Cerebral small vessel disease: from a focal to a global perspective

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Abstract | Cerebral small vessel disease (SVD) is commonly observed on neuroimaging among elderly individuals and is recognized as a major vascular contributor to dementia, cognitive decline, gait impairment, mood disturbance and stroke. However, clinical symptoms are often highly inconsistent in nature and severity among patients with similar degrees of SVD on brain imaging. Here, we provide a new framework based on new advances in structural and functional neuroimaging that aims to explain the remarkable clinical variation in SVD. First, we discuss the heterogeneous pathology present in SVD lesions despite an identical appearance on imaging and the perilesional and remote effects of these lesions. We review effects of SVD on structural and functional connectivity in the brain, and we discuss how network disruption by SVD can lead to clinical deficits. We address reserve and compensatory mechanisms in SVD and discuss the part played by other age-related pathologies. Finally, we conclude that SVD should be considered a global rather than a focal disease, as the classically recognized focal lesions affect remote brain structures and structural and functional network connections. The large variability in clinical symptoms among patients with SVD can probably be understood by taking into account the heterogeneity of SVD lesions, the effects of SVD beyond the focal lesions, the contribution of neurodegenerative pathologies other than SVD, and the interaction with reserve mechanisms and compensatory mechanisms.

Life expectancy is higher than ever before and is predicted to increase continuously in industrialized countries[1]. As a result, age-related diseases will increasingly pose challenges to societies and health-care systems. Globally, over 40 million people currently have dementia, and this number is predicted to almost double every 20 years[2]. Cerebral small vessel disease (SVD), which was once thought to be innocuous, is now recognized to be the most important vascular contributor to dementia[3]. Furthermore, this condition causes ~20% of all ischaemic strokes and is associated with gait impairment and mood disturbances[4–7]. Consequently, a proper understanding of how SVD exerts its action on the ageing brain and leads to clinical symptoms is urgently needed.

SVD is present to some extent in virtually every individual aged 60 years or older[8]. SVD affects the smallest cerebral blood vessels, including the perforating arterioles, capillaries and venules[9]. Although in vivo assessment of the smallest blood vessels is not yet possible with conventional imaging techniques, a spectrum of radiological manifestations can be detected that are thought to result from SVD. Common radiological markers of SVD include white matter hyperintensities (WMHs), lacunes, enlarged perivascular spaces, microbleeds, recent small subcortical infarcts and brain atrophy, and the detection of these features is now complemented by the examination of losses in microstructural integrity of the white matter and the presence of cortical microinfarcts[5] (FIG. 1).

SVD historically has been perceived as a slowly progressing disease that affects frontal–subcortical networks, leading to corresponding frontal symptoms[10]. These symptoms include loss of mental processing speed and executive function and affect cognitive function, motor performance and mood regulation. Compared with the healthy ageing population, individuals with SVD are at an increased risk of cognitive decline and, ultimately, dementia[6,11]. In addition, slowing of gait is a frequent observation in people with SVD and can result in parkinsonism[4,12–14]. Finally, apathy (defined as a lack of motivation expressed by reduced initiative, diminished interest and lowered emotional responsiveness to stimuli[15,16]) and depressive symptoms are common in individuals with SVD[7,17,18].

At least two reasons support re-evaluation of this classic concept of SVD. First, despite loss of executive control and speed in behavioural performance, the spectrum of cognitive symptoms attributable to SVD

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Key points

- Cerebral small vessel disease (SVD) is associated with a remarkable degree of variation in clinical symptoms — both in nature and in severity — that cannot be explained fully by conventional markers of SVD.
- Conventional MRI does not capture the heterogeneity present in SVD lesions with a similar appearance and reveals only the tip of the iceberg of the total SVD-related brain damage.
- SVD affects brain tissue beyond the commonly recognized focal lesions by inducing a cascade of events that spread from the initial lesion to remote brain areas, which probably contributes to clinical outcome.
- SVD disturbs structural and functional network connectivity and thereby disrupts efficient communication in brain networks, which is necessary for functional performance.
- Brain resilience protects against clinical deterioration caused by SVD via reserve and compensatory mechanisms, which explains the clinical variation observed in patients with apparently equal SVD lesion burden.
- The clinical notion that SVD mostly constitutes a subcortical disease of focal lesions requires reconsideration.

is more diverse than previously thought and can also include deficits in language, memory, attention and visuospatial abilities[19–24]. These symptoms typically have not been attributed to SVD as they are considered to result from cortical lesions rather than subcortical lesions. This view is also consistent with findings in case studies, which have reported the occurrence of acute memory loss in patients with an isolated lacunar infarct in the thalamus[25,26] or internal capsule[27,28]. Second, clinicians often observe a remarkable heterogeneity in clinical symptoms among patients with a similar radiological degree of SVD-associated features on brain imaging. In a hospital-based cohort of individuals with SVD, the 5.5-year cumulative risk of dementia was 11%, which indicates that SVD might go unnoticed or result in only mild functional deficits in the majority of people[29].

Advances in structural and functional neuroimaging have now begun to shed light on these remarkable clinical observations in SVD. In this Review, we summarize these advances and provide a new framework for clinical observations in patients with SVD on the basis of an analysis of the latest literature on this topic. First, we discuss the heterogeneous pathology present in SVD lesions that seem radiologically identical and the effects of SVD on perilesional and remote brain regions. Second, we review the effects of SVD on structural and functional networks in the brain and provide reasons supporting the notion that SVD is a disconnection syndrome. We address the clinical variation in SVD from the perspective of brain resilience, comprising brain reserve and compensatory mechanisms, and briefly address mixed age-related pathologies in SVD. We conclude with a discussion on methodological considerations and future perspectives. The focus of this Review is on the most frequently occurring, sporadic form of SVD — that is, SVD with predominantly ischaemic manifestations (BOX 1) provoked by ageing and vascular risk factors[9]. Illustrative examples of mechanisms of action that have been demonstrated in other types of SVD, such as cerebral amyloid angiopathy (CAA) or inherited SVD, are sometimes used as a model.

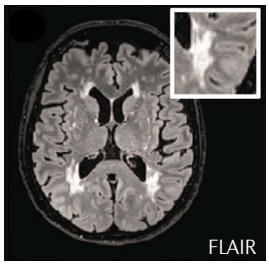
Focal and remote effects of SVD

Heterogeneity of SVD lesions with an identical appearance on imaging. MRI-based markers of SVD have a homogeneous appearance on conventional imaging. However, post-mortem histopathology studies have shown that these markers are in fact heterogeneous with regard to disease severity and aetiology[30–33].

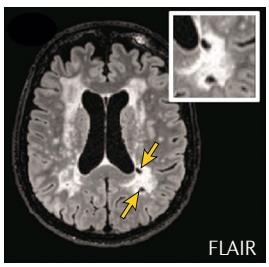
Pathological examination of WMHs has shown different degrees of demyelination, gliosis and loss of fibres and oligodendrocytes in different lesions, with more extensive abnormalities in more severe and confluent lesions[30]. Periventricular and deep WMHs are characterized by vessel wall thickening, enlarged perivascular spaces, decreased vascular density, increased vessel tortuosity and the presence of plasma proteins. Furthermore, activated endothelial cells within capillaries, especially in deep WMHs, and immunologically activated microglial cells, particularly in periventricular WMHs, have been observed[30]. On the basis of these different pathological observations, ischaemia and blood–brain barrier breakdown have been suggested as mechanisms that contribute to the origin of WMHs[30]. However, new hypotheses on the pathophysiology of WMHs include the dysfunction of oligodendrocyte precursor cells, which are involved in the formation of myelin, and failure of the glymphatic system, responsible for clearance of neurotoxic waste products[34,35]. In addition, evidence increasingly suggests a role for pathological changes of the venules in the origin of WMHs, especially venous collagenosis[36]. Thickening of the walls of venules due to collagen deposition could contribute to failure of interstitial fluid drainage and might also increase vascular resistance, which can cause perfusion deficits in deep white matter areas[36,37].

On histopathological examination, lacunes are irregularly shaped fluid-filled cavities that are surrounded by some degree of myelin and axonal loss and gliosis[30,38]. Different pathological findings have been described with respect to the age of the lacune. In contrast to more recently formed lacunes, older lacunes are characterized by a decreased concentration of macrophages and of necrotic waste and an increased density of gliosis[30,38]. In addition, a distinct type of lacunar infarcts has been proposed; these so-called incomplete infarcts are either not cavitated or are only minimally cavitated but show evidence of myelin loss and neuronal loss as well as a variable extent of gliosis[31].

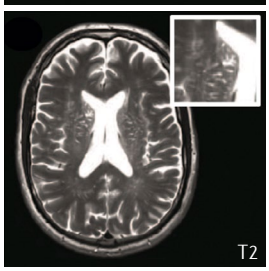
MRI-defined microbleeds have also been associated with various degrees of gliosis and tissue loss, and different pathological correlates have been identified. A pathology study that examined patients with CAA distinguished between acute and old microbleeds by the presence of intact red blood cells in acute lesions and of haemosiderin-laden macrophages in older microbleeds[33]. Histopathological evidence suggests that the majority of microbleeds reflect true microhaemorrhages caused by vessel wall disruption[30,32,33]. However, some microbleed mimics have been identified that reflect a vasculopathy rather than a parenchymal haemorrhage, including vessel wall dissection, microaneurysms or vessel wall thickening due to accumulation of fibrin and red blood cells in the vessel wall[30,32,33]. Finally,



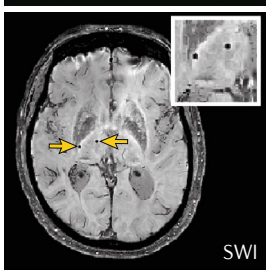
White matter hyperintensities
Bilateral hyperintensities (often symmetrical) visible on T2-weighted sequences (e.g. FLAIR). They are of variable size and are mostly located in the periventricular and deep white matter.



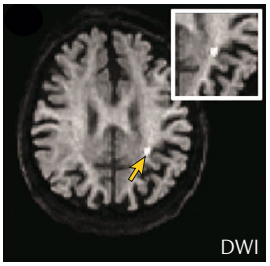
Lacunes
Round or ovoid subcortical cavitations (3–15 mm in diameter) presumed to be of vascular origin. Lacunes have a signal intensity similar to CSF and often, although not always, have a surrounding hyperintensive rim. They are thought to result from acute, small subcortical infarcts or haemorrhages in the territory of a single perforating artery.



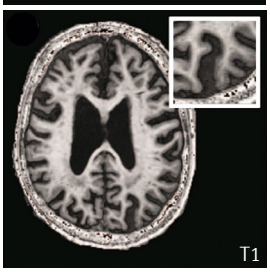
Enlarged perivascular spaces
Extensions of extracerebral fluid space surrounding the perforating vessels. These features are visible on MRI as CSF-like fluid-filled spaces that follow the course of penetrating vessels, with a linear or round shape depending on whether imaged parallel or perpendicular to the vessel orientation, respectively.



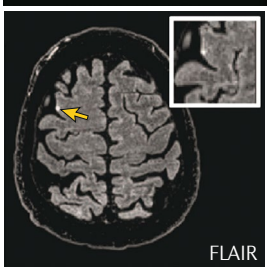
Cerebral microbleeds
Small depositions of haemosiderin consistent with blood cell leakage into brain tissue. Microbleeds are detectable on paramagnetic resonance sequences (e.g. T2*-weighted sequences or SWI), as small (2–10 mm in diameter) hypointense lesions.



Recent small subcortical infarcts
Can be revealed by DWI as a small (≤20 mm on axial slice) hyperintensity in the territory of a single perforating arteriole. Lesions <5 mm (that is, subcortical microinfarcts) are detectable only with high-resolution (3T and higher field strengths) imaging[65].



Brain atrophy
Cortical or subcortical brain volume loss unrelated to large traumatic injuries or infarctions.



Cortical microinfarcts
Small ischaemic lesions varying between 50 µm and a few millimetres[139] that are revealed on high-resolution structural MRI and DWI.

Fig. 1 | **Features of cerebral SVD on MRI.** Cerebral small vessel disease (SVD) is associated with a wide range of tissue alterations detectable with MRI (highlighted by yellow arrows), which are reported here according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria[5]. CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging.

markers of an underlying ischaemic process have been observed in some microbleeds, suggesting haemorrhagic transformation of a previous infarct[30,33].

These pathological findings indicate heterogeneous SVD lesions with a radiologically similar appearance, which is also increasingly being recognized in vivo on MRI[39–42]. Conventional MRI techniques, such as fluid-attenuated inversion recovery (FLAIR), coarsely dichotomize tissue into abnormal and normal tissue and do not, for example, reliably reflect the degree of demyelination[43], whereas quantitative imaging techniques, including magnetization transfer imaging and diffusion tensor imaging (DTI), can provide a detailed evaluation of the underlying tissue alterations at the voxel level[44]. DTI is a technique that applies a tensor-based model to acquired diffusion-weighted imaging (DWI) scans, an MRI sequence sensitive to the diffusion of water molecules, and thereby provides information on the microstructural organization of white matter[45]. In a study that investigated DTI changes within WMHs that had not changed on FLAIR imaging over a 3-year period, diffusion metrics showed a significant change over time in these WMHs[40]. Similarly, within acute or subacute incidental DWI-positive lesions that were suggestive of infarction, diffusion metrics were significantly changed on follow-up imaging after 7 months compared with the pre-lesional scan[39]. Interestingly, this ongoing change in diffusion parameters occurred irrespective of whether or not an infarct remained visible on FLAIR or T1-weighted MRI[39].

In addition to showing heterogeneity with regard to disease severity, MRI is increasingly able to contribute to our understanding of the various mechanisms implicated in the origin of SVD, including perfusion deficits, blood–brain barrier breakdown and venous pathology[46–48]. Finally, imaging evidence has converged on a shared origin of different types of SVD lesions. Acute DWI-positive lesions have now been shown to evolve into a WMH, lacune, microbleed or normal-appearing tissue[39,49,50].

Box 1 | **Different types of cerebral SVD**

Although the pathological processes that underlie MRI markers of cerebral small vessel disease (SVD) are incompletely understood, changes that result in disorganization of the vessel structure and function of the intraparenchymal and leptomeningeal blood vessel walls are key[9]. A previous report described six types of SVD[9]. The most prevalent type of SVD comprises a set of pathological changes under the influence of age and vascular risk factors — especially hypertension — that mainly affect the perforating arterioles[9,132,133]. This type is characterized by arteriolar wall thickening (mainly due to deposition of collagen, plasma proteins and inflammatory cells in the vessel wall), loss of smooth muscle cells involved in the regulation of arterial pressure and blood flow[134] and leakage of plasma proteins into the perivascular tissue[9,132,133]. Arteriolosclerosis represents an early stage of the disease, whereas lipohyalinosis and fibroid necrosis are observed at later stages — although these early and late stages can occur simultaneously in one vessel[9,132,133]. The second most common type of SVD is cerebral amyloid angiopathy (CAA), which is characterized by the deposition of amyloid-β in the walls of small arteries, arterioles and, infrequently, capillaries and venules, predominantly in the cerebral cortex and leptomeninges[9,132]. In addition, vasculopathic changes observed in CAA include vessel wall thickening, loss of smooth muscle cells, fibrinoid necrosis and exudation of blood breakdown products into perivascular tissue[132,135]. In both of these types of SVD, the described vessel wall alterations are associated with enlarged perivascular spaces[132]. Furthermore, occlusion or rupture of the blood vessel can occur, which leads to infarction or haemorrhage, although CAA is typically associated with lobar haemorrhages[132,135]. Microatheroma and microaneurysms are sometimes formed, which can also cause an infarct or haemorrhage[9,132]. The remaining four types of SVD result from rare causes and consist of hereditary forms of SVD (such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)), inflammatory and immunologically mediated SVD, venous collagenosis and, finally, a category of other causes of SVD (such as post-radiation angiopathy)[9].

In summary, the histopathological characteristics of lesions with similar appearances on MRI can vary. Consequently, the effects that these lesions have on the cerebral tissue can also vary (FIG. 2a,b).

Perilesional effects of SVD. In addition to overlooking the heterogeneous pathology present in SVD lesions with a similar appearance, conventional MRI manifestations of SVD are well known to represent only the tip of the iceberg with regards to SVD-related brain damage. In fact, DTI studies have shown that SVD lesions, such as WMHs, are surrounded by areas with altered diffusion metrics that otherwise look normal on conventional MRI, the so-called SVD penumbra[51,52] (FIG. 2b). Diffusion abnormalities in penumbral areas are associated with the overall WMH load and depend on the distance from the WMH, with more severe abnormalities in regions proximal to WMHs than in distant regions[51,52].

A cross-sectional study demonstrated that a gradient of diffusion abnormalities also surrounds lacunes and extends up to centimetres from the lacune into the white matter tract containing that lacune[53] (FIG. 2b). In a longitudinal study on the effect of acute and subacute DWI-positive lesions on the DTI characteristics of the perilesional tissue, water diffusion in perilesional tissue was slightly less anisotropic at the post-lesional scan than at the pre-lesional scan — albeit not to a significant extent, perhaps because only six patients demonstrated a lesion[39]. An autopsy study in six patients with a lacunar infarct suggested the presence of a penumbra surrounding the lacunar infarct, confirming previous imaging findings. The investigators revealed axonal damage in the penumbral area of the lacunar infarct at a distance 1.5 times the diameter of the lacune[54]. Changes included loss of nodes of Ranvier and increased length between each node. Although the axon and myelin sheath were preserved, the investigators argued that the injured axons could be susceptible to future axonal degeneration[54].

In addition to WMHs and lacunes, a penumbra can also surround cerebral microbleeds and perivascular spaces, although this phenomenon requires further investigation. One case report observed a temporary perilesional oedema surrounding an acute microbleed, which was thought to cause the transient clinical symptoms observed in this individual[55]. The dilatation of perivascular spaces could affect the integrity of surrounding grey or white matter tissue, although this idea remains to be proved.

Interestingly, in contrast to conventional markers of SVD such as WMHs or lacunar volume, which have consistently shown only weak relations with clinical symptoms, diffusion metrics generally yield robust relations with cognitive, motor and mood symptoms associated with SVD, which remain after adjustment for the typical SVD imaging markers in statistical analyses[56–58]. A DTI study demonstrated an association between abnormal diffusion metrics in the penumbra surrounding lacunes and deficits on tests of executive functioning and information processing speed, independent of the size and side (that is, left or right hemisphere) of the lacune and independent of total WMH load[53]. This finding indicates that cognitive performance is determined not only by SVD lesions that are visible on conventional MRI but also by the extent to which diffusion metrics in the penumbra are affected. In the past few years, two global brain DTI-derived metrics — the peak width of skeletonized mean diffusivity (which is based on skeletonization of white matter tracts and histogram analysis[59]) and the segmentation of DTI images[60] — have been shown to be strongly related with processing speed[59,60] and executive functioning[60] in patients with SVD, well beyond the associations with classic SVD makers such as WMHs and lacunar volume. These findings illustrate that SVD truly exerts its action outside the visible lesion, which contributes to clinical outcome.

A penumbra seems to surround not only conventional SVD markers but also cortical microinfarcts[61–63] (FIG. 2b). Cortical microinfarcts are frequently observed at brain autopsy in elderly people, are associated with cognitive decline and dementia[64] and, within the past

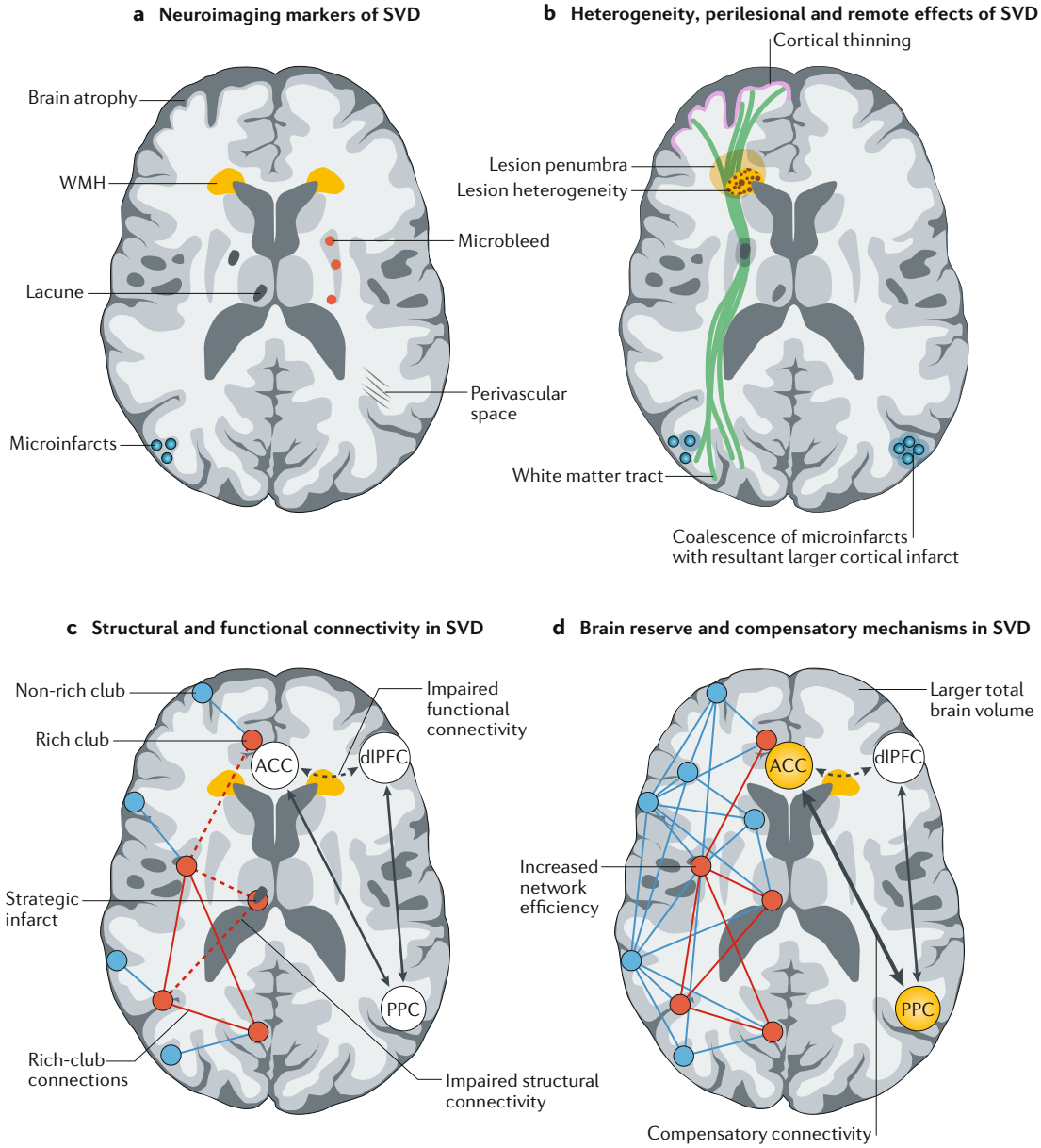


Fig. 2 | **What you see is not what you get. a** | MRI markers of cerebral small vessel disease (SVD), including white matter hyperintensities (WMHs; yellow), lacunes, enlarged perivascular spaces, microbleeds (orange), cortical microinfarcts (blue) and brain atrophy. **b** | Pathology studies show heterogeneity with regard to underlying disease severity and nature in SVD lesions with a similar appearance on MRI (shown for WMHs). A penumbra (lighter areas around the lesions) can surround SVD lesions. When penumbras of cortical microinfarcts overlap, these microinfarcts can coalesce with a resultant larger cortical infarct. In addition to having perilesional effects, SVD is also associated with remote effects, such as cortical thinning (purple) caused by lacunes and possibly WMHs via the disconnection of white matter tracts (green). **c** | SVD lesions can impair structural (left) and functional (right) connectivity by affecting the nodes of a network or the connections between them. Strategic infarcts affect rich clubs (red circles) or rich-club connections (red lines). Dotted lines denote impaired connectivity. **d** | A larger total brain volume, increased network efficiency and compensatory (increased) functional connectivity can make the brain resilient to a certain degree of damage. ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex.

few years, have also been recognized on MRI[65]. Two studies in rodents demonstrated that the occlusion of a single penetrating arteriole to induce a cortical microinfarct led to structural, functional and haemodynamic changes that were measurable millimetres away from the infarct core[62,63]. In fact, decreased neuronal activity was estimated to extend over a cortical region at least 12 times larger than the volume of the microinfarct core itself, whereas MRI could visualize only the core[63]. Remarkably, when perilesional areas of multiple, isolated microinfarcts overlapped, a coalescence of infarcts was observed, resulting in a larger cortical infarct[62] (FIG. 2b). An ex vivo study in human brain tissue showed that, similar to what was observed

in the penumbra surrounding lacunar infarcts, cortical microinfarcts caused disruption in the organization of adjacent axons, which was characterized predominantly by a loss of axon initial segments and increased length between nodes of Ranvier[61]. The investigators suggested that these changes ultimately reduce the capability of the axons to conduct action potentials[61]. The debilitating effect of cortical microinfarcts on axonal communication might be yet another mechanism by which the accumulation of cortical microinfarcts can induce clinical deficits[61] (FIG. 2b).

Remote effects of SVD. Previous studies have demonstrated suppression of brain function in areas far from subcortical infarcts and WMHs, as indicated by reduced perfusion and glucose metabolism on PET, suggesting the presence of sequelae of SVD remote from subcortical MRI markers[21,26,66]. In addition to these functional changes, a growing body of evidence suggests that SVD is accompanied by structural changes remote from the initial SVD MRI markers. Several cross-sectional studies have shown negative associations between WMHs and cortical thickness[67–69]. More specifically, one study demonstrated a particular pattern of frontal–parietal–occipital grey matter atrophy related to WMH progression, which was thought to be responsible for the observed decline in total brain volume[70]. However, among patients less severely affected by SVD, a longitudinal association between progression of WMHs and reduction of cortical thickness could not be confirmed[67].

A study of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic form of SVD, demonstrated that incident lacunar infarcts cause thinning in cortical tissue connected to the infarct area, providing the first direct proof for SVD-induced secondary degeneration in remote cortex[71]. Cortical thinning was most pronounced in areas that had a high probability of connectivity via the lacune-affected white matter tract (FIG. 2b). Indeed, in a subsequent study, this group demonstrated that infarcts are accompanied by DTI changes in white matter tracts connecting to the infarct area, with larger changes of white matter microstructure associated with more cortical thinning[72]. Interestingly, cortical thinning was independent of the final infarct fate — that is, whether the infarct was cavitating (complete or partial tissue loss) or non-cavitating (no visible tissue loss) — suggesting that less-severe infarcts can also induce long-term remote effects[72].

Brain atrophy is an important predictor of cognitive decline and has been shown to mediate the relationship between the presence of WMHs and cognitive decline in individuals[73,74]. Similar to lacunar infarcts, WMHs can affect the cortex via disruption of white matter tracts (FIG. 2b) and consequently can lead to cognitive symptoms, although this hypothesis remains to be proved in longitudinal studies. We previously showed that the decreased cortical thickness associated with WMHs mediated the associations between WMH volume and deficits in various cognitive domains (namely, global cognition, verbal memory, psychomotor speed, attention and executive functioning)[69]. In line with our observations, others have identified an intermediate role for cortical thickness of the left medial frontal lobe in the relationship between lacunar infarct volume within the anterior thalamic radiation and reductions in processing speed, whereas anterior thalamic radiation lacunar volume itself was not related to processing speed[75]. The role of cortical thickness in SVD is probably not limited to its effects on cognitive performance: another study showed that periventricular WMHs affected gait impairment via disruption of white matter tracts and cortical thinning[76].

Structural and functional connectivity

Functional performance results from the complex interplay between brain regions connected with each other through the white matter tracts, together forming brain networks. Advances in human connectomics have led to a better understanding of how SVD might give rise to clinical symptoms through its effects on structural or functional connected brain networks (BOX 2).

Structural connectivity in SVD. The white matter tracts are crucial for information transfer between brain regions. These tracts can be reconstructed using DTI tractography techniques and represent the connections in structural brain networks. Subsequently, the organizational properties of a network, such as its global efficiency of information transfer (a measure of how well connected the brain regions are), can be quantified using principles from graph theory (BOX 2). Several studies demonstrated structural network changes in patients with SVD through the application of this approach[77–80]. These network changes were characterized by a reduction in the number of connections, reduced strength of connectivity and decreased local and global efficiency. The degree of brain network disruption was associated with the extent of MRI markers of SVD, including WMH volume, number of lacunes and number of microbleeds, and with brain volume and microstructural integrity.

With respect to the specific connections being disrupted in patients with severe SVD, a study revealed a subnetwork comprising the most impaired connections, which included predominantly interhemispheric and prefrontal connections[77]. Whereas the distribution of SVD near the ventricles and within the centrum semiovale could explain the reduced connectivity of interhemispheric tracts, the disruption of frontal connections was interpreted as remote effects of SVD. Additional insights into the extent and location of structural network disruption in SVD have been provided by rich-club analyses (BOX 2). Rich-club organization of a network refers to the presence of nodes (brain regions) that are rich in connections that are more densely connected to each other than to other nodes[81]. The connections between the rich-club regions are centrally located in the network and are thereby the most important connections for integration of information[82]. Rich-club nodes identified in SVD comprise the precuneus, putamen, thalamus, superior occipital gyrus and regions in the superior frontal gyrus[78]. Reduced connectivity was predominantly observed for connections

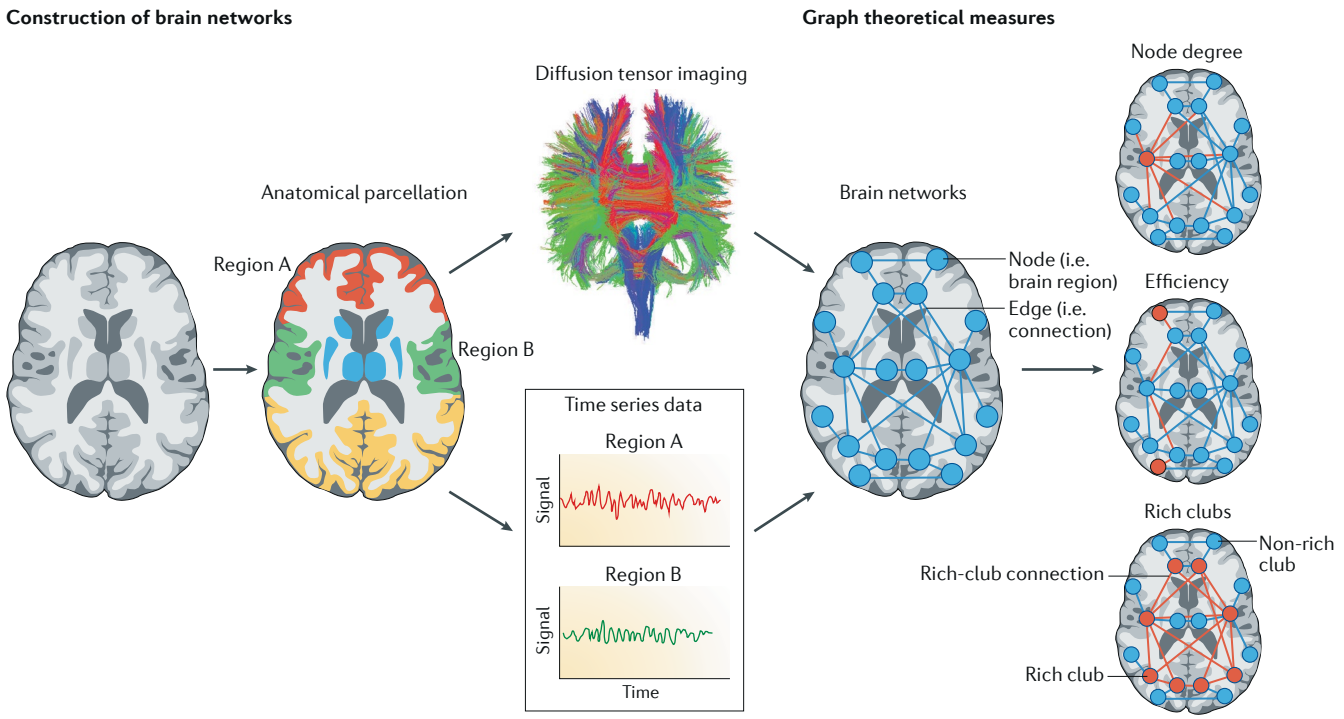
between the rich-club nodes rather than a generalized, random reduction of the white matter connectivity[78] (FIG. 2c). This observation might be explained in part by the location of SVD damage, which often overlaps with the location of rich clubs.

Several studies in patients with SVD have demonstrated that the degree of brain network disruption, reflected by decreased global efficiency, was related to increased cognitive impairment[77,79,83] and depressive symptoms[84]. Furthermore, decreased global efficiency was linked to an increased risk of all-cause dementia over a 5-year period[85]. In addition, associations between the presence of conventional MRI markers of SVD and decreased cognitive functions were, at least in part, mediated through network disruption[69,77,79]. In particular, rich-club connectivity strength mediated the association of WMHs with processing speed and executive functioning, in that higher rich-club connectivity strength was associated with better cognitive performance[78]. These findings were corroborated by others, who found that only microstructural changes in central network connections, as opposed to non-central connections, mediated the association between WMH volume and executive functioning[86]. Owing to their central role in brain networks and high connectivity with other nodes, damage to rich clubs or central connections might have a more widespread effect on network function than damage to peripheral nodes or peripheral connections in a network. Consequently, strategic infarctions, even when small in size, could result in a highly heterogeneous clinical phenotype that deviates from the typical 'subcortical' clinical picture when they are located near rich clubs or central connections[87] (FIG. 2c).

Functional connectivity in SVD. Functional neuroimaging enables the functional neuroanatomy of specific brain functions to be probed. Our brain consists of spatially distributed but functionally linked regions that continuously share information with each other. Functional connectivity is defined as the temporal

Box 2 | **Brain networks and graph theory**

Brain networks can be explored using graph theory, which conceptualizes the brain as a network (that is, a graph) with connections that mediate the interaction between brain regions. A network consists of nodes (brain regions) linked by edges (the connections between nodes), in which nodes are defined by a parcellation scheme (arbitrary scheme shown in figure). Brain networks can be constructed using structural and functional neuroimaging data. In structural imaging, connectivity between nodes A and B is retrieved from diffusion tensor tractography and thereby represents their anatomical connections. In functional imaging, connectivity between nodes A and B is based on the correlation between their functional MRI blood-oxygen-level-dependent time series. Functionally connected regions might or might not have a structural underpinning. Regions with correlated activity are likely to form a network, and several such brain networks have been identified, including the default-mode network, dorsal attention network and frontoparietal control network[89,136]. Once brain networks are constructed, the topological organization and properties of these networks can be explored[137,138], of which some are discussed here. Node degree refers to the number of connections that link a node to the rest of the network (connections to the node shown in orange, other connections shown in blue). Path length is defined as the shortest distance or minimum number of connections between two nodes (orange connections). Network efficiency is inversely related to path length, whereby global efficiency of the network is reflected by the average efficiency for all node pairs. The human brain consists of a few central connected regions, known as hubs. Several hubs are also highly interconnected with each other and with the rest of the network and represent rich clubs. Connections between the rich-club nodes are referred to as rich-club connections and play an important part in the integration of information by creating short paths[81,82].



dependency of neuronal activation patterns in anatomically separated brain regions[88]. Functional connectivity thus refers to correlated activity between functionally related brain regions rather than to connections via existing white matter tracts, as is the case in structural connectivity based on diffusion tensor tractography (BOX 2).

Functional neuroimaging studies have reported reduced functional connectivity across distributed networks in SVD (FIG. 2c). Three networks that are commonly affected in SVD are the default-mode network (DMN), the dorsal attention network (DAN) and the frontoparietal control network (FPCN), which play an important part in goal-directed attention and executive functions[89,90]. Patients with SVD showed reduced functional connectivity between nodes within the FPCN and the DAN[91–96], which was related to SVD severity[91,92,96–99]. These findings suggest that damage to long association fibres, caused by SVD, can manifest as reductions in functional connectivity between major nodes of the attentional networks. Furthermore, brain regions within the DMN normally show highly correlated brain activity during rest and reduced activity during attentionally demanding tasks, which is considered to be important for the maintenance of task-related goals. However, patients with SVD showed hyperactivation or impaired DMN deactivation during attentionally demanding tasks[100–103]. For example, WMH severity was associated with hyperactivation of the anterior cingulate cortex, a key structure of the DMN[100].

These alterations to functional networks provide novel insights into the mechanisms of cognitive decline in SVD. Several studies have reported that reduced functional connectivity within the FPCN, DAN and DMN was related to an increased degree of cognitive impairment[91,97–99,104]. Evidence suggests that cognitive impairments due to SVD result from disruption of frontal–subcortical circuits and long association fibres that in turn impairs communication between crucial neural networks responsible for cognitive control or attention, such as the DMN, FPCN and DAN[90] (FIG. 2c).

Brain resilience

In the previous sections, we described the clinical consequences of SVD and discussed the mechanisms by which SVD might lead to these clinical deficits. Nevertheless, these clinical deficits cannot entirely be explained by SVD alone as many individuals remain functionally independent despite a considerable burden of SVD. An alternative approach might be to look not only at the sum of SVD burden and brain damage but also explicitly at brain resilience, which is the capacity for patients to tolerate a certain degree of brain damage before clinical symptoms become manifest. Brain resilience can be separated into reserve mechanisms, including brain reserve (referring to structural or functional metrics of the brain, such as intracranial volume) and cognitive reserve (referring to lifetime experiences, such as education), which offer protection against brain pathology, and compensatory mechanisms through which the brain actively compensates for clinical deterioration in the presence of pathology[105] (FIG. 2d).

The concept of brain reserve states that individuals with a larger brain reserve tolerate a greater burden of pathology before clinical symptoms arise than do individuals with lower brain reserve[106]. One study reported a lower risk of dementia in patients with a larger brain volume[107], and another study reported that patients with WMHs who had no cortical atrophy had a lower risk of dementia than did those with cortical atrophy[108]. Structural network efficiency can also be viewed as a form of brain reserve, whereby more efficient networks might protect against clinical deterioration in the presence of brain pathology. In other words, patients with highly efficient networks (for example, networks with many connections between nodes) could cope well with pathology, as these individuals are able to compensate for the disruption of white matter tracts by using alternative connections. This hypothesis is supported by the finding that patients with SVD who did not develop dementia had higher global network efficiency than did patients who converted to dementia, independent of SVD markers, including WMH volume, presence of lacunes and microbleeds and brain atrophy[85].

The concept of cognitive reserve is that high intellectual enrichment or high cognitive reserve (usually operationalized as IQ and level of education) offers increased protection against age-related brain pathology[105,106,109–111]. Specifically, in the context of cognitive impairment associated with SVD, several studies reported that high cognitive reserve attenuated the negative effects of SVD on cognition[106,109,112–117]. Higher cognitive reserve was associated with a slower rate of decline in processing speed, executive functions and memory, independently of WMH severity, which supports the hypothesis that cognitive reserve protects against the clinical manifestations of SVD and could partly explain the variation in cognitive performance in patients with a similar burden of SVD markers[118].

Compensatory functional connectivity refers to the ability of the brain to adapt to pathology by the use and development of compensatory networks when the primary networks are no longer capable of executing a certain task[110,119]. A functional neuroimaging study reported associations between decreased grey matter volume within the primary network and increased use of an alternative network to maintain task performance[120], supporting the theory of compensatory connectivity. In addition, a ‘less wiring, more firing’ hypothesis has been proposed, which states that neurons compensate for age-related impairments in white matter via greater synaptic responsiveness[121]. Altered functional connectivity patterns in patients with SVD have been observed in several studies, with compensatory activation in networks found to be important to maintain cognitive performance[91,97–99].

Mixed age-related pathologies

The variability in clinical symptoms between patients with apparently similar degrees of SVD might also be explained by the presence of other neurodegenerative pathologies, such as Alzheimer disease (AD). A neuroimaging study in patients with AD has reported reductions in network integrity that were associated with increased volume

of WMH and lacunes, specifically in networks important for cognitive functioning, such as in executive networks and DMNs as well as in connections between the hippocampus, thalamus, putamen and cortical regions[122].

The question remains to what extent these pathologies truly interact. Some neuroimaging studies have found a synergistic effect between WMHs and markers suggestive of AD pathology (for example, hippocampal volume) on cognitive performance[123,124]. Studies using AD transgenic mouse models have suggested that neurovascular dysfunction potentiates the production of amyloid-β[125]. However, longitudinal evidence on the directionality of associations between vascular pathology and AD pathology in humans is limited[125,126]. Neuroimaging studies in cognitively normal elderly individuals and in patients with cognitive impairment have suggested that cerebrovascular pathology and AD pathology negatively affect cognition independently of each other[116,127]. The same conclusion was also reached by two recent reviews[125,126].

Methodological considerations

Several methodological considerations must be addressed regarding the studies discussed in this article. We discuss factors related to neuroimaging and to study design as well as possible solutions to tackle these methodological issues in future studies.

The reproducibility of SVD imaging markers is a major concern, especially across different centres[128]. One review identified several aspects — from acquisition of imaging data to processing — that influence the reproducibility[128]. Quantification of SVD markers depends on magnetic field strength, choice of MRI sequence, image resolution and the segmentation method used, the latter of which can range from qualitative visual rating scales to quantitative automatic segmentation routines[128,129]. With the publication of the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE), which provides definitions of visible SVD features and recommendations for image acquisition, analyses and scientific reporting to reduce the large variation between studies, a higher consistency between studies has been reached[5]. Nonetheless, variation between studies is still considerable, hampering progress in our understanding of how SVD might contribute to clinical symptoms.

In connectivity analyses, the presence of SVD lesions, such as WMHs, affects the reconstruction of white matter fibre tracts with the use of DTI data and consequently affects the investigation of remote effects via white matter tracts connected to the lesion or the assessment of structural connectivity. In functional connectivity, brain activity is measured by blood-oxygen-level-dependent imaging that relies on regional differences in cerebral blood flow, which is often affected in patients with SVD. Additionally, cerebral blood flow can be affected by antihypertensive treatment[130].

With regards to the design of the discussed studies, most are cross-sectional and consequently cannot elaborate on causality or on the directionality of the associations. Furthermore, studies might be susceptible to selection bias, as patients with the most severe SVD lesion load are often institutionalized and might not have been able to participate. Finally, study populations vary between different studies — ranging from pure SVD to SVD with concomitant AD pathology and from population-based studies to studies including patients with symptomatic lacunar stroke — and this variability should be taken into account when interpreting results on the clinical consequences of SVD.

Future directions

Comprehensive studies with in-depth phenotyping of patients are warranted to further unravel the mechanisms by which SVD might lead to clinical deficits. Studies should include patients of a younger age (as currently patients older than 60 years of age are often studied), which would enable elaboration on the factors involved in the origin of SVD. Future studies should also take into account all neuroimaging markers of SVD and include advanced multimodal structural and functional magnetic resonance sequences with high spatial resolution. Moreover, studies with longitudinal designs, including those with short interscan intervals of weeks or months, are of utmost importance to elucidate the directionality of associations and the sequence of events from focal SVD towards global remote effects and clinical symptoms. Furthermore, rather than solely focusing on vascular dementia or AD as isolated diseases, the field would benefit from a focus on the interaction of SVD pathology with other neurodegenerative pathologies. Finally, the pathological correlates of MRI-defined SVD lesions should be further investigated.

Conclusion

SVD is associated with a remarkable variation of clinical symptoms that differ both in nature and in severity. In this Review, we elaborate on how SVD affects the brain, and we provide a framework to explain the remarkable disparities between patients. SVD markers visible on conventional MRI reveal only the tip of the iceberg with regards to the changes associated with the disease. Despite an identical appearance on MRI, SVD lesions are pathologically heterogeneous, and a cascade of events seems to spread from the initial SVD lesion to remote areas with an as yet unknown time course. Furthermore, SVD disturbs structural and functional network integrity, especially in central connections, thereby disrupting efficient communication in brain networks. Consequently, even a small focal lesion can lead to widespread effects. In addition, reserve and compensatory mechanisms enable patients to maintain cognitive and motor performance at the premorbid level until these mechanisms are exhausted and functional performance drops. Finally, other neurodegenerative pathologies can be present and probably contribute to the clinical presentation.

Although SVD lesions mostly occur in subcortical areas, they exert their effect throughout the brain. Consequently, the clinical notion of SVD being a focal subcortical disease must be reconsidered. Following the identification of SVD markers on MRI, clinicians should be aware that the entire brain is affected, despite the presence of focal subcortical lesions. Hence, what we see is not what we get. This notion has also become apparent

in other neurological diseases — for instance, in multiple sclerosis, in which the clinical course is increasingly understood from the perspective of a global, rather than a focal, brain disease[131].

In conclusion, advances in structural and functional imaging and network analyses have increased our understanding of the clinical symptoms in SVD beyond the classic spectrum and of the heterogeneity of these symptoms between individuals. Future prospective studies with in-depth phenotyping of patients and multimodal structural and functional MRI with high temporal and spatial resolution will shed light on the sequence of events in SVD from the very first MRI manifestation of focal SVD to its global remote effects.

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A.t.T. and E.M.C.v.L. researched the data for the article and wrote the text. A.t.T., K.W. and A.M.T. researched the data and created the boxes and figures. A.t.T., E.M.C.v.L., K.W., C.J.M.K., A.M.T. and F.-E.d.L. provided substantial contributions to discussions of the content. All authors reviewed and/or edited the manuscript before submission.

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Review criteria
Articles were selected from PubMed. To select articles on small vessel disease, we used the following search terms appearing in the title and abstract: "cerebral small vessel disease", "cerebral microangiopath*", "white matter hyperintensities", "leukoaraiosis", "lacunar stroke", "lacunar infarct", "perivascular spaces" or "microbleeds". We combined these searches with search terms covering the topics in this Review, including "cognition", "motor", "cerebral cortex", "network" or "connect*". We included only articles in English and focused on articles published within the past decade to discuss the most recent scientific findings. Furthermore, reference lists of cited articles and articles in our personal databases were screened for eligibility.

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