMI also reflects total lean mass, it is risky to conclude that there is a protective effect of obesity alone in the functional recovery after stroke; nevertheless, it is possible that a minimum body mass is necessary to prevent severe disability in stroke survivors [23].

Contradictory results were reported in study from 2007 published in American Journal of Medicine and Rehabilitation, showing that the functional improvement scores in normal weighted patients were better than those in overweight/obese patients [24].

In a retrospective cohort study on 53,104 stroke patients from the Danish Stroke Register, data on BMI, age, sex, civil status, stroke severity, stroke subtype, a predefined cardiovascular profile, and socioeconomic status became available. This reported no evidence of an obesity paradox in patients with stroke reported. However stroke occurred at a significantly younger age in patients with higher BMI.

More recently, study analyzed 451 patients hospitalized for ischemic stroke and found that BMI on admission had no relationship to functional recovery on discharge [25]. Most likely, the association between higher BMI and favorable functional recovery might be influenced by stroke severity because patients with high BMI seemed to have had less severe strokes [20] and more lacunar infarctions [26].

## Depression and Inflammation

Major depressive disorder (MDD) is a severe psychiatric illness that is associated with significant morbidity and mortality. About one in six individuals will succumb to clinical depression during their lifetime [27]. In addition to mortality associated with suicide, depressed patients are more likely to develop coronary artery disease and type 2 diabetes [28]. Depression also complicates the prognosis of other chronic diseases [29,30]. However, biological mechanisms underlying depression remains poorly understood due to lack of biomarkers, relatively low rates of heritability, and heterogeneity of precipitating factors, including stress [27,31,32].

Despite advances in the treatment of major depression, one-third of depressed patients fail to respond to conventional antidepressant medication [33]. One pathophysiologic mechanism hypothesized to contribute to treatment resistance in depression is inflammation. Inflammation has been linked to depression by a number of putative mechanisms involving neuroinflammation, oxidative stress, endothelial nitric oxide synthase uncoupling, and hyperglutamatergia, as well as their relationships to indirect evidence of neurovascular dysfunction in MDD [34].

Recent evidence has shown that MDD is associated with increased levels of inflammatory markers in the periphery. A number of inflammatory biomarkers (including inflammatory cytokines, acute phase proteins, chemokines, and adhesion molecules) in the periphery have been found to be reliably elevated in one third of all depressed patients with a decreased likelihood of response to conventional antidepressants [35-37]. Conversely, patients treated with cytokines for various illnesses are at increased risk of developing major depressive illness [38]. A recent study reported that treatment-resistant depression (TRD) who have highly increased inflammation (i.e. elevated baseline hs-CRP concentration) responded preferentially to infliximab while infliximab-treated participants with a low level of inflammation appeared to do worse than placebo-treated participants [39]. Of note, increased inflammatory markers in depressed patients have also been associated and may also be associated with remitted stages of depression in response to treatment with conventional antidepressant medications [36,40-44]. Neuroinflammation has been associated with greater rates of major depression. On a background of systemic inflammation, proinflammatory cytokines can access the central nervous system and interfere with serotonin metabolism, and reduce both synaptic plasticity and hippocampal neurogenesis [45,46]. Behavioral consequences of these effects of the immune system on the brain include depression [39,47]. Cross-sectional [48-50] and prospective [51-53] epidemiological studies have focused on peripheral inflammatory markers, such as cytokines, on the assumption that peripheral inflammatory markers are etiological factors in the development of depressive symptoms [54,44] as well as induce neurotransmitter changes in the brain as seen in depression [55]. The most consistent finding has been the association of elevated cytokines IL-6 and IL-8 with depressive symptoms [38,48-50,56]. Specifically, there was a significant linear relationship between increasing levels of IL-6 and depressive symptoms at baseline, whereas IL-8 was associated with depressed symptoms at baseline and at 2 years follow-up [44]. More recently, a prospective association of IL-1b and interleukin 1 receptor antagonist (IL1ra) with depressive symptoms in the elderly was also suggested [51,52].

Patients undergoing cytokine therapy are at increased risk of developing major depressive illnesses. For example, IFN-alpha has been frequently associated with significant psychiatric morbidity, notably in the form of the development of major depression in up to 45 percent of patients [57-59]. This findings strongly support the inflammatory hypothesis in the pathophysiology of depression.

Successful antidepressant treatment may reduce proinflammatory markers by improving perfusion or restore endothelial function [35,60,61]. Etanercept, a soluble tumor necrosis factor- $\alpha$  receptor, and celecoxib, a cyclo-oxygenase-2 inhibitor, may reduce depressive symptoms in patients with inflammatory diseases [62,63] and infliximab may improve depression in patients with greater pre-treatment inflammation [39].

## Microglia, synaptic plasticity and depressive behaviour

A large body of post-mortem [64,65] and neuroimaging [64,66] studies of depressed patients have reported reductions in grey-matter volume and glial density in the prefrontal cortex and the hippocampus, regions thought to mediate the cognitive aspects of depression. Further, the Wnt/ $\beta$ -catenin pathway –that is implicated in synaptic plasticity it is downregulated in major depression and upregulated after antidepressant treatment. Likewise, the mTOR pathway which is controlling synaptic plasticity, is disrupted in major depression, and the target of some drugs with fast-acting potential antidepressant action. Finally, recent studies suggest that microglia may play a role in synaptic remodeling and plasticity in the healthy brain [67-72]. Furthermore, disrupting microglia-specific CR3/C3 signaling resulted in sustained deficits in synaptic connectivity [72]. Taken together these results highly suggest that there is a deep connection between inflammation, microglia, neuroplasticity and mood regulation. However, it remains less clear what role microglia play in the uninjured brain. A recent report has shown that in the normal brain microglia synaptic remodeling and plasticity in the healthy brain and play a major role in synaptic pruning during postnatal development in mice by actively engulfing synaptic material [69]. Signaling through a phagocytic receptor, complement receptor 3 (CR3/CD11b-CD18/Mac-1) is a key molecular mechanism underlying engulfment of synapses. CR3 is expressed on the surface of microglia and its ligand, complement component C3 is localized to synaptically-enriched regions. Conversely, disruption of CR3/C3 signaling was specific to microglia in the CNS and resulted in sustained deficits in brain wiring and structural remodeling.

## Depression and Aging

The prevalence of depression and cognitive dysfunction is particularly elevated in the elderly and obese subjects. Aging is one of the most challenging public health issue facing the developed countries today. With the growth in aged population, there has been a growing interest to promote successful aging and to reduce disparities in attaining maximum healthy life expectancy [73].

Depression is an independent risk factor for early mortality [74]. Patients with major depression have an increased onset risk of aging-related diseases affecting the cardiovascular, cerebrovascular, neuroendocrine, metabolic, and immune systems [75-78]. Depression can thus significantly compromise successful aging defined subjectively as freedom from chronic disease and disability, along with high physical and cognitive functioning and social engagement [79,80].

Among elderly individuals, depressive symptoms are common and burdensome [27,81,82]. In a given year, between 1 to 2% of individuals over the age of 65 will meet the criteria for major depressive disorder [83]. Even though this 12-month prevalence seems quite low compared to the about 6% observed in adults, several parameters have to be taken into account. First, it has recently been demonstrated that the apparently lower prevalence estimates of depression in older adults might be biased by incorrect inclusions of individuals, notably patients with sub-threshold hypomania; and to a lesser extent, to the increase in general medical condition depressive disorders with age. Second, another 15-25% of elders experience depressive symptoms that, while not meeting criteria for major depressive disorder, do cause significant distress and interfere with daily functioning [84]. Third, with the ongoing demographic changes, an ever increasing number of older adults with mental illnesses, notably late life depression, is expected [85]. Overall, among the aging population, individuals experiencing late life depression display greater functional disability [86] and cognitive decline than healthy ones [87].

Normal aging is a situation characterized by a chronic low-grade, pro-inflammatory state [88], with an over-expression of systemic inflammatory factors, including pro-inflammatory cytokines [89,90]. Age-associated inflammation in the brain manifests primarily by the chronic activation of perivascular and

parenchymal macrophages/microglia expressing proinflammatory cytokines and an increased number of astrocytes [91-93].

Given the potential role of inflammation in psychopathology, it is thus highly possible that chronically activated inflammatory signals in aging may contribute to increased vulnerability to neuropsychiatric disorders [94]. Inflammation in obese women is associated with increased concentrations of inflammatory markers (IL-6, CRP and adipokines) that correlated with increased symptoms of depression and anxiety [95]. Conversely, removal of fat tissue surgically was associated with reduced inflammation [96,97].

## Post-stroke depression

Emerging evidence suggests that stroke and traumatic brain injury confer vulnerability to a late-onset of neuropsychiatric and neurocognitive symptoms [98,99]. Brain injury initiates an exaggerated neuroinflammation by activation of an immune-reactive microglial population as a possible triggering mechanism for the development of depressive-like behavior after injury that may last for weeks and months after the event [99]. Importantly, a recent meta-analysis found that the frequency of depressive symptoms even tends to increase in the long-term phase of recovery [100]. Depression persists after 20 months in 34% of elderly patients with acute stroke and has been linked to both worse cognitive and physical outcome [101].

Post-stroke depression (PSD) has been shown to increase mortality for more than 5 years after stroke [102]. Emotional distress caused by stroke-induced motor disabilities may contribute to the development of PSD. However, other non-psychological factors such as the ischemia-induced brain lesion itself and/or secondary degenerative changes may play a major etiological role. Despite the fact that a high proportion of stroke patients develop mood disorders, the mechanisms underlying PSD have so far received little attention from the field of neurobiology. One major factor involving the development of post-stroke depression is an age-related microglia activation in response to stroke.

Persistent neuronal death causes a prolonged neuroinflammatory response in the infarcted area and may contribute substantially to post-stroke depression. After stroke and traumatic brain injury microglia move toward the site of damage and engulf and clear damaged cellular debris [68,103,104]. Previously we have shown that aged rats showed a fulminant microglia reaction during the acute phase of stroke that persists for weeks thereafter [99,105,106]. Since microglia has been involved in scavenging synapses, these findings suggest that CR3/C3 signaling is a major determinant of post-stroke depression therefore a major target of intervention.

## Conclusions

Worldwide cerebrovascular diseases are increasing in parallel with modernization, changes in lifestyle, and the growing elderly population. Understanding how aging and life style precipitate the development of cerebrovascular diseases is fundamental for prevention, diagnosis and for the development of safe and efficient therapies. Recent work suggest that perfusion deficits in the elderly can trigger microglial activation and subsequent neuroinflammation and shifts the CNS into a proinflammatory state ultimately resulting in demyelination and neurodegeneration.

### Question for further research

Given the potential role of inflammation in psychopathology, it is thus highly possible that chronically activated inflammatory signals in aging may contribute to increased vulnerability to neuropsychiatric disorders.

## The review in brief

|                   |                                                                                                                                                                                                                                            |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical question | To indagate the association between aging, inflammation and depressive behavior                                                                                                                                                            |
| Type of review    | Narrative                                                                                                                                                                                                                                  |
| Conclusions       | Recent work suggest that perfusion deficits in the elderly can trigger microglial activation and subsequent neuroinflammation and shifts the CNS into a proinflammatory state ultimately resulting in demyelination and neurodegeneration. |
| Limitation        | It remains less clear what role microglia play in the uninjured brain.                                                                                                                                                                     |

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