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The impact of vascular burden on late-life depression

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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

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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 cm³) 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 Snowden 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) $\epsilon 4$ 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 $\epsilon 4$ 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 transsulfuration 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)-1 β , 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 comorbidities, 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.

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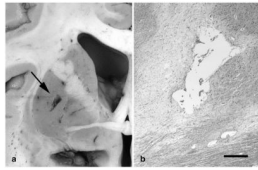


Fig. 1. Macroscopic (a) and histological (b) views of basal ganglia lacune (b: hematoxylineosin staining, scale bar: 200 μ m).

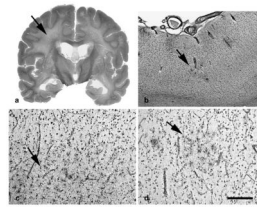


Fig. 2. Representative examples of ischemic vascular lesions. (a) Demyelination of the deep white matter. (b) Cortical microinfarct. (c) Subcortical white matter gliosis. (d) Focal cortical gliosis (a: Luxol–van Gieson staining, b–d: Globus silver impregnation). Scale bars, 800 μm (b) and 200 μm (c and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