Title: The impact of vascular burden on late-life depression.
Authors: Santos M, Kövari E, Hof PR, Gold G, Bouras C, Giannakopoulos P
Journal: Brain research reviews
Year: 2009 Dec 11
Volume: 62
Issue: 1
Pages: 19-32
DOI: 10.1016/j.brainresrev.2009.08.003

Published in final edited form as:
Brain Res Rev. 2009 December 11; 62(1): 19–32. doi:10.1016/j.brainresrev.2009.08.003.

The impact of vascular burden on late-life depression

Micaela Santos[a], **Enikö Kövari**[a], **Patrick R. Hof**[d], **Gabriel Gold**[c], **Constantin Bouras**[a], and **Panteleimon Giannakopoulos**[a,b,*]

[a] Department of Psychiatry, University Hospitals and Faculty of Medicine of Geneva, Belle-Idée, Geneva, Switzerland [b] Service of Old Age Psychiatry, Department of Psychiatry, University of Lausanne School of Medicine, Lausanne, Switzerland [c] Department of Geriatrics, University Hospitals and Faculty of Medicine of Geneva, Belle-Idée, Geneva, Switzerland [d] Department of Neuroscience and Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY, USA

Abstract

Small vessel pathology and microvascular lesions are no longer considered as minor players in the fields of cognitive impairment and mood regulation. Although frequently found in cognitively intact elders, both neuroimaging and neuropathological data revealed the negative impact on cognitive performances of their presence within neocortical association areas, thalamus and basal ganglia. Unlike cognition, the relationship between these lesions and mood dysregulation is still a matter of intense debate. Early studies focusing on the role of macroinfarct location in the occurrence of post-stroke depression (PSD) led to conflicting data. Later on, the concept of vascular depression proposed a deleterious effect of subcortical lacunes and deep white matter demyelination on mood regulation in elders who experienced the first depressive episode. More recently, the chronic accumulation of lacunes in thalamus, basal ganglia and deep white matter has been considered as a strong correlate of PSD. We provide here a critical overview of neuroimaging and neuropathological sets of evidence regarding the affective repercussions of vascular burden in the aging brain and discuss their conceptual and methodological limitations. Based on these observations, we propose that the accumulation of small vascular and microvascular lesions constitutes a common neuropathological platform for both cognitive decline and depressive episodes in old age.

Keywords

Vascular burden; Cognitive impairment; Aging; Mood; Microvascular pathology; Lacunes

1. Introduction

The first reports of the impact of vascular lesions on cognitive functions date from 1672, when Thomas Willis (1621–1675) described, in his book *De Anima Brutorum*, a series of cases of post-apoplexy dementia (Roman, 2003). Already in 1845, Griesinger postulated that senility can be attributed to arteriosclerosis (Loeb, 1995) but vascular dementia (VaD) was clearly delineated by Otto Binswanger and Alois Alzheimer who first recognized its specificity by separating it from neurosyphilis (Roman, 2003). Since then, arteriosclerotic lesions of cerebral blood vessels were considered a major cause of dementia even though the

*Corresponding author. Division of Geriatric Psychiatry, 2 chemin du Petit-Bel-Air, CH-1225 Chêne-Bourg, Switzerland. Fax: +41 22 3055044. Panteleimon.Giannakopoulos@unige.ch (P. Giannakopoulos).

biological mechanisms surrounding this phenomenon remained poorly understood. Paralleling the debate about the cognitive repercussions of vascular lesions, their role on mood came to light, mainly through studies of depression after stroke (Robinson, 1986). More recently, the concept of vascular depression was proposed combining late-onset depressive syndromes with cerebrovascular lesions and cardiovascular risk factors (Alexopoulos et al., 1997). An increased prevalence of magnetic resonance imaging (MRI) punctuate hyperintensities (MRIHs) in the subcortical gray matter and in deep and periventricular white matter was described in patients with late-onset depression (Krishnan et al., 1997). However, subsequent studies demonstrated that MRIHs were often present in normal brain aging raising doubts about their clinical significance in elderly cohorts (Guttmann et al., 1998). One main limitation of the MRI studies that may explain these contradictory findings is related to the "impure" nature of radiological lesions. In fact, MRI hyperintensities previously referred to as leucoencephalopathy, leukoaraïosis and subcortical encephalomalacia correspond to various combinations of small macrovascular lesions such as lacunes and demyelination and microvascular lesions such as cortical microinfarcts (Fazekas et al., 1993). Autopsy studies in clinically well-documented cohorts are thus crucial to isolate the consequences of each type of vascular lesions in old age.

After a brief summary of current knowledge regarding the cognitive impact of vascular lesions mainly based on neuropathological observations, the present review offers a detailed analysis of their repercussions on mood with special reference to the complex methodological limitations that should be considered when interpreting the experimental data in this field. Taking into account the main etiological theories relative to the clinical impact of vascular burden in emotional regulation, we also comment on recent evidence implying that the chronic accumulation of small vascular changes may be a common denominator of both neuropsychological and mood changes in old age.

2. Vascular burden and cognitive decline in old age: the contribution of neuropathology

Tomlinson et al.'s (1968 1970) seminal work establishing a link between VaD and the volume of cerebral infarcts larger than 100 ml was rapidly contested by the results of Hachinski et al. (1974) that changed the focus from the volume of the lesions to their location and proposed the landmark notion of "strategic macroinfarcts." More recently, the definition of vascular cognitive impairment (VCI) pointed first to the possible role of small vessel disease in white and deep gray matter as a cause of cognitive decline. According to a recent multi-centre study, the importance of small vessel disease as a cause of VaD has been underestimated. A recent epidemiological study revealed that among patients with VaD, 74% had small vessel disease and only 18% presented with large vessel disease while 8% had both (Staekenborg et al., 2008). The concept of subcortical ischemic vascular dementia represents the most recent attempt to focus on the cognitive impact of MRI detectable small vessel-related lesions in old age. Clinically, this syndrome is characterized by predominant frontal symptoms such as a dysexecutive syndrome and aberrant behaviors. Lacunar infarcts or deep white matter lesions (WML) may lead to the disruption of three frontosubcortical circuits involved in non-motor behavior: the dorsomedial prefrontal circuit related to executive function, the medial prefrontal circuit involved in initiation and drive and the orbital prefrontal circuit that subserves social behavior. Deep WML may also affect cortico–cortical connections known to play a key role in cognitive and emotional regulation (Chui, 2007).

Lacunes are defined as complete or cavitating infarcts resulting from definitive ischemic necrosis and measuring 1–15 mm in diameter, seen in MRI and upon gross examination at autopsy and largely confined to cerebral white matter and subcortical structures including

thalamus, basal ganglia and brainstem (Gold et al., 2005; Kalaria et al., 2004) (Fig. 1). The exact clinical significance of lacunes remains doubtful (Jellinger and Attems, 2003; Lee et al., 2000; Vinters et al., 2000). Although subcortical lacunes (i.e., in the thalamus, basal ganglia and deep white matter) have repeatedly been associated with cognitive impairment (Snowdon et al., 1997; van der Flier et al., 2005), other datasets emphasize the common presence of clinically silent lacunes in very old individuals (Jellinger and Attems, 2003; Vermeer et al., 2003).

The prevalence of WML or hyperintensities (referred to as leukoaraïosis) increases as a function of age and vascular risk factors (Breteler et al., 1994; Jeerakathil et al., 2004; Longstreth et al., 1996). Neuropathologically, WMLs correspond to a heterogeneous group of histological changes such as demyelination and pallor, lacunar infarcts, dilated periventricular spaces, astrogliosis and cerebral amyloid angiopathy (Bronge et al., 2002; Fazekas et al., 1993; Gurol et al., 2006; Munoz et al., 1993; Scheltens et al., 1995; van Swieten et al., 1991; Udaka et al., 2002). In a first study including volumetric measures of WML in autopsy cases, Jagust et al. (2008) reported no association between WML and AD lesions or cerebral amyloid angiopathy but confirmed the positive association between WML and complete or incomplete infarction. Data from *in vivo* studies addressing the WML impact on cognition remain challenging (Enzinger et al., 2007; Hentschel et al., 2007; Stewart et al., 2008). Both the Rotterdam Scan study (de Groot et al., 2002) and the Cache County study (Bigler et al., 2002) showed a strong correlation between periventricular WML and cognitive decline. For other authors, the relationship between WML on MRI and cognitive status was significant for both periventricular and subcortical WML (Garde et al., 2000). In a recent study of AD patients, periventricular WML were related to impaired executive function and subcortical WML with depressed mood (Bracco et al., 2005). Other neuroimaging studies did not reveal significant correlations between WMLs and cognitive changes (Bracco et al., 1993; Schmidt et al., 2002).

The first ambitious neuropathological investigation in this domain was the Nun study based on the data of 678 catholic sisters 75–107 years of age who consented to clinical archives consultation (including early- and middle-life risk factors), annual cognitive and physical function evaluation and postmortem brain donation for neuropathologic examination (Snowdon et al., 1997). These early results documented the relationship between cognitive deterioration and the presence of lacunar infarcts in the basal ganglia, thalamus and deep white matter. They also suggested that a few small infarcts in strategic regions of the brain might be sufficient to produce dementia solely in individuals with substantial AD lesion formation within the neocortex.

Unlike its macrovascular counterparts discussed above, the possible cognitive impact of microvascular lesions not detectable with classical neuroimaging methods has been overlooked. Thought to cause only limited damage in brain tissue, cortical microinfarcts (CMI) were frequently considered as benign consequences of brain aging (Del Ser et al., 1990). The possible contribution of microinfarcts to the cognitive decline was first pointed out by the pioneer neuropathological work of Esiri et al. (1997) and Vinters et al. (2000). Other autopsy studies confirmed the cognitive impact of microvascular lesions in deep white and gray matters and raised the possibility that microvascular lesions contribute to lower the threshold at which AD pathology becomes clinically evident (Esiri et al., 1999; Esiri, 2000; Zekry et al., 2002). This view was, however, challenged by the results of a neuropathological and neuropsychological examination performed by Lee et al. (2000). In this series, the presence of concomitant small infarcts (less than 10 cm^3) neither worsened dementia severity near death nor increased the observed rate of cognitive decline.

The controversy surrounding the relevance of microvascular pathology in cognitive deterioration may be partly explained by four factors. First, the heterogeneity of these lesions (including microinfarcts, focal cortical and white matter gliosis and diffuse white matter and periventricular demyelination), possibly with distinct patterns of clinical impact, should be taken into account. Second, given their diffuse nature, a systematic bilateral assessment in cortical regions known to be involved in dementia such as hippocampus and neocortical association areas is recommended (Giannakopoulos et al., 1997). Third, both microvascular (Vernooij et al., 2007) and AD neurodegenerative lesions (Snowdon, 2003) occur in cognitively intact individuals and their cognitive impact depends on the subject's ability to use his cognitive reserve (Stern, 2006). Most importantly, the concomitant presence of AD or macrovascular pathology may mask the effect of microvascular lesions mainly in very old patients with mixed pathology (Esiri et al., 1999; Neuropathology Group of the Medical Research Council Cognitive Function and Ageing, 2001). Studies of cases with pure microvascular pathology are thus mandatory to isolate the cognitive impact of these lesions in brain aging (Giannakopoulos et al., 2003; Gold et al., 2000; Gold et al., 2001).

To address this issue, we recently performed a series of prospective clinicopathological evaluations of autopsy cases aged from 63 to 100 years with various degrees of cognitive impairment but without significant neurofibrillary tangle (NFT) pathology or macrovascular lesions (Kovari et al., 2004, Gold et al., 2005). All the subjects in this autopsy sample had been clinically evaluated for the presence and severity of dementia with classification according to the clinical dementia rating scale (CDR) (Hughes et al., 1982) within 3 months of their death. The neuropathologic analysis included bilateral assessment of all types of microvascular lesions (microinfarcts, demyelination, focal cortical gliosis and white matter gliosis; Fig. 2) and lacunes. Multivariate models were used to control for the most probable confounders (i.e., the interaction between microvascular pathology, age and amyloid deposits). The results showed no significant association between CDR score and focal and diffuse gliosis. Conversely, a strong positive association was found between the severity of cortical microinfarct formation and CDR scores. This relationship persisted after adjustment for age and β-amyloid protein deposition staging in a multivariate model, the microinfarcts score explaining approximately 20% of the clinical variability (Gold et al., 2007). Lacunes and demyelination (deep white matter and periventricular) contributed equally to cognitive function and explained each 6% of clinical variability. In the multivariate analysis, however, only lacunes explained 17% of the clinical variability in cognitive function. These autopsy data confirm the role of basal ganglia and thalamic lacunes as significant independent predictors of cognitive decline in the elderly. They also provided evidence that, in disagreement with most neuroimaging studies (Longstreth et al., 1996; Roman et al., 2002; Schmidt et al., 2007; Ylikoski et al., 1993), the relationship between cognitive function and both deep white matter and periventricular demyelination was no longer significant after controlling for lacune severity in multivariate models.

3. From cognition to mood: a new dimension of vascular burden

In the last 2 decades, several lines of evidence have converged to establish a bidirectional relationship between vascular disease and depression. The concepts of "vascular depression" (Alexopoulos et al., 1997; Krishnan et al., 1997), "depression-executive dysfunction syndrome of late life" (Alexopoulos et al., 2002b) and "subcortical ischemic depression" (Krishnan et al., 2004) represent the first attempts to provide a clinicoradiologic definition of vascular burden-related mood disorders in the elderly.

Depression can be seen as a risk factor for vascular disease since it exacerbates vascular morbidity and increases mortality from vascular disease. But it may also be a consequence

of vascular lesions, mainly those affecting frontosubcortical structures. Despite some rare negative findings (Kumar et al., 1997; Lyness et al., 2000), depression is overall considered not only as a frequent co-morbidity after coronary heart disease (Frasure-Smith et al., 1995), heart failure (Williams et al., 2002) and myocardial infarction (Forrester et al., 1992; Frasure-Smith et al., 1993; Penninx et al., 2001), but also a strong determinant of mortality risk in both adult and elderly cohorts (Morris et al., 1993; Murphy et al., 1987; Robinson et al., 1983b).

But depression can also precede vascular disease. One study showed that approximately 50% of patients suffering from coronary disease and major depression had one or more prior episodes of major depression (Carney et al., 1999). A prospective study also reported that pre-existing depressive symptoms predicted the occurrence of coronary heart disease and stroke (Ohira et al., 2001) and major depression has been shown to signal increased risk for onset of type II diabetes (Eaton et al., 1996). In fact, diagnosis of depression at index evaluation is associated with an increased odds ratio (OR) for adverse outcome in type II diabetes (OR of 2.2), myocardial infarction (OR of 4.5) and stroke (OR of 2.7) (Eaton et al., 2006).

From a lesional viewpoint, macroscopic vascular lesions have been related to depressive symptoms in post-stroke depression (PSD) and WMLs have been associated with depressed mood in old age (O'Brien et al., 2000; Stewart et al., 2008; van der Flier et al., 2005; Vataja et al., 2001). Moreover, disruption of frontosubcortical circuits by subcortical lacunes and WML has been involved in the pathogenesis of vascular depression (Alexopoulos et al., 2000; Carey et al., 2008; Chui, 2007; Mayberg et al., 1988; Naarding et al., 2007; Robinson and Bloom, 1977). The next chapters summarize the main neuropathological evidence regarding the differential role of various types of vascular lesions in late-life depression.

4. Pathological substrates of post-stroke depression

Since Meyer's (1904) observations more than 100 years ago on the relationship between depression and brain injury, it has become increasingly clear that psychiatric and cognitive abnormalities following stroke are interconnected. The prevalence of depressive symptoms in the 3- to 6-month post-stroke period ranges from 29% to 36% (Hackett et al., 2005; Whyte and Mulsant, 2002). Even though prevalence seems to decrease between 12 and 24 months post-stroke, 20% of patients display depressive symptoms more than 2 years after initial stroke (Whyte et al., 2004). The occurrence of a PSD adversely affects recovery and rehabilitation (Burvill et al., 1995; Lenze et al., 2001), increases cognitive impairment (Austin et al., 2001) and suicidality (Schulz et al., 2000) and raises three-fold the risk of death over the 10 years following stroke (Everson et al., 1998). Physical disability, stroke severity, cognitive impairment, female gender and previous cerebrovascular or depressive episodes have been consistently identified as risk factors for PSD (Hackett and Anderson, 2005; Paolucci et al., 2006). Clinically, PSD seems to display a common pattern with late-life depression characterized by anxiety, loss of libido, feelings of guilt, mood lability and social isolation (Paradiso et al., 1997).

Both biological and psychosocial factors have been evoked in the pathogenesis of PSD. For the same degree of functional disability, major depression is more common after stroke compared to other chronic disorders (Folstein et al., 1977). Partisans of the biological model explain this fact by the interruption of biogenic amine pathways by ischemic lesions (Robinson and Bloom, 1977) or by the negative effect on mood of proinflammatory cytokines released as a response to acute cerebral ischemia [for review see Spalletta et al. (2006)]. In contrast, others see PSD as a psychological response to acute disability (Kotila et al., 1999; Paolucci et al., 1999; Parikh et al., 1990).

Neuroimaging studies have attempted to resolve the controversy, but led to conflicting results. Stroke location in left frontal lobe, bilateral prefrontal cortex, right occipital pole and basal ganglia has been thought to increase PSD risk (Robinson and Szetela, 1981; Robinson et al., 1983a; Robinson, 1986; Starkstein et al., 1987), but these data have been challenged (Aben et al., 2006; Berg et al., 2003; Bhogal et al., 2004; Carson et al., 2000; Leentjens et al., 2006; Nys et al., 2005; Singh et al., 1998). Methodological issues such as sampling differences between hospital-based versus community-based cohorts, doubtful neuroimaging in oldest-old cases, lack of standardization in the clinical diagnosis of depression and frequent use of univariate analysis without correction for demographic factors may partly explain these discrepancies.

We recently carried out the first neuropathological study of 95 autopsied patients with stroke (21 cases who developed first-onset depression within 2 years after index stroke and 74 patients without PSD). After controlling for multiple comparisons, age at onset of PSD and post-stroke survival period, no relationship was found between diffuse or focal macrovascular pathology in a specific brain area and PSD (Bozikas et al., 2005).

5. The neuroanatomical model of vascular depression

Paralleling the debate on the origin of PSD, the abundant literature on “vascular depression” hypothesis is increasingly emphasizing the possible role of small vessel and microvascular chronic burden in triggering depressive episodes. The idea is, however, not new. Introducing the concept of “arteriosclerotic depressive disease” in his 1905 treatise “Depressive states in old age,” Gaupp was the first to describe the possible link between the accumulation of vascular lesions and depression. In an attempt to integrate vascular lesions in a neurobiologic model of depression, the “vascular depression hypothesis” postulated the existence of vascular lesions affecting brain circuits responsible for mood regulation. Alexopoulos et al. (1997) based their assumptions on the co-morbidity of depressive syndromes with cerebrovascular lesions and with cardiovascular risk factors and on the increased incidence of depressive episodes after stroke. Simultaneously, Krishnan et al. (1997) described a similar concept based on the MRI observation of punctuate hyperintensities of the subcortical gray matter and deep and periventricular white matter in late-life depression. The presence of these lesions was associated with a significantly higher probability of being elderly, nonpsychotic and having a late-onset depression compared to patients with nonvascular depression.

Small vascular lesions might critically affect frontal and subcortical regions known to play a role in depression. For instance, lesions in three prefrontal pathways have major behavioral correlates such as executive dysfunctions (dorsolateral prefrontal circuit), apathy (anterior cingulate circuit) as well as mood lability and disinhibition (orbitofrontal circuit) (Tekin and Cummings, 2002; West, 1996). Alternatively, the diffuse accumulation of lesions exceeding a threshold in patients with neurologically silent lesions or previous stroke can lead to depression.

Early epidemiological data support the concept of vascular depression. Patients with vascular disease often have depressive symptoms and a high percentage of depressed elderly patients have vascular disease [i.e., depression is highly prevalent in patients with hypertension, coronary heart disease and vascular dementia (Fujikawa et al., 1994)]. Moreover, silent strokes are frequently found in patients with late-onset major depression, about 25% of Caucasian and 80% of Japanese elderly patients (Geroldi et al., 2003), and lesions in the thalamus and basal ganglia are also strongly related to depression [more than 40% in depressed elders compared to only 5% in age-matched controls (Fujikawa et al., 1993)]. Ischemic brain damage that affects the integrity of frontal structures and subcortical

connections is accompanied by severe deficits in planning, organization and abstraction, three common features in late-life depression (Alexopoulos, 2001). Furthermore, patients with MRI-defined subcortical lacunes and white matter hyperintensities are not only more frequently depressed than patients with other types of stroke but also more prone to develop major executive dysfunctions (51% vs. 39%) (Pohjasvaara et al., 2003).

Very recent epidemiological and MRI studies provided additional evidence in favor of the concept of vascular depression (Herrmann et al., 2008). In a longitudinal study, depression, cognition and vascular risk factors were evaluated at baseline and a mean of over 2 years later in a group of 631 Korean patients (Kim et al., 2006). Incident stroke, baseline ischemic heart disease and low high-density lipoprotein cholesterol were all associated with the development of depression, independently of cognitive changes. Interestingly, Cherr and collaborators (2007) pointed out that depression at baseline was associated with worse patency of the revascularization and greater risk for return to symptomatic disease in elderly patients operated for peripheral arterial disease. Recent MRI data revealed reduced orbitofrontal volumes and greater severity of white matter lesions in elderly patients with depression (Taylor et al., 2007). Moreover, these patients exhibited lower fractional anisotropy in the white matter of the right superior frontal gyrus (indicative of microstructural white matter abnormalities) compared to age-matched controls (Taylor et al., 2004). Interestingly, elderly patients with poor response to anti-depressive treatment also had lower fractional anisotropy in several cortico–striato–limbic areas, in comparison with depressed elders that achieved remission (Alexopoulos et al., 2008).

In contrast to the profusion of neuroimaging data, the scarceness of studies on the neuropathological correlates of mood disorders has motivated Harrison's (2002) statement that "if schizophrenia has been a neuropathological graveyard, primary mood disorders have remained an uncharted wilderness." However, given the accumulation of radiological evidence for structural brain abnormalities in mood disorders, some groups have searched for postmortem histological and cellular correlates of MRI volumetric abnormalities. Although a homogeneous pathology within the cerebral cortex is improbable, given the negative results in sensory cortices (Bouras et al., 2001; Ongur et al., 1998), some positive data should be mentioned. For example, histopathological analyses of the pregenual anterior cingulate cortex (Cotter et al., 2001), dorsal anterolateral prefrontal cortex (Cotter et al., 2002; Uranova et al., 2004) and amygdala (Bowley et al., 2002; Hamidi et al., 2004) have shown abnormal reductions in glial (mainly oligodendrocyte) cell counts, neuron size and/or synaptic proteins (Rajkowska, 2000). Consistent with a global stress–vulnerability etiopathogenic model, elevated glucocorticoid secretion and glutamatergic transmission during depressive and manic episodes may lead to the loss of glial cells (Drevets et al., 2008). However, bidirectional causality cannot be excluded given the growing body of evidence supporting a central role of glial cells in regulating central nervous system energy homeostasis, glutamate concentrations, trophic factor release and synapse development and maintenance (Davidson et al., 2002).

Clinico-pathological studies in late-life depression are still lacking with the exception of the pioneer work of Thomas et al. (2001). In order to clarify the relationship between the radiologically observed lesions and their pathological substrate, these authors assessed AD, Lewy body and vascular pathology in 20 patients with a history of major depression and 20 controls. An increased frequency of cerebrovascular atheromatous lesions in cerebral arteries was found in the depressed group. In contrast, there was no evidence supporting an increase of the global vascular, AD and Lewy body burden in late-life depression.

6. Small vascular and microvascular lesions in brain aging: impact on mood regulation

In their recent work, Brodaty and colleagues (2007) recommended to move from single ischemic events to chronic vascular burden stating that “depression after stroke is related to cumulative vascular brain pathology rather than to side and severity of single strokes.” This affirmation clearly reminds that of Snowdon and collaborators (1997) in the Nun study about the impact of small vascular lesions on cognition: “It is possible that our findings have less to do with the location of the infarct and more to do with the disease process that produced the lacunar infarcts.” According to this perspective, the lasting accumulation of microvascular lesions may be associated with lower rate of spontaneous recovery and higher risk of chronic depression in PSD.

Given the limited information provided by structural neuroimaging, *in vivo* studies are not the most appropriate to assess the impact of small vascular and microvascular lesions on mood. We recently performed a detailed analysis of lacunes and microvascular lesions in 41 consecutively autopsied stroke cases. Twenty patients developed PSD and 21 did not. Basal ganglia, thalamic and deep white matter lacunes were the only significant neuropathological correlates of PSD. This was the case for neither CMI nor deep white matter and periventricular demyelination. In fact, the combined lacune score (thalamic+basal ganglia +deep white matter) was strongly related to PSD and explained 25% of the variability of this occurrence (Santos et al., 2009 Santos et al., in press). These first neuropathological data support the idea that lacunes in basal ganglia and thalamic nuclei can contribute to the development of depressive symptoms after stroke possibly by disrupting biogenic amine-containing axons ascending from brainstem to cerebral cortex thought to be involved in mood regulation (Robinson and Bloom, 1977; Mayberg et al., 1988).

7. Vascular burden and mood disorders: the molecular mechanisms

An increasing body of experimental data strengthens the hypothesis that AD pathology and cerebrovascular disease may have a synergistic impact on the emergence of cognitive and mood pathologies in old age. The coexistence of AD and vascular lesions in old age already addressed in the previous chapters as well as the presence of common risk factors for both AD and VaD represent the first lines of evidence supporting this idea. In addition, cerebral amyloid angiopathy (CAA) that affects most AD patients and almost 30% of cognitively intact controls is a significant risk factor for cerebral infarction and ischemic leucoencephalopathy independently of apolipoprotein E (ApoE) ε4 genotype (Olichney et al., 1995; Olichney et al., 2000). This distinction is relevant since this genetic risk factor for sporadic AD (Chalmers et al., 2003; Love et al., 2009) is closely related to lipid profile and vascular disease (Mahley, 1988) both within AD and non-AD samples (Greenberg et al., 1995; Olichney et al., 1996; Premkumar et al., 1996) but also to myelin formation and neuronal regeneration (Boyles et al., 1989). Moreover, MRI evidence of subacute ischemic infarction has been observed in 15% of patients suffering from advanced CAA independently of conventional vascular risk factors (Kimberly et al., 2009).

The bidirectional link between neurodegeneration and late-life depression is still unclear. A positive relationship exists between the presence of the ApoE ε4 allele and an increased risk of late-life depression (Rigaud et al., 2001) even after controlling for cardiovascular conditions and lipid profile (Yen et al., 2007). Moreover, Rapp and colleagues (2006) demonstrated that patients with neuropathologically confirmed AD who have a history of major depression before the onset of dementia exhibit more pronounced neurodegenerative changes (neuritic plaques and neurofibrillary tangles) in the hippocampus than AD patients without life history of depression. Longitudinal follow-up of elderly cohorts with the newly

developed *in vivo* protein imaging of senile plaques and neurofibrillary tangles will certainly help to clarify this issue (Kumar et al., 2008).

Unlike AD pathology, the accumulation of cardiovascular risk factors constitutes a widely accepted vulnerability background for late-life depression (Isingrini et al., 2009; Kamphuis et al., 2009; Kim et al., 2009; Lu et al., 2009; Muhtz et al., 2009; Smith et al., 2009). Vascular disease and depression share both environmental (e.g., smoking, poor diet and reduced exercise) and genetic risk factors (e.g., polymorphism of the 5–10-methylenetetrahydrofolate reductase gene—MTHFR C677T). However, even after controlling for some of these factors, the association of depression with coronary heart disease persists (Rugulies, 2002). The presence of clinical depression may in turn induce a "stress burden" (Kopp and Rethelyi, 2004) that will have a negative impact on cardiovascular parameters closing a pathogenic circle that can possibly explain why late-onset depression is associated with a poor outcome and has been seen as a prodromal state of dementia (Korczyn and Halperin, 2009; Thomas and O'Brien, 2008).

Three main etiopathogenetic pathways have consistently been implicated in both cardiovascular pathologies and late-life depression: homocysteine regulation, endothelial dysfunction and inflammation. Homocysteine is a sulfur-containing amino acid derived from the ingested essential amino acid methionine through demethylation (Hankey, 2006). It may be toxic to neurons and blood vessels through the induction of oxidative stress, DNA strand breakage and apoptosis. Its catabolic pathway includes remethylation to methionine using as cofactors B12 vitamin and folates, whereas its clearance depends on transulfuration to cysteine and glutathione requiring vitamins B6 and B12. Elevated levels of homocysteine are usually considered as indirect indicator of Vitamin B deficiency (Folstein et al., 2007). Hyperhomocysteinemia has been associated with carotid stenosis (Sacco, 2001; Streifler et al., 2001), AD (Seshadri et al., 2002) and depression (Bell et al., 1991; Bottiglieri et al., 2000), although negative results also exist (Morris et al., 2003; Seshadri et al., 2002). Almeida et al. (2007) have recently investigated the link between prevalent late-life depression and several cardiovascular risk factors in 4204 elderly individuals. Plasma total homocysteine (tHcy) had the highest population attributed fraction (15% of cases could be attributed to tHcy, assuming the relation to be causal). Higher concentrations of tHcy increase the risk of depression whereas lowering tHcy by 0.19 mg/L could reduce the depression risk by 20% (Almeida et al., 2008). Despite these positive data, longitudinal studies are warranted to explore whether there is a causal relationship between hyperhomocysteinemia and late-life depression. One among the possible mechanisms involved in the vascular toxicity of hyperhomocysteinemia is oxidative stress-related endothelial dysfunction (Welch and Loscalzo, 1998).

Endothelial dysfunction is defined as the loss of the capacity of nitric oxide (NO) to induce vasodilatation, but the term is also used to describe the unbalance of other relaxing and contracting endothelium-derived factors. Several methods have been used to assess the level of endothelial dysfunction, including flow-mediated vasodilatation (FMD) (Celermajer et al., 1992) and pulse wave velocity (PWV) (Naka et al., 2006). Impaired FMD was observed in adults and elders with history of moderate to severe depression (Broadley et al., 2002; Rajagopalan et al., 2001) and PWV shows significant changes in patients suffering from unipolar and bipolar depression (Rybakowski et al., 2006). In line with the vascular depression hypothesis, increased intima-media thickness (IMT) is associated with depressive symptoms (Kim et al., 2006; Sherwood et al., 2005), executive dysfunctions (Smith et al., 2007) and WML severity (Chen et al., 2006). Later onset of first depressive episode and fewer previous depressive episodes have been described in this sample independently of cardiovascular co-morbidities (Smith et al., 2009). Interestingly, a recent study highlights the bilateral relationship between endothelial dysfunction and depression by demonstrating

that patients with normal coronary artery and depressive symptoms show significant vasoconstriction in response to acetylcholine infusion compared to age-matched controls (Kim et al., 2009). If further studies confirm these data in community-based cohorts, FMD, PWV and IMT could be used to assert vulnerability to late-onset depression.

The impairment of endothelial function may also be a final consequence of the inflammatory phenomena that occur in elderly patients with depression (Myers et al., 1994). The link between the immune system and atherosclerosis was first established by the pioneer work of Virchow and Rokitansky. Later on, the role of immunological factors in arterial lipid deposition as well as proliferation and migration of smooth muscle cells came to light and inflammatory processes were seen as key determinants of coronary disease progression (Kop and Gottdiener, 2005). For example, interleukin-6 has been implicated in the progress of coronary heart disease (Yudkin et al., 2000) and its administration can produce endothelial dysfunction (Craddock and Thomas, 2006). The immunological correlates of emotional distress and depression have been reliably investigated (Dantzer et al., 2008; Herbert and Cohen, 1993b; Irwin and Miller, 2007; Maes, 1995; Segerstrom and Miller, 2004; van West and Maes, 1999; Zorrilla et al., 2001), although a causal relationship is not widely accepted (Janszky et al., 2005, Vaccarino, 2008; Whooley et al., 2007). Overall, depression is associated with activation of the inflammatory response, including elevation of peripheral leucocytes (Maes, 1999; Maes et al., 1999), acute-phase proteins such as C-reactive protein (CRP) (O'Brien et al., 2006) and pro-inflammatory cytokine production [e.g., interleukin (IL)-1β, IL-2, IL-6 and tumor necrosis factor alpha (TNF-α)] (O'Brien et al., 2007; Thomas et al., 2005) as well as with a decrease of the proliferative response of lymphocytes to mitogenic stimulation (Herbert and Cohen, 1993a). Post-mortem studies have documented higher levels of pro-inflammatory factors such as vascular cellular adhesion molecules (VCAMs) and intercellular adhesion molecules (ICAMs) in the dorsolateral prefrontal cortex of patients with late-onset depression suggesting that inflammatory activation may be one among the possible causal pathways of vascular depression (Thomas et al., 2000; Thomas et al., 2002). However, when controlling for confounding factors such as adiposity, alcohol and smoking the association between proinflammatory factors and depression did not consistently persist (Kop et al., 2002; Tiemeier et al., 2003).

Both the bidirectional causality described above and the interdependence of homocysteine, endothelial dysfunction and inflammation as possible etiopathogenic bridges between vascular disease and depression point to a multifactorial stress–vulnerability model that can be mediated by the activation of the hypothalamo–pituitary–adrenal (HPA) system. This possibility is consistent with the recent "glucocorticoid cascade hypothesis" of chronic stress that postulates the presence of progressive hippocampal damage due to the neurotoxic effect of HPA up-regulation (Bao et al., 2008; Jacobs et al., 2000; Wang et al., 2008).

The relationship between vascular burden and late-life depression may also be explained by the activation of alternative mechanisms such as modifications in platelet function (Bruce and Musselman, 2005; Ziegelstein et al., 2009), abnormal autonomic tone (Carney et al., 2005; Veith et al., 1994) and dietary habits such as low intake of n-3 long chain fatty acids (Riediger et al., 2009). Although not consensual (Ziegelstein et al., 2009), this perspective is corroborated by several recent articles indicating that the association of depression and cardiovascular mortality may reflect a cumulative risk related to the subjective health status (Hamer et al., 2007; Kamphuis et al., 2009; Lu et al., 2009; Mast et al., 2008; Muhtz et al., 2009).

8. Conclusions

Structural and functional neuroimaging have certainly offered new perspectives in the domain of aging research, even though the initial expectations of a direct lesion–syndrome relationship are far from being fulfilled. Despite strong epidemiological evidence supporting a close relationship between vascular disease and mood dysregulation in old age (Alexopoulos et al., 2002a; Alexopoulos, 2003; Fuhrer et al., 2003; Korczyn and Halperin, 2009; Reeves and Rose, 2006), neuroimaging studies focusing on acute ischemic events failed to identify an unequivocal structural background for late-life depression. The concept of vascular depression was the first to suggest a shift of focus proposing that the chronic accumulation of small vascular and microvascular lesions is not a benign aging-related phenomenon. Concomitantly, systematic neuropathological analyses showed that thalamic and basal ganglia lacunes and cortical microinfarcts have a deleterious impact on cognition confirming further the relevance of these lesions in brain aging. More recently, a first autopsy study indicated that the severity of subcortical lacunes is also a strong determinant of PSD. A chronic accumulation of small vessel pathology and microvascular lesions, related to genetic predisposition, behavioral patterns and medical and psychiatric co-morbidities, might thus constitute a common platform in the development of cognitive impairment and mood disorders in elders. From a neurobiological viewpoint, two recent findings aim to provide a molecular background to this hypothesis. Firstly, although still controversial (Navailles et al., 2008), the conceptually attractive “neurogenesis and depression theory” gathers data from human and animal studies and postulates that vascular stress-induced decrease of neurogenesis in hippocampal dentate gyrus may precipitate depressive episodes (Jacobs et al., 2000), supporting the key role of hippocampus not only in cognitive but also affective processes in the elderly. Secondly, one of the most recent theorizations of depression points to the role of behavioral and genetic patterns in determining plasma homocysteine levels and, interestingly, hyperhomocysteinemia has been associated with vascular disease, depression, AD and cognitive impairment (Folstein et al., 2007). This new vascular burden/vulnerability model constitutes a less deterministic perspective that can provide an interesting conceptual framework for the very active research on emotional regulation in old age.

Acknowledgments

This work was supported by NIH grants AG05138 and AG02219 (P.R.H.) and the Foundation Jérôme Tissières (P.G.).

References

Aben I, Lodder J, Honig A, Lousberg R, Boreas A, Verhey F. Focal or generalized vascular brain damage and vulnerability to depression after stroke: a 1-year prospective follow-up study. Int Psychogeriatr. 2006; 18:19–35. [PubMed: 16403249]

Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. ‘Vascular depression’ hypothesis. Arch Gen Psychiatry. 1997; 54:915–922. [PubMed: 9337771]

Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, Sirey JA, Hull J. Executive dysfunction and long-term outcomes of geriatric depression. Arch Gen Psychiatry. 2000; 57:285–290. [PubMed: 10711915]

Alexopoulos GS. New concepts for prevention and treatment of late-life depression. Am J Psychiatry. 2001; 158:835–838. [PubMed: 11384886]

Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. Biol Psychiatry. 2002a; 52:543–558. [PubMed: 12361668]

Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML. Clinical presentation of the "depression-executive dysfunction syndrome" of late life. Am J Geriatr Psychiatry. 2002b; 10:98–106. [PubMed: 11790640]

Alexopoulos GS. Vascular disease, depression, and dementia. J Am Geriatr Soc. 2003; 51:1178–1180. [PubMed: 12890087]

Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, Lim KO, Hoptman MJ. Microstructural white matter abnormalities and remission of geriatric depression. Am J Psychiatry. 2008; 165:238–244. [PubMed: 18172016]

Almeida OP, Flicker L, Norman P, Hankey GJ, Vasikaran S, van Bockxmeer FM, Jamrozik K. Association of cardiovascular risk factors and disease with depression in later life. Am J Geriatr Psychiatry. 2007; 15:506–513. [PubMed: 17158633]

Almeida OP, McCaul K, Hankey GJ, Norman P, Jamrozik K, Flicker L. Homocysteine and depression in later life. Arch Gen Psychiatry. 2008; 65:1286–1294. [PubMed: 18981340]

Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry. 2001; 178:200–206. [PubMed: 11230029]

Bao AM, Meynen G, Swaab DF. The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev. 2008; 57:531–553. [PubMed: 17524488]

Bell IR, Edman JS, Morrow FD, Marby DW, Mirages S, Perrone G, Kayne HL, Cole JO. B complex vitamin patterns in geriatric and young adult inpatients with major depression. J Am Geriatr Soc. 1991; 39:252–257. [PubMed: 2005338]

Berg A, Palomaki H, Lehtihalmes M, Lonnqvist J, Kaste M. Poststroke depression: an 18-month follow-up. Stroke. 2003; 34:138–143. [PubMed: 12511765]

Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. Stroke. 2004; 35:794–802. [PubMed: 14963278]

Bigler ED, Kerr B, Victoroff J, Tate DF, Breitner JC. White matter lesions, quantitative magnetic resonance imaging, and dementia. Alzheimer Dis Assoc Disord. 2002; 16:161–170. [PubMed: 12218647]

Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. J Neurol Neurosurg Psychiatry. 2000; 69:228–232. [PubMed: 10896698]

Bouras C, Kovari E, Hof PR, Riederer BM, Giannakopoulos P. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. Acta Neuropathol. 2001; 102:373–379. [PubMed: 11603813]

Bowley MP, Drevets WC, Ongur D, Price JL. Low glial numbers in the amygdala in major depressive disorder. Biol Psychiatry. 2002; 52:404–412. [PubMed: 12242056]

Boyles JK, Zoellner CD, Anderson LJ, Kosik LM, Pitas RE, Weisgraber KH, Hui DY, Mahley RW, Gebicke-Haerter PJ, Ignatius MJ, et al. A role for apolipoprotein E, apolipoprotein A-I, and low density lipoprotein receptors in cholesterol transport during regeneration and remyelination of the rat sciatic nerve. J Clin Invest. 1989; 83:1015–1031. [PubMed: 2493483]

Bozikas VP, Gold G, Kovari E, Herrmann F, Karavatos A, Giannakopoulos P, Bouras C. Pathological correlates of poststroke depression in elderly patients. Am J Geriatr Psychiatry. 2005; 13:166–169. [PubMed: 15703326]

Bracco L, Campani D, Baratti E, Lippi A, Inzitari D, Pracucci G, Amaducci L. Relation between MRI features and dementia in cerebrovascular disease patients with leukoaraiosis: a longitudinal study. J Neurol Sci. 1993; 120:131–136. [PubMed: 8138800]

Bracco L, Piccini C, Moretti M, Mascalchi M, Sforza A, Nacmias B, Cellini E, Bagnoli S, Sorbi S. Alzheimer's disease: role of size and location of white matter changes in determining cognitive deficits. Dement Geriatr Cogn Disord. 2005; 20:358–366. [PubMed: 16192726]

Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, van Harskamp F, Tanghe HL, de Jong PT, van Gijn J, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology. 1994; 44:1246–1252. [PubMed: 8035924]

Broadley AJ, Korszun A, Jones CJ, Frenneaux MP. Arterial endothelial function is impaired in treated depression. Heart. 2002; 88:521–523. [PubMed: 12381649]

Brodaty H, Withall A, Altendorf A, Sachdev PS. Rates of depression at 3 and 15 months poststroke and their relationship with cognitive decline: the Sydney Stroke Study. Am J Geriatr Psychiatry. 2007; 15:477–486. [PubMed: 17545448]

Bronge L, Bogdanovic N, Wahlund LO. Postmortem MRI and histopathology of white matter changes in Alzheimer brains. A quantitative, comparative study. Dement Geriatr Cogn Disord. 2002; 13:205–212. [PubMed: 12006730]

Bruce EC, Musselman DL. Depression, alterations in platelet function, and ischemic heart disease. Psychosom Med. 2005; 67 (Suppl 1):S34–S36. [PubMed: 15953798]

Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Prevalence of depression after stroke: the Perth Community Stroke Study. Br J Psychiatry. 1995; 166:320–327. [PubMed: 7788123]

Carey CL, Kramer JH, Josephson SA, Mungas D, Reed BR, Schuff N, Weiner MW, Chui HC. Subcortical lacunes are associated with executive dysfunction in cognitively normal elderly. Stroke. 2008; 39:397–402. [PubMed: 18096844]

Carney RM, Freedland KE, Veith RC, Jaffe AS. Can treating depression reduce mortality after an acute myocardial infarction? Psychosom Med. 1999; 61:666–675. [PubMed: 10511015]

Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Domitrovich PP, Jaffe AS. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. Arch Intern Med. 2005; 165:1486–1491. [PubMed: 16009863]

Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, Sharpe M. Depression after stroke and lesion location: a systematic review. Lancet. 2000; 356:122–126. [PubMed: 10963248]

Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992; 340:1111–1115. [PubMed: 1359209]

Chalmers K, Wilcock GK, Love S. APOE epsilon 4 influences the pathological phenotype of Alzheimer's disease by favouring cerebrovascular over parenchymal accumulation of A beta protein. Neuropathol Appl Neurobiol. 2003; 29:231–238. [PubMed: 12787320]

Chen CS, Chen CC, Kuo YT, Chiang IC, Ko CH, Lin HF. Carotid intima-media thickness in late-onset major depressive disorder. Int J Geriatr Psychiatry. 2006; 21:36–42. [PubMed: 16323250]

Cherr GS, Wang J, Zimmerman PM, Dosluoglu HH. Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization. J Vasc Surg. 2007; 45:744–750. [PubMed: 17303367]

Chui HC. Subcortical ischemic vascular dementia. Neurol Clin. 2007; 25:717–740. vi. [PubMed: 17659187]

Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Arch Gen Psychiatry. 2001; 58:545–553. [PubMed: 11386983]

Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. Cereb Cortex. 2002; 12:386–394. [PubMed: 11884354]

Craddock D, Thomas A. Cytokines and late-life depression. Essent Psychopharmacol. 2006; 7:42–52. [PubMed: 16989292]

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008; 9:46–56. [PubMed: 18073775]

Davidson RJ, Lewis DA, Alloy LB, Amaral DG, Bush G, Cohen JD, Drevets WC, Farah MJ, Kagan J, McClelland JL, Nolen-Hoeksema S, Peterson BS. Neural and behavioral substrates of mood and mood regulation. Biol Psychiatry. 2002; 52:478–502. [PubMed: 12361665]

de Groot JC, de Leeuw FE, Oudkerk M, Van Gijn J, Hofman A, Jolles J, Breteler MM. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol. 2002; 52:335–341. [PubMed: 12205646]

Del Ser T, Bermejo F, Portera A, Arredondo JM, Bouras C, Constantinidis J. Vascular dementia. A clinicopathological study. J Neurol Sci. 1990; 96:1–17. [PubMed: 2351984]

Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008; 213:93–118. [PubMed: 18704495]

Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population-based study. Diabetes Care. 1996; 19:1097–1102. [PubMed: 8886555]

Eaton, WW.; Fogel, J.; Armenian, HK. Medical and psychiatric comorbidity over lifespan. American Psychiatric Publishing; Washington: 2006. The consequences of psychopathology in the Baltimore epidemiologic catchment area follow-up.

Enzinger C, Fazekas F, Ropele S, Schmidt R. Progression of cerebral white matter lesions—clinical and radiological considerations. J Neurol Sci. 2007; 257:5–10. [PubMed: 17321549]

Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. J Neurol Neurosurg Psychiatry. 1997; 63:749–753. [PubMed: 9416809]

Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet. 1999; 354:919–920. [PubMed: 10489957]

Esiri MM. Which vascular lesions are of importance in vascular dementia? Ann NY Acad Sci. 2000; 903:239–243. [PubMed: 10818512]

Everson SA, Roberts RE, Goldberg DE, Kaplan GA. Depressive symptoms and increased risk of stroke mortality over a 29-year period. Arch Intern Med. 1998; 158:1133–1138. [PubMed: 9605786]

Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993; 43:1683–1689. [PubMed: 8414012]

Folstein M, Liu T, Peter I, Buell J, Arsenault L, Scott T, Qiu WW. The homocysteine hypothesis of depression. Am J Psychiatry. 2007; 164:861–867. [PubMed: 17541043]

Folstein MF, Maiberger R, McHugh PR. Mood disorder as a specific complication of stroke. J Neurol Neurosurg Psychiatry. 1977; 40:1018–1020. [PubMed: 591971]

Forrester AW, Lipsey JR, Teitelbaum ML, DePaulo JR, Andrzejewski PL. Depression following myocardial infarction. Int J Psychiatry Med. 1992; 22:33–46. [PubMed: 1577547]

Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. JAMA. 1993; 270:1819–1825. [PubMed: 8411525]

Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation. 1995; 91:999–1005. [PubMed: 7531624]

Fuhrer R, Dufouil C, Dartigues JF. Exploring sex differences in the relationship between depressive symptoms and dementia incidence: prospective results from the PAQUID Study. J Am Geriatr Soc. 2003; 51:1055–1063. [PubMed: 12890066]

Fujikawa T, Yamawaki S, Touhouda Y. Incidence of silent cerebral infarction in patients with major depression. Stroke. 1993; 24:1631–1634. [PubMed: 8236334]

Fujikawa T, Yamawaki S, Touhouda Y. Background factors and clinical symptoms of major depression with silent cerebral infarction. Stroke. 1994; 25:798–801. [PubMed: 8160223]

Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HB. Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. Lancet. 2000; 356:628–634. [PubMed: 10968435]

Geroldi C, Ferrucci L, Bandinelli S, Cavazzini C, Zanetti O, Guralnik JM, Frisoni GB. Mild cognitive deterioration with subcortical features: prevalence, clinical characteristics, and association with cardiovascular risk factors in community-dwelling older persons (The InCHIANTI Study). J Am Geriatr Soc. 2003; 51:1064–1071. [PubMed: 12890067]

Giannakopoulos P, Hof PR, Michel JP, Guimon J, Bouras C. Cerebral cortex pathology in aging and Alzheimer's disease: a quantitative survey of large hospital-based geriatric and psychiatric cohorts. Brain Res Brain Res Rev. 1997; 25:217–245. [PubMed: 9403139]

Giannakopoulos P, Herrmann FR, Bussiere T, Bouras C, Kovari E, Perl DP, Morrison JH, Gold G, Hof PR. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology. 2003; 60:1495–1500. [PubMed: 12743238]

Gold G, Bouras C, Kovari E, Canuto A, Glaria BG, Malky A, Hof PR, Michel JP, Giannakopoulos P. Clinical validity of Braak neuropathological staging in the oldest-old. Acta Neuropathol (Berl). 2000; 99:579–582. discussion 583–4. [PubMed: 10805104]

Gold G, Kovari E, Corte G, Herrmann FR, Canuto A, Bussiere T, Hof PR, Bouras C, Giannakopoulos P. Clinical validity of A beta-protein deposition staging in brain aging and Alzheimer disease. J Neuropathol Exp Neurol. 2001; 60:946–952. [PubMed: 11589425]

Gold G, Kövari E, Herrmann FR, Canuto A, Hof PR, Michel JP, Bouras C, Giannakopoulos P. Cognitive consequences of thalamic, basal ganglia, and deep white matter lacunes in brain aging and dementia. Stroke. 2005; 36:1184–1188. [PubMed: 15891000]

Gold G, Giannakopoulos P, Herrmann FR, Bouras C, Kovari E. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain. 2007; 130:2830–2836. [PubMed: 17878206]

Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol. 1995; 38:254–259. [PubMed: 7654074]

Gurol ME, Irizarry MC, Smith EE, Raju S, Diaz-Arrastia R, Bottiglieri T, Rosand J, Growdon JH, Greenberg SM. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. Neurology. 2006; 66:23–29. [PubMed: 16401840]

Guttmann CR, Jolesz FA, Kikinis R, Killiany RJ, Moss MB, Sandor T, Albert MS. White matter changes with normal aging. Neurology. 1998; 50:972–978. [PubMed: 9566381]

Hachinski VD, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet. 1974; 2:207–210. [PubMed: 4135618]

Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005; 36:2296–2301. [PubMed: 16179565]

Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. Stroke. 2005; 36:1330–1340. [PubMed: 15879342]

Hamer M, Tanaka G, Okamura H, Tsuda A, Steptoe A. The effects of depressive symptoms on cardiovascular and catecholamine responses to the induction of depressive mood. Biol Psychol. 2007; 74:20–25. [PubMed: 16860921]

Hamidi M, Drevets WC, Price JL. Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. Biol Psychiatry. 2004; 55:563–569. [PubMed: 15013824]

Hankey GJ. Is plasma homocysteine a modifiable risk factor for stroke? Nat Clin Pract Neurol. 2006; 2:26–33. [PubMed: 16932518]

Harrison PJ. The neuropathology of primary mood disorder. Brain. 2002; 125:1428–1449. [PubMed: 12076995]

Hentschel F, Damian M, Krumm B, Froelich L. White matter lesions—age-adjusted values for cognitively healthy and demented subjects. Acta Neurol Scand. 2007; 115:174–180. [PubMed: 17295712]

Herbert TB, Cohen S. Depression and immunity: a meta-analytic review. Psychol Bull. 1993a; 113:472–486. [PubMed: 8316610]

Herbert TB, Cohen S. Stress and immunity in humans: a meta-analytic review. Psychosom Med. 1993b; 55:364–379. [PubMed: 8416086]

Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. J Neurol Neurosurg Psychiatry. 2008; 79:619–624. [PubMed: 17717021]

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Brit J Psychiat. 1982; 140:566–572.

Irwin MR, Miller AH. Depressive disorders and immunity: 20 yearsof progress and discovery. Brain Behav Immun. 2007; 21:374–383. [PubMed: 17360153]

Isingrini E, Desmidt T, Belzung C, Camus V. Endothelial dysfunction: a potential therapeutic target for geriatric depression and brain amyloid deposition in Alzheimer's disease? Curr Opin Investig Drugs. 2009; 10:46–55.

Jacobs BL, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry. 2000; 5:262–269. [PubMed: 10889528]

Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW, Ellis WG, Zarow C, Mungas D, Reed BR, Kramer JH, Schuff N, DeCarli C, Chui HC. Neuropathological basis of magnetic resonance images in aging and dementia. Ann Neurol. 2008; 63:72–80. [PubMed: 18157909]

Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. Brain Behav Immun. 2005; 19:555–563. [PubMed: 16214026]

Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. Stroke. 2004; 35:1857–1861. [PubMed: 15218158]

Jellinger KA, Attems J. Incidence of cerebrovascular lesions in Alzheimer's disease: a postmortem study. Acta Neuropathol (Berl). 2003; 105:14–17. [PubMed: 12471455]

Kalaria RN, Kenny RA, Ballard CG, Perry R, Ince P, Polvikoski T. Towards defining the neuropathological substrates of vascular dementia. J Neurol Sci. 2004; 226:75–80. [PubMed: 15537525]

Kamphuis MH, Geerlings MI, Giampaoli S, Nissinen A, Grobbee DE, Kromhout D. The association of depression with cardiovascular mortality is partly explained by health status. The FINE Study. J Affect Disord. 2009; 114:184–192. [PubMed: 18694600]

Kim JH, Kim JW, Ko YH, Choi CU, Na JO, Kim EJ, Rha SW, Park CG, Seo HS, Oh DJ. Coronary endothelial dysfunction associated with a depressive mood in patients with atypical angina but angiographically normal coronary artery. Int J Cardiol. 2009 (Electronic publication ahead of print).

Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Vascular risk factors and incident late-life depression in a Korean population. Br J Psychiatry. 2006; 189:26–30. [PubMed: 16816302]

Kimberly WT, Gilson A, Rost NS, Rosand J, Viswanathan A, Smith EE, Greenberg SM. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. Neurology. 2009; 72:1230–1235. [PubMed: 19349602]

Kop WJ, Gottdiener JS, Tangen CM, Fried LP, McBurnie MA, Walston J, Newman A, Hirsch C, Tracy RP. Inflammation and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. Am J Cardiol. 2002; 89:419–424. [PubMed: 11835923]

Kop WJ, Gottdiener JS. The role of immune system parameters in the relationship between depression and coronary artery disease. Psychosom Med. 2005; 67 (Suppl 1):S37–S41. [PubMed: 15953799]

Kopp MS, Rethelyi J. Where psychology meets physiology: chronic stress and premature mortality—the Central–Eastern European health paradox. Brain Res Bull. 2004; 62:351–367. [PubMed: 15168900]

Korczyn AD, Halperin I. Depression and dementia. J Neurol Sci. 2009; 283:139–142. [PubMed: 19345960]

Kotila M, Numminen H, Waltimo O, Kaste M. Post-stroke depression and functional recovery in a population-based stroke register. The Finnstroke study. Eur J Neurol. 1999; 6:309–312. [PubMed: 10210911]

Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Michel JP, Bouras C, Giannakopoulos P. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. Stroke. 2004; 35:410–414. [PubMed: 14707236]

Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997; 154:497–501. [PubMed: 9090336]

Krishnan KR, Taylor WD, McQuoid DR, MacFall JR, Payne ME, Provenzale JM, Steffens DC. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry. 2004; 55:390–397. [PubMed: 14960292]

Kumar A, Miller D, Ewbank D, Yousem D, Newberg A, Samuels S, Cowell P, Gottlieb G. Quantitative anatomic measures and comorbid medical illness in late-life major depression. Am J Geriatr Psychiatry. 1997; 5:15–25. [PubMed: 9169241]

Kumar A, Ajilore O, Kepe V, Barrio JR, Small G. Mood, cognition and in vivo protein imaging: the emerging nexus in clinical neuroscience. Int J Geriatr Psychiatry. 2008; 23:555–563. [PubMed: 18044797]

Lee JH, Olichney JM, Hansen LA, Hofstetter CR, Thal LJ. Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer disease. Arch Neurol. 2000; 57:1474–1479. [PubMed: 11030800]

Leentjens AF, Aben I, Lodder J, Verhey FR. General and disease-specific risk factors for depression after ischemic stroke: a two-step Cox regression analysis. Int Psychogeriatr. 2006; 18:739–748. [PubMed: 16805924]

Lenze EJ, Rogers JC, Martire LM, Mulsant BH, Rollman BL, Dew MA, Schulz R, Reynolds CF III. The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. Am J Geriatr Psychiatry. 2001; 9:113–135. [PubMed: 11316616]

Loeb C. The history of vascular dementia. J Hist Neurosci. 1995; 4:121–126. [PubMed: 11619018]

Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke. 1996; 27:1274–1282. [PubMed: 8711786]

Love S, Miners S, Palmer J, Chalmers K, Kehoe P. Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy. Front Biosci. 2009; 14:4778–4792. [PubMed: 19273389]

Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS ONE. 2009:e4144, 4. [PubMed: 19127292]

Lyness JM, King DA, Conwell Y, Cox C, Caine ED. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. Am J Psychiatry. 2000; 157:1499–1501. [PubMed: 10964868]

Maes M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry. 1995; 19:11–38. [PubMed: 7708925]

Maes M. Major depression and activation of the inflammatory response system. Adv Exp Med Biol. 1999; 461:25–46. [PubMed: 10442165]

Maes M, Van Bockstaele DR, Gastel A, Song C, Schotte C, Neels H, DeMeester I, Scharpe S, Janca A. The effects of psychological stress on leukocyte subset distribution in humans: evidence of immune activation. Neuropsychobiology. 1999; 39:1–9. [PubMed: 9892853]

Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science. 1988; 240:622–630. [PubMed: 3283935]

Mast BT, Miles T, Penninx BW, Yaffe K, Rosano C, Satterfield S, Ayonayon HN, Harris T, Simonsick EM. Vascular disease and future risk of depressive symptomatology in older adults: findings from the Health, Aging, and Body Composition study. Biol Psychiatry. 2008; 64:320–326. [PubMed: 18367153]

Mayberg HS, Robinson RG, Wong DF, Parikh R, Bolduc P, Starkstein SE, Price T, Dannals RF, Links JM, Wilson AA, et al. PET imaging of cortical S2 serotonin receptors after stroke: lateralized changes and relationship to depression. Am J Psychiatry. 1988; 145:937–943. [PubMed: 3394877]

Meyer A. The anatomical facts and clinical varieties of traumatic insanity. Am J Insanity. 1904; 60:373–442.

Morris MS, Fava M, Jacques PF, Selhub J, Rosenberg IH. Depression and folate status in the US population. Psychother Psychosom. 2003; 72:80–87. [PubMed: 12601225]

Morris PL, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of depression with 10-year poststroke mortality. Am J Psychiatry. 1993; 150:124–129. [PubMed: 8417554]

Neuropathology Group of the Medical Research Council Cognitive Function and Ageing. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet. 2001; 357:169–175. [PubMed: 11213093]

Muhtz C, Zyriax BC, Klahn T, Windler E, Otte C. Depressive symptoms and metabolic risk: effects of cortisol and gender. Psychoneuroendocrinology. 2009; 34:1004–1011. [PubMed: 19278789]

Munoz DG, Hastak SM, Harper B, Lee D, Hachinski VC. Pathologic correlates of increased signals of the centrum ovale on magnetic resonance imaging. Arch Neurol. 1993; 50:492–497. [PubMed: 8489405]

Murphy JM, Monson RR, Olivier DC, Sobol AM, Leighton AH. Affective disorders and mortality. A general population study. Arch Gen Psychiatry. 1987; 44:473–480. [PubMed: 3555383]

Myers PR, Parker JL, Tanner MA, Adams HR. Effects of cytokines tumor necrosis factor alpha and interleukin 1 beta on endotoxin-mediated inhibition of endothelium-derived relaxing factor bioactivity and nitric oxide production in vascular endothelium. Shock. 1994; 1:73–78. [PubMed: 7743332]

Naarding P, de Koning I, van Kooten F, Janzing JG, Beekman AT, Koudstaal PJ. Post-stroke dementia and depression: frontosubcortical dysfunction as missing link? Int J Geriatr Psychiatry. 2007; 22:1–8. [PubMed: 17117393]

Naka KK, Tweddel AC, Doshi SN, Goodfellow J, Henderson AH. Flow-mediated changes in pulse wave velocity: a new clinical measure of endothelial function. Eur Heart J. 2006; 27:302–309. [PubMed: 16267075]

Navailles S, Hof PR, Schmauss C. Antidepressant drug-induced stimulation of mouse hippocampal neurogenesis is age-dependent and altered by early life stress. J Comp Neurol. 2008; 509:372–381. [PubMed: 18512685]

Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Kappelle LJ. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. J Neurol Sci. 2005; 228:27–33. [PubMed: 15607207]

O'Brien J, Perry R, Barber R, Gholkar A, Thomas A. The association between white matter lesions on magnetic resonance imaging and noncognitive symptoms. Ann NY Acad Sci. 2000; 903:482–489. [PubMed: 10818542]

O'Brien SM, Scott LV, Dinan TG. Antidepressant therapy and C-reactive protein levels. Br J Psychiatry. 2006; 188:449–452. [PubMed: 16648531]

O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. J Psychiatr Res. 2007; 41:326–331. [PubMed: 16870211]

Ohira T, Iso H, Satoh S, Sankai T, Tanigawa T, Ogawa Y, Imano H, Sato S, Kitamura A, Shimamoto T. Prospective study of depressive symptoms and risk of stroke among japanese. Stroke. 2001; 32:903–908. [PubMed: 11283390]

Olichney JM, Hansen LA, Hofstetter CR, Grundman M, Katzman R, Thal LJ. Cerebral infarction in Alzheimer's disease is associated with severe amyloid angiopathy and hypertension. Arch Neurol. 1995; 52:702–708. [PubMed: 7619027]

Olichney JM, Hansen LA, Galasko D, Saitoh T, Hofstetter CR, Katzman R, Thal LJ. The apolipoprotein E epsilon 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. Neurology. 1996; 47:190–196. [PubMed: 8710076]

Olichney JM, Hansen LA, Hofstetter CR, Lee JH, Katzman R, Thal LJ. Association between severe cerebral amyloid angiopathy and cerebrovascular lesions in Alzheimer disease is not a spurious one attributable to apolipoprotein E4. Arch Neurol. 2000; 57:869–874. [PubMed: 10867785]

Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A. 1998; 95:13290–13295. [PubMed: 9789081]

Paolucci S, Antonucci G, Pratesi L, Traballesi M, Grasso MG, Lubich S. Poststroke depression and its role in rehabilitation of inpatients. Arch Phys Med Rehabil. 1999; 80:985–990. [PubMed: 10488996]

Paolucci S, Gandolfo C, Provinciali L, Torta R, Toso V. The Italian multicenter observational study on post-stroke depression (DESTRO). J Neurol. 1997; 253:556–562. [PubMed: 16767539]

Paradiso S, Ohkubo T, Robinson RG. Vegetative and psychological symptoms associated with depressed mood over the first two years after stroke. Int J Psychiatry Med. 2006; 253:556–562.

Parikh RM, Robinson RG, Lipsey JR, Starkstein SE, Fedoroff JP, Price TR. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. Arch Neurol. 1990; 47:785–789. [PubMed: 2357159]

Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry. 2001; 58:221–227. [PubMed: 11231827]

Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Clinical features of MRI-defined subcortical vascular disease. Alzheimer Dis Assoc Disord. 2003; 17:236–242. [PubMed: 14657788]

Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN. Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. Am J Pathol. 1996; 148:2083–2095. [PubMed: 8669492]

Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. Am J Cardiol. 2001; 88:196–198. A7. [PubMed: 11448425]

Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry. 2000; 48:766–777. [PubMed: 11063973]

Rapp MA, Schnaider-Beeri M, Grossman HT, Sano M, Perl DP, Purohit DP, Gorman JM, Haroutunian V. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry. 2006; 63:161–167. [PubMed: 16461859]

Reeves RR, Rose ES. Depression and vascular disease: conceptual issues, relationships and clinical implications. Vasc Dis Prevention. 2006; 3:193–203.

Riediger ND, Othman RA, Suh M, Moghadasian MH. A systemic review of the roles of n-3 fatty acids in health and disease. J Am Diet Assoc. 2009; 109:668–679. [PubMed: 19328262]

Rigaud AS, Traykov L, Caputo L, Coste J, Latour F, Couderc R, Moulin F, Boller F, Forette F. Association of the apolipoprotein E epsilon4 allele with late-onset depression. Neuroepidemiology. 2001; 20:268–272. [PubMed: 11684904]

Robinson RG, Bloom FE. Pharmacological treatment following experimental cerebral infarction: implications for understanding psychological symptoms of human stroke. Biol Psychiatry. 1977; 12:669–680. [PubMed: 588647]

Robinson RG, Szetela B. Mood change following left hemispheric brain injury. Ann Neurol. 1981; 9:447–453. [PubMed: 7271239]

Robinson RG, Kubos KL, Starr LB, Rao K, Price TR. Mood changes in stroke patients: relationship to lesion location. Compr Psychiatry. 1983a; 24:555–566. [PubMed: 6653097]

Robinson RG, Starr LB, Kubos KL, Price TR. A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. Stroke. 1983b; 14:736–741. [PubMed: 6658957]

Robinson RG. Post-stroke mood disorders. Hosp Pract (Off Ed). 1986; 21:83–89. [PubMed: 3007550]

Roman G. Vascular dementia: a historical background. Int Psychogeriatr. 2003; 15(Suppl 1):11–13. [PubMed: 16191211]

Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol. 2002; 1:426–436. [PubMed: 12849365]

Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med. 2002; 23:51–61. [PubMed: 12093424]

Rybakowski JK, Wykretowicz A, Heymann-Szlachcinska A, Wysocki H. Impairment of endothelial function in unipolar and bipolar depression. Biol Psychiatry. 2006; 60:889–891. [PubMed: 16730331]

Sacco RL. Newer risk factors for stroke. Neurology. 2001; 57:S31–S34. [PubMed: 11552052]

Santos M, Gold G, Kövari E, Herrmann FR, Bozikas VP, Bouras C, Giannakopoulos P. Differential impact of lacunes and microvascular lesions on poststroke depression. Stroke. 2009 Aug 20. (Electronic publication ahead of print).

Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W. Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. Neurology. 1995; 45:883–888. [PubMed: 7746401]

Schmidt R, Schmidt H, Kapeller P, Lechner A, Fazekas F. Evolution of white matter lesions. Cerebrovasc Dis. 2002; 13:16–20. [PubMed: 11901238]

Schmidt R, Petrovic K, Ropele S, Enzinger C, Fazekas F. Progression of leukoaraiosis and cognition. Stroke. 2007; 38:2619–2625. [PubMed: 17673724]

Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults: the Cardiovascular Health Study. Arch Intern Med. 2000; 160:1761–1768. [PubMed: 10871968]

Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004; 130:601–630. [PubMed: 15250815]

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. 2002; 346:476–483. [PubMed: 11844848]

Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. J Am Coll Cardiol. 2005; 46:656–659. [PubMed: 16098431]

Singh A, Herrmann N, Black SE. The importance of lesion location in poststroke depression: a critical review. Can J Psychiatry. 1998; 43:921–927. [PubMed: 9825164]

Smith PJ, Blumenthal JA, Babyak MA, Hoffman BM, Doraiswamy PM, Waugh R, Hinderliter A, Sherwood A. Cerebrovascular risk factors, vascular disease, and neuropsychological outcomes in adults with major depression. Psychosom Med. 2007; 69:578–586. [PubMed: 17634564]

Smith PJ, Blumenthal JA, Babyak MA, Doraiswamy PM, Hinderliter A, Hoffman BM, Waugh R, Sherwood A. Intima-media thickness and age of first depressive episode. Biol Psychol. 2009; 80:361–364. [PubMed: 19041688]

Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997; 277:813–817. [PubMed: 9052711]

Snowdon DA. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med. 2003; 139:450–454. [PubMed: 12965975]

Spalletta G, Bossu P, Ciaramella A, Bria P, Caltagirone C, Robinson RG. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. Mol Psychiatry. 2006; 11:984–991. [PubMed: 16894392]

Staekenborg SS, van Straaten EC, van der Flier WM, Lane R, Barkhof F, Scheltens P. Small vessel versus large vessel vascular dementia: risk factors and MRI findings. J Neurol. 2008; 255:1644–1651. [PubMed: 18677637]

Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain. 1987; 110 (Pt 4):1045–1059. [PubMed: 3651794]

Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord. 2006; 20:112–117. [PubMed: 16772747]

Stewart R, Dufouil C, Godin O, Ritchie K, Maillard P, Delcroix N, Crivello F, Mazoyer B, Tzourio C. Neuroimaging correlates of subjective memory deficits in a community population. Neurology. 2008; 70:1601–1607. [PubMed: 18443310]

Streifler JY, Rosenberg N, Chetrit A, Eskaraev R, Sela BA, Dardik R, Zivelin A, Ravid B, Davidson J, Seligsohn U, Inbal A. Cerebrovascular events in patients with significant stenosis of the carotid artery are associated with hyperhomocysteinemia and platelet antigen-1 (Leu33Pro) polymorphism. Stroke. 2001; 32:2753–2758. [PubMed: 11739968]

Taylor WD, MacFall JR, Payne ME, McQuoid DR, Provenzale JM, Steffens DC, Krishnan KR. Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. Am J Psychiatry. 2004; 161:1293–1296. [PubMed: 15229065]

Taylor WD, Macfall JR, Payne ME, McQuoid DR, Steffens DC, Provenzale JM, Krishnan KR. Orbitofrontal cortex volume in late life depression: influence of hyperintense lesions and genetic polymorphisms. Psychol Med. 2007; 37:1763–1773. [PubMed: 17335636]

Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res. 2002; 53:647–654. [PubMed: 12169339]

Thomas AJ, Ferrier IN, Kalaria RN, Woodward SA, Ballard C, Oakley A, Perry RH, O'Brien JT. Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. Am J Psychiatry. 2000; 157:1682–1684. [PubMed: 11007725]

Thomas AJ, Ferrier IN, Kalaria RN, Perry RH, Brown A, O'Brien JT. A neuropathological study of vascular factors in late-life depression. J Neurol Neurosurg Psychiatry. 2001; 70:83–87. [PubMed: 11118253]

Thomas AJ, Ferrier IN, Kalaria RN, Davis S, O'Brien JT. Cell adhesion molecule expression in the dorsolateral prefrontal cortex and anterior cingulate cortex in major depression in the elderly. Br J Psychiatry. 2002; 181:129–134. [PubMed: 12151283]

Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in interleukin-1beta in late-life depression. Am J Psychiatry. 2005; 162:175–177. [PubMed: 15625217]

Thomas AJ, O'Brien JT. Depression and cognition in older adults. Curr Opin Psychiatry. 2008; 21:8–13. [PubMed: 18281834]

Tiemeier H, Hofman A, van Tuijl HR, Kiliaan AJ, Meijer J, Breteler MM. Inflammatory proteins and depression in the elderly. Epidemiology. 2003; 14:103–107. [PubMed: 12500057]

Tomlinson BE, Blessed G, Roth M. Observations on the brains of non-demented old people. J Neurol Sci. 1968; 7:331–356. [PubMed: 5707082]

Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. J Neurol Sci. 1970; 11:205–242. [PubMed: 5505685]

Udaka F, Sawada H, Kameyama M. White matter lesions and dementia: MRI-pathological correlation. Ann NY Acad Sci. 2002; 977:411–415. [PubMed: 12480780]

Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr Res. 2004; 67:269–275. [PubMed: 14984887]

Vaccarino V, Brennan ML, Miller AH, Bremner JD, Ritchie JC, Lindau F, Veledar E, Su S, Murrah NV, Jones L, Jawed F, Fazekas F, Dai J, Goldberg J, Hazen SL. Association of major depressive disorder with serum myeloperoxidase and other markers of inflammation: a twin study. Biol Psychiatry. 2008; 64:476–483. [PubMed: 18514165]

van der Flier WM, van Straaten EC, Barkhof F, Verdelho A, Madureira S, Pantoni L, Inzitari D, Erkinjuntti T, Crisby M, Waldemar G, Schmidt R, Fazekas F, Scheltens P. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. Stroke. 2005; 36:2116–2120. [PubMed: 16141425]

van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. Brain. 1991; 114 (Pt. 2):761–774. [PubMed: 2043948]

van West D, Maes M. Activation of the inflammatory response system: a new look at the etiopathogenesis of major depression. Neuro Endocrinol Lett. 1999; 20:11–17. [PubMed: 11473226]

Vataja R, Pohjasvaara T, Leppavuori A, Mantyla R, Aronen HJ, Salonen O, Kaste M, Erkinjuntti T. Magnetic resonance imaging correlates of depression after ischemic stroke. Arch Gen Psychiatry. 2001; 58:925–931. [PubMed: 11576030]

Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, Murburg MM, Ashleigh EA, Castillo S, Peskind ER, et al. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. Arch Gen Psychiatry. 1994; 51:411–422. [PubMed: 8179465]

Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003; 348:1215–1222. [PubMed: 12660385]

Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A. Incidental findings on brain MRI in the general population. N Engl J Med. 2007; 357:1821–1828. [PubMed: 17978290]

Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ, Mack WJ, Chui HC. Neuropathologic substrates of ischemic vascular dementia. J Neuropathol Exp Neurol. 2000; 59:931–945. [PubMed: 11089571]

Wang SH, Zhang ZJ, Guo YJ, Teng GJ, Chen BA. Hippocampal neurogenesis and behavioural studies on adult ischemic rat response to chronic mild stress. Behav Brain Res. 2008; 189:9–16. [PubMed: 18258314]

Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med. 1998; 338:1042–1050. [PubMed: 9535670]

West RL. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull. 1996; 120:272–292. [PubMed: 8831298]

Whooley MA, Caska CM, Hendrickson BE, Rourke MA, Ho J, Ali S. Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. Biol Psychiatry. 2007; 62:314–320. [PubMed: 17434456]

Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry. 2002; 52:253–264. [PubMed: 12182931]

Whyte EM, Mulsant BH, Vanderbilt J, Dodge HH, Ganguli M. Depression after stroke: a prospective epidemiological study. J Am Geriatr Soc. 2004; 52:774–778. [PubMed: 15086660]

Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. Psychosom Med. 2002; 64:6–12. [PubMed: 11818580]

Yen YC, Rebok GW, Gallo JJ, Yang MJ, Lung FW, Shih CH. ApoE4 allele is associated with late-life depression: a population-based study. Am J Geriatr Psychiatry. 2007; 15:858–868. [PubMed: 17911363]

Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Raininko R, Tilvis R. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. Arch Neurol. 1993; 50:818–824. [PubMed: 8352667]

Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis. 2000; 148:209–214. [PubMed: 10657556]

Zekry D, Duyckaerts C, Moulias R, Belmin J, Geoffre C, Herrmann F, Hauw JJ. Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. Acta Neuropathol (Berl). 2002; 103:481–487. [PubMed: 11935264]

Ziegelstein RC, Parakh K, Sakhuja A, Bhat U. Platelet function in patients with major depression. Intern Med J. 2009; 39:38–43. [PubMed: 19220540]

Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun. 2001; 15:199–226. [PubMed: 11566046]

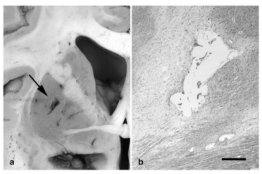

Fig. 1.
Macroscopic (a) and histological (b) views of basal ganglia lacune (b: hematoxylineosin staining, scale bar: 200 μm).

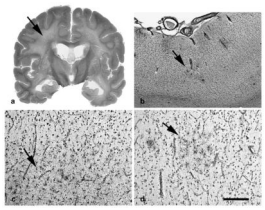

Fig. 2.
Representative examples of ischemic vascular lesions. (a) Demyelination of the deep white matter. (b) Cortical microinfarct. (c) Subcortical white matter gliosis. (d) Focal cortical gliosis (a: Luxol–van Gieson staining, b–d: Globus silver impregnation). Scale bars, 800 μm (b) and 200 μm (c and d).