



Published in final edited form as:

*Neuron*. 2013 November 20; 80(4): . doi:10.1016/j.neuron.2013.10.008.

## The pathobiology of vascular dementia

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### Abstract

Vascular cognitive impairment defines alterations in cognition, ranging from subtle deficits to full-blown dementia, attributable to cerebrovascular causes. Often coexisting with Alzheimer's disease, mixed vascular and neurodegenerative dementia has emerged as the leading cause of age-related cognitive impairment. Central to the disease mechanism is the crucial role that cerebral blood vessels play in brain health, not only for the delivery of oxygen and nutrients, but also for the trophic signaling that links inextricably the well being of neurons and glia to that of cerebrovascular cells. This review will examine how vascular damage disrupts these vital homeostatic interactions, focusing on the hemispheric white matter, a region at heightened risk for vascular damage, and on the interplay between vascular factors and Alzheimer's disease. Finally, preventative and therapeutic prospects will be examined, highlighting the importance of midlife vascular risk factor control in the prevention of late-life dementia.

### Introduction

Age related dementia, an irreversible condition resulting in progressive cognitive decline, has emerged as one of the leading health problems of our time. Advances in prevention and healthcare have increased life expectancy and produced a shift in the burden of disease worldwide. Thus, non-communicable diseases, including dementia, have been recognized for the first time as the major threat to the world population (World Health Organization, 2012). The World Health Organization estimates that 35.6 million people live with dementia, a number that is anticipated to triple by 2050 (World Health Organization, 2012). Every year 7.7 million new cases of dementia are diagnosed, imposing a tremendous burden on families, the primary caregivers, and financial cost to society. Although recent data suggest a decline in prevalence (Matthews et al., 2013), dementia remains a devastating and costly disease. In the US such cost has already surpassed that of cancer and heart diseases (Hurd et al., 2013). The realization of its paramount public health impact has led nations, including the US, to develop national plans to cope with dementia and attempt to reduce its devastating effects (National Alzheimer's Project Act; Public Law 111-375).

Vascular dementia, a heterogeneous group of brain disorders in which cognitive impairment is attributable to cerebrovascular pathologies, is responsible for at least 20% of cases of dementia, being second only to Alzheimer's disease (AD) (Gorelick et al., 2011). Recent clinical-pathological studies have highlighted the role of cerebrovascular disease, not only as a primary cause of cognitive impairment, but also as an adjuvant to the expression of

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dementia caused by other factors, including AD and other neurodegenerative pathologies (Gorelick et al., 2011; Schneider et al., 2007a; Toledo et al., 2013). At the same time, new experimental findings have revealed a previously unrecognized functional and pathogenic synergy between neurons, glia and vascular cells (Iadecola, 2010; Quaegebeur et al., 2011; Zlokovic, 2011), providing a new framework to reevaluate how alterations in cerebral blood vessels could contribute to the neuronal dysfunction underlying cognitive impairment. These advances call for a re-appraisal of the role of vascular factors in cognitive health. To this end, the major cerebrovascular causes of cognitive dysfunction will be briefly reviewed, focusing on neuropathology, emerging mechanisms and overlap with neurodegeneration.

## Dementia through the ages

In Alois Alzheimer's time (1900s), dementia was thought to be caused predominantly by "hardening of the arteries" (arteriosclerotic dementia) (Bowler, 2007; Jellinger, 2006). Vascular factors were considered a major player in dementia well into the 20<sup>th</sup> century, until, in the 1980s, the A $\beta$  peptide was identified as the main component of parenchymal (amyloid plaque) and vascular (amyloid angiopathy) amyloid deposits, pathological hallmarks of AD (Glennner and Wong, 1984; Kang et al., 1987). Shortly after, mutations in the amyloid precursor protein (APP) gene were identified in familial forms AD (Bertram and Tanzi, 2008). Since then, the emphasis shifted from vascular dementia to AD, a process defined as the "Alzheimerization of dementia" (fig. 1) (Bowler, 2007). However, an increasing appreciation of the impact of cerebrovascular lesions on AD brought to the forefront the importance of cerebrovascular health in cognitive function (Esiri et al., 1999; Gold et al., 2007; Snowden et al., 1997). Furthermore, community based clinical-pathological studies revealed that the largest proportion of dementia cases have mixed pathology, comprising features of AD (amyloid plaques and neurofibrillary tangles) as well as ischemic lesions (Launer et al., 2008; Schneider et al., 2009). These developments have promoted an interest to gain a better understanding of how vascular brain lesions affect cognition, and how vascular pathology and neurodegeneration interact to amplify their respective pathogenic contribution.

## Defining dementia on vascular bases: From arteriosclerotic dementia to vascular cognitive impairment

The concept of dementia caused by cerebrovascular pathology has evolved considerably over the years (fig. 2). For many decades vascular dementia was attributed to sclerosis of cerebral arteries leading to diffuse ischemic injury and brain atrophy (Jellinger, 2006). The first significant departure from this concept, inspired by the work of Tomlinson and colleagues (Tomlinson et al., 1970), was proposed by Hachinski and colleagues (Hachinski et al., 1974), who suggested that dementia on vascular bases was caused by multiple and discrete ischemic lesions in patients with vascular risk factors, such as hypertension (multi-infarct dementia) (figs. 2, 3). The construct of multi-infarct dementia, by attributing cognitive impairment to multiple strokes, raised the possibility that preventing cerebrovascular diseases could also prevent dementia (Hachinski et al., 1974). The introduction of brain imaging led to the realization that diffuse white matter lesions, termed leukoaraiosis (Hachinski et al., 1987), were a frequent correlate of cognitive impairment, much more common than multiple infarcts, which turned out to be a rare cause of dementia (Hulette et al., 1997) (fig. 2, 3). Genetic causes of white matter lesions were discovered, the prototypical one being the Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (Chabriat et al., 2009). In the early 90s the criteria for diagnosis of vascular dementia were largely based on those used for AD, which emphasized memory impairment, irreversibility of the deficits, and impaired activities of daily living (Roman et al., 1993). This definition was felt to be restrictive since it did not

take into due consideration cognitive deficits more commonly associated with cerebrovascular lesions, such as executive dysfunction and psychomotor slowing (supplemental table 1). Therefore, the term vascular cognitive impairment (VCI) was introduced to better reflect the full range of cognitive alterations resulting from vascular factors (Hachinski and Bowler, 1993) (fig. 2). By doing so, it was hoped that the vascular nature of the cognitive deficit could be recognized early, providing the opportunity to slow down disease progression by controlling vascular risk factors (Hachinski and Bowler, 1993). The concept of VCI has gained wide acceptance and is currently defined as “*a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain*” (Gorelick et al., 2011), vascular dementia being the most severe form of VCI.

## The neurovascular unit: blood flow regulation and beyond

The fundamental role that cerebral blood vessels play in the broad spectrum of pathologies underlying cognitive impairment highlights the importance of vascular structure and function in brain health. Owing to its high energy needs and lack of fuel reserves, the brain requires a continuous and well-regulated supply of blood (Iadecola, 2004). Most energy is used by neurons to fuel ionic pumps to maintain and restore the ionic gradients dissipated by synaptic activity (Harris et al., 2012). Due to fewer synapses, white matter energy usage, and consequently blood flow, is 1/3 lower of that of the gray matter (Harris and Attwell, 2012). The brain vasculature has an intimate developmental, structural and functional relationship with the brain tissue, their cellular elements forming a functional domain termed the neurovascular unit (Iadecola, 2004). Due to their intimate association with brain cells, cerebral blood vessels have unique characteristics that sets them apart from vessels in other organs (Abboud, 1981; Bevan, 1979; Quaegebeur et al., 2011). The salient structural and functional features of the cerebral circulation are briefly examined next.

## The brain vascular network and neurovascular unit

The brain is supplied by arteries arising from the circle of Willis, a polygon of interconnected vessels at the base of the brain formed by the confluence of the internal carotid arteries and the basilar artery (fig. 4). The main vessels arising from the circle of Willis - the anterior middle and posterior cerebral arteries, and their branches - give rise to a rich anastomotic network on the brain surface (pial arteries and arterioles). Pial vessels are endowed with a smooth muscle cell coat, which surrounds a monolayer of endothelial cells (fig. 4). Pial arterial branches dive into the brain substance, giving rise to smaller arterioles still surrounded by an extension of the subarachnoid space filled with cerebrospinal fluid (perivascular space or Virchow-Robin space) (fig. 4). Delimited by the vascular basement membrane and the basement membrane of the glia limitans (fig. 4) (Dyrna et al., 2013), the perivascular space has emerged as critically important for the disposal of unwanted proteins and peptides, e.g., A $\beta$  (Carare et al., 2013; Iliff et al., 2013; Laman and Weller, 2013). As intracerebral arterioles reach deeper into the brain parenchyma and become smaller (diameter <100 $\mu$ m), the perivascular space disappears and the vessel's basement membrane enters in direct contact with the glial basement membrane enveloping the end-feet of astrocytes (fig. 4). In capillaries, smooth muscle cells are replaced by pericytes, contractile cells that are particularly abundant in brain vessels and are involved in the development and maintenance of the BBB (Armulik et al., 2010; Bell et al., 2010; Quaegebeur et al., 2011).

The “outside in” vascularization pattern of the brain differs from that of other major organs, like the kidney and liver that are vascularized from the “inside out”, and places key vessels regulating intracerebral blood flow, the pial arterioles, outside the brain parenchyma. Consequently, elaborate vascular signaling mechanisms coordinate changes in vascular diameter of pial arterioles on the brain's surface with those of the intracerebral

microvasculature (Bagher and Segal, 2011; Iadecola, 2004). Another consequence of this vascular arrangement is that occlusion of penetrating arterioles or venules, unlike pial vessels, cannot be effectively compensated by anastomotic branches (Blinder et al., 2013), and results in reductions in flow sufficient to produce small ischemic lesions akin to microinfarcts (Nguyen et al., 2011; Nishimura et al., 2010; Shih et al., 2013). In addition, regions of the deep white matter are supplied by long penetrating arterioles arising from the pial cortical network at the border between non-overlapping vascular territories of the anterior and middle cerebral arteries, and as such are more vulnerable to reductions in blood flow (Brown and Thore, 2011; De Reuck, 1971) (fig. 4). On the other hand, the basal ganglia and brainstem are supplied by penetrating arterioles arising directly from the circle of Willis and its proximal branches (fig. 4), rendering these vessels more susceptible to the mechanical stresses imposed by chronic hypertension or stiffening of large arteries (Scuteri et al., 2011; Sörös et al., 2013).

### Neurovascular control mechanisms

The brain is endowed with vasoregulatory mechanisms that assure that it receives enough blood to support the energy needs to its cellular constituents. Consequently, neural activity, which uses most of the brain's energy budget, is the major determinant of the dynamic regulation of CBF. The increases in blood flow induced by activation depend on the concerted action of neurons, astrocytes and vascular cells through a wide variety of molecular signals including ions, arachidonic acid metabolites, nitric oxide (NO), adenosine, neurotransmitters and neuropeptides (Drake and Iadecola, 2007). The hemodynamic changes underlying the increases in blood flow are mediated by vasoactive agents with opposing vascular actions (vasodilatation or vasoconstriction), generated by synaptic activity, astrocytes, interneurons, and afferent projections from the basal forebrain and brainstem (Cauli and Hamel, 2010; Drake and Iadecola, 2007; Kleinfeld et al., 2011). These highly coordinated signals converge on specific sites of the cerebrovascular network to shape the hemodynamic response to neural activation with a remarkable degree of spatial and temporal precision (Iadecola, 2004). Thus, the regional hemodynamic changes induced by activation are widely used to localize neuronal activity in the living brain using functional imaging (Attwell and Iadecola, 2002).

Like in other organs, endothelial cells regulate vascular tone by releasing vasoactive factors in response to chemical signals, e.g., transmitters (Andresen et al., 2006), or mechanical forces, e.g., shear stress (Ando and Yamamoto, 2013). Unlike other organs, cerebral endothelial cells in most brain regions are adjoined by intricate junctional complexes formed by occludins and claudins (tight junctions) that prevent the bidirectional exchange of hydrophilic substances between blood and the brain, a key feature of the BBB (Dyrna et al., 2013). Rather, specialized transport proteins on the endothelial cell membrane control the traffic of solutes in and out of the brain. For example, GLUT1 and amino acid transporters regulate the transfer of glucose and amino acids into the brain, whereas "efflux transporters", such as LRP-1, ABC transporters and others, remove drugs and metabolic by-products from the brain, including A and lactate (Neuwelt et al., 2011).

Vascular smooth muscle cells, owing to their ability to constrict when intravascular pressure increases (myogenic tone), adjust vascular tone in response to changes in arterial pressure to maintain CBF relatively constant within a range of pressures (cerebrovascular autoregulation) (Cipolla, 2010). Autoregulation protects cerebral blood vessels from the wide swings in arterial pressure associated with the activities of daily living, and provides a stable CBF baseline on which the dynamic changes induced by neurovascular coupling and endothelium are superimposed. These neurovascular control mechanisms work in concert to assure that the brain receives sufficient blood flow to meet the metabolic needs of its active cellular constituents.

## Trophic coupling in the neurovascular unit

Neurons, astrocytes, oligodendrocytes, as well as vascular and perivascular cells are in state of close trophic and metabolic co-dependence that plays a defining role in brain development, function and reaction to injury. In the developing nervous system, prototypical neural guidance signals, ephrins, netrins, slit glycoproteins and semaphorins, also contribute to endothelial tip cell guidance (Carmeliet and Jain, 2011). In turn, classical angiogenic molecules, such as VEGF, participate in neurogenesis (neurovascular niche), neuronal cell migration, axon guidance, dendritogenesis, and oligodendrocyte precursor migration (Butler et al., 2010; Carmeliet and Ruiz de Almodovar, 2013; Quaegebeur et al., 2011). In the adult nervous system, neuroblasts migrate along blood vessels, a process dependent on BDNF secretion by endothelial cells (Snapyan et al., 2009). Endothelial cells have the potential to stimulate the proliferation of neuronal precursors and to stir their differentiation toward the neuronal lineage (Shen et al., 2004). Furthermore, through BDNF, insulin growth factor 2, chemokine (C-X-C motif) ligand 12, and pleiotrophin, endothelial cells support neuronal survival and protect them from injury (Dugas et al., 2008; Guo et al., 2008). Endothelial cells can also promote the proliferation and survival of oligodendrocytes (oligovascular niche) by activating the Akt/PI3 kinase pathway through BDNF and FGF (Arai and Lo, 2009). In addition to their well established interactions with neurons, astrocytes are also needed for the development and maintenance of BBB characteristics in endothelial cells (Wolburg et al., 2009), and for the reorganization of vascular networks after brain injury (Hayakawa et al., 2012). In turn, endothelial cells regulate glycolytic metabolism in astrocytes through the production of NO (Brix et al., 2012). Therefore, neurovascular cells are trophically and metabolically interdependent, such that damage to one cell type removes a vital source of support to the whole unit and has deleterious consequences also for the other cell types.

## Immune trafficking and regulation

The cells of the neurovascular unit are involved in the initiation and expression of adaptive and innate immune responses of the brain. Pericytes and perivascular macrophages have the potential for antigen presentation, the first step in adaptive immunity, whereas endothelial cells and microglia are richly endowed with innate immunity receptors including CD36, toll like receptors (TLR) and the receptor for advanced glycation end-products (RAGE) (Lampron et al., 2013; Park et al., 2011). The perivascular space, which drains into the subarachnoid space and then into cervical lymph nodes (Laman and Weller, 2013), is the “afferent arm” through which brain antigens reach the systemic immune system (Galea et al., 2007). The cells of the neurovascular unit also regulate the “efferent arm” of the immune system, which relies on the transfer of effector immune cells into the brain. In conditions of hypoxia-ischemia, endothelial cells express adhesion receptors, such as P-selectin, E-selectin, ICAM, VCAM, instrumental for the transfer of circulating leukocytes into the perivascular space (Iadecola and Anrather, 2011). In turn, perivascular macrophages, located in contact with the vascular basement membrane, are required for inflammatory cells, such as lymphocytes, to cross the glial basement membrane and move from the perivascular space into the brain parenchyma (Tran et al., 1998). Astrocytes express “death” ligands (CD95L) on their perivascular end feet, and control immune trafficking by triggering apoptosis of CD95+ lymphocytes attempting to enter the brain (Bechmann et al., 1999). Therefore, the neurovascular unit is an important checkpoint regulating the afferent and efferent arms of the immune system and shaping the immune responses of the brain. Vital to vascular homeostasis are circulating endothelial progenitor cells (EPC), hematopoietic stem cells involved in the maintenance and repair of endothelial cells (Hill et al., 2003). EPC development and function is controlled by CD31+ T-cells (angiogenic T-cells) through the release proangiogenic cytokines (Hur et al., 2007; Kushner et al., 2010). Thus, immune cells are also involved in the maintenance of vascular homeostasis.



## Cerebrovascular pathologies underlying cognitive impairment are diverse

Considering the vital importance of the cerebral blood supply for the structural and functional integrity of the brain, it is not surprising that alterations in cerebral blood vessels have a profound impact on cognitive function. The vascular alterations that cause cognitive impairment are diverse, and include systemic conditions affecting global cerebral perfusion or alterations involving cerebral blood vessels, most commonly small size arterioles or venules (fig. 5). Table 1 describes some of the most common conditions, their vascular bases, and neuropathological correlates (see (Jellinger, 2013) for a more complete list).

### Reduced cerebral perfusion and post-stroke dementia

Reduction in global cerebral perfusion caused by cardiac arrest, arrhythmias, cardiac failure, or hypotension can produce brain dysfunction and impair cognition transiently or permanently (table 1) (Alosco et al., 2013; Justin et al., 2013; Marshall, 2012; Stefansdottir et al., 2013). High-grade stenosis or occlusion of the internal carotid arteries is associated with chronic ischemia and can lead to cognitive impairment even in the absence of ischemic lesions (Balestrini et al., 2013; Cheng et al., 2012; Johnston et al., 2004; Marshall, 2012) (fig. 5).

On the other hand, if the reduction in CBF is sustained and severe, ischemic stroke ensues (Moskowitz et al., 2010). Stroke doubles the risk for dementia (post-stroke dementia), and approximately 30% of stroke patients go on to develop cognitive dysfunction within 3 years (Allan et al., 2011; Leys et al., 2005; Pendlebury and Rothwell, 2009). The association between stroke and dementia is also observed in patients younger than 50 years, up to 50% of whom exhibit cognitive deficits after a decade (Schaapsmeeders et al., 2013). As mentioned, multiple infarcts, caused by multiple arterial occlusions over time, are well known to impair cognition (multi-infarct dementia), as can a single infarct located in a brain region critical for cognitive function, such as frontal lobe or thalamus (table 1) (strategic infarct dementia) (fig. 3). However, ischemic strokes are often associated with many of the vascular pathologies described below, which also contribute to the total vascular burden.

### Small vessel disease, leukoaraiosis and lacunar infarcts

By far, the most prevalent vascular lesions associated with VCI are related to alterations in small vessels in the hemispheric white matter (Jellinger, 2013). These microvascular alterations result in different neuropathological lesions, which can occur in isolation but, more typically, coexist in the same brain (table 1). Confluent white matter lesions, the imaging correlate of which is termed leukoaraiosis (fig. 3), and lacunes, small (<1.5 cm) white matter infarcts typically in the basal ganglia, are common occurrence in VCI and are strongly associated with cardiovascular risk factors, especially hypertension, diabetes, hyperlipidemia and smoking (Gorelick et al., 2011; Wardlaw et al., 2013b). The vascular pathologies underlying these lesions consist of atherosclerotic plaques affecting small cerebral vessels, deposition of a hyaline substance in the vascular wall (lipohyalinosis), fibrotic changes in the vessel wall resulting in stiffening and microvascular distortion (arteriolosclerosis), and total loss of integrity of the vascular wall (fibrinoid necrosis) (fig. 5) (Thal et al., 2012). Arterioles become tortuous, have thickened basement membranes and are surrounded by enlarged perivascular spaces (Brown and Thore, 2011). Capillaries are reduced in number and “string vessels”, non-functional capillaries that have lost endothelial cells and have only a basement membrane, are observed (Brown and Thore, 2011). Collagen deposits are observed in venules (venous collagenosis) (Black et al., 2009; Brown and Thore, 2011). The white matter damage resulting from these lesions consists of vacuolation, demyelination, axonal loss, and lacunar infarcts. The white matter lesions generally correspond to hyperintensities observed on MRI, which, however, can also reflect other

pathological substrates (Gouw et al., 2011). The white matter lesions evolve over time by expansion of existing lesions, rather than formation of new foci (Maillard et al., 2012), resembling the patterns of progression of amyloid angiopathy (Alonzo et al., 1998; Robbins et al., 2006). The expansion of the white matter lesions correlates with the evolution of the cognitive impairment (Maillard et al., 2012), new lacunes causing a steeper decline, especially in motor speed and executive functions (Jokinen et al., 2011). White matter lesions and lacunar infarcts are also present in uncommon genetic conditions resulting in VCI and vascular dementia (Federico et al., 2012; Schmidt et al., 2012). The better studied of these, CADASIL, is associated with extensive leukoariosis and lacunar infarcts (Chabriat et al., 2009). CADASIL vascular lesions are related to accumulation of granular osmiophilic material (GOM) in vascular and perivascular cells, which include the Notch 3 ectodomain (Yamamoto et al., 2013).

### **Microinfarcts and microhemorrhages**

Microscopic infarcts (microinfarcts) and hemorrhages (microbleeds) (fig. 5) are independent predictors of cognitive dysfunction, but are commonly associated with other vascular pathologies, such as leukoariosis, lacunar infarcts, large infarcts, and hemorrhage (Smith et al., 2012; van Norden et al., 2013), as well as CADASIL and AD (table 1). Microinfarcts are sharply delineated lesions consisting of pallor, necrosis, cavitation and inflammation (astrocytosis, microgliosis and macrophage infiltration) (Thal et al., 2012), caused by the small vessel pathology described above (table 1). Microbleeds are microscopic areas of blood extravasation from leaky arterioles, which are restricted to the perivascular space and do not disrupt the brain parenchyma (De Reuck, 2012). Observed in 17% of demented patients (Cordonnier and van der Flier, 2011), cortical microbleeds are frequently associated with cerebral amyloid angiopathy (CAA), whereas microbleeds in deep regions tend to be associated with white matter disease secondary to vascular risk factors (De Reuck, 2012; Park et al., 2013a).

### **Cerebral amyloid angiopathy**

It is well known that deposits of A $\beta$  in cerebral blood vessels or CAA are associated with vascular cognitive impairment. Although inherited forms of CAA have been described, CAA is most prevalent in AD, being present in over 90% of cases (Attems et al., 2011; Charidimou et al., 2012). CAA is also observed in demented (50–60%) and non-demented (20–40%) elderly people (Attems et al., 2011; Charidimou et al., 2012). The major risk factor for CAA is advanced age, and cardiovascular risk factors seem to play a lesser role (Charidimou et al., 2012). CAA is a major cause of microbleeds and large hemorrhages, typically located in the cortex (lobar hemorrhages) (Auriel and Greenberg, 2012). The amyloid accumulation occurs in the media and the adventitia of cerebral vessels, leading to degeneration of smooth muscle cells and pericytes (Thal et al., 2012). In extreme cases, the vascular wall develops fibrinoid necrosis and the vessels assume a characteristic double barrel appearance (Thal et al., 2012).

### **Mixed lesions**

Overlap of AD neuropathology (amyloid plaques and neurofibrillary tangles) with cerebrovascular lesions is observed in up to 50% of cases of dementia (Jellinger, 2013). These lesions include atherosclerosis of the circle of Willis and its branches, leukoariosis and lacunar infarcts, microbleeds, microinfarcts, and CAA (Benedictus et al., 2013; Charidimou et al., 2012; Honig et al., 2005; Jellinger, 2013; Richardson et al., 2012; Roher et al., 2004; Toledo et al., 2013; Yarchoan et al., 2012). Ischemic lesions in regions between arterial territories (watershed infarcts) have also been reported in AD, implicating hypoperfusion and CAA in their mechanisms (Miklossy, 2003; Suter et al., 2002). Vascular lesions are also present in other age related neurodegenerative diseases, such as

synucleinopathies, hippocampal sclerosis and frontotemporal lobar degeneration linked to tau or TDP-43, but the coexistence with AD is the most frequent (Toledo et al., 2013).

### How do vascular factors cause cognitive impairment?

As reviewed above, VCI can stem from a wide variety of cardiovascular and cerebrovascular pathologies, but it has been difficult to pin down the contribution of each condition to cognitive dysfunction because of the coexistence of the different lesions and overlap with neurodegenerative pathology (Gorelick et al., 2011). Reductions in global cerebral perfusion, such as those caused by heart diseases or carotid artery stenosis/occlusion, if below a critical threshold, can impair cognition independently of brain lesions (Marshall et al., 2012). Reductions in CBF by 40–50% are associated with suppression of brain activity and cognitive dysfunction, which are reversible upon re-establishing normal CBF levels (Marshall et al., 1999; Marshall, 2012; Tatemichi et al., 1995). As for the other pathologies underlying VCI, there is a general correlation between the total burden of vascular pathology and cognitive deficits (Gelber et al., 2012; Gorelick et al., 2011; Inzitari et al., 2009). A caveat is that, due to confounding factors, such as overlap with AD, differences in educational level (see below), and microscopic pathology not seen by *in vivo* imaging, the exact parameters of the relationship have been hard to define (Black et al., 2009; Brickman et al., 2011). However, there is general consensus that cognitive impairment results from the brain dysfunction caused by cumulative tissue damage (Gorelick et al., 2011), as originally proposed by Tomlinson et al. for large cerebral infarcts (Tomlinson et al., 1970).

In addition to gray matter damage, disruption of the white matter can have profound effects on the precision and fidelity of the information transfer underlying brain function and cognitive health (Nave, 2010a). Fast-conducting myelinated white matter tracts are responsible for long range connectivity, interhemispheric synchronization and neurotrophic effects through spike timing dependent plasticity and axonal transport (Dan and Poo, 2004; Nave, 2010a; Stone and Tesche, 2013). Indeed, white matter lesions affect brain structure and function broadly, and are associated with reductions in frontal lobe glucose utilization (Decarli et al., 1995; Haight et al., 2013; Tullberg et al., 2004), global reduction in cortical blood flow (Appelman et al., 2008; Chen et al., 2013a; Dam et al., 2007; Kobari et al., 1990), disruption of brain connectivity (Lawrence et al., 2013; Sun et al., 2011) and cerebral atrophy (Appelman et al., 2009). In addition, since myelination of previously naked fibers participates in neuroplasticity and skilled motor learning (Fields, 2010; Richardson et al., 2011), myelin damage could also compromise these important functions and contribute to cognitive impairment.

### Risk factors for vascular cognitive impairments

Ascertaining the genetic and modifiable risk factors of VCI is problematic due to the multiplicity of underlying pathologies, coexistence with cardiovascular diseases, and the frequent overlap with AD and other neurodegenerative diseases (Gorelick et al., 2011). Therefore, the risk attributable to specific factors remains unclear, although the recent development of biomarkers for *in vivo* AD diagnosis (Hampel et al., 2012) promises to alleviate this problem.

Advanced age is a powerful risk factor for VCI, and the prevalence and incidence of cognitive impairment increases exponentially after age 65 (Gorelick et al., 2011). The level of education, a surrogate marker of cognitive reserves (Stern, 2012), is an important determinant of the expression of VCI, such that for a given level of neuropathology higher education is associated with less cognitive deficits (Zieren et al., 2013). However, the education level does not influence the rate of progression of VCI and no longer has an



impact in advanced disease (Elbaz et al., 2013; Zieren et al., 2013). Although education could account for individual differences in the susceptibility to cognitive impairment given comparable burdens of disease, socioeconomic status, coexisting chronic diseases, ethnicity, and pre-morbid intellectual capacity are important confounders (Gorelick et al., 2011).

Vascular risk factors, including hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, and hyperhomocystinemia, increase the risk of dementia independently of the associated increase in stroke risk (Sahathevan et al., 2012). Furthermore, the metabolic syndrome, including insulin resistance, hypertension and dyslipidemia, has been associated with lower cognitive performance (Yates et al., 2012). However, recurrent stroke is one of the strongest predictors of dementia onset (Pendlebury and Rothwell, 2009). Remarkably, in VCI as in AD, the increase in risk afforded by vascular risk factors is observed decades later, a finding that may explain why some studies did not find a cognitive improvement with risk factor control later in life (Sahathevan et al., 2012).

A host of rare genetic mutations are associated with VCI (Federico et al., 2012; Schmidt et al., 2012). The most common of these is the CADASIL syndrome caused by a frame shift mutation of *Notch-3* that either creates or eliminates a cysteine residue (Chabriat et al., 2009). Other hereditary cerebral vasculopathies include familial CAAs caused by mutations or duplications of *APP* (Auriel and Greenberg, 2012; Rannikmäe et al., 2013), the cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) caused by mutation of the TGF $\beta$  repressor *HTRA1*, the autosomal dominant retinal vasculopathy with cerebral leukodystrophy caused by frameshift deletions in the exonuclease *TREX1*, and mutations of the *COL4A1* gene encoding the type IV collagen alpha 1 chain (Federico et al., 2012; Gorelick et al., 2011; Lanfranconi and Markus, 2010). The ApoE 4 allele is a well-established susceptibility gene for increased cardiovascular risk and Alzheimer disease (Verghese et al., 2011). The ApoE4 allele is associated with increased risk of CAA, whereas both ApoE2 and 4 increase the risk of lobar hemorrhages (Charidimou et al., 2012). Nevertheless, a strong link between ApoE and sporadic VCI has not been established (Lee and Kim, 2013; Yu et al., 2013). Studies of candidate genes have revealed weak associations with genes involved in the renin-angiotensin system, endothelial nitric oxide synthase, oxidative stress, lipid metabolism and inflammation, but have not been replicated (Fornage et al., 2011; Lee and Kim, 2013; Markus, 2008). GWAS of vascular dementia have shown small effect of SNPs in the androgen receptor gene locus (Schrijvers et al., 2012), a finding not observed in all ethnic groups (Lee and Kim, 2013). The diversity of pathologies underlying VCI and the overlap with AD complicate the interpretation of these studies. Linkage studies in patients with white matter lesions on MRI have discovered several loci (Schmidt et al., 2012), but no specific gene has been identified and the findings await replication and validation (Lee and Kim, 2013; Markus, 2008).

## Pathogenic mechanisms responsible for white matter injury

Although as described in the previous section severe ischemia resulting from arterial occlusion can lead to brain damage and VCI, e.g., multi-infarct dementia, cognitive dysfunction is most often associated with more subtle vascular alterations targeting predominantly the deep hemispheric white matter (fig. 5). Here we examine the major pathogenic mechanisms leading to white matter damage, inferred either from brain imaging and post-mortem studies in humans, or animal models (fig. 6).

### Hypoperfusion and hypoxia

Owing to their location at the distal border between different vascular territories (De Reuck, 1971) (fig 4) and to the susceptibility of their vasculature to risk factors (Brown and Thore, 2011), deep white matter tracts are particularly vulnerable to vascular insufficiency. Even in

healthy individuals, hypercapnia, a potent vasodilator, does not increase, but reduces, CBF in the periventricular white matter, suggesting that vasodilatation of upstream vessels diverts blood flow to other regions (intracerebral steal) (Mandell et al., 2008). This finding highlights the hemodynamic precariousness of the periventricular white matter, even in the absence of vascular damage.

Increasing evidence suggests that the white matter cerebral blood supply is compromised in VCI (fig. 6). Resting flow is reduced in areas of leukoaraiosis and vascular reactivity attenuated (Kobari et al., 1990; Makedonov et al., 2013; Markus et al., 2000; 1994; Marstrand et al., 2002; O'Sullivan et al., 2002; Yao et al., 1992). In patients with VCI risk factors, like hypertension and diabetes, the ability of neural activity to increase blood flow in brain or retina is compromised (Delles et al., 2004; Jennings et al., 2005; Sorond et al., 2011). Cerebrovascular autoregulation is impaired, increasing the susceptibility of the white matter to damage during fluctuation in blood pressure (Matsushita et al., 1994). Interestingly, CBF alterations have also been described in normal appearing white matter (O'Sullivan et al., 2002), suggesting that the flow reduction precedes and, as such, may contribute to the white matter damage. Indeed, in the general population, lower global CBF and lower cerebrovascular reactivity to hypercapnia is associated with a greater volume of white matter lesions (Bakker et al., 1999; Vernooij et al., 2008). The CBF reduction is observed prior to the onset of dementia (Ruitenberget al., 2005). Due to their hemodynamic vulnerability, deep white matter regions are marginally perfused, and, in the presence of vascular risk factors, their vessels may be unable to adapt CBF to the metabolic needs of the tissue. Consistent with this hypothesis, post-mortem studies have shown that areas of leukoaraiosis are chronically hypoxic, as indicated by the expression of hypoxia inducible factors and related hypoxia-inducible genes (Fernando et al., 2006; Rosenberg et al., 2001).

In addition to local factors affecting white matter microvessels, broader-acting systemic factors are also involved. White matter lesions and lacunar strokes are associated with increases in circulating levels of the NO synthase inhibitor asymmetric dimethylarginine (ADMA) (Notsu et al., 2009; Pikula et al., 2009; Rufa et al., 2008). ADMA may contribute to the impairment of NO-dependent vasodilatation in peripheral and cerebral arteries (Chen et al., 2006; Knottnerus et al., 2009; Pretnar-Oblak et al., 2006; Stevenson et al., 2010). Furthermore, stiffness of large vessels and increased pulsatility are associated with reduced white matter CBF and are strong predictors of leukoaraiosis and lacunes (Brisset et al., 2013; Tarumi et al., 2011; Webb et al., 2012), independently of vascular risk factors (Kearney-Schwartz et al., 2009). These findings implicate loss of large artery elasticity and increased pulsatile stress on microvessels, especially those branching directly from the circle of Willis, in the microvascular damage underlying white matter lesions (Scuteri et al., 2011). Similar microvascular changes occur also in other organs, suggesting that small vessel disease in brain may be the manifestation of a systemic vasculopathy (Thompson and Hakim, 2009).

### **Increased blood-brain barrier permeability**

Reflecting another aspect of endothelial dysfunction, alterations in BBB permeability are also associated with leukoaraiosis and lacunar stroke (Wardlaw et al., 2013a; Yang and Rosenberg, 2011). Several lines of evidence indicate that the BBB is disrupted in the course of the disease. First, the plasma protein albumin is increased in the CSF of patient with VCI, reflecting BBB breakdown (Candelario-Jalil et al., 2011). Second, plasma proteins, including complement, fibrinogen, albumin and immunoglobulins are detected in astrocytes in white matter lesions (Akiguchi et al., 1998; Alafuzoff et al., 1985; Simpson et al., 2007; Tomimoto et al., 1996). Third, the permeability to MRI tracers is increased in white matter lesions (Hanyu et al., 2002; Taheri et al., 2011; Wardlaw et al., 2009) and in normal appearing white matter (Topakian et al., 2010). The latter finding suggests that the BBB

disruption could precede white matter injury and contribute to its development. BBB leakiness in white matter was found in lacunar strokes, but not cortical strokes (Wardlaw et al., 2008), raising the possibility of a specific association with small vessel disease of the deep white matter.

Several factors could contribute to the BBB disruption (Rosenberg, 2012). Hypoxia-ischemia, which has been demonstrated in white matter lesions, is well known to damage endothelial cells leading to increased BBB leakage in vitro (Ahmad et al., 2012). In vivo, hypoperfusion produced by bilateral carotid stenosis in rat increases BBB permeability (Ueno et al., 2002). In a similar model, the BBB alteration was found to be due to MMP9 production by oligodendrocyte precursors, which are increased in ischemic white matter injury in rodent models (Seo et al., 2013) and in patients with VCI (Candelario-Jalil et al., 2011). In stroke prone spontaneously hypertensive rats, which have a strong vascular risk factor profile, a high salt diet induces fast-developing vasculopathy with BBB leakage that leads to ischemic injury in the absence of arterial occlusions (Schreiber et al., 2013). This finding indicates that chronic BBB disruption has the potential of induce ischemic damage. Indeed, vascular risk factors, and the associated oxidative stress and vascular inflammation also alter BBB permeability and could play a role.

### Oxidative stress and inflammation

Pathological studies have shown markers of oxidative stress (isoprostanes) and inflammation (cytokines and adhesion molecules) in the damaged white matter associated with VCI (Back et al., 2011; Candelario-Jalil et al., 2011; Fernando et al., 2006). Furthermore, microglial activation and reactive astrocytes are also present in the lesions (Akiguchi et al., 1998; Simpson et al., 2007; Tomimoto et al., 1996) (fig. 6). Markers of endothelial activation, hemostasis, inflammation and oxidative stress are also upregulated in blood, consistent with more widespread effects in the systemic circulation (Gallacher et al., 2010; Knottnerus et al., 2010; Markus et al., 2005; Rouhl et al., 2012a; Shibata et al., 2004; Xu et al., 2010) (fig. 6). The mechanisms of these responses have not been fully elucidated, but several factors may play a role. Cerebral hypoperfusion is associated with white matter inflammation and oxidative stress in rodent models (Dong et al., 2011; Huang et al., 2010; Ihara et al., 2001; Juma et al., 2011; Masumura et al., 2001; Reimer et al., 2011; Yoshizaki et al., 2008), indicating that hypoxia-ischemia is sufficient to trigger these responses. Vascular risk factors for VCI, such as hypertension, insulin resistance and diabetes, lead to vascular oxidative stress and inflammation, both in animal models and in humans (Cohen and Tong, 2010; Iadecola and Davisson, 2008; Yates et al., 2012), which, in turn, impair the factors regulating the cerebral circulation (Faraci, 2011). Thus, functional hyperemia and endothelium dependent responses are attenuated in models of aging, hypertension, and diabetes (Ergul, 2011; Kazama et al., 2004; Park et al., 2007), whereas the ability of the vessels to adjust cerebral perfusion in response to changes in blood pressure (autoregulation) is blunted in patients with diabetes or hypertension (Kim et al., 2008b; Novak et al., 2003). Such neurovascular dysfunction would aggravate the CBF reduction in critically perfused deep white matter regions and contribute to the white matter damage. Accordingly, scavenging of free radicals or approaches to suppress inflammation counteract white matter damage and behavioral deficits in rodent models of cerebral hypoperfusion (Dong et al., 2011; Kim et al., 2008a; Maki et al., 2011; Ueno et al., 2009; Wakita et al., 2008; Wang et al., 2010; Washida et al., 2010; Zhang et al., 2011). NADPH oxidase, a multiunit enzyme particularly enriched in cerebral blood vessels (Miller et al., 2005), has emerges as an important source in vascular oxidative stress in aging, hypertension, hyperlipidemia and diabetes (Faraci, 2011), and inhibition or genetic inactivation of this enzyme has been shown to ameliorate the vascular dysfunction (Drummond et al., 2011). Extravasation of plasma proteins, due to the BBB alterations, is also likely to play a role, since fibrinogen,

immunoglobulins, and complement are potent activators of inflammation and free radical production (Crehan et al., 2013; Davalos and Akassoglou, 2012; Yoshida et al., 2002). In particular, fibrinogen extravasation activates inflammatory pathway through its interaction with integrin (CD11b/CD18) and non-integrin receptors (TLRs), leading to activation of microglia and astrocytes (Davalos and Akassoglou, 2012; Davalos et al., 2012) (fig. 6). As discussed next, inflammation and oxidative stress have also deleterious effects on the trophic interaction among the cells of the neurovascular unit.

### Trophic uncoupling

ROS and inflammation suppress the prosurvival action of endothelial cells on neurons by reducing BDNF levels, an effect mediated by impairing integrin linked kinase signaling (Guo et al., 2008). In models of diabetes, advanced glycation end-products lead to MMP9 secretion by endothelial cells and cleavage of the ectodomain of the BDNF receptor TRKB on neurons, reducing neurotrophic signaling (Navaratna et al., 2013). Owing to their trophic support of vascular cells, dysfunction and damage to neurons and glia is associated with endothelial cell atrophy and microvascular rarefaction (Brown and Thore, 2011). Systemic factor also play a role in the mechanisms of trophic uncoupling. EPC are reduced by stroke risk factors (Hill et al., 2003) and predict cardiovascular morbidity and mortality (Werner et al., 2005). EPC are reduced in age associated white matter lesions, the reduction correlating with lesion burden (Jickling et al., 2009). In addition, EPC may be less functionally competent in patients with vascular risk factors and stroke. For example, the ability of colony forming units, a subset of EPC, to form vascular tubes in a matrigel assay is impaired in patients with large artery atherosclerosis or lacunar stroke (Chu et al., 2008). Interestingly, EPC colony forming units are also reduced in AD patients, in whom the magnitude of the reduction correlates with the degree of cognitive impairment (Lee et al., 2009). Angiogenic T-cells are reduced in patients with vascular risk factors (Hur et al., 2007; Weil et al., 2011), and in hypertensive patients with small vessels disease (Rouhl et al., 2012b). Furthermore, angiogenic T-cells migration *in vitro* is positively correlated with preservation of endothelium-dependent vasodilatation in patients with cardiovascular risk factors (Weil et al., 2011), highlighting their protective role in vascular function. These findings, raise the possibility that vascular risk factors suppress the production of angiogenic T-cells, reduce the repair potential of EPC, and contribute to the microvascular degeneration underlying leukoaraiosis and lacunar stroke. Accordingly, capillary density is reduced not only at lesioned sites, but also in normal appearing white matter in patients with VCI (Brown et al., 2007). Vessels devoid of endothelium (string vessels) are often observed, reflecting a failure of endothelial repair, possibly due to EPC dysfunction or loss of neuron and/or glial-derived growth factors.

Lesions of white matter tracts also lead to distant effects resulting from loss of trophic support at their site of termination. Leukoaraiosis is associated with focal cortical thinning especially in frontal cortex, a finding correlated with executive dysfunction (Seo et al., 2012). Focal cortical thinning was also observed in a prospective study of patients with CADASIL subsequent to a subcortical infarct (Duering et al., 2012), indicating a causal link between white matter lesions and cortical atrophy. These processes are likely to play a role in the progressive cerebral atrophy observed in patients with leukoaraiosis, who experience a brain volume loss of 1% per year, twice that of age matches controls (Nitkunan et al., 2011). However, it has not been established whether white matter lesions cause the atrophy independently of age and other risk factors (Appelman et al., 2009; 2010). Trophic interactions are also critically involved in the demyelination and remyelination associated with leukoaraiosis, which are examined next.

## Demyelination and remyelination

One of the consequences of the oxidative and proinflammatory environment induced by hypoperfusion and BBB breakdown is damage to the myelin sheath and demyelination. Myelination allows axons to conduct 100 times faster, and reduce energy expenditures by restricting the depolarization of the axonal membrane to the Na<sup>+</sup> channel rich Ranvier nodes (Nave, 2010b). Some of the energy saving afforded by myelination is offset by the cost of maintaining the resting potential of oligodendrocytes, which is estimated to be high (Harris and Attwell, 2012). Loss of myelin has important consequences for the white matter tracts. In addition to the brain dysfunction caused by slowing down the transmission of axon potentials, demyelination threatens the integrity of the axons and leads to axonal loss (Franklin and Ffrench-Constant, 2008; Matute and Ransom, 2012). Several factors contribute to the demise of the axons. Oligodendrocytes release growth factors, such as IGF-1 and glial cell-derived neurotrophic factor that support the survival of axons (Wilkins et al., 2003). Thus, loss of myelin deprives the axons of trophic support and increases their vulnerability. In addition, demyelination exposes the axons to the deleterious effects of cytokine and free radicals in the hypoxic white matter, which may impair axonal energy production leading to failure of the Na<sup>+</sup>/K<sup>+</sup> ATPase. The resulting accumulation of intracellular Na<sup>+</sup> reverses the operation of the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, resulting in intracellular Ca<sup>2+</sup> accumulation (Matute and Ransom, 2012; Stys et al., 1992). Furthermore, the adaptive upregulation of voltage-dependent Na<sup>+</sup> channels (VNa<sup>+</sup>) in the denuded internodal axoplasm, attempting to preserve impulse propagation in demyelinated axons, leads to Na<sup>+</sup> entry and aggravates the energy deficit and Ca<sup>2+</sup> overload. Upregulation of VNa<sup>1.2</sup> channels increases the activity of the Na<sup>+</sup>/K<sup>+</sup> ATPase, stressing further the energy budget of the marginally perfused white matter (Trapp and Stys, 2009). In turn, excess intracellular Ca<sup>2+</sup> activates protease dependent processes that lead to microtubule fragmentation and perturbation of axonal flow (Franklin and Ffrench-Constant, 2008; Matute and Ransom, 2012).

Attempts to remyelinate are present in the damaged white matter in leukoaraiosis (Jonsson et al., 2012). Oligodendrocytes are responsible for the formation and maintenance of the myelin sheath. A large pool of oligodendrocyte progenitor cells (OPC) is present in the brain, which goes through several stages of development before becoming mature and competent to lay down myelin (Fancy et al., 2011a). However, in demyelinating diseases, including leukoaraiosis, axons fail to fully remyelinate (Franklin and Ffrench-Constant, 2008). Several factors are thought to be responsible (fig. 7). First, OPC in the late stage of development are particularly susceptible to injury in conditions of chronic hypoxia and oxidative stress existing in the ischemic white matter (Back et al., 2011; 2002; Fernando et al., 2006; French et al., 2009). Oligodendrocytes are also susceptible to damage caused by extracellular ATP, which increases in hypoxia-ischemia, through activation of the P2X7 purinergic receptors (Domercq et al., 2010). Second, withdrawal of trophic support from damaged endothelial cells and astrocytes could reduce the vitality of the OPC pool and contribute to their demise in the hypoxic environment of the vulnerable white matter (Arai and Lo, 2010). Third, failure to remyelinate could be related to an arrest in OPC maturation. OPC are abundant in areas of leukoaraiosis, which are enriched with hyaluronan (HA), a high molecular weight glycosaminoglycan produced by reactive astrocytes and other cells (Back et al., 2011). HA is a component of the matrix and is involved in neurodevelopment promoting neuronal migration (Sherman and Back, 2008). In white matter lesions, HA is degraded by the hyaluronidase PH20 and its cleavage products inhibit the maturation of OPC into oligodendrocytes capable of myelination (Preston et al., 2013) (fig. 7). Dysregulation of the Wnt signaling pathway could also play a role in the OPC developmental arrest (Fancy et al., 2011b). In addition, OPC produce MMP9, which, as seen in the previous sections, promotes



BBB breakdown perpetuating the cytotoxic milieu underlying demyelination (Seo et al., 2013).

### Putting it all together

The evidence reviewed above suggests a convergence of pathogenic factors on cerebral blood vessels, which in turn leads to white matter damage (figs. 6, 7). Oxidative stress-induced endothelial dysfunction caused by risk factors is most likely an early event leading to white matter damage. Endothelial dysfunction has two major pathogenic consequences: reductions in resting CBF in the marginally perfused white matter, and alterations in the permeability of the BBB. In turn, hypoperfusion and BBB disruption lead to additional oxidative stress by inducing tissue hypoxia and by extravasation of plasma proteins, such as fibrinogen. Tissue edema resulting from increased BBB permeability may exacerbate these alterations by compressing blood vessels and reducing CBF further. Tissue hypoxia and oxidative stress activate inflammatory pathways through NF- $\kappa$ B-dependent transcription, leading to production of cytokines and adhesion molecules in vascular cells, reactive astrocytes and activated microglia. Hypoxia, inflammation and oxidative stress damage oligodendrocytes and leads to trophic uncoupling in the neurovascular unit, which, in turn, contribute to the damage to vascular cells and oligodendrocytes. Oligodendrocyte damage, oxidative stress and inflammation lead to demyelination and attempted remyelination through OPC proliferation. Developmental arrest of OPC, due to HA degradation products, leads to accumulation of these cells which secrete MMP9 and worsen the BBB impairment (fig. 7). Once demyelination occurs, the increased energy requirement of the denuded axons aggravates the hypoxic stress of the tissue, leading to a vicious circle that perpetuates these pathogenic processes and exacerbates the tissue damage.

### Is hypoperfusion involved also in inherited and autoimmune white matter diseases?

There is emerging evidence that reduced cerebral perfusion may contribute to other diseases characterized by white matter damage. Multiple sclerosis (MS) is the prototypical neuroinflammatory disease in which demyelination is thought to be related to a T-cell mediated autoimmune attack on myelin (McFarland and Martin, 2007). However, in MS patients CBF is reduced in the normal appearing white matter (Law et al., 2004), as well as in the gray matter (D'haeseleer et al., 2011). In contrast, in active lesions displaying BBB disruption CBF is increased, consistent with vasodilatation caused by inflammation (D'haeseleer et al., 2011). The reduction in CBF in the normal white matter could be caused by a primary vascular dysfunction pathogenically linked to the disease process, or could be secondary to loss of white matter elsewhere, due to distal Wallerian degeneration, or reduced synaptic activity (De Keyser et al., 2008). Studies in which CBF measurements in the normal appearing white matter were coupled to diffusion tensor imaging, revealed that the reductions in CBF are associated with restricted diffusion and not with increased fractional anisotropy, as anticipated if the CBF changes were secondary to Wallerian degeneration (Saindane et al., 2007). Although the possibility that the reduction in CBF is secondary to reduced local synaptic activity has not been ruled out, the fact that the hypoperfusion is normalized by an endothelin receptor antagonist suggest a primary vascular cause (D'haeseleer et al., 2013). Consistent with the hypoperfusion hypothesis, HIF-1 $\alpha$  and dependent genes are upregulated in normal appearing white matter (Graumann et al., 2003).

Reductions in white matter CBF has also been found X-linked adrenoleukodystrophy (ALD), a disease caused by mutations in *ABCD1*, which encodes a peroxisomal membrane transporter protein, leading to accumulation of very long chain fatty acids in brain, spinal cord and adrenal glands (Moser et al., 2000). In its infantile form, the disease starts between

4 and 8 years of age and is characterized by a progressive cognitive decline associated with rampant inflammatory demyelination of the white matter (Moser et al., 2000). BBB alterations predict disease progression (Melhem et al., 2000). Cerebral blood volume, assessed by susceptibility contrast MRI (Musolino et al., 2012), or CBF, assessed by single photon emission tomography (Suhaili et al., 1994), is reduced in the normal appearing and abnormal white matter. The mechanisms of the white matter hypoperfusion remain to be defined. Reductions in CBF prior to white matter damage were also observed in a patient with Alexander disease, a rare childhood disease caused by a dominant mutation of the GFAP gene (Ito et al., 2009).

It is noteworthy that, despite fundamental differences in their pathogenesis, inherited and autoimmune diseases of the white matter exhibit cerebrovascular alterations before pathology develops, just like in white matter disease caused by vascular factors. Thus, hypoperfusion and BBB disruption seem necessary correlates of the process leading to white matter damage independently of the primary disease cause. Collectively, these observations highlight the importance of neurovascular factors in maintaining white matter health.

## Overlap between vascular and neurodegenerative dementia

The realization that most cases of dementia have mixed pathological features has raised the intriguing possibility that vascular factors play role in AD and other neurodegenerative diseases. As discussed in the section on “Mixed lesions”, AD brains have a wide variety of vascular lesions, suggesting a potential pathogenic interaction between vascular factors and AD. However, since cerebrovascular diseases and AD are common in the aged, the coexistence of the two pathologies could simply be coincidental (Hachinski, 2011). The overall effect on cognition would result from the combined burden of vascular and neurodegenerative pathology, according to an additive model. Alternatively, vascular disease could promote AD and vice-versa, resulting in a reciprocal interaction amplifying their pathogenic effects. The cognitive impact of vascular and AD neuropathology depends on the severity of the AD pathology and location of the vascular lesions (Gold et al., 2007). In advanced cases of AD, vascular lesions do not seem to have a major influence on the progression of the cognitive deficits, suggesting the AD pathology is the major driver of the cognitive dysfunction (Chui et al., 2006; Jellinger, 2001). On the other hand, in older individuals with moderate AD pathology subcortical vascular lesions are a major determinant of the expression of the dementia (Esiri et al., 1999; Schneider et al., 2007b; Snowden et al., 1997).

## Cerebrovascular factors and AD

Cerebrovascular function is reduced in patients with early AD or at risk for AD (Claassen et al., 2009; Gao et al., 2013; Luckhaus et al., 2008; Mentis et al., 1996; Niedermeyer, 2006; Ruitenberget al., 2005; Sabayan et al., 2012; Tanaka et al., 2002), implicating reduced cerebral perfusion in the pathobiology of the disease (Iadecola, 2004). Conversely, some studies (Jendroska et al., 1995; Ly et al., 2012), but not others (Aho et al., 2006; Mastaglia et al., 2003), have reported increased amyloid deposition in stroke patients, implicating that ischemia promotes AD pathology. Furthermore, AD and cerebrovascular diseases may have common risk factors, such as hypertension, insulin resistance, diabetes, obesity, hyperhomocystinemia, hyperlipidemia, etc. (Craft, 2009; Fillit et al., 2008; Honjo et al., 2012; Purnell et al., 2009). However, the correlation was most evident when the risk factors were considered together and not individually (Chui et al., 2012). Furthermore, the correlation was strongest for vascular dementia and weakest for AD, suggesting that vascular risk factors may independently increase the likelihood of dementia without exacerbating AD pathology (Chui et al., 2012). In contrast, studies that have prospectively evaluated representative patients cohorts with confirmation of the clinical diagnosis at

autopsy failed to establish a link between the burden of AD pathology and vascular risk factors (Chui et al., 2012). It is, therefore, conceivable that in cases in which AD was diagnosed clinically there might have been a component of vascular pathology. New imaging and CSF biomarkers for the in vivo diagnosis of AD may provide additional insights into whether vascular factors are pathogenically linked to AD (Chui et al., 2012; Haight et al., 2013; Purnell et al., 2009).

### Vascular effects of A $\beta$

Mounting evidence that A $\beta$  has powerful vascular effects also suggests a link between AD and vascular disease. A $\beta_{42}$  constrict isolated cerebral and systemic blood vessels (Niwa et al., 2001; Paris et al., 2003; Thomas et al., 1996), whereas application of A $\beta_{42}$  to the exposed cerebral cortex of mice reduces CBF and impairs the increase in CBF induced by endothelium-dependent vasodilators and functional hyperemia (Niwa et al., 2000a; 2000b). Similarly, functional hyperemia, endothelium-dependent responses and autoregulation are profoundly impaired in young mice overexpressing mutated forms of APP, in which brain A $\beta$  is elevated, but there are no plaques, behavioral alterations, or reductions in resting glucose utilization (Niwa et al., 2000b; 2002; Tong et al., 2012). These data suggest that the cerebrovascular effects of A $\beta$  are not attributable to CAA or amyloid plaques, and are not a consequence of neuronal energy hypometabolism. APP-overexpressing mice have increased brain damage following occlusion of the middle cerebral artery (Koistinaho et al., 2002; Zhang et al., 1997), an effect in part related to poor collateral circulation due to vascular dysregulation (Zhang et al., 1997). The vascular alterations induced by A $\beta$  are abrogated by overexpression of the ROS scavenging enzyme superoxide dismutase or deficiency of the NADPH oxidase subunit NOX2 (Iadecola et al., 1999; Park et al., 2005; 2008), implicating ROS produced by the enzyme NADPH oxidase in the vascular dysfunction. The mechanisms of NADPH oxidase activation involve the A $\beta$ -binding scavenger receptor CD36 (Park et al., 2011). Aged APP mice deficient in CD36 are protected from cerebrovascular alterations and behavioral deficits, effects associated with reduced CAA compared to controls, but no reduction of amyloid plaques (Park et al., 2013b). Thus, CD36, which is located in vascular and perivascular cells, may contribute to the accumulation of A $\beta$  in cerebral blood vessels.

### A $\beta$ production and clearance

Hypoperfusion and hypoxia caused by vascular insufficiency may also facilitate A $\beta$  production by activating the APP cleavage enzyme  $\gamma$ -secretase (Kitaguchi et al., 2009; Sun et al., 2006; Tesco et al., 2007; Wen et al., 2004a). Cerebral ischemia promotes amyloid plaque formation (Garcia-Alloza et al., 2011; Kitaguchi et al., 2009; Okamoto et al., 2012), and tau phosphorylation (Koike et al., 2010; Wen et al., 2007; 2004b). The vascular effects of A $\beta$  may also impair the clearance of the peptide, a key factor in brain A $\beta$  accumulation in sporadic AD (Mawuenyega et al., 2010). The vascular pathway is estimated to be a major route of removal of A $\beta$  from the brain (Castellano et al., 2012; Shibata et al., 2000). Brain A $\beta$  is transported along the perivascular pathway draining into the cervical lymphnodes (Carare et al., 2013; Iliff et al., 2013). In addition, A $\beta$  is cleared from the brain through a transvascular transport system involving LRP-1 (Shibata et al., 2000), a protein that acts in concert with P-glycoprotein, ApoE, ApoJ, and  $\alpha$ 2-macroglobulin to regulate brain A $\beta$  homeostasis (Zlokovic, 2008). Interestingly, ApoE4, a major genetic risk factor for AD, leads to BBB disruption through a proinflammatory pathway involving cyclophilin A in pericytes (Bell et al., 2012). Activation of this pathway causes MMP-9-mediated degradation of endothelial tight junctions and basement membrane proteins, as shown in human ApoE4 targeted replacement mice (Bell et al., 2012). ApoE4 positive individuals may develop a similar age-dependent BBB breakdown prior to cognitive decline (Halliday et al., 2013). In patients with vascular risk factors, such as hypertension, sedentary life style,

or ApoE4 genotype, there is a greater tendency for amyloid accumulation (Head et al., 2012; Rodrigue et al., 2013), whereas amyloid accumulation is reduced in patients who exercise regularly (Liang et al., 2010). Experimental studies indicate that this clearance mechanism is altered in the presence of vascular dysfunction and damage, contributing to parenchymal and vascular A $\beta$  accumulation (Deane et al., 2004; Park et al., 2013b). In particular, suppression of LRP1 in vascular smooth muscle cells due to upregulation of serum response factor and myocardin, is a key factor in the clearance impairment (Bell et al., 2009). Collectively, these observations suggest a link between cerebrovascular health and brain A $\beta$  clearance.

These lines of evidence suggest that AD is frequently associated with cerebral macro- and micro-vascular pathology, which can contribute to the expression of the dementia. Vascular risk factors can increase amyloid accumulation and the risk of clinically defined AD. The vasoactivity of A $\beta$  and the influence of cerebral perfusion on APP processing and A $\beta$  clearance suggest that cerebral blood vessels can have a role in the accumulation of A $\beta$  in the brain parenchyma and cerebral blood vessels. Preliminary evidence suggests that control of vascular risk factors reduces vascular lesions in AD (Richard et al., 2010), and may delay disease progression (Deschaintre et al., 2009), at least early in the disease course (Richard et al., 2010). Although replication in representative cohorts in which AD is confirmed pathologically or with biomarkers is needed, these observations provide initial evidence that improving vascular health may also help in AD.

## Prospects for prevention and therapy

The development of treatments for VCI has been hampered by the lack of a suitable animal model recapitulating the multifaceted features of the disease (Gorelick et al., 2011). Although several animal models have been developed (Hainsworth et al., 2012; Lee et al., 2012), the most widely used has been white matter damage produced by chronic forebrain ischemia (Ihara and Tomimoto, 2011). These models have demonstrated that counteracting some of the pathogenic factors, including chronic ischemia, inflammation and oxidative stress, reduce white matter damage and/or behavioral deficits (Dong et al., 2011; Ihara and Tomimoto, 2011; Maki et al., 2011). Other approaches have attempted to promote remyelination by stimulating the survival and differentiation of OPC (Miyamoto et al., 2010). Despite these positive results in models of hypoperfusion-induced white matter damage, there are no FDA approved treatments for VCI and vascular dementia (Butler and Radhakrishnan, 2012). Treatment with antioxidants, anti-inflammatory agents or agents increasing cerebral perfusion have not led to consistent results (Butler and Radhakrishnan, 2012). Some agents, like the neurotrophic factor cerebrolysin, showed a modest cognitive improvement, but the evidence is not sufficiently strong to justify clinical use (Chen et al., 2013b). Clinical trials are currently exploring other agents, including cholinergic stimulants (choline alphoscerate), vasodilators (udenafil), inhibitor of platelet aggregation (cilostazol) and delta-9-tetrahydrocannabinol (a complete list can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

On the other hand, increasing evidence indicates that the risk of VCI and vascular dementia can be reduced by preventive measures. A study in the UK population suggests that the prevalence of dementia may be decreasing, a finding interpreted to reflect the beneficial effects of controlling blood pressure and other risk factors (Matthews et al., 2013). Indeed, rigorous blood pressure control reduces white matter damage and staves off cognitive decline (Sharp et al., 2011; Sörös et al., 2013). Physical and mental activity, social engagement, and a diet rich in antioxidants or polyunsaturated fatty acids reduce dementia risk (Aarsland et al., 2010; Akinyemi et al., 2013; Middleton and Yaffe, 2009; Verdelho et al., 2012). Therefore, controlling vascular risk factors and promoting a healthy diet, exercise and mental activity are promising strategies to reduce VCI. This hypothesis is supported by a study indicating that weight control, a healthy diet, nonsmoking, physical activity, and

keeping total cholesterol, blood pressure, and fasting glucose at goal levels are associated with better cognitive performance later in life (Reis et al., 2013). However, most of the evidence is based on observational studies, which have not been confirmed by randomized clinical trials of risk factor modification, stressing the need for further large scale studies (Dichgans and Zietemann, 2012; Middleton and Yaffe, 2009).

## Conclusions

VCI and vascular dementia are major contributors to age-related dementing illnesses and comprise a heterogeneous group of cognitive disorders attributable to vascular causes. Vascular pathology is also an integral part of AD and other late-life neurodegenerative conditions associated with dementia, and play a defining role in the expression of the cognitive dysfunction. Despite the diversity of the underlying brain pathology, the vascular alterations have a similar pathogenic bases, resulting from hypoperfusion, oxidative stress and inflammation, which in turn lead to endothelial damage, BBB breakdown, activation of innate immunity and disruption of trophic coupling between vascular and brain cells. The hemispheric white matter, which is particularly susceptible to the deleterious effects of vascular risk factors, is a major target of these vascular alterations. The resulting demyelination and axonal loss plays a role in the broad functional brain changes underlying cognitive impairment and in the associated cerebral atrophy. This chain of events highlights the critical role that vascular cells play in the maintenance of the health of neurons, glia and myelin.

However, several fundamental questions remain to be addressed. The predilection of the vascular pathology for the deep hemispheric white matter, a remarkable constant in conditions as diverse as CADASIL and sporadic white matter disease, remains incompletely understood. Although its peculiar vascular topology and precarious blood supply are likely to play a role, the cellular and molecular bases determining the characteristic vascular lesions remain to be defined. In particular, how aging and vascular risk factors interact with the vascular wall to induce vascular lesions preferentially in the white matter remains unclear. The relative contribution of hypoperfusion, BBB damage and oxidative stress to vascular and parenchymal damage remain to be defined. Furthermore, what determines the pathological diversity, e.g., lacunes, microinfarcts, microhemorrhages, etc., and spatial localization of the brain lesions resulting from similar vascular pathology remain unexplained. A better understanding of ischemic demyelination and abortive remyelination is needed. Fundamental questions concerning the interaction of AD pathology with vascular pathology also remains unanswered. Studies elucidating the vascular biology of the white matter and the interaction with risk factors and AD pathology would be needed to shed light on some of these issues and provide better insight into potential therapeutic targets. These mechanistic studies can benefit from the increasing availability of cell specific conditional genetic models, viral-based gene delivery methods, and novel approaches for targeted cell replacement/modification in the brain, e.g., (Goldman et al., 2012).

Developing treatments for VCI remains a challenge. In addition to the lack of predictive animal models to guide target selection, the heterogeneity of the underlying pathology represents a therapeutic challenge. The role of hypoperfusion, BBB disruption, oxidative stress and inflammation is well established in animal models of white matter damage, but therapies based on these pathogenic mechanisms have not been successful. Although it has been difficult to prove that these approaches achieved the intended effect on cerebral perfusion, ROS production and inflammation in the white matter at risk, other considerations make the development of treatments particularly challenging. For example, the long preclinical phase of dementia is problematic, since, in VCI as in AD, initiating therapy when patients become symptomatic may be too late. Furthermore, due to frequent



overlap with AD, the diagnosis of VCI can be challenging, complicating the choice of the best therapeutic approach (Wang et al., 2012). Novel imaging modalities, including amyloid and tau imaging, as well as high resolution MRI, will go a long way in addressing some of these challenges, and will make possible to characterize the pathology in vivo with an unprecedented spatial, temporal and morphological accuracy. At the same time, these approaches offer the prospect of developing new biomarkers that will be critical for identifying patients at risk, staging the progression of the disease, and assessing therapeutic efficacy.

Considering that mixed dementia is the most common cause of dementia in the elderly, it has become increasingly important to harmonize basic science, translational, and clinical approaches in AD and vascular dementia. Thus, the impact of both pathologies should be considered, independently of whether their contribution is additive or synergistic. In the absence of effective therapies, promoting and maintaining vascular health seems critical to prevent both the vascular and neurodegenerative components of the disease and is probably the best possible course of action at the present.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We gratefully acknowledge the support from the NIH (NINDS: NS37853, NHLBI: HL96571) and the Alzheimer's Association (ZEN-11-202707). Dr. Giuseppe Faraco provided invaluable help with the figures.

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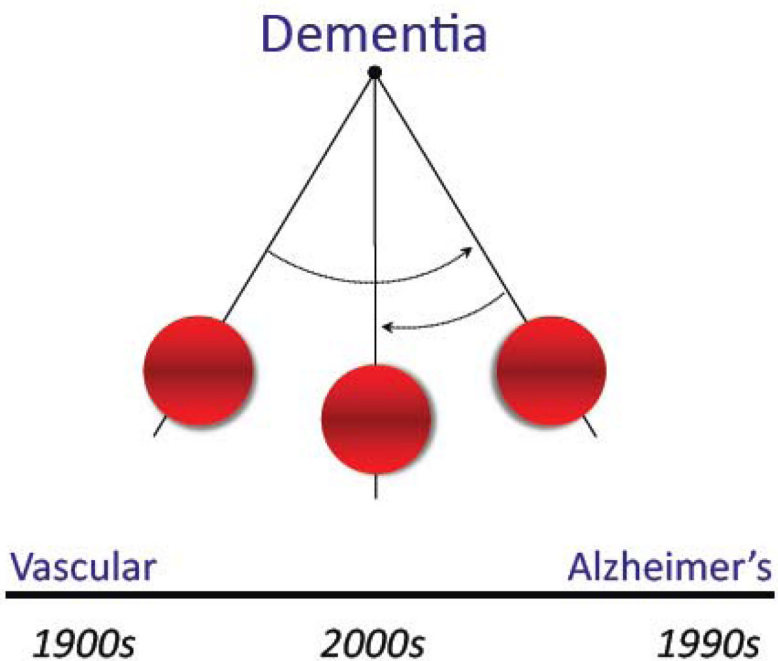


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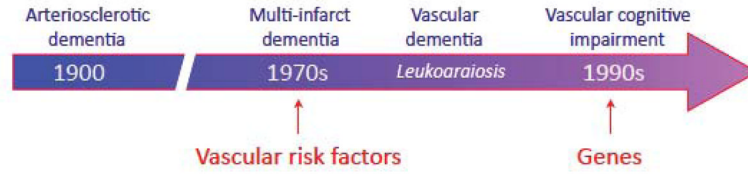
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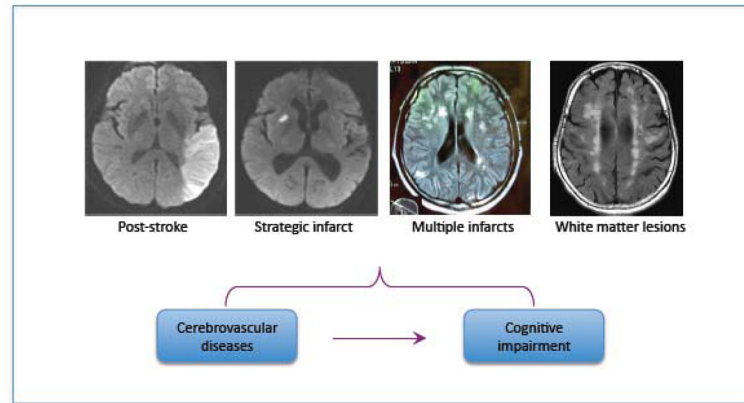


**Figure 1.** Changing views about dementia through the years. In the early 1900s vascular factors were thought to be the main cause of dementia. Over the next several decades Alzheimer's disease was felt to be the main cause. Clinical-pathological studies have revealed that mixed dementia, combining feature of vascular dementia and AD, is currently the most common cause of cognitive impairment in the aged.

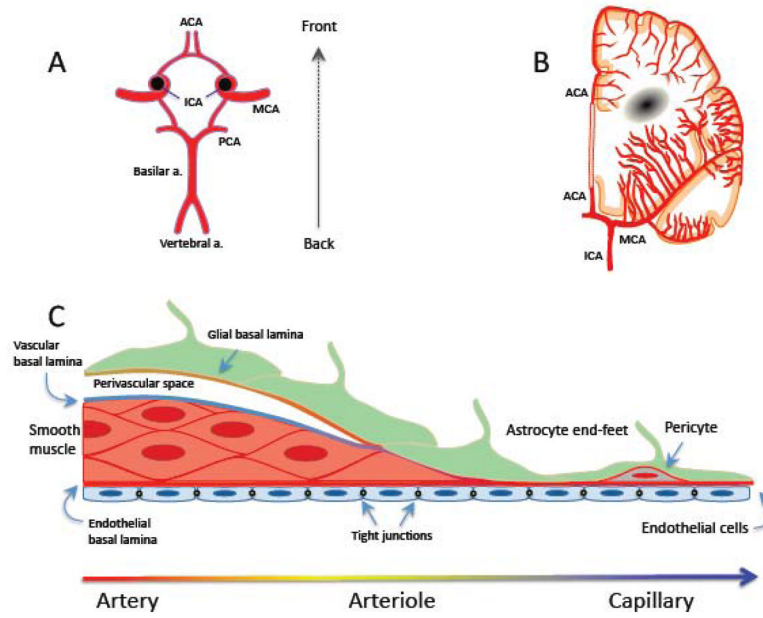




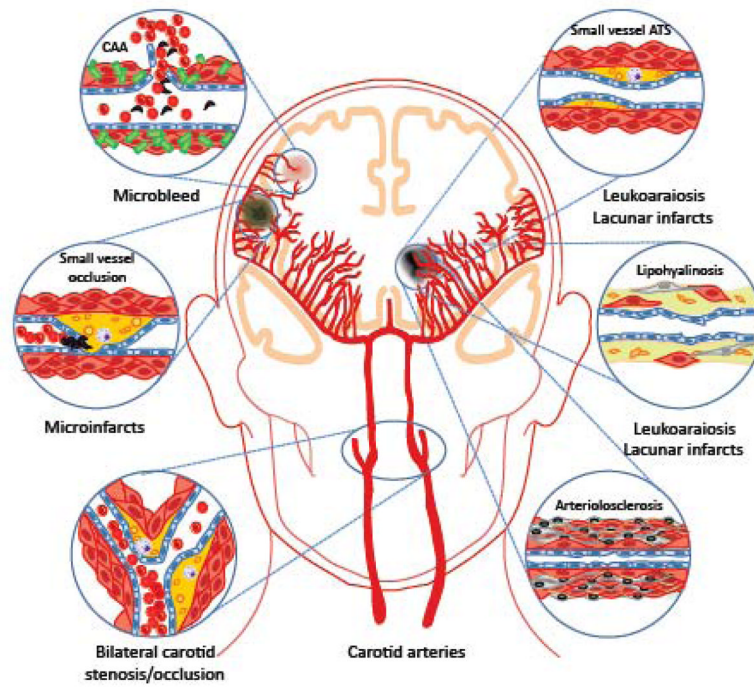
**Figure 2.** Evolution of the concept of cognitive impairment on vascular bases. Hardening of the arteries was considered the main cause in the early 1900s. The concept of multi-infarct dementia introduced the possibility of preventing dementia by controlling vascular risk factors. The introduction of brain imaging modalities (computer tomography, then magnetic resonance imaging) led to the realization that white matter disease, termed leukoaraiosis, was a major cause of cognitive impairment. In the 1990s the term VCI was introduced to broaden the spectrum of cognitive deficits caused by vascular factors. At this time, genetic causes of vascular damage causing dementia were also discovered, CADASIL being the first monogenic cause of vascular cognitive impairment, identified by M-G. Bousser and colleagues.



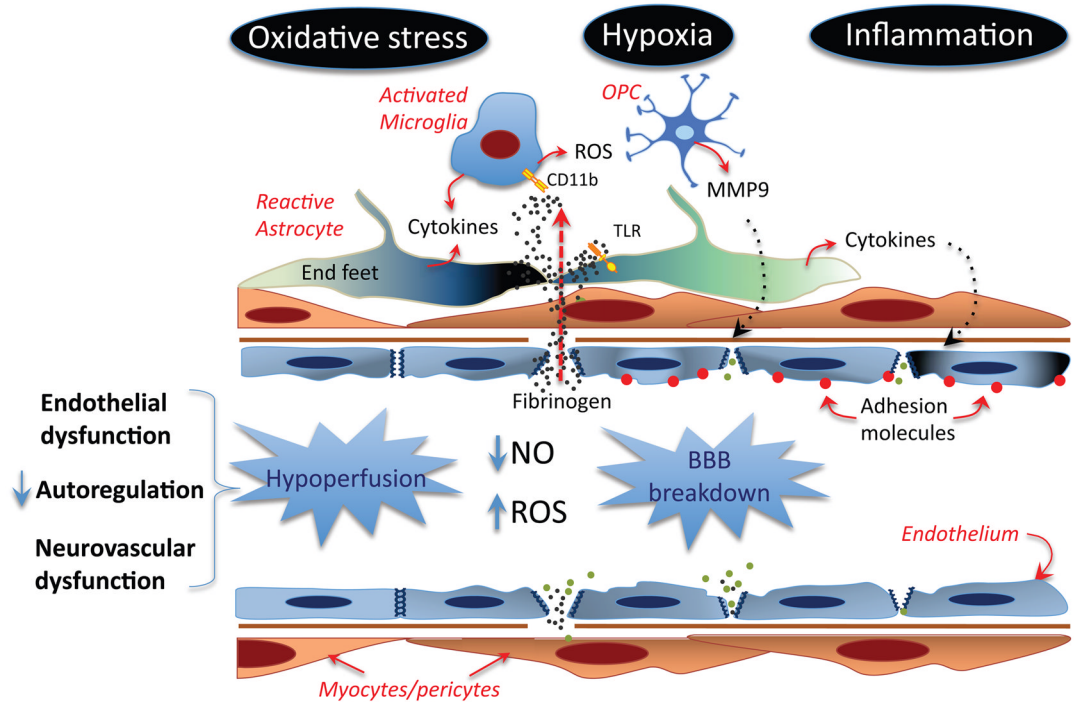
**Figure 3.** Brain lesions responsible for vascular cognitive impairment. All MRI sequences are diffusion weighted imaging, except for the white matter lesions, which is a fluid attenuated inversion recovery sequence. Images are courtesy of Dr. Hooman Kamel.



**Figure 4.** Anatomy of the cerebral blood supply. **A:** Circle of Willis. **B:** The arterial supply of the deep white matter arises from branches of the ACA and the MCA. The supply of the basal ganglia white matter is provided by arteries arising directly from the circle of Willis and its proximal branches. **Abbreviations:** ACA: anterior cerebral artery; ICA: internal carotid artery; MCA: middle cerebral artery; PCA: posterior cerebral artery. **C:** Anatomy of the wall of arteries, arterioles and capillaries.

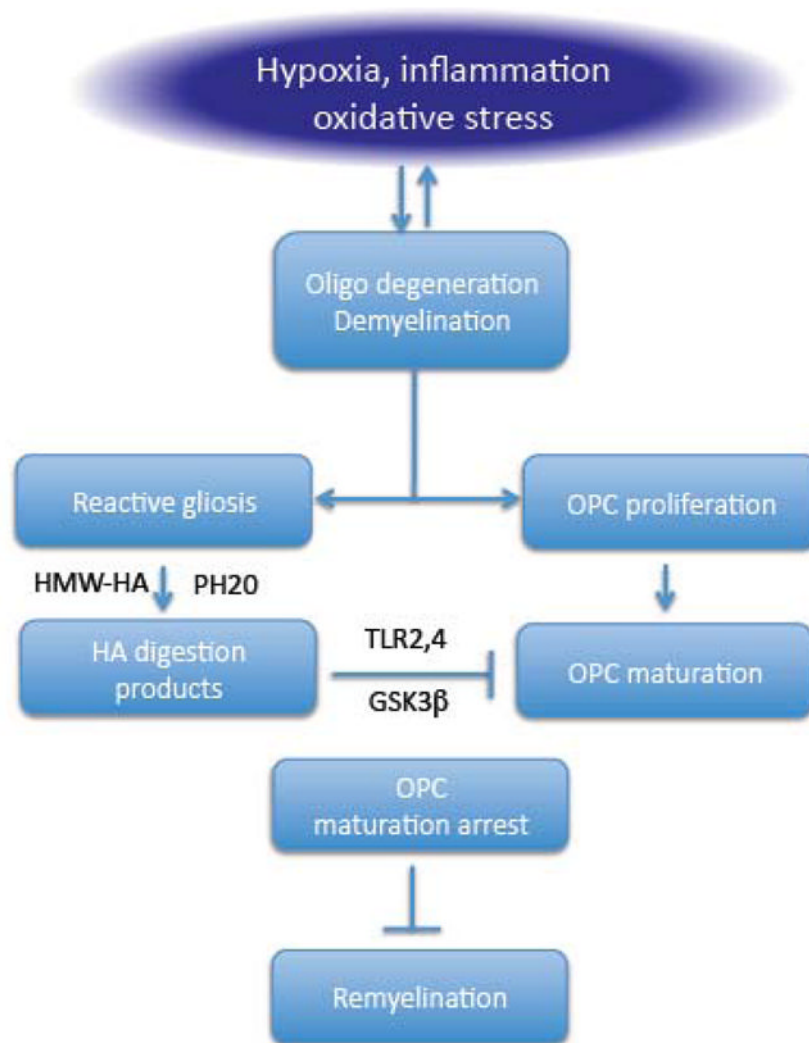


**Figure 5.** Vascular lesions leading to VCI and their effects on the brain. See text for details. CAA: cerebral amyloid angiopathy; ATS: atherosclerosis.



**Figure 6.** Potential mechanisms of the blood vessel damage induced by vascular risk factors. Endothelial dysfunction, impairment of autoregulation and dysfunction of neurovascular coupling, partly mediated by oxidative stress and NO deficit, reduce CBF resulting in hypoperfusion and tissue hypoxia. In addition to hypoperfusion, a critical consequence of endothelial dysfunction is increased BBB permeability, which leads to extravasation of plasma proteins, including fibrinogen, into the brain. Fibrinogen activates CD11b and TLR leading to production of ROS, proinflammatory cytokines and MMPs from activated microglia, reactive astrocytes and OPCs. Inflammation, in turn, aggravates the BBB breakdown and induces expression of adhesion molecules in endothelial cells, contributing to leukocyte and platelet adhesion and microvascular occlusion.





**Figure 7.** Potential mechanisms of failure to remyelinate the damaged white matter. Inflammation, oxidative stress and hypoxia induced demyelination. OPC proliferate to attempt remyelination. High molecular weight hyaluronic acid (HMW-HA) produced by reactive astrocytes is cleaved by the hyaluronidase PH20 generating digestion products that inhibit OPC maturation through mechanisms involving TLR2 and 4 and GSK3. The resulting OPC maturation arrest prevents efficient remyelination.

Table 1

Selected causes of cognitive impairment related to vascular factors

Condition	Predominant association/cause	Target vessel and vascular pathology	Resulting brain lesions	Refs.
<b>Hypoperfusion dementia</b>	<ul style="list-style-type: none"> <li>Cardiac arrest/failure</li> <li>Hypotension</li> <li>Carotid occlusion</li> </ul>	<ul style="list-style-type: none"> <li>Large vessel ATS</li> <li>Vascular stiffening</li> </ul>	<ul style="list-style-type: none"> <li>“Watershed” infarcts</li> <li>Cortical laminar necrosis</li> <li>Incomplete white matter infarcts</li> </ul>	(Jellinger, 2013; Johnston et al., 2004; Marshall et al., 2012)
<b>“Strategic infarct” dementia</b>	<ul style="list-style-type: none"> <li>Arterial occlusion</li> </ul>	<ul style="list-style-type: none"> <li>Large-medium size arteries</li> </ul>	<ul style="list-style-type: none"> <li>Infarct in regions involved in cognition, e.g., frontal lobe, thalamus, etc.</li> </ul>	(Jellinger, 2013)
<b>Multiinfarct dementia</b>	<ul style="list-style-type: none"> <li>Multiple arterial occlusions (embolic thrombotic)</li> </ul>	<ul style="list-style-type: none"> <li>Large-medium size arteries and arterioles</li> </ul>	<ul style="list-style-type: none"> <li>Multiple large infarcts</li> <li>Lacunar infarcts</li> <li>Microinfarcts</li> </ul>	(Thal et al., 2012)
<b>White matter lesions (Leukoaraiosis) and lacunes</b>	<ul style="list-style-type: none"> <li>Vascular risk factors</li> <li>CADASIL and other genetic causes</li> </ul>	<ul style="list-style-type: none"> <li>Arterioles (&lt;300µm Ø)</li> <li>Small vessel ATS</li> <li>Arteriosclerosis</li> <li>Lipohyalinosis</li> <li>Venous collagenosis</li> </ul>	<ul style="list-style-type: none"> <li>Axonal damage</li> <li>Demyelination</li> <li>Lacunar infarcts</li> <li>Microinfarcts</li> <li>Microbleeds</li> </ul>	(Black et al., 2009; Brown and Thore, 2011; Thal et al., 2012)
<b>Microinfarcts</b>	<ul style="list-style-type: none"> <li>CADASIL</li> <li>CAA, AD</li> <li>Vascular risk factors</li> </ul>	<ul style="list-style-type: none"> <li>Arterioles (&lt;300µm Ø)</li> <li>Small vessel ATS</li> <li>Arteriosclerosis</li> </ul>	<ul style="list-style-type: none"> <li>Infarcts not visible by naked eye</li> </ul>	(Smith et al., 2012)
<b>Microbleeds and hemorrhages</b>	<ul style="list-style-type: none"> <li>CAA, AD</li> <li>CADASIL</li> <li>Vascular risk factors</li> </ul>	<ul style="list-style-type: none"> <li>Arterioles (&lt;300µm Ø)</li> <li>Vascular rupture</li> </ul>	<ul style="list-style-type: none"> <li>Small hemorrhage in perivascular space</li> <li>Lobar or basal ganglia hemorrhage</li> </ul>	(Charidimou and Werring, 2012; Henskens et al., 2008)
<b>CADASIL</b>	<ul style="list-style-type: none"> <li>Notch 3 mutations</li> </ul>	<ul style="list-style-type: none"> <li>Arterioles (&lt;300µm Ø)</li> <li>Thickened wall</li> <li>Smooth muscle cell GOM</li> <li>pericyte loss</li> </ul>	<ul style="list-style-type: none"> <li>White matter lesions</li> <li>Lacunar infarcts</li> <li>Microinfarcts</li> <li>Microbleeds</li> <li>Brain atrophy</li> </ul>	(Chabriat et al., 2009; Federico et al., 2012; Schmidt et al., 2012)
<b>Cerebral amyloid angiopathy</b>	<ul style="list-style-type: none"> <li>Hereditary</li> <li>Sporadic</li> <li>AD</li> </ul>	<ul style="list-style-type: none"> <li>Amyloid deposits in arteries (&lt;2mm Ø), arterioles, capillaries</li> <li>Smooth muscle degeneration</li> <li>Vascular rupture</li> </ul>	<ul style="list-style-type: none"> <li>Hemorrhage</li> <li>White matter lesions</li> <li>Microinfarcts</li> <li>Microbleeds</li> </ul>	(Attems et al., 2011; Charidimou and Werring, 2012)

Condition	Predominant association/cause	Target vessel and vascular pathology	Resulting brain lesions	Refs.
<b>Post-stroke dementia</b>	<ul style="list-style-type: none"> <li>Ischemic stroke of any cause</li> </ul>	<ul style="list-style-type: none"> <li>Large-medium size arteries</li> <li>perivascular immune cells (?)</li> </ul>	<ul style="list-style-type: none"> <li>Silent infarcts</li> <li>White matter lesions</li> <li>Lacunar infarcts</li> <li>Neuronal loss</li> <li>Brain atrophy</li> </ul>	(Leys et al., 2005) (Iadecola and Anrather, 2011)
<b>Mixed AD vascular dementia</b>	<ul style="list-style-type: none"> <li>Sporadic</li> <li>Vascular risk factors</li> </ul>	<ul style="list-style-type: none"> <li>Large-medium size arteries and arterioles</li> </ul>	<ul style="list-style-type: none"> <li>AD pathology</li> <li>White matter lesions</li> <li>Lacunar infarcts</li> <li>Microinfarcts</li> <li>Microbleeds</li> </ul>	(Jellinger, 2013; Thal et al., 2012)

Large infarct: >1cm Ø; Lacunar infarct: 5–15 mm Ø; microinfarct: <1mm Ø; microbleeds: <5mm Ø; ATS: atherosclerosis; GOM: granular osmophilic material; Vascular risk factors: hypertension, diabetes, smoking, etc.