Cognitive and affective repercussions of vascular burden in the elderly

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Funding / competing conflicts of interest: This work has been supported by an unrestricted grant from La Fondation Vachoux (MS).

Summary

Initial investigations of the impact of cerebrovascular pathology on cognition and mood predominantly focused on macrovascular lesions. Progressively, however, the role of a chronic accumulation of small vascular and microvascular lesions on both cognitive status and mood regulation came to light. Recent contributions have pointed to the main role of cortical microinfarcts and subcortical lacunes in dementia, providing the first pathological substrates of mixed dementia.

With respect to mood regulation, the research focus has equally shifted from the localisation of macrovascular infarcts to the impact of a chronic cerebrovascular lesion burden. However, empirical results from the wider field of the "vascular depression hypothesis" remain contradictory and the relative contributions of biological and psychosocial factors are still a matter of debate.

We review here the currently available datasets and theories regarding the cognitive and affective repercussions of cerebrovascular lesions while considering the methodological limitations of neuroimaging and neuropathological studies. In contrast to the initial neuroanatomically inspired lesion models, the current conception of the clinical expression of vascular burden is based on a vulnerability model. This encourages a multidimensional approach that takes into account not only lesions and risk factors but also the possibilities of early detection and intervention, thus integrating the emergent concepts of healthy aging and cognitive reserve and emphasising the role of psychosocial factors.

Keywords: vascular burden; cognitive impairment; aging; mood; macroinfarcts; lacunes; microvascular; neuropathology

List of abbreviations

AD:	Alzheimer's Disease
ADDTC:	Alzheimer's Disease Diagnostic and Treatment Centre
CT:	Computed Tomography
DSM-IV:	Diagnostic and Statistic Manual of Mental Disorders, 4th Edition
ICD-10:	International Classification of Diseases, 10th Revision
LOD:	Late-onset Depression
MRI:	Magnetic Resonance Imaging
NFT:	Neurofibrillary Tangles
NINSD-AIREN:	"National Institute of Neurological Disorders and Stroke" and "Association Internationale pour la Recherche et L'Enseignement en Neurosciences"
PSD:	Post-stroke Depression
VaD:	Vascular Dementia
VCI:	Vascular Cognitive Impairment
WML:	White Matter Lesions

Introduction

The impact of cerebrovascular lesions has intrigued researchers for more than a century. The notion of "post-apoplexy dementia" appeared as one of the first attempts to link these lesions to the sudden decline of cognitive function observed after a stroke [1].

Interestingly, the pioneer description of Auguste D by Alois Alzheimer [2] already contained a commonly overlooked description of the concomitant presence in dementia of arteriosclerotic changes as well as neurodegenerative lesions. Later on, the descriptions by Otto Biswanger of severe cognitive deterioration associated with chronic hypoperfusion constituted an important step in the demarcation of vascular dementia (VaD) from neurosyphilis [1]. In the 1960s, the landmark studies of Tomlinson et al. [3, 4] pointed to the importance of the volume of brain tissue loss during stroke while Hachinski et al. [5] highlighted the impact of its localisation. More recently, the accumulation of small vascular and even microvascular lesions was identified as an aetiologic factor of cognitive impairment (for review see [6]).

The impact of vascular lesions on mood regulation progressively came to light through the frequent observation of anxious and depressive symptoms as well as behavioural disturbances in patients with VaD. On the other hand, the early observations of behavioural changes and decreased brain catecholamines after ligation of the middle cerebral artery in rats [7] set the tone for the very active field of research on depression of vascular origin [8, 9]. Although globally supported by neuroimaging studies (for review see [10]), the neuropathological explorations of the concept of vascular depression have yielded conflicting results [11, 12].

The present article provides not only a detailed overview of current evidence regarding the impact of cerebrovascular lesions on cognition, but also a concise summary of the available studies addressing the relationship between vascular risk factors and mood regulation. In our critical analysis

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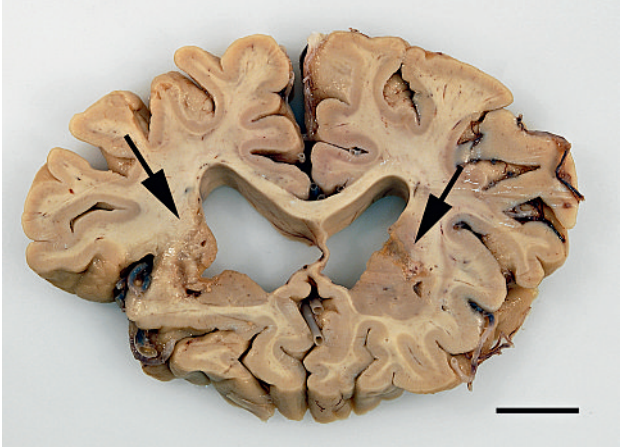
Figure 1 The figure displays a bilateral old basal ganglia ischemic infarct that resulted in post-stroke dementia. Scale bar = 1.5 cm.



of both fields, we will integrate data from neuropathological and neuroimaging studies, and comment on their potential implication for clinical practice.

Large vessel disease and cognition: in search of a comprehensive approach

Tomlinson's pioneering studies established a traditional view of VaD associated with a volume of cerebral infarcts larger than 100 ml [3, 4]. Later on, Hachinski et al. pointed out stroke location as a major determinant of its differential impact on cognition [5] and introduced the concepts of "multi-infarct dementia" and "strategic macroinfarcts". Classical multi-infarct encephalopathy more frequently involves the dominant hemisphere and accounts for about 15% of VaD (for review see [13]) (fig. 1).

Several recent studies have confirmed the role of a single stroke as a very strong risk factor for the development of dementia [14–17]. Depending on the population under study, on the selected set of diagnostic criteria and on the timing of the neuropsychological assessment, the prevalence of post-stroke dementia ranges from 6 to 32%. Both hospital and community-based studies show that the risk of developing dementia is doubled by the occurrence of a stroke, both in short- and long-term post-stroke assessments (for review see [18]). Moreover, patients with post-stroke dementia develop not only a major functional impairment (with dependence for daily living activities) [19], but also a high mortality rate (independently of age and co-morbidities) [20].

The first attempts to define VaD evolved from the classic criteria for Alzheimer's disease (AD) such as the presence of a prominent loss of memory and markedly impaired activities of daily living, along with the observation of progressive deterioration and irreversibility of symptoms. Later on, the semi-quantitative Hachinski ischemic score attempted to distinguish between VaD and AD [21]. Mainly based on stroke history and the presence of focal neurological signs, this scale provided a good tool to differentiate multi-infarct VaD from AD but a recent clinicopathological study in nonagenarians and centenarians pointed out its relative low specificity (only 66%) [22]. Moreover, it is important to note that the most commonly used sets of diagnostic criteria for VaD [ADDTC (the Alzheimer's Disease Diagnostic and Treatment Center) and NINSD-AIREN (the National Institute of Neurological Disorders and Stroke, and the *Association Internationale pour la Recherche et L'Enseignement en Neurosciences*) criteria] have very different sensitivities and specificities, with variable inter-rater reliabilities (for review see [23]; table 1). With regard to psychiatric classifications, clinicopathological data have demonstrated that DSM-IV (Diagnostic and Statistical Manual of Mental disorders, fourth edition) criteria [24] perform better than ICD-10 (International Classification of Diseases, 10th revision) criteria [25] in identifying cases of VaD, as 80% of the cases of VaD were undetected by ICD-10 [26] (table 2).

A recent clinicopathological study suggests that the inclusion of neuroimaging in ADDTC VaD criteria [27] for probable dementia might lead to a significantly better sensitivity [22]. Due to a greater specificity and due to the fact that they include all forms of cerebrovascular disease (complete and incomplete ischemia, haemorrhagic stroke and

Table 1 Summary of DSM-IV and ICD-10 research criteria for vascular dementia.

DSM-IV criteria	ICD research criteria
Cognitive deficits manifested by both: – Memory impairment (either in anterograde or retrograde memory) – One or more of the following disturbances – Aphasia, – Apraxia, – Agnosia, – Disturbance in executive functioning.	Dementia as defined by: – A decline in memory and other cognitive abilities that has been present for at least six months. – Intact consciousness. – A decline in emotional control or motivation, or a change in social behaviour manifested as at least one of the following: emotional lability, irritability, apathy, coarsening of social behaviour.
Significant impairment in social or occupational functioning as a result of the above cognitive deficits, representing a decline from a previous level of functioning.	Uneven distribution of deficits in higher cognitive functions (thus memory may be quite markedly affected while thinking, reasoning and information processing may show only modest impairment).
Focal neurological signs and symptoms or laboratory evidence of cerebrovascular disease that are judged to be aetiologically related to the disturbance.	Focal brain damage, manifested as at least one of the following: unilateral spastic weakness of the limbs, unilaterally increased tendon reflexes, an extensor plantar response, pseudobulbar palsy.
The deficits do not occur exclusively during the course of a delirium.	Evidence from the history, examination or tests of significant cerebrovascular disease, which may reasonably be judged to be aetiologically related to the dementia.

Table 2 Summary of ADDTC and NINDS-AIREN clinical criteria.

	ADDTC criteria	NINDS-AIREN criteria
Dementia definition	Cognitive deterioration interfering with customary affairs of life, not isolated to a single category of intellectual performance and independent of the level of consciousness.	Decline in intellectual function affecting memory and at least two other cognitive domains, sufficient to interfere with activities of daily living and independent of the level of consciousness.
Probable VaD	Dementia. Evidence of two or more strokes by history, neurological signs, and/or neuroimaging; or a single stroke with a clear temporal relationship to the onset of dementia. Evidence of at least one infarct outside the cerebellum by CT or T1-weighted MRI.	Dementia. Cerebrovascular disease defined by focal signs upon neurological examination and evidence of relevant cerebrovascular disease by CT or MRI. Relationship between the above two disorders, manifested by: – Dementia onset within three months of a stroke, or – Abrupt deterioration in cognitive functions, or – Fluctuating stepwise course.
Possible VaD	Dementia. History or evidence of a single stroke without a clear temporal relationship with dementia onset. Biswanger's disease which includes the following: – Early onset of urinary incontinence or gait disturbances, – Vascular risk factors and extensive white matter changes on neuroimaging.	Dementia and focal neurological signs. No neuroimaging. Absence of clear temporal relationship between stroke and the onset of dementia. Subtle onset and variable course of cognitive deficit and evidence of cerebrovascular disease.
Mixed dementia	Presence of one or more other systemic or brain disorders that are thought to be causally related to the dementia.	Possible AD and clinical or brain imaging evidence of relevant cerebrovascular disease.

cardiogenic VaD), NINDS-AIREN criteria [28] are the most widely used in clinical and treatment studies. They are among the first to propose clear neuroimaging criteria as a requirement for the diagnosis of probable VaD. However, even though these sets of criteria have undoubtedly contributed to a significant progress in the field of VaD, they also proved to have limited accuracy when used in routine clinical settings [22, 26, 29, 30].

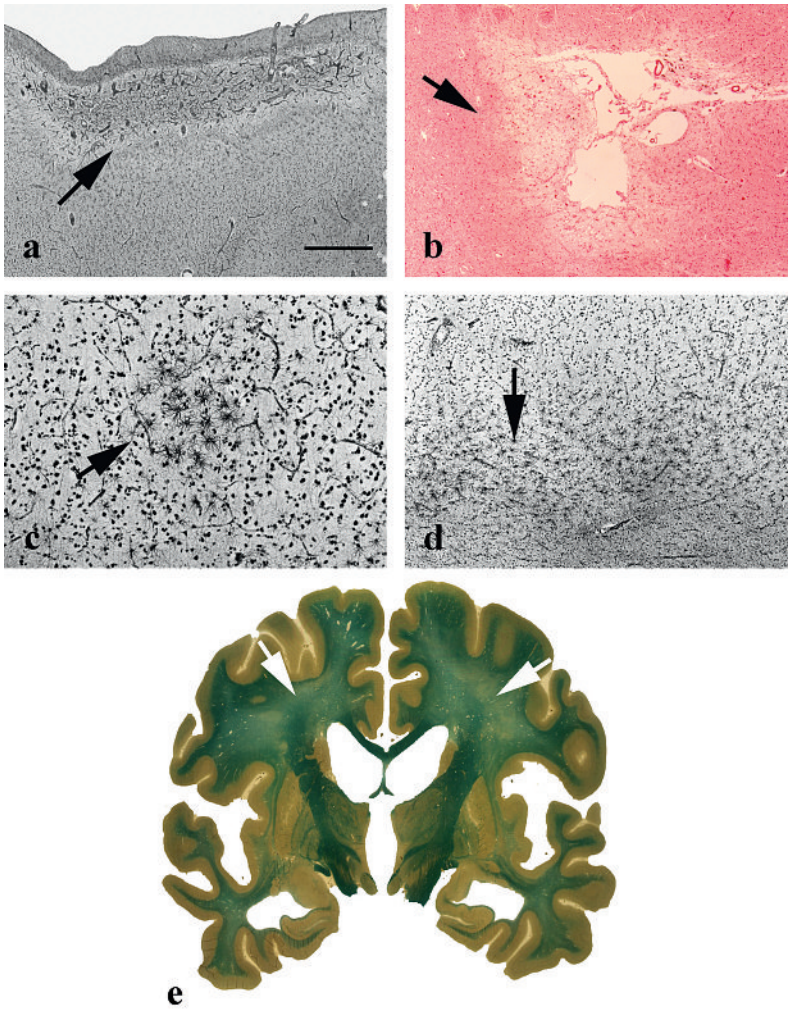
The concept of vascular cognitive impairment (VCI) tried to move away from these limitations by taking into account the existence of a continuum between subjects showing no clear cognitive decline and those presenting a demented state. Nevertheless, even after the adoption of this concept by the International Psychogeriatric Association, its use remains ambiguous (for review see [31,32]). From a neurocognitive standpoint, a definition of the clinical profile of VCI remains a matter of debate [33–36]. Unlike AD, VCI is characterised by a relative preservation of language and memory coexisting with significant executive deficits. The conceptualisation of VCI reflected a growing interest in the impact of subcortical small vessel disease on cognitive decline and dementia.

The relatively recent concept of subcortical ischemic vascular dementia constitutes an attempt to focus on the cognitive impact of lacunar lesions and deep white matter changes in the elderly. In fact, according to a recent multi-centre study, the importance of small vessel-disease seems to have been underestimated. Among 706 patients with VaD, 522 (74%) had small vessel disease and only 126 (18%) presented large vessel disease, while 56 patients (8%) had both [37]. Clinically, this syndrome presents with predominantly frontal type behavioural features including a dysexecutive syndrome, short-term memory deficits and deterioration in daily living activities. One possible interpretation proposes that lacunar infarctions or deep white matter changes lead to the disruption of three fronto-subcortical circuits involved in non-motor behaviour (dorsomedial prefrontal circuit related to executive function, medial prefrontal circuit involved in initiation and drive and orbital prefrontal circuit linked to social behaviour). Another study postulates that deep white matter lesions disrupt cortico-cortical connections known to play a key role in cognitive and emotional regulation (for review see [38]).

Small vessel disease and cognitive impairment: insights from neuroimaging

In contrast to macrovascular lesions such as ischemic and haemorrhagic brain infarcts, which are visible to the naked eye, microvascular lesions (which include cortical microinfarcts, gliosis and demyelination) are smaller and typically observable uniquely in histological preparations. Between these two types of lesions, lacunar infarcts (fig. 2b) are visible by neuroimaging, as well as upon gross examination at autopsy [13, 39]. They are usually classified among microvascular lesions given their possible link to microangiopathy. In contrast to macroangiopathic lesions (also referred to as atherosclerosis), microangiopathic lesions include arteriolosclerosis as well as hyalinosis and fibrinoid necrosis of arterioles. Lacunes appear increasingly central to the development of vascular burden-related cognitive impairment in brain aging. They measure, by definition, between 1 and 15 mm and are the result of definitive ischemic necrosis. They appear almost exclusively in the cerebral white matter and in subcortical structures including the thalamus, basal ganglia and brainstem. Although lacunar lesions are thought to result from hypertensive angiopathy, this association seems to be overemphasised [40] and recent studies with diffusion-weighted MRI have stressed the role of embolism from the heart or extracranial arteries in the pathogeny of these lesions [41, 42]. The exact clinical significance of lacunes in the aging brain remains a matter of debate [43–45]. Although subcortical lacunes have repeatedly been associated with cognitive impairment [46–49], other datasets emphasise the common presence of clinically silent lacunes in very old

Figure 2 Representative examples of vascular lesions: cortical microinfarct (a; arrow), putaminal lacunar infarct (b; arrow), focal cortical gliosis (c; arrow), subcortical gliosis in the frontal cortex (d; arrow) and areas of demyelination of the deep white matter (e; white arrows) are displayed. Sections were stained with Globus silver-impregnation (a,c and d), Hematoxylin-eosin (b) and Luxol-van Gieson stain (e). Scale bar: 500 µm (a, b); 125 µm (c); 250 µm (d) and 1.5 cm (e).



individuals [43, 50] and in 30 to 100% of a group of healthy, non-demented elderly subjects, age being the strongest predictor of their presence and severity [51–57].

Similarly to what was observed for lacunar infarcts, the prevalence of MRI white matter lesions (WML) (also referred to as hyper-intensities and leukoaraïosis) increases as a function of age and vascular risk factors [51, 54, 58] and these lesions are often the consequence of stenosis or occlusion of small cerebral vessels with sudden or chronic ischemia leading to incomplete white matter infarction [59].

Neuropathologically, WML may correspond to different types of histological changes such as myelin loss, axonal loss, astrogliosis, scattered microinfarcts, lacunar infarcts, dilated periventricular spaces and cerebral amyloid angiopathy [60–67]. Although a recent review validated the association between WML's progression and cognitive decline [68], their deleterious effect on cognition is by far not unanimously accepted [69–73]. Besides the heterogeneity of their pathological substrates, sampling differences and inter-rater variability in WML classification and sensitivity of cognitive evaluation may underlie the discordant reported results [66].

Interestingly, some MRI assessments of patients with micro- and macroangiopathy versus control subjects seem to indicate that a chronic vascular burden expressed by the occurrence of micro- and macrovascular lesions may be linked to the presence of these types of angiopathy. Namely, Preul and collaborators [74] reported an association between cerebral microangiopathy and a decrease in cortical thickness that was also correlated with neuropsychological performances. Hund-Georgiadis and collaborators [75] demonstrated a close relationship between age, obesity and hypertension, and the presence of magnetic resonance imaging alterations in patients affected by micro- and macroangiopathy.

Small vascular and microvascular lesions in cognitive aging: the realm of neuropathology

Increasingly evoked concepts of vascular burden [76, 77], successful aging [78–82] and cognitive reserve [83–85] point to a new "brain-at-risk" concept that progressively takes over the previous "end-stage" definitions of brain vascular lesions [86]. In a seminal study in this domain, Snowdon and collaborators [46] clearly demonstrated the link between cognitive deterioration and the presence of lacunar infarcts in the basal ganglia, thalamus and deep white matter by analysing a large database consisting of both regular clinical assessments and the donated post-mortem brains of 678 Catholic sisters, 75 to 107 years of age.

In contrast to its macrovascular counterparts discussed above, the possible cognitive impact of cerebral microvascular lesions not detectable with classical neuroimaging methods, has been rather overlooked. Cortical microinfarcts (fig. 2a) constitute a striking example. Thought to cause only limited damage in brain tissue, they were frequently considered as benign consequences of brain aging [87] until their significant role was unveiled by the pioneering work of Esiri et al. [88], showing that microvascular brain damage was closely related to a history of dementia in cases of cerebrovascular disease without substantial AD pathology [89, 90]. In line with these observations, Vinters et al. [45] reported a consistent development of microinfarcts involving both cortical and subcortical structures in a group of 20 demented patients. However, in the very frequent cases with mixed pathology it is important to consider that the consequences of microvascular pathology can be masked by the concomitant presence of age-related AD pathology such as amyloid deposits and neurofibrillary tangles (NFT).

To address the cognitive impact of the burden of microvascular lesions in the absence of AD, we performed a prospective clinicopathological evaluation of 45 patients, 63 to 100 years of age, with various degrees of cognitive impairment but without significant NFT pathology or macrovascular lesions including lacunes [91]. The neuropathologic analysis included bilateral assessment of all types of microvascular lesions [cortical microinfarcts (fig. 2a), focal cortical gliosis (fig. 2c), diffuse white matter gliosis (fig. 2d) and white matter demyelination (fig. 2e)] and multivariate mod-

els 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 Clinical Dementia Rating scale scores and focal and diffuse gliosis. Conversely, a strong association was found between the extent of cerebral damage due to microinfarcts and cognitive assessment [92].

In a second step, we analysed the impact of lacunar lesions on cognition in a series of 45 patients without cortical macroinfarcts aged 63 to 100 years [39]. Results showed that lacunes (fig. 2b) and deep white matter (fig. 2e) and periventricular demyelination contributed in equal parts to cognitive function and explained each 6% of clinical variability. In the multivariate analysis, lacunes explained as much as 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.

The interaction between vascular and neurodegenerative changes in cognitive decline: a field in motion

Over the last decades, the increasing coexistence of AD and vascular lesions in old age as well as the presence of common risk factors for both AD and VaD have raised a growing interest among neurobiologists and clinical researchers [46, 93–97]. Although compelling evidence that AD might be a vascular disorder with neurodegenerative consequences is missing (for review see [98]), it is widely accepted that brain aging is characterised by the concomitant development of cortical lesions of both AD and vascular type [47, 67, 71, 72, 82, 83, 99].

In this context, the definition of mixed dementia constitutes a challenge for both clinical practice and research. This entity was initially diagnosed in the presence of both AD pathology and large infarcts [100]. Progressively, the concomitant presence of lacunes and small vessel disease with AD lesions was associated with the development of clinically overt dementia [46, 89] and the concept of mixed dementia currently covers a wide spectrum of combinations between AD and VaD. At one end of the spectrum, one can find subjects with minimal AD-related pathology and substantial small macrovascular and microvascular changes, and at the other end are subjects with severe AD pathological changes and mild vascular lesions. The main difficulty preventing the establishment of neuropathological criteria for mixed dementia arises from the interconnection of distinct neuropathological dimensions such as the type, location and number of AD and vascular lesions [94].

To assess these issues, a recent series of 156 prospectively documented cases with various degrees of AD pathology was submitted to a detailed neuropathological analysis that included Braak NFT and Abeta-protein deposition staging and bilateral semi-quantitative assessment of microvascular ischemic pathology and lacunes [92]. Results showed that four independent variables were significant predictors of cognitive status, explaining 48.9% of the presence of dementia. The vascular scores including cortical microinfarcts and thalamic and basal ganglia lacunes explained 15% of the variability of the outcome variable (presence of dementia), Braak NFT staging explained 30.4% and Abeta deposition staging explained 3.5%. A threshold value with the best combination of sensitivity and specificity allowed for a highly accurate distinction between demented and non-demented cases. These results are encouraging in the perspective of proposing an operational definition of neuropathological criteria for mixed dementia that takes into account both degenerative and vascular changes occurring in the aging brain.

Cerebrovascular lesions and mood regulation: the groundbreaking concept of post-stroke depression

Macroscopic vascular lesions have been related to depressive symptoms in cases of post-stroke depression (for review see [101]) and WML have been associated with both cognitive decline and depressed mood [47, 99, 102, 103]. Moreover, disruption of fronto-subcortical circuits by lacunes and WML has been implicated in the pathogenesis of vascular depression, and subcortical vascular changes are increasingly being associated not only with cognitive impairment but also with anxiety and depression [7, 38, 48, 104–106].

In the last decades, stroke has been recognised as the most common severe neurological disorder and the third leading cause of mortality among adults worldwide [107]. According to a recent review, 51 adequately designed studies using depression scales and DSM-IV criteria for minor and major depression observed the presence of depressive symptoms in the three to six months following stroke in one third of the patients [108, 109], with 20% of the stroke patients displaying depressive symptoms even more than two years later [110]. Robinson and collaborators proposed an association between the ligation of the middle cerebral artery and the development of behavioural changes and alterations in the levels of brain catecholamines in a rat animal model. They hypothesised that the ischemic injury might adversely affect ascending biogenic amine pathways related to mood regulation [111]. However, when this hypothesis was tested in stroke patients, no cortical localisation was consistently associated with depressive symptoms (for review see [112]). Others have argued that pro-inflammatory cytokines released during stroke can be depressiogenic by increasing the activity of the hypothalamus-pituitary-adrenal axis or altering biogenic amine neurotransmission, and a recent study did confirm the role of interleukin-1 alpha in the pathogenesis of depression [113]. Yet no other perspective stresses the role of psychosocial aspects contributing to the development of a depressive episode after stroke (for review see [101]). Physical disability, stroke severity, cognitive impairment, female gender and previous cerebrovascular or depressive episodes are among the consistently identified risk factors for post-stroke depression (PSD) [114, 115].

Unlike neuroimaging, neuropathological studies allow for the assessment of different types of vascular lesions and for a more subtle delimitation of the stroke-affected area. In a first study of 95 autopsied patients with stroke, we reported no association between diffuse or focal macrovascular

pathology and PSD (even though younger age at death was significantly related to the occurrence of PSD) [116]. However, as previously emphasised in the realm of cognitive decline, the role of small vascular and microvascular lesions constituting a "vascular burden" with comparable repercussions in mood regulation progressively came to light.

Could post-stroke depression be linked to the chronic accumulation of lacunes (fig. 2b) and microvascular lesions [cortical microinfarcts (fig. 2a), white matter demyelination (fig. 2e), subcortical (fig. 2d) and focal (fig. 2c) gliosis]? In order to explore this hypothesis, we recently analysed 41 post-mortem brains of stroke patients and showed that the chronic accumulation of lacunar infarcts within the thalamus, basal ganglia and deep white matter was significantly related to the occurrence of post-stroke depression explaining 25% of its variability [99].

Other types of cerebrovascular disorders such as normal pressure hydrocephalus and traumatic brain injury are also thought to be associated with depressive symptoms. Normal pressure hydrocephalus was originally described in 1965 as a progressive syndrome characterised by a triad of gait disturbance, cognitive impairment and urinary dysfunction and is accompanied by landmark depressive symptoms such as apathy (present in 70.3% of the patients affected with normal pressure hydrocephalus) and anxiety (in 25% of the patients) [117]. With regard to exposure to physical trauma, Hudak et al. have recently reported an association between brain atrophy following traumatic injury and depressive symptoms [118]. It is interesting to note that, consistent with the limbic-frontal model of depression, the cortical regions that correlate with depressive symptoms, when affected, are the rostral anterior cingulate and the orbitofrontal cortices [119].

Long-term vascular risk and late onset depression: does neuropathology confirm the "vascular depression" hypothesis?

The concept that vascular lesions may increase older patients' vulnerability to depression was already present in Gaupp's 1905 treatise, "Depressive states in old age", in which he discussed "arteriosclerotic depressive disease" [120]. More recent neuroimaging data showed that, even in the absence of a clinical stroke, older depressed patients may present with two main imaging patterns: white matter fronto-subcortical lesions and bilateral hypometabolism in anterior frontal areas (for review see [121]). In addition, several datasets have reported an association between cardiovascular pathology such as hypertension and coronary heart disease and depressive symptoms, and demonstrated that silent strokes were frequently present in late-onset depression [122–124].

Based on the converging evidence that lesions affecting fronto-subcortical connections are associated with deficits in executive function and depressive symptoms in late life [122, 125–127], two research groups proposed the "vascular depression hypothesis". Alexopoulos et al. [8] based their assumptions on the co-morbidity of depressive syndromes with cerebrovascular lesions and cardiovascular risk factors as well as on the increased incidence of depressive episodes after stroke. Simultaneously, Krishnan et al. [9] observed that patients presenting MRI lesions in the subcortical gray matter and deep and periventricular white matter had a higher probability of presenting with late-onset depression.

Patients with vascular depression display an onset of depression after 65 years of age or, in the case of early-onset depression, a change in depression course after the onset of vascular disease. They also present with co-morbid cardiovascular risk factors such as history of stroke or transient ischemic attacks, focal neurologic signs, atrial fibrillation, carotid bruit, hypertension and hyperlipidemia [8]. The fact that these patients show major impairments in executive functions such as planning, organising, and abstracting was consistently demonstrated leading to the concept of "Depression-Executive Dysfunction Syndrome" proposed by Alexopoulos et al. [128]. Other common characteristics of vascular depression include the presence of psychomotor retardation, limited or absent depressive (such as guilt feelings) or psychotic ideation, apathy and an absence of family history of mood disorders [129].

How can vascular lesions impact mood regulation? Certain authors have suggested that small vascular lesions affected three prefrontal pathways with major behavioural correlates, namely executive dysfunction (dorsolateral prefrontal circuit), apathy/abulia (anterior cingulate circuit) and mood lability or disinhibition (orbitofrontal circuit) [8, 130, 131]. In fact, subcortical ischemic lesions that may include silent lacunar infarctions and/or hyperintense lesions (WML) in these prefrontal pathways had already been implicated in age-related cognitive decline [29], and vascular risk factors are significantly associated with deficits in planning, organisation and abstraction, common in late-life depression. Moreover, patients with MRI-defined subcortical ischemic vascular disease are not only more frequently depressed than patients with other types of stroke but they are more prone to develop major executive dysfunction (51% vs 39%) [127].

Several recent studies emphasised that the accumulation of risk factors constitute the vulnerability background potentially implicated in the development of depression [132–137]. It is probable that vascular disease and depression both share environmental (e.g., smoking, poor diet, reduced exercise) and genetic risk factors (e.g., polymorphism of the 5–10-methylenetetrahydrofolate reductase gene – MTHFR C677T or of the ApoE4 allele). However, even after controlling for some of these factors, the association of depression with coronary heart disease persists [138]. The presence of clinical depression may in turn induce a "stress burden" [139] 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 [140, 141].

Even though most neuroimaging explorations have confirmed the "vascular depression hypothesis", the implication of cardiovascular factors in late-onset depression remains a matter of debate [142–144] and explorations of MRI WML in mood disorders are scarce [61, 145–147]. Thomas et al.

performed a series of neuropathological explorations in a group of 20 patients with late-life depression and 20 controls with conflicting results: late-onset depression (LOD) was associated with an increase of deep WML of ischemic origin in the dorsolateral prefrontal cortex [148] but not with small vascular or microvascular lesions [12, 149]. In order to address this question, we recently undertook an exploration of the neuropathological underpinnings of late-onset depression in a post-mortem series of 38 subjects who had suffered from LOD and 29 age- and gender-matched controls. Unlike Thomas et al., we performed a bilateral assessment in different cortical areas of each type of small vascular and microvascular lesion in order to assess the global vascular burden in each subject. Our results showed that neither the presence of subcortical lacunes nor the presence of microvascular lesions (cortical microinfarcts, white matter demyelination and gliosis) was related to the development of depression in late life [11].

Cerebrovascular lesions and bipolar disorder: an emerging debate

Recently, the link between mood elation and presence of cerebrovascular lesions is receiving increasing attention. The relationship between the burden of cerebrovascular lesions and bipolar disorder has been established by neuroimaging studies and grounded in the observation of a higher frequency of WML in bipolar patients in comparison to controls [150–152]. Similarly to the contrast between early-onset depression (EOD) and LOD symptomatic constellations, patients with late-onset bipolar disorder have a less frequent familial history and more marked medical co-morbidities [153], including cerebrovascular pathology [154], as compared to younger cases. Moreover, elderly bipolar patients have a significantly higher risk of developing stroke [155], which contributed to the emergence of the notion of "Vascular Mania" [156].

Conclusions

Even though recent neuroimaging structural and functional methods offer an outstanding research window to the aging brain, unimaginable just half a century ago, expectations of direct lesion-syndrome relationships are not plainly fulfilled. With the exception of post-stroke dementia where the cognitive repercussions of vascular lesions seem to be unequivocal, the clinical significance of small macrovascular and microvascular lesions is just beginning to be uncovered [39, 55, 71, 72, 157]. In the case of AD, autopsy data point to the absence of a systematic co-occurrence of high scores of neurodegenerative lesions and the clinical phenotype of dementia [83, 158]. Moreover, even though the increasing research efforts on the issue of mixed dementia highlight the cumulative effects of vascular and neurodegenerative lesions in cognitive decline [92], the differential impact of these two types of lesions is still controversial. Interestingly, the clear-cut definitions of depressive disorders and dementia syndromes have also been challenged and are being increasingly interconnected by several observations, with vascular disease constituting one of the conceptual bridges between these two entities. For example, depressive symptoms have been shown to raise the risk of dementia in men, mainly in those with hypertension [159] and to increase the likelihood for later development of AD [160]. The vascular depression literature has extensively shown that vascular disease promotes development of depression but that the opposite sequence is also true (for review see [161, 162]).

Paralleling this debate, in the field of the impact of vascular lesions on mood, the neuro-anatomical model of PSD has equally failed to provide us with a clear lesion-syndrome correlation. In contrast to what was originally thought, single stroke localisation does not predict the occurrence of PSD. The main pathological determinant of PSD seems to be the progressive accumulation of subcortical lacunes in the thalamus, basal ganglia and deep white matter [163]. Moreover, even though most neuroimaging studies support the concept of vascular depression [10, 164], our recent neuropathologic exploration of the impact of small vascular and microvascular lesions on late-onset depression did not confirm this hypothesis and in the new field of "Vascular Mania Hypothesis" the neuropathologic underpinnings of neuroimaging findings are still to be addressed. Taken together, these contributions indicate that a chronic burden of subcortical lacunes may be a common denominator in the development of cognitive decline and mood dysregulation. However, in what concerns the development of depressive symptoms, the accumulation of small vascular lesions seems to play a role solely in the presence of acute brain compromise such as when of a clinical stroke occurs.

The "lesional" view of cognitive and affective disorders seems to progressively give place to a vulnerability model that puts together the traditionally opposed views of biologic versus psychosocial determinants. A chronic accumulation of small vessel pathology and microvascular lesions, related to both genetic predisposition, behavioural patterns and medical and psychiatric co-morbidities seems to constitute a common platform in the development of both cognitive impairment and mood disorders in elders.

Acknowledgements: This work has been supported by an unrestricted grant from La Fondation Vachoux (MS).

References

1 Roman G. Vascular dementia: a historical background. Int Psychogeriatr. 2003;15 Suppl1:11–3.
2 Graeber MB, Kosel S, Grasbon-Frodl E, Moller HJ, Mehraein P. Histopathology and APOE genotype of the first Alzheimer disease patient, Auguste D. Neurogenetics. 1998;1(3):223–8.
3 Tomlinson BE, Blessed G, Roth M. Observations on the brains of non-demented old people. J Neurol Sci. 1968;7(2):331–56.
4 Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. J Neurol Sci. 1970;11(3):205–42.
5 Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet. 1974;2(7874):207–10.
6 Chui H. Vascular dementia, a new beginning: shifting focus from clinical phenotype to ischemic brain injury. Neurol Clin. 2000;18(4):951–78.
7 Robinson RG, Bloom FE. Pharmacological treatment following experimental cerebral infarction: implications for understanding psychological symptoms of human stroke. Biol Psychiatry. 1977;12(5):669–80.
8 Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry. 1997;54(10):915–22.

9 Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997;154(4):497–501.
10 Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. J Neurol Neurosurg Psychiatry. 2008;79(6):619–24.
11 Santos M, Gold G, Kovari E, Herrmann FR, Hof PR, Bouras C et al. Neuropathological analysis of lacunes and microvascular lesions in late-onset depression. Neuropathol Appl Neurobiol. 2010;36 (7):661–72.
12 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(1):83–7.
13 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(1–2):75–80.
14 Tang WK, Chan SS, Chiu HF, Ungvari GS, Wong KS, Kwok TC. Emotional incontinence in Chinese stroke patients–diagnosis, frequency, and clinical and radiological correlates. J Neurol. 2004;251(7):865–9.
15 Zhou DH, Wang JY, Li J, Deng J, Gao C, Chen M. Study on frequency and predictors of dementia after ischemic stroke: the Chongqing stroke study. J Neurol. 2004;251(4):421–7.
16 Tatemichi TK, Paik M, Bagiella E, Desmond DW, Stern Y, Sano M et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. Neurology. 1994;44:1885–91.
17 Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. J Neurol Neurosurg Psychiatry. 1994;57(2):202–7.
18 Henon H, Pasquier F, Leys D. Poststroke dementia. Cerebrovasc Dis. 2006;22(1):61–70.
19 Lin JH, Lin RT, Tai CT, Hsieh CL, Hsiao SF, Liu CK. Prediction of post-stroke dementia. Neurology. 2003;61(3):343–8.
20 Desmond DW, Moroney JT, Sano M, Stern Y. Mortality in patients with dementia after ischemic stroke. Neurology. 2002;59(4):537–43.
21 Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J et al. Cerebral blood flow in dementia. Arch Neurol. 1975;32(9):632–7.
22 Bacchetta JP, Kovari E, Merlo M, Canuto A, Herrmann FR, Bouras C et al. Validation of clinical criteria for possible vascular dementia in the oldest-old. Neurobiol Aging. 2007;28(4):579–85.
23 Jellinger KA. Morphologic diagnosis of "vascular dementia" – a critical update. J Neurol Sci. 2008;270(1–2):1–12.
24 American Psychiatric Association (APA), Diagnostic and statistical Manual of Mental Disorders. 4th ed. 1994, Washington: American Psychiatric Association.
25 World Health Organization (WHO), The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines. 1992, Geneva: World Health Organization.
26 Gold G, Bouras C, Canuto A, Bergallo MF, Herrmann FR, Hof PR et al. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. Am J Psychiatry. 2002;159(1):82–7.
27 Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology. 1992;42(3 Pt 1):473–80.
28 Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250–60.
29 O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L et al. Vascular cognitive impairment. Lancet Neurol. 2003;2(2):89–98.
30 van Straaten EC, Scheltens P, Barkhof F. MRI and CT in the diagnosis of vascular dementia. J Neurol Sci.2004;226(1–2):9–12.
31 O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry. 2006;14(9):724–33.
32 Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments. Lancet Neurol. 2008;7(3):246–55.
33 Arango-Lasprilla JC, Rogers H, Lengenfelder J, Deluca J, Moreno S, Lopera F. Cortical and subcortical diseases: do true neuropsychological differences exist? Arch Clin Neuropsychol. 2006;21(1):29–40.
34 Frisoni GB, Galluzzi S, Bresciani L, Zanetti O, Geroldi C. Mild cognitive impairment with subcortical vascular features: clinical characteristics and outcome. J Neurol. 2002;249(10):1423–32.
35 Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. J Neurol Neurosurg Psychiatry. 2004;75(1):61–71.
36 Laukka EJ, Jones S, Small BJ, Fratiglioni L, Backman L. Similar patterns of cognitive deficits in the preclinical phases of vascular dementia and Alzheimer's disease. J Int Neuropsychol Soc. 2004;10(3):382–91.
37 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;255:1644–51.
38 Chui HC. Subcortical ischemic vascular dementia. Neurol Clin. 2007; 25(3):717–40, vi.
39 Gold G, Kövari E, Herrmann FR, Canuto A, Hof PR, Michel JP et al. Cognitive consequences of thalamic, basal ganglia, and deep white matter lacunes in brain aging and dementia. Stroke. 2005;36(6): 1184–8.
40 Franke CL, van Swieten JC, Algra A, van Gijn J. Prognostic factors in patients with intracerebral haematoma. J Neurol Neurosurg Psychiatry. 1992;55(8):653–7.
41 Caso V, Budak K, Georgiadis D, Schuknecht B, Baumgartner RW. Clinical significance of detection of multiple acute brain infarcts on diffusion weighted magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2005;76(4):514–8.
42 Wessels T, Rottger C, Jauss M, Kaps M, Traupe H, Stolz E. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. Stroke. 2005;36(4):757–61.
43 Jellinger KA, Attems J. Incidence of cerebrovascular lesions in Alzheimer's disease: a postmortem study. Acta Neuropathol (Berl). 2003;105(1):14–7.
44 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 [In Process Citation]. Arch Neurol. 2000;57(10):1474–9.
45 Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ, Mack WJ et al. Neuropathologic substrates of ischemic vascular dementia. J Neuropathol Exp Neurol. 2000;59(11):931–45.
46 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(10):813–7.
47 van der Flier WM, van Straaten EC, Barkhof F, Verdelho A, Madureira S, Pantoni L et al. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. Stroke. 2005;36(10): 2116–20.
48 Carey CL, Kramer JH, Josephson SA, Mungas D, Reed BR, Schuff N et al. Subcortical lacunes are associated with executive dysfunction in cognitively normal elderly. Stroke. 2008;39(2):397–402.
49 Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol. 1998;55(9): 1217–25.
50 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(13):1215–22.
51 Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology. 1994;44(7):1246–52.
52 Liao D, Cooper L, Cai J, Toole J, Bryan N, Burke G et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology. 1997;16(3):149–62.
53 Lindgren A, Roijer A, Rudling O, Norrving B, Larsson EM, Eskilsson J et al. Cerebral lesions on magnetic resonance imaging, heart disease, and vascular risk factors in subjects without stroke. A population-based study. Stroke. 1994;25(5):929–34.
54 Longstreth WT Jr., Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke. 1996;27(8):1274–82.
55 Soderlund H, Nyberg L, Adolfsson R, Nilsson LG, Launer LJ. High prevalence of white matter hyperintensities in normal aging: relation to blood pressure and cognition. Cortex. 2003;39(4–5):1093–105.
56 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(8):818–24.
57 Ylikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R, Tilvis R. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke. 1995;26(7):1171–7.
58 Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. Stroke. 2004;35(8):1857–61.
59 Mok VC, Liu T, Lam WW, Wong A, Hu X, Guo L et al. Neuroimaging predictors of cognitive impairment in confluent white matter lesion: volumetric analyses of 99 brain regions. Dement Geriatr Cogn Disord. 2008;25(1):67–73.
60 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(4):205–12.
61 Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993;43(9):1683–9.
62 Gurol ME, Irizarry MC, Smith EE, Raju S, Diaz-Arrastia R, Bottiglieri T et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. Neurology. 2006;66(1):23–9.
63 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(5):492–7.
64 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(5):883–8.

65 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):761–74.
66 Udaka F, Sawada H, Kameyama M. White matter lesions and dementia: MRI-pathological correlation. nn N Y Acad Sci. 2002;977:411–5.
67 Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW et al. Neuropathological basis of magnetic resonance images in aging and dementia. Ann Neurol. 2008;63(1):72–80.
68 Enzinger C, Fazekas F, Ropele S, Schmidt R. Progression of cerebral white matter lesions -clinical and radiological considerations. J Neurol Sci. 2007;257(1–2):5–10.
69 Bracco L, Campani D, Baratti E, Lippi A, Inzitari D, Pracucci G et al. Relation between MRI features and dementia in cerebrovascular disease patients with leukoaraiosis: a longitudinal study. J Neurol Sci. 1993; 120(2):131–6.
70 Schmidt R, Schmidt H, Kapeller P, Lechner A, Fazekas F. Evolution of white matter lesions. Cerebrovasc Dis. 2002;13(Suppl 2):16–20.
71 Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP et al. Incidental findings on brain MRI in the general population. N Engl J Med. 2007;357(18):1821–8.
72 van de Pol LA, Korf ES, van der Flier WM, Brashear HR, Fox NC, Barkhof F et al. Magnetic resonance imaging predictors of cognition in mild cognitive impairment. Arch Neurol. 2007;64(7):1023–8.
73 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(9230):628–34.
74 Preul C, Lohmann G, Hund-Georgiadis M, Guthke T, von Cramon DY. Morphometry demonstrates loss of cortical thickness in cerebral micro-angiopathy. J Neurol. 2005;252(4):441–7.
75 Hund-Georgiadis M, Ballaschke O, Scheid R, Norris DG, von Cramon DY. Characterization of cerebral microangiopathy using 3 Tesla MRI: correlation with neurological impairment and vascular risk factors. J Magn Reson Imaging. 2002;15(1):1–7.
76 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(6): 477–86.
77 Norrving B. Lacunar infarcts: no black holes in the brain are benign. Pract Neurol. 2008;8(4):222–8.
78 Depp CA, Glatt SJ, Jeste DV. Recent advances in research on successful or healthy aging. Curr Psychiatry Rep. 2007;9(1):7–13.
79 Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry. 2006;14(1):6–20.
80 Rowe JW, Kahn RL. Human aging: usual and successful. Science. 1987; 237(4811):143–9.
81 Seeman T, McAvay G, Merrill S, Albert M, Rodin J. Self-efficacy beliefs and change in cognitive performance: MacArthur Studies of Successful Aging. Psychol Aging. 1996;11(3):538–51.
82 Tyas SL, Snowdon DA, Desrosiers MF, Riley KP, Markesbery WR. Healthy ageing in the Nun Study: definition and neuropathologic correlates. Age Ageing. 2007;36(6):650–5.
83 Snowdon DA. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med. 2003;139(5 Pt 2):450–4.
84 Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002;8(3): 448–60.
85 Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord. 2006;20(2):112–7.
86 Ferro JM. Welcome harmonizations. Stroke. 2006;37(9):2197.
87 Del Ser T, Bermejo F, Portera A, Arredondo JM, Bouras C, Constantinidis J. Vascular dementia. A clinicopathological study. J Neurol Sci. 1990; 96(1):1–17.
88 Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. J Neurol Neurosurg Psychiatry. 1997;63(6):749–53.
89 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(9182):919–20.
90 Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. 2001;357(9251):169–75.
91 Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Michel JP et al. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. Stroke. 2004;35(2):410–414.
92 Gold G, Giannakopoulos P, Herrmann FR, Bouras C, Kovari E. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain. 2007;130(Pt 11):2830–6.
93 de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? Neurol Res. 1993;15(3):146–53.
94 Giannakopoulos P, Gold G, Kovari E, von Gunten A, Imhof A, Bouras C et al. Assessing the cognitive impact of Alzheimer disease pathology and vascular burden in the aging brain: the Geneva experience. Acta Neuropathol. 2007;113(1):1–12.
95 Jellinger KA. Is Alzheimer's disease a vascular disorder? J Alzheimers Dis. 2003;5(3):247–62.
96 Sheng B, Cheng LF, Law CB, Li HL, Yeung KM, Lau KK. Coexisting cerebral infarction in Alzheimer's disease is associated with fast dementia progression: applying the National Institute for Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences Neuroimaging Criteria in Alzheimer's Disease with Concomitant Cerebral Infarction. J Am Geriatr Soc. 2007; 55(6):918–22.
97 Silvestrini M, Pasqualetti P, Baruffaldi R, Bartolini M, Handouk Y, Matteis M et al. Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. Stroke. 2006;37(4):1010–5.
98 Jellinger KA. The pathology of "vascular dementia": a critical update. J Alzheimers Dis. 2008;14(1):107–23.
99 Stewart R, Dufouil C, Godin O, Ritchie K, Maillard P, Delcroix N et al. Neuroimaging correlates of subjective memory deficits in a community population. Neurology. 2008;70(18):1601–7.
100 Jellinger KA. Understanding the pathology of vascular cognitive impairment. J Neurol Sci. 2005;229–230:57–63.
101 Santos M, Gold G, Kövari E, Herrmann FR, Bozikas VP, Bouras C et al. Differential impact of lacunes and microvascular lesions on Poststroke depression. Stroke. 2009;40(11):3557–62.
102 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 N Y Acad Sci. 2000;903:482–9.
103 Vataja R, Pohjasvaara T, Leppavuori A, Mantyla R, Aronen HJ, Salonen O et al. Magnetic resonance imaging correlates of depression after ischemic stroke. Arch Gen Psychiatry. 2001;58(10):925–31.
104 Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M et al. Executive dysfunction and long-term outcomes of geriatric depression. Arch Gen Psychiatry. 2000;57(3):285–90.
105 Mayberg HS, Robinson RG, Wong DF, Parikh R, Bolduc P, Starkstein SE et al. PET imaging of cortical S2 serotonin receptors after stroke: lateralized changes and relationship to depression. Am J Psychiatry. 988;145(8):937–43.
106 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): 1–8.
107 World Health Organization (WHO), Stroke-1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke. 1989; 20(10):1407–31.
108 Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. Stroke. 2005; 36(6):1330–40.
109 Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry. 2002;52(3): 253–64.
110 Whyte EM, Mulsant BH, Vanderbilt J, Dodge HH, Ganguli M. Depression after stroke: a prospective epidemiological study. J Am Geriatr Soc. 2004;52(5):774–8.
111 Robinson RG, Shoemaker WJ, Schlumpf M, Valk T, Bloom FE. Effect of experimental cerebral infarction in rat brain on catecholamines and behaviour. Nature. 1975;255(5506):332–4.
112 Provinciali L, Coccia M. Post-stroke and vascular depression: a critical review. Neurol Sci. 2002;22(6):417–28.
113 Lee KS, Chung JH, Lee KH, Shin MJ, Oh BH, Lee SH et al. Simultaneous measurement of 23 plasma cytokines in late-life depression. Neurol Sci. 2009;30(5):435–8.
114 Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005;36(10): 2296–301.
115 Paolucci S, Gandolfo C, Provinciali L, Torta R, Toso V. The Italian multicenter observational study on post-stroke depression (DESTRO). J Neurol. 2006;253(5):556–62.
116 Bozikas VP, Gold G, Kovari E, Herrmann F, Karavatos A, Giannakopoulos P et al. Pathological correlates of poststroke depression in elderly patients. Am J Geriatr Psychiatry. 2005;13(2):166–9.
117 Kito Y, Kazui H, Kubo Y, Yoshida T, Takaya M, Wada T et al. Neuropsychiatric symptoms in patients with idiopathic normal pressure hydrocephalus. Behav Neurol. 2009;21(3):165–74.
118 Hudak A, Warner M, Marquez de la Plata C, Moore C, Harper C, Diaz-Arrastia R. Brain morphometry changes and depressive symptoms after traumatic brain injury. Psychiatry Res. 2011;191(3):160–5.
119 Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci. 1997;9(3):471–81.
120 Kales HC, Maixner DF, Mellow AM. Cerebrovascular disease and late-life depression. Am J Geriatr Psychiatry. 2005;13(2):88–98.
121 Vaishnavi S, Taylor WD. Neuroimaging in late-life depression. Int Rev Psychiatry. 2006;18(5):443–51.

122 Fujikawa T, Yamawaki S, Touhouda Y. Incidence of silent cerebral infarction in patients with major depression. Stroke. 1993;24(11): 1631–4.
123 Fujikawa T, Yamawaki S, Touhouda Y. Background factors and clinical symptoms of major depression with silent cerebral infarction. Stroke. 1994;25(4):798–801.
124 Geroldi C, Ferrucci L, Bandinelli S, Cavazzini C, Zanetti O, Guralnik JM et al. 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(8):1064–71.
125 Oh BH, Cheon JS. White matter lesions on magnetic resonance imaging in late-life depression. Psychogeriatrics. 2004;4:72–81.
126 Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging. 2002;23(3):421–31.
127 Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Clinical features of MRI-defined subcortical vascular disease. Alzheimer Dis Assoc Disord. 2003;17(4):236–42.
128 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. 2002;10(1):98–106.
129 Ellison JM, Kyomen HH, Verma S (eds). Mood Disorders in Later Life. Medical Psychiatry Series. 2009, Informa Healthcare USA: New York.
130 Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res. 2002;53(2):647–54.
131 West RL. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull. 1996;120(2):272–92.
132 Muhtz C, Zyriax BC, Klahn T, Windler E, Otte C. Depressive symptoms and metabolic risk: Effects of cortisol and gender. Psychoneuroendocrinology. 2009;34(7)1004–11.
133 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(1):46–55.
134 Kim JH, Kim JW, Ko YH, Choi CU, Na JO, Kim EJ et al. Coronary endothelial dysfunction associated with a depressive mood in patients with atypical angina but angiographically normal coronary artery. Int J Cardiol. 2009;143(2):154–7.
135 Smith PJ, Blumenthal JA, Babyak MA, Doraiswamy PM, Hinderliter A, Hoffman BM et al. Intima-media thickness and age of first depressive episode. Biol Psychol. 2009;80(3):361–4.
136 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(1–3):184–92.
137 Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS ONE. 2009; 4(1):e4144.
138 Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. Am J Prev Med. 2002;23(1):51–61.
139 Kopp MS, Rethelyi J. Where psychology meets physiology: chronic stress and premature mortality–the Central-Eastern European health paradox. Brain Res Bull. 2004;62(5):351–67.
140 Thomas AJ, O'Brien JT. Depression and cognition in older adults. Curr Opin Psychiatry. 2008;21(1):8–13.
141 Korczyn AD, Halperin I. Depression and dementia. J Neurol Sci. 2009; 283(1–2):139–42.
142 Lenze E, Cross D, McKeel D, Neuman RJ, Sheline YI. White matter hyperintensities and gray matter lesions in physically healthy depressed subjects. Am J Psychiatry. 1999;156(10):1602–7.
143 Lyness JM, Caine ED, Cox C, King DA, Conwell Y, Olivares T. Cerebrovascular risk factors and later-life major depression. Testing a small-vessel brain disease model. Am J Geriatr Psychiatry. 1998;6(1):5–13.
144 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(9):1499–501.
145 Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology. 2. Hyperintense white-matter foci in the elderly. AJR Am J Roentgenol. 1988;151(3):559–66.
146 Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology. 1. Lacunar infarction and Virchow-Robin spaces. AJR Am J Roentgenol. 1988;151(3):551–8.
147 Chimowitz MI, Estes ML, Furlan AJ, Awad IA. Further observations on the pathology of subcortical lesions identified on magnetic resonance imaging. Arch Neurol. 1992;49(7):747–52.
148 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;181:129–34.
149 Thomas AJ, O'Brien JT, Barber R, McMeekin W, Perry R. A neuropathological study of periventricular white matter hyperintensities in major depression. J Affect Disord. 2003;76(1–3):49–54.
150 Stuart BC, Simoni-Wastila L, Zhao L, Lloyd JT, Doshi JA. Increased persistency in medication use by U.S. Medicare beneficiaries with diabetes is associated with lower hospitalization rates and cost savings. Diabetes Care. 2009;32(4):647–9.
151 Tamashiro JH, Zung S, Zanetti MV, de Castro CC, Vallada H, Busatto GF et al. Increased rates of white matter hyperintensities in late-onset bipolar disorder. Bipolar Disord. 2008;10(7):765–75.
152 de Asis JM, Greenwald BS, Alexopoulos GS, Kiosses DN, Ashtari M, Heo M et al. Frontal signal hyperintensities in mania in old age. Am J Geriatr Psychiatry. 2006;14(7):598–604.
153 Depp CA, Jeste DV. Bipolar disorder in older adults: a critical review. Bipolar Disord. 2004;6(5):343–67.
154 Subramaniam H, Dennis MS, Byrne EJ. The role of vascular risk factors in late onset bipolar disorder. Int J Geriatr Psychiatry. 2007;22(8):733–7.
155 Lin HC, Tsai SY, Lee HC. Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study. J Affect Disord. 2007;100(1–3):49–54.
156 Wijeratne C, Malhi GS. Vascular mania: an old concept in danger of sclerosing? A clinical overview. Acta Psychiatr Scand Suppl. 2007; (434):35–40.
157 Gold G, Kovari E, Hof PR, Bouras C, Giannakopoulos P. Sorting out the clinical consequences of ischemic lesions in brain aging: a clinicopathological approach. J Neurol Sci. 2007;257(1–2):17–22.
158 Freeman SH, Kandel R, Cruz L, Rozkalne A, Newell K, Frosch MP et al. Preservation of Neuronal Number Despite Age-Related Cortical Brain Atrophy in Elderly Subjects Without Alzheimer Disease. J Neuropathol Exp Neurol. 2008;67(12):1205–12.
159 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(8):1055–63.
160 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. 2002;52(6): 543–58.
161 Alexopoulos GS. Vascular disease, depression, and dementia. J Am Geriatr Soc. 2003;51(8):1178–80.
162 Reeves RR, Rose ES. Depression and Vascular Disease: Conceptual Issues, Relationships and Clinical Implications. Vascular Disease Prevention. 2006;3:193–203.
163 Santos M, Kövari E, Gold G, Bozikas VP, Hof PR, Bouras C et al. The neuroanatomical model of post-stroke depression: towards a change of focus? Journal of the Neurological Sciences. 2009;283:158–162.
164 O'Brien JT, Firbank MJ, Krishnan MS, van Straaten EC, van der Flier WM, Petrovic K et al. White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: the LADIS study. Am J Geriatr Psychiatry. 2006;14(10):834–41.