



# Detection, risk factors, and functional consequences of cerebral microinfarcts

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Cerebral microinfarcts are small lesions that are presumed to be ischaemic. Despite the small size of these lesions, affected individuals can have hundreds to thousands of cerebral microinfarcts, which cause measurable disruption to structural brain connections, and are associated with dementia that is independent of Alzheimer's disease pathology or larger infarcts (ie, lacunar infarcts, and large cortical and non-lacunar subcortical infarcts). Substantial progress has been made with regard to understanding risk factors and functional consequences of cerebral microinfarcts, partly driven by new in-vivo detection methods and the development of animal models that closely mimic multiple aspects of cerebral microinfarcts in human beings. Evidence from these advances suggests that cerebral microinfarcts can be manifestations of both small vessel and large vessel disease, that cerebral microinfarcts are independently associated with cognitive impairment, and that these lesions are likely to cause damage to brain structure and function that extends beyond their actual lesion boundaries. Criteria for the identification of cerebral microinfarcts with in-vivo MRI are provided to support further studies of the association between these lesions and cerebrovascular disease and dementia.

## Introduction

Cerebral microinfarcts are small lesions presumed to be of ischaemic origin. Although the lesions are often not visible to the naked eye on autopsy, definitions of specific size cutoffs vary and depend on different detection modalities. Cerebral microinfarcts are a common finding at brain autopsy, particularly in individuals with dementia and in individuals with other manifestations of cerebrovascular disease.<sup>1,2</sup> A systematic review<sup>2</sup> of neuropathological studies reported a cerebral microinfarct prevalence of 62% in patients with a diagnosis of vascular dementia, 43% in Alzheimer's disease, and 24% in individuals aged around 75 years or older without a diagnosis of dementia before autopsy. Affected individuals are estimated to have hundreds to thousands of cerebral microinfarcts.<sup>3,4</sup> A 2012 review<sup>1</sup> highlighted the importance of these lesions, which are considered to be the most widespread form of brain infarction, with effects that extend beyond the tissue injury identified at autopsy. Cerebral microinfarcts cause measurable disruption to structural brain connections, and are associated with dementia that is independent of Alzheimer's disease pathology. These findings suggest that cerebral microinfarcts represent an important mechanistic link between cerebrovascular disease and dementia.<sup>5</sup>

In 2012, cerebral microinfarcts were considered to be so-called invisible lesions,<sup>1</sup> but high-resolution structural

MRI has enabled the largest cerebral microinfarcts to be visualised in vivo. Additionally, animal models have been established to study the effect of cerebral microinfarcts on the brain with unprecedented temporal and spatial resolution. This Review describes these recent developments and provides an update on the frequency, risk factors, and functional consequences of cerebral microinfarcts. We propose criteria for identification of cerebral microinfarcts with MRI and provide a framework to translate candidate cerebral microinfarct mechanisms and outcome markers from animal models to MRI-guided clinical trials.

## Detection of microinfarcts

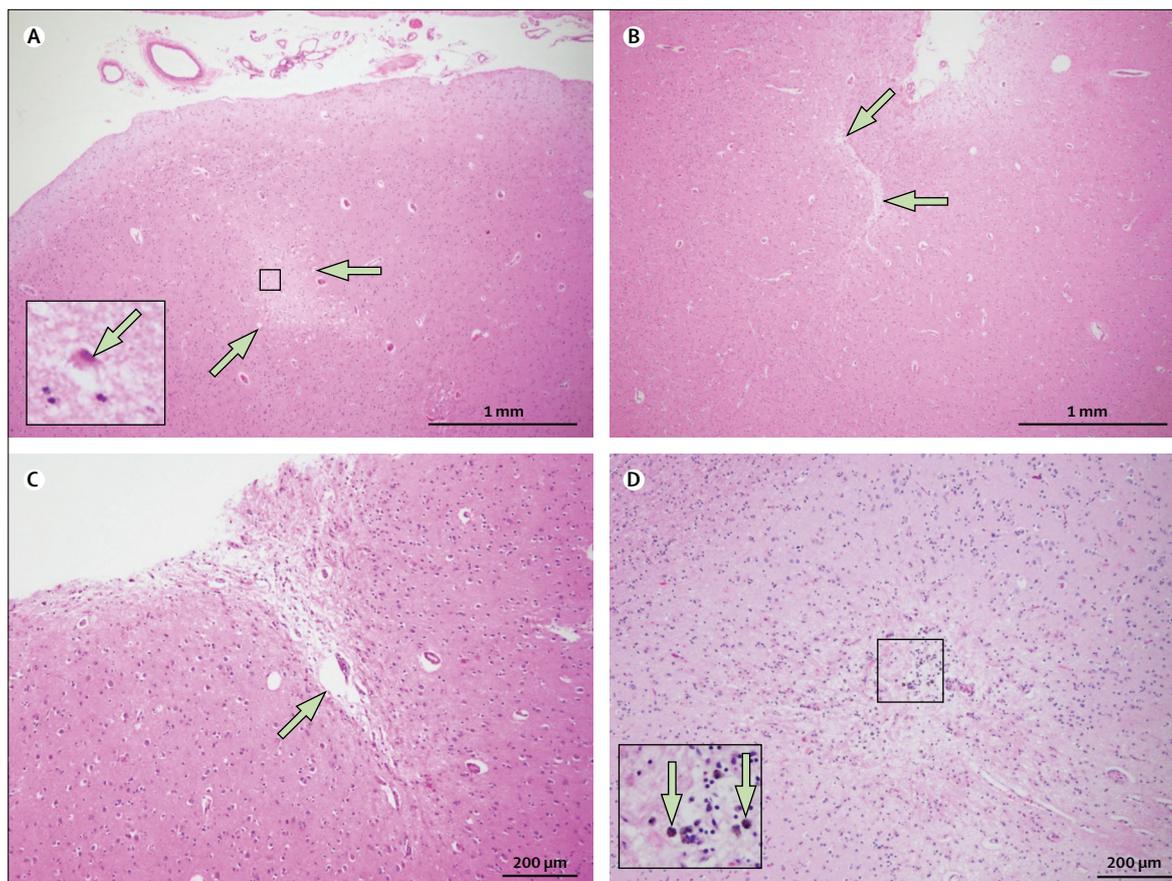
Three different modalities are available for the detection of cerebral microinfarcts: neuropathological examination, diffusion-weighted imaging, and high-resolution structural MRI. An important consideration is that none of these three modalities capture the entire cerebral microinfarct burden in the brain (table). It is therefore important to note that neuropathological assessment—currently considered the reference standard—is not directly translatable to neuroimaging definitions. Furthermore, whether the different subtypes of cerebral microinfarcts—detected by different modalities—have the same causes and functional implications remains unclear. Further cross-modal studies are warranted to investigate this.

### Neuropathological examination

Neuropathological examination can detect the smallest acute (<24 h-old) and subacute to chronic (>24 h-old) cerebral microinfarcts. However, detection by most neuropathological methods has restricted brain coverage. In a standard autopsy of the brain, only a few samples (usually  $\leq 20$ ) are taken for processing into paraffin sections (approximately 4–6  $\mu\text{m}$ -thick) for histopathological analysis; thus, less than 0.01% of the entire brain is sampled. Therefore, the detection of one or several cerebral microinfarcts at routine brain autopsy might

	Neuropathological examination	Diffusion-weighted MRI	High-resolution structural MRI
Spatial resolution	High	Moderate	Moderate
Microinfarct size	100 $\mu\text{m}$ –few mm	>1 mm	>1 mm
Temporal resolution	High	Low	High
Microinfarct stage	Hyperacute to chronic	Hyperacute (<2 weeks)	Acute to chronic (within hours on T2, within days on T1)
Brain coverage	Low	High	Partial
Volume assessed	<0.01%, few sections	Whole brain	Cortical grey matter

**Table:** Comparison of the three modalities available for the detection of cerebral microinfarcts



**Figure 1: Haematoxylin and eosin-stained sections of cerebral microinfarcts on neuropathological examination**

(A) An acute microinfarct (arrows) in the midfrontal cortex and a red hypoxic neuron (inset; arrow). (B) A chronic slit-like microinfarct with puckering in the inferior parietal cortex (arrows). (C) A chronic microinfarct with cavitation (arrow) in the inferior parietal cortex. (D) A chronic microinfarct with haemosiderin deposits in the inferior parietal cortex (inset; arrows).

indicate the presence of hundreds to thousands of cerebral microinfarcts throughout the brain that remain undetected.<sup>3</sup> On microscopic examination of standard histological haematoxylin and eosin-stained sections, typical older (chronic) cerebral microinfarcts can be discriminated as focal lesions of tissue cavitation with evidence of gliosis and often a few remaining macrophages—a histological signature suggestive of ischaemia. Less extensive chronic lesions might show only neuronal cell loss with or without macrophages or substantial gliosis, with tissue pallor or puckering (figure 1). Evidence of previous haemorrhage in the form of haemosiderin or haematoidin might also be present, but unlike microhaemorrhages, the presence of such blood-breakdown products is not the primary feature of these lesions. Recent (acute) cerebral microinfarcts have well defined foci of cell injury (red neurons in the grey matter on haematoxylin and eosin staining) without cavitation or cell loss (figure 1). Most neuropathological studies focus on chronic cerebral microinfarcts because these lesions are most readily associated with cognitive impairment, often observed in the months before death.

Acute cerebral microinfarcts might also be associated with peri-mortem events rather than factors relevant during life. Some studies report immunohistochemical approaches for the enhanced detection of cerebral microinfarcts, such as glial fibrillary acidic protein for gliosis, CD68 for macrophages, human leucocyte antigen markers for microglia,<sup>2</sup> and calcineurin.<sup>6</sup> However, the sensitivity and specificity of these approaches for the detection of cerebral microinfarcts is not clear.

The differences between pathological subtypes of cerebral microinfarcts (cavitated, slit-like, haemorrhagic, or recent; figure 1) have not yet been linked to specific pathogenic mechanisms, but do affect the appearance on MRI and the detectability of the lesions (panel 1). Conventionally, cerebral microinfarcts are only considered microinfarcts (as opposed to larger infarcts), when they are not visible to the naked eye on gross pathology. The reported sizes of microinfarcts vary between 100 µm and a few mm.<sup>2</sup> Of note, standard neuropathological evaluation might underestimate the actual sizes of cerebral microinfarcts, because often only part of the lesion is included in a single thin paraffin section.

### Panel 1: Proposed detection and visual rating criteria for cerebral microinfarcts on in-vivo MRI

#### Acute cerebral microinfarcts on diffusion-weighted imaging (ie, small incidental diffusion-weighted imaging lesions) should meet all of the following criteria:

- Hyperintense on diffusion-weighted imaging
- Apparent diffusion coefficient should be isointense or hypointense at the same location (to rule out so-called T2-shine-through of high-T2 signal)
- Isointense or hyperintense on T2\*-weighted MRI or blood-sensitive scans (eg, gradient echo or susceptibility-weighted imaging)
- Any brain parenchymal location
- Operationally defined as less than 5 mm in greatest dimension

#### Durable cortical cerebral microinfarcts on structural MRI should meet all of the following criteria:

- Hyperintense on T2-weighted MRI (ie, fluid-attenuated inversion recovery, T2), with or without cavitation on fluid-attenuated inversion recovery
- Hypointense on T1-weighted MRI
- Isointense on T2\*-weighted MRI or blood-sensitive scans (eg, gradient echo or susceptibility-weighted imaging)
- Operationally defined as strictly intracortical and less than 4 mm in greatest dimension
- Distinct from enlarged perivascular spaces
- Visible in at least two planes (eg, sagittal, transversal, coronal)

Important mimics for cortical cerebral microinfarcts are enlarged perivascular spaces in the immediate underlying juxtacortical areas that might extend into the cortical ribbon, leptomeningeal vessels (especially in the temporal lobes), anatomical variations (eg, gyral curvatures), and cortical cerebral microbleeds (signal on blood-sensitive scans should always be verified). We suggest that cerebral microinfarcts in close proximity (ie, <1 cm in the same gyrus) to larger strokes should not be considered as independent cerebral microinfarcts.

### Diffusion-weighted imaging

Diffusion-weighted imaging detects recent brain infarction with high sensitivity (figure 2).<sup>7</sup> Because of the signal generated by diffusion-weighted imaging, even very small infarcts can be detected, including those 1–2 mm in diameter, which represent the upper limit of lesions that would be pathologically defined as cerebral microinfarcts. However, a disadvantage of diffusion-weighted imaging is that the signal fades over 2 weeks.<sup>8</sup> Therefore, although diffusion-weighted imaging offers full brain coverage, temporal resolution for microinfarct detection is poor. A study published in 2015<sup>4</sup> used mathematical models to estimate the annual incidence of new cerebral microinfarcts according to the presence of incidental diffusion-weighted imaging lesions. The estimations indicated that the detection of one or two incidental small lesions on diffusion-weighted imaging—presumed to be acute cerebral microinfarcts large enough to produce a diffusion-weighted imaging signal—could reflect an annual incidence of hundreds of new cerebral microinfarcts of any size.<sup>4</sup>

Incidental small diffusion-weighted imaging lesions have been reported in 23–41% of patients with a recent intracerebral haemorrhage (<3 months) in whom they

are associated with MRI manifestations of small vessel disease.<sup>9–12</sup> These lesions have also been identified in 15% of patients with cerebral amyloid angiopathy and recent intracerebral haemorrhage,<sup>13</sup> 6% of patients with ischaemic stroke,<sup>14</sup> 14% of patients after carotid endarterectomy,<sup>15</sup> and 1–4% of patients with cognitive impairment or dementia.<sup>16,17</sup>

On the basis of these prevalence data, the average patient with cerebral amyloid angiopathy is estimated to develop as many as eight asymptomatic diffusion-weighted imaging lesions per year.<sup>13</sup> By contrast, the prevalence of incidental small diffusion-weighted imaging lesions in the general population appears much lower. In a population-based study of 793 participants aged 40–75 years, no incidental diffusion-weighted imaging lesions were found (95% confidence upper limit 0.5%),<sup>18</sup> whereas in a community-based study of 623 older individuals (mean age 71 years) with more vascular risk factors, the prevalence was 1%.<sup>17</sup>

Most studies of incidental small diffusion-weighted imaging lesions have been cross-sectional. A notable exception was a small study<sup>19</sup> of five patients with extensive white matter hyperintensities who had weekly MRI scans over 16 weeks, during which three patients had a total of nine incidental subcortical diffusion-weighted imaging lesions. Another longitudinal study<sup>11</sup> found incidental diffusion-weighted imaging lesions in 30 (27%) of 113 patients with intracerebral haemorrhage scanned 30 days after admission.

The long-term outcomes of incidental small diffusion-weighted imaging lesions (ie, their MRI signature after weeks or months) are largely unknown. Preliminary data suggest that these lesions can evolve into a small cavity, a T2 hyperintensity without cavitation (figure 2), or become radiologically inapparent.<sup>20</sup> In some patients, acute small diffusion-weighted imaging lesions resolved into cavities less than 3 mm in diameter, which in their chronic stage would not be classifiable as infarcts according to STRIVE criteria.<sup>21</sup>

Most studies of incidental small diffusion-weighted imaging lesions do not report their actual size, and instead use a cutoff (eg, <5 mm in diameter). However, representative figures from previous publications<sup>9,10,13,20</sup> suggest that most small diffusion-weighted imaging lesions are only a few mm in size and potentially consistent with cerebral microinfarcts. Whether upper size cutoffs for diffusion-weighted imaging lesions compatible with acute cerebral microinfarcts can distinguish them from acute lacunar infarcts or large acute cortical infarcts remains unclear. The STRIVE criteria<sup>21</sup> for recent small subcortical infarcts include an upper size cutoff of 20 mm, a criterion designed to identify lacunar infarcts in their acute stage, without providing a lower size cutoff and without criteria for classification of cortical small infarcts. Another issue is that size of diffusion-weighted imaging lesions depends on field strength and the parameters of the diffusion-weighted imaging sequence.

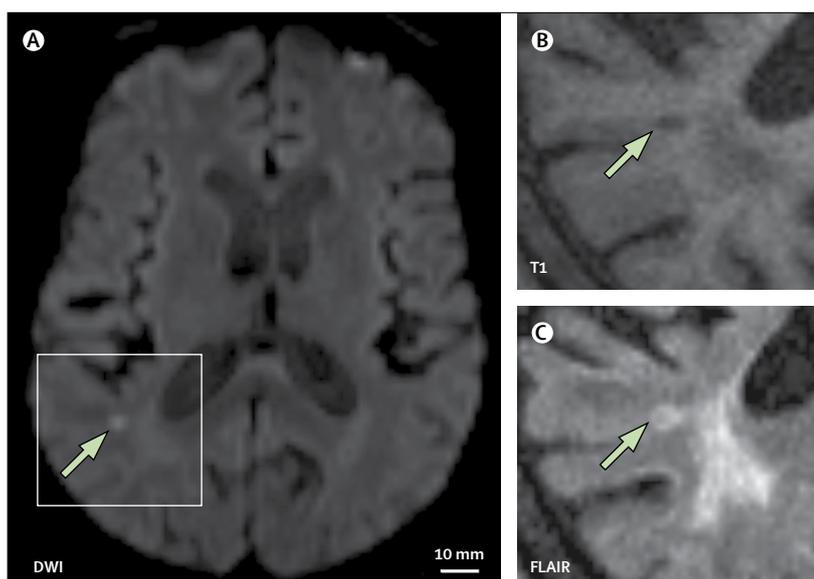
On the basis of the available evidence, we postulate that diffusion-weighted imaging lesions with an axial diameter of 5 mm or more are unlikely to evolve into what would be considered a cerebral microinfarct on structural brain imaging or neuropathological examination, and should not be described as cerebral microinfarct. Hence, we propose a size criterion of less than 5 mm for acute cerebral microinfarcts (panel 1). Notably, this cutoff was operationally defined and might need to be refined in the future as more data about the long-term MRI signature of incidental small diffusion-weighted imaging lesions and the association between radiological and pathological findings become available.

### High-resolution structural MRI

Detection of cerebral microinfarcts on structural MRI provides a major step forward in determining the causes and consequences of these small ischaemic lesions. Evidence from radiological–histopathological correlation studies<sup>22–24</sup> using high-field strength 7T MRI suggested that durable (ie, not just visible in the subacute or acute stage) cerebral microinfarcts of at least 1–2 mm in size in the cortical grey matter can be discerned on structural MRI scans (figure 3, panel 1). These post-mortem verification studies<sup>22–24</sup> indicated high specificity (26 of 27 lesions on post-mortem MRI were verified as cerebral microinfarcts on the corresponding histological sections). These initial studies used a pragmatic approach to specifically focus on the detection of cerebral microinfarcts in cortical areas of the brain because in the white matter it is difficult to distinguish cerebral microinfarcts from other lesions such as white matter hyperintensities, lacunar infarcts, and enlarged perivascular spaces. Indeed, in juxtacortical areas (directly adjacent to, rather than within, cortical grey matter), lesions that had an appearance similar to cortical cerebral microinfarcts were enlarged perivascular spaces on histological examination.<sup>23</sup> Hence, we consider punctate subcortical lesions on structural MRI—without previous information about diffusion-weighted imaging positivity—currently unclassifiable as cerebral microinfarcts.

The first studies<sup>22,25–27</sup> to detect cortical cerebral microinfarcts in vivo used 7T MRI. A later 7T MRI study<sup>28</sup> of 23 patients showed that 27% of the lesions were also visible on 3T MRI scans done on the same day. Subsequently, cortical cerebral microinfarcts were examined in several studies<sup>14,28–30</sup> using 3T MRI. Cerebral microinfarcts have also occasionally been observed using 1.5T MRI (appendix), so this possibility should not be overlooked. In addition to field strength, the sensitivity of detection depends on the scan protocol and level of scrutiny used during examination.

Proposed rating criteria for the detection of durable cerebral microinfarcts on in-vivo MRI and representative examples are provided in panel 1, figure 3, and the appendix. The shape of durable cortical cerebral microinfarcts on in-vivo structural MRI generally matches



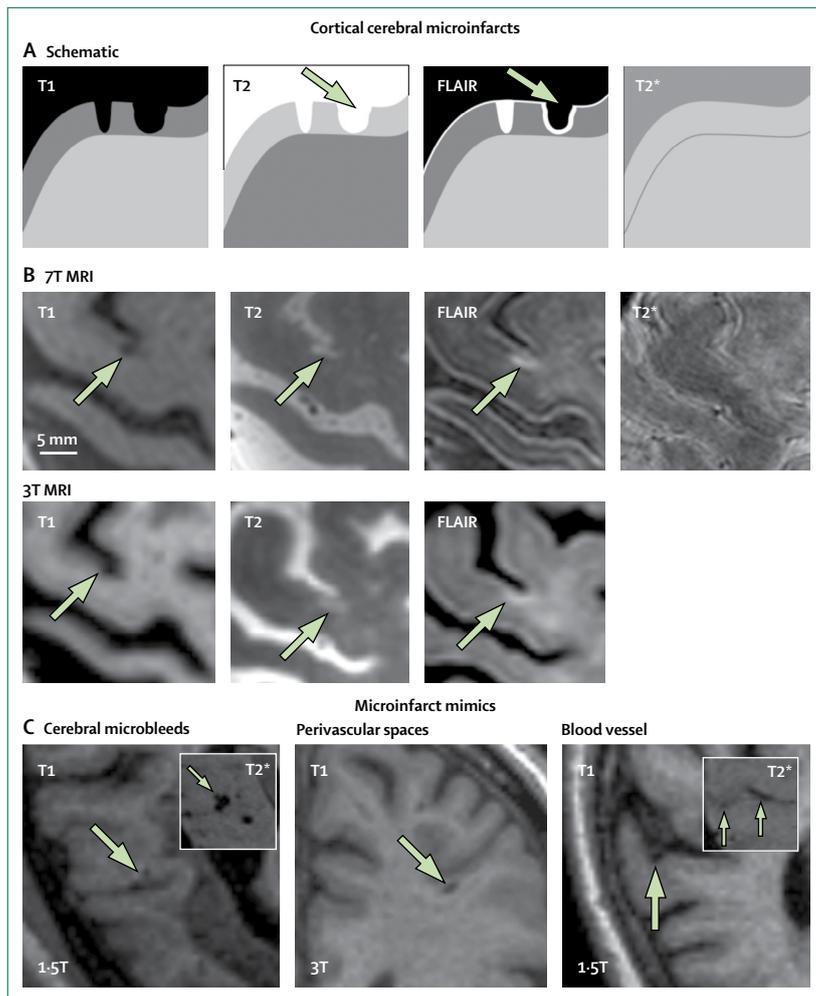
**Figure 2: Incidental small diffusion-weighted imaging lesion**

(A) DWI 1.5T MRI shows a hyperintense subcortical lesion (arrow). Follow-up imaging at 3 months shows that the lesion (arrows) is still visible, appearing hypointense on T1 (B) and hyperintense on FLAIR (C). DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery. T1=T1-weighted MRI.

the perfusion territory of small, single penetrating cortical arterioles (ie, a cylindrical shape perpendicular to the cortical surface extending towards the border with the white matter). Importantly, such cerebral microinfarcts can be detected using existing datasets from large cohort studies, which provides an important opportunity to advance this field. For reliable detection of cortical cerebral microinfarcts on structural MRI, datasets should ideally include high-resolution ( $\leq 1 \times 1 \times 1$  mm voxel size) three-dimensional (3D) T1-weighted and 3D T2-weighted (ie, fluid-attenuated inversion recovery or T2) MRI, and blood-sensitive scans to rule out cerebral microinfarct mimics, such as cerebral microbleeds. Because most existing datasets from 1.5–3T MRI studies include only one 3D scan—often the T1—detection of cortical cerebral microinfarcts in those datasets on T1 is recommended, aided by two-dimensional (2D) T2-weighted images, to rule out possible microinfarct mimics (ie, a lesion that is compatible with a microinfarct on 3D T1-weighted images but cannot be detected as a hyperintense lesion on 2D T2-weighted imaging, because of lesion orientation or slice thickness, can be accepted as a microinfarct if the T2\* image is not hypointense at the same site). Two 3T MRI studies measured the actual size of such lesions smaller than 5 mm: one study<sup>28</sup> reported a median lesion size of 3 mm in 75 patients, with only 8% of lesions larger than 3 mm. Similarly, the other study<sup>31</sup> of 209 patients reported a mean lesion size of 2.8 mm (SD 0.8; 95% CI 1.1–4.5). We therefore propose a size criterion for durable cortical cerebral microinfarcts of less than 4 mm (panel 1).

Additional methodological details and examples of cerebral microinfarcts are available,<sup>32</sup> which includes a

See Online for appendix



**Figure 3: Durable cortical cerebral microinfarcts and mimics on structural MRI**  
(A) Schematic representation of a cortical cerebral microinfarct (left schematic lesion), which is hypointense on T1, hyperintense on T2 and FLAIR, and isointense on T2\*-weighted images. The right schematic lesion (arrow) represents a cortical cerebral microinfarct with cavitation, which appears hypointense on FLAIR with a hyperintense rim. (B) Examples of a cortical cerebral microinfarct (arrows) without cavitation imaged in the same individual on the same day using 7T and 3T MRI. (C) Examples of common cerebral microinfarct mimics, such as cerebral microbleeds (arrows), which are distinct from cerebral microinfarcts because they appear hypointense on T2\*-weighted MRI (inset); enlarged perivascular spaces (arrow), which are distinct from cortical cerebral microinfarcts because they are located in juxtacortical areas; and blood vessels (arrow), which are distinct from cortical cerebral microinfarcts because they appear hypointense on T2\*-weighted MRI and can be traced over several slices (inset; arrows). FLAIR=fluid-attenuated inversion recovery. T1=T1-weighted MRI. T2=T2-weighted MRI. T2\*=T2\*-weighted MRI.

video instruction to guide detection of cortical cerebral microinfarcts on both 7T and 3T in-vivo structural MRI. Currently, visual rating of cortical cerebral microinfarcts is time intensive (approximately 30 min per patient), and inter-rater agreement is modest (two studies reported intraclass correlation coefficients of 0.39<sup>33</sup> and 0.76,<sup>26</sup> and another study<sup>30</sup> reported a kappa of 0.83). Development of semi-automated detection techniques is ongoing<sup>26,34</sup> and would greatly improve observer reliability and the efficiency of evaluation of existing 3T MRI datasets from large cohort studies.

### Causes and risk factors of microinfarcts

Cerebral microinfarcts have multiple underlying causes, which can coexist in a single patient. The three main causes are cerebral small vessel disease (eg, cerebral amyloid angiopathy, arteriolosclerosis), microemboli, and hypoperfusion. Neuropathological studies have shown that cerebral microinfarcts are common in the presence of severe cerebral amyloid angiopathy at autopsy.<sup>35–37</sup> Subsequently, cerebral microinfarcts have been assessed with regard to manifestations of cerebral amyloid angiopathy in living patients where durable cortical cerebral microinfarcts were associated with lobar cerebral microbleeds on 7T MRI<sup>25,26</sup> and 3T MRI.<sup>28,38,39</sup> A study<sup>40</sup> that assessed cortical cerebral microinfarcts on in-vivo 7T MRI in patients with hereditary cerebral amyloid angiopathy showed that cerebral microinfarcts were one of the earliest markers of the disease, compared with other clinical and MRI manifestations.

Neuropathological studies have further explored the association between cerebral microinfarcts and cerebral amyloid angiopathy, atherosclerosis, and arteriolosclerosis. In one study,<sup>41</sup> which examined the brains of approximately 1000 community-dwelling individuals at autopsy, cortical cerebral microinfarcts were associated with cerebral amyloid angiopathy, whereas subcortical cerebral microinfarcts were associated with atherosclerosis and arteriolosclerosis. In a smaller study of 80 patients at autopsy,<sup>42</sup> all of whom had multiple cerebral microinfarcts on routine pathological examination, cerebral microinfarcts in the occipital cortex were associated with local cerebral amyloid angiopathy pathology, whereas cerebral microinfarcts in the frontal cortex and hippocampus were not.

In addition to cerebral amyloid angiopathy, cerebral microinfarcts are also associated with other manifestations of small vessel disease on MRI. Both in patients who attended a memory clinic<sup>28</sup> and in population-based cohorts,<sup>29,30</sup> cerebral microinfarcts co-occur with lacunar infarcts<sup>28,30</sup> and the presence of cerebral microinfarcts is associated with a higher volume of white matter hyperintensities<sup>28–30</sup> and cerebral atrophy.<sup>28</sup> The presence of cerebral microinfarcts has been linked to a history of stroke in population-based cohorts,<sup>29,30</sup> but also among patients admitted to hospital for stroke<sup>14,31,43</sup> and in patients attending a memory clinic with various diagnoses, including subjective cognitive complaints, Alzheimer's disease, and vascular dementia.<sup>28</sup> This association between cerebral microinfarcts and stroke might also be linked to large vessel disease, because large cortical infarcts on MRI and cerebral microinfarcts have been found to co-occur.<sup>28,30</sup> Notably, cerebral microinfarcts have been associated with intracranial stenosis in studies of patients recruited from a memory clinic<sup>28</sup> and in patients with ischaemic stroke,<sup>31,43</sup> and commonly occur ipsilateral to the stenosis.<sup>28,43</sup> A 2017 study<sup>15</sup> reported that the incidence of acute cerebral microinfarcts was 14% on diffusion-weighted imaging in patients who had carotid

endarterectomy. Atrial fibrillation has also been identified as an important risk factor for cortical cerebral microinfarcts.<sup>14,28,44</sup> Moreover, biomarkers of cardiac disease, particularly N-terminal pro-brain natriuretic peptide and high-sensitivity cardiac troponin T, were associated with cortical cerebral microinfarcts on 3T MRI in patients attending a memory clinic.<sup>44</sup> Whether these links between cerebral microinfarcts and both large vessel atherosclerosis and cardiac disease reflect microemboli as a causative mechanism or even hypoperfusion—which has been proposed as an alternative mechanism of cerebral microinfarct formation—remains unclear.<sup>45,46</sup>

Literature has emerged about the association between vascular risk factors and cerebral microinfarcts on MRI. A 7T MRI study<sup>33</sup> that assessed cortical cerebral microinfarcts in 48 patients with type 2 diabetes mellitus and 49 control participants found no difference in occurrence or number of cortical cerebral microinfarcts between patients with diabetes and controls. This observation is consistent with two neuropathological studies<sup>47,48</sup> that assessed 1228 and 2365 patient autopsies, which showed an association between diabetes and large infarcts, but not between diabetes and cerebral microinfarcts. In a 3T MRI study<sup>28</sup> of 238 patients who attended a memory clinic, cerebral microinfarcts were not associated with diabetes or hypertension, but were significantly associated with hyperlipidaemia. By contrast, in a study<sup>14</sup> of 231 patients with ischaemic stroke or transient ischaemic attack, none of these risk factors were associated with the presence of cerebral microinfarcts, whereas in a cohort<sup>30</sup> of 861 participants from the general population, cerebral microinfarcts were associated with hypertension. These inconsistent results indicate that identification of risk factor patterns for cerebral microinfarcts may be influenced by the setting in which they are studied, and this is an area that warrants further investigation.

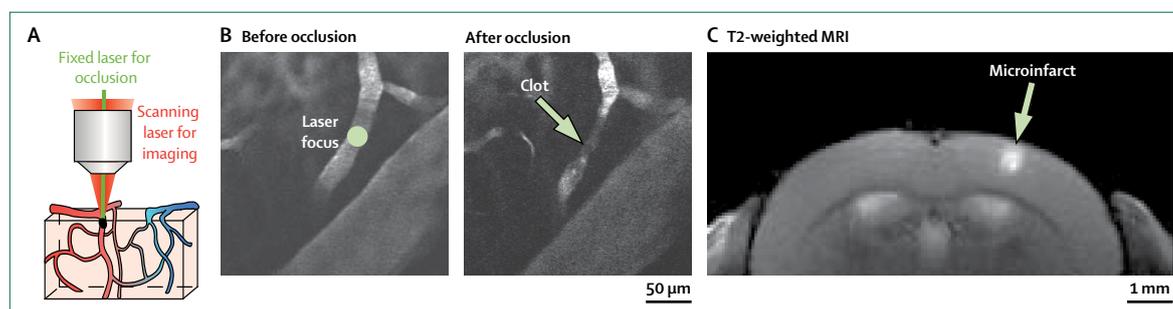
Taken together, these studies clearly show that the cause of cerebral microinfarcts is heterogeneous, and is linked to different manifestations of small vessel disease, large vessel disease, and cardiac disease. In

most settings, the presence of cerebral microinfarcts cannot be regarded as a marker of specific causes. However, in specific patient subgroups with a high burden of one particular pathology—eg, patients diagnosed with probable cerebral amyloid angiopathy—presence of cerebral microinfarcts might be regarded as a likely marker of that pathology. Whether particular cerebral microinfarct features, such as location, size, or shape might be indicative of specific causes requires investigation. Autopsy studies do indeed suggest that a link might exist between cerebral microinfarct location and different subtypes of small vessel diseases, but such studies are limited by restricted brain coverage. MRI data<sup>26,28,31</sup> from cohorts of patients who attended a memory clinic or had a stroke suggest a predisposition for cerebral microinfarcts to occur in parietal and frontal areas (appendix). However, MRI studies are restricted by the fact that durable subcortical lesions and lesions smaller than 1–2 mm cannot be detected with current techniques.

With the development of semi-automated cerebral microinfarct detection techniques, a wealth of MRI data from existing, large population, and clinic-based cohorts with detailed information about risk factors and comorbidities is expected to become available. Additionally, studies that combine post-mortem MRI and histopathological examination are ongoing. These techniques and studies might provide more unbiased data about risk factors and causes of cerebral microinfarcts.

### Functional effect of microinfarcts on the brain

The presence of cerebral microinfarcts on brain autopsy has been associated with ante-mortem cognitive dysfunction.<sup>1</sup> Neuropathological studies<sup>49–54</sup> have confirmed the link between cerebral microinfarcts on autopsy and ante-mortem dementia and cognitive impairment, although the trajectories of cognitive decline later in life with regard to cerebral microinfarcts and other co-occurring pathologies are complex and might require further investigation. Studies suggest a strong association



**Figure 4: Modelling microinfarcts in rodent cortex by targeted photothrombotic occlusion of individual penetrating arterioles**

(A) Under the guidance of multiphoton imaging, a single penetrating arteriole is visualised with a scanning laser and occluded with a second fixed green laser after intravenous injection of rose bengal (a photosensitising agent). (B) In-vivo multiphoton images of a single penetrating arteriole, before and after occlusion.

(C) A cortical microinfarct visualised using in-vivo T2-weighted MRI. Despite a large difference in brain size, rodent microinfarcts are similar in absolute size to human microinfarcts because microvascular topology is relatively well conserved between species.<sup>64,65</sup>

between cerebral microinfarcts and age,<sup>51,52</sup> race,<sup>53</sup> and additive effects with comorbid pathologies.<sup>53</sup>

Advances in cerebral microinfarct detection during life greatly facilitate studies of their functional effect. In one of the first studies<sup>25</sup> that investigated the detection of cerebral microinfarcts using in-vivo 7T MRI, a higher number of cerebral microinfarcts was found in 14 patients with Alzheimer's disease compared with 18 healthy controls, although the proportion of participants with cerebral microinfarcts did not differ between the groups (86 vs 72%). Similarly, another 7T MRI study<sup>26</sup> found no difference in cerebral microinfarct occurrence between 29 patients with early Alzheimer's disease and 22 healthy controls (55 vs 45%), but did not confirm differences in cerebral microinfarct numbers between groups. Both of these initial studies were limited by small numbers of participants, which is inherent to most in-vivo 7T MRI studies. Moreover, one of the studies<sup>25</sup> also considered juxtacortical lesions, which might include cerebral microinfarct mimics, particularly enlarged perivascular spaces.<sup>23</sup> Cerebral microinfarcts can also be detected on 3T MRI scans, which allows assessment of the association between these lesions and cognition in larger cohorts, with findings that are likely to have greater generalisability than findings from small cohorts. In a cohort<sup>28</sup> which included 238 patients who had attended a memory clinic, cerebral microinfarcts were associated with dementia, most strongly with vascular dementia (cerebral microinfarcts occurred in 12 [55%] of 22 patients with vascular dementia). In particular, cerebral microinfarcts were associated with worse global cognition and poorer performance on tasks associated with visuoconstructive abilities and language. In a sample of patients<sup>14</sup> with ischaemic stroke or transient

ischaemic attack both cortical cerebral microinfarcts and acute cerebral microinfarcts at baseline predicted worse cognitive performance at 2 year follow-up than in patients without cerebral microinfarcts, especially in the domain of visuospatial functioning. In an Asian study<sup>30</sup> of 861 participants at risk of developing cognitive impairment, the presence of cortical cerebral microinfarcts on in-vivo 3T MRI was independently associated with dementia. Furthermore, cortical cerebral microinfarcts were significantly associated with worse global cognition and poorer performance on tasks in the domains of executive function, visual memory, and verbal memory.<sup>30</sup> Notably, these studies considered confounding effects of other markers of vascular damage and neurodegeneration, such as atrophy.

One neuropathology study<sup>55</sup> of 850 patients at autopsy found that cerebral microinfarcts were associated with impaired motor function before death. The effect of cerebral microinfarcts on motor function has not yet been investigated using in-vivo MRI.

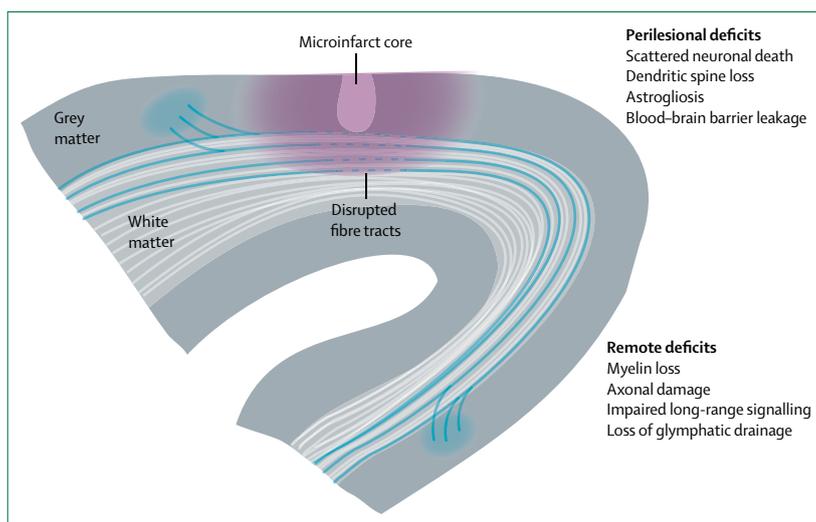
Taken together, these initial in-vivo MRI studies support neuropathological observations that cerebral microinfarcts are associated with worse cognition, independent of other age-associated pathologies. However, whether such associations are causal remains unclear. It is possible that, as a result of the high numbers and widespread distribution of cerebral microinfarcts throughout the brain, these lesions might cause sufficient disruption resulting in functional impairment, which has been supported by animal studies. Alternatively, cerebral microinfarcts might be a marker of other underlying vascular pathologies that are even more widespread than the lesions themselves, and thus also affect the brain without visible focal injury.

## Animal models of microinfarcts

### Mechanisms

Cerebral microinfarcts have been successfully modelled in the brains of rodents by occluding penetrating arterioles that form bottlenecks in microvascular perfusion.<sup>56–62</sup> Penetrating arterioles have emerged as a key locus for occlusion, because unlike the interconnected pial and capillary systems, blood flow through a penetrating arteriole cannot be efficiently re-routed around a localised clot.<sup>63</sup> Cerebral microinfarcts induced in rodents show remarkable similarity to human cerebral microinfarcts, with respect to their range of shapes, size, and location, and their temporal evolution (figure 4). For example, the core of a cerebral microinfarct in an animal model becomes packed with microglia and is surrounded by reactive astrocytes, which is also observed in cerebral microinfarcts in human beings.<sup>56</sup>

Two distinct but complementary strategies have been used to model cerebral microinfarcts. One method involves the intra-arterial injection of occlusive microbeads,<sup>57</sup> cholesterol crystals,<sup>58,59</sup> or microthrombi.<sup>60</sup> This sudden influx of microemboli produces cerebral



**Figure 5: Functional deficits in tissues beyond the non-viable microinfarct core**

Perilesional deficits are caused by secondary effects of ischaemic injury, such as spreading depression, blood-brain barrier disruption, and neuroinflammation. Remote deficits arise when microinfarcts damage white matter fibres, or occur in areas that are connected to, and are crucial for, the function of other brain regions.

microinfarcts that are broadly distributed, with shapes ranging from wedge or column-like lesions in the cortex to smaller, circumscribed cerebral microinfarcts in both cortical and subcortical tissues. A second, more recently developed model of cortical microinfarction enables the location and size of cerebral microinfarcts to be targeted reproducibly in rodent cortex. Typically coupled with in-vivo multiphoton imaging, single penetrating arterioles are selectively occluded by inducing clots with precise laser irradiation, with and without intravenous photosensitising agents.<sup>61,62,66–68</sup>

Cerebral microinfarcts that occur spontaneously have also been identified in mouse models. When subjected to forebrain hypoperfusion with bilateral carotid stenosis, the Tg-SwDI mouse model of cerebral amyloid angiopathy develops cortical and subcortical cerebral microinfarcts between the age of 18 and 32 weeks.<sup>45</sup> Application of carotid stenosis to non-transgenic C57BL/6 mice also led to spontaneous cerebral microinfarct formation and microhaemorrhages, but with a lower incidence than observed in Tg-SwDI mice.<sup>69</sup> Mice deficient in endothelial nitric oxide synthase have cerebral hypoperfusion and also develop both cortical and subcortical cerebral microinfarcts.<sup>70</sup> These models can provide important clues about the cause of cerebral microinfarcts in human beings, and the vascular changes responsible for cerebral microinfarct formation require thorough investigation.

### Perilesional and remote effects of microinfarcts

Animal studies have provided evidence that the physiological effect of cerebral microinfarcts extends beyond the non-viable lesion core observed by MRI or in neuropathological studies (figure 5). By strategically targeting cerebral microinfarcts in the mouse sensory or motor cortices, in-vivo imaging studies<sup>71</sup> have reported deficits in both neural and haemodynamic function in tissue surrounding the cerebral microinfarct that can last for weeks. These deficits involved persistent alterations in neuronal circuitry, observed by displacement and disorganisation of sensorimotor maps.<sup>72</sup> A study published in 2017<sup>56</sup> estimated that a single cerebral microinfarct, with a mean lesion core of 0.2 mm<sup>3</sup> in volume (approximately 0.5 mm in diameter), could impair neuronal function over cortical regions at least 12 times larger in size than the lesion core. However, this calculation is likely to be an underestimate because cerebral microinfarcts in both grey and white matter can also disrupt neighbouring fibres of passage, with demyelination and damage of axonal structure.<sup>57–59</sup> Consistent with cerebral microinfarcts having a considerable effect on brain function, rodent studies using unilateral<sup>58,59</sup> or repeated bilateral cholesterol crystal injections<sup>73</sup> have reported deficits in cognitive tasks, despite the actual cerebral microinfarct load being small compared with overall brain size. Two of these studies<sup>59,74</sup> also showed brain-wide impairment of glymphatic

pathways, a perivascular network for clearance of amyloid- $\beta$  and other cytotoxic metabolites from the brain.

Examination of the perilesional areas of experimentally induced cerebral microinfarcts has revealed numerous pathological changes that are likely to be substrates for observed functional and behavioural deficits. Evidence supports delayed, selective neuronal loss (5–10% decrease),<sup>58</sup> thinning of dendritic processes, and reduced dendritic spine density.<sup>56,59</sup> Non-neuronal changes include widespread astrogliosis, reduced expression of aquaporin 4, and myelin loss.<sup>56,58,59,61,75</sup> Blood–brain barrier disruption is also evident on the basis of extravasation of plasma proteins and nitrosative stress at the capillary walls.<sup>61,73</sup> One striking manifestation of this pathology is the coalescence of isolated cerebral microinfarcts into larger contiguous infarcts when their perilesional zones begin to overlap.<sup>61</sup> This finding emphasises the susceptibility of tissues in perilesional areas, and suggests that injury can be shifted towards further exacerbation, or rescued by therapeutic agents.

### Panel 2: Directions for future research

#### Identification and definition of microinfarcts

- Refine operational rating criteria for the detection of acute cerebral microinfarcts on diffusion-weighted MRI (eg, size cutoff)
- Verify the ischaemic nature of these small incidental diffusion-weighted imaging lesions by comparing MRI scans with histopathological examinations
- Establish sensitivity, specificity, and rater reliability for proposed criteria for detection of cerebral microinfarcts on MRI accounting for differences in field strength and other imaging parameters
- Establish MRI detection methods for durable subcortical cerebral microinfarcts
- Investigate topographical distribution of cerebral microinfarcts (eg, lobar distribution, grey matter vs white matter, and underlying small vessel diseases)
- Do crossmodal studies that investigate different pathological subtypes of cerebral microinfarcts (eg, cavitated, haemorrhagic, slit-like), lesion sizes, and MRI appearance<sup>77</sup>

#### Causes, risk factors, and functional effects

- Do longitudinal MRI studies in different populations, including the general population and specific patient cohorts, with rich phenotyping of risk factors, causes, and functional outcomes
- Identify pathophysiological mechanisms underlying cerebral microinfarct formation in different patient populations focusing on the roles of vascular risk factors, small vessel diseases, microemboli, and hypoperfusion
- Establish whether features such as size, distribution, and appearance of cerebral microinfarcts reflect different pathogenic mechanisms
- Study the remote effects of cerebral microinfarcts on brain structure and function, and translate insights from animal models to human beings
- Use animal models that spontaneously develop cerebral microinfarcts to better understand vascular factors that lead to cerebral microinfarcts

#### Treatment

- Establish whether cerebral microinfarcts can be used as reliable and informative biomarkers in multicentre clinical trials
- Study the involvement of aggressive blood pressure reduction and other vascular interventions in the formation of cerebral microinfarcts

### Search strategy and selection criteria

We searched PubMed to identify articles for this Review, focusing on papers published in English between Jan 1, 2012, and April 10, 2017. The search terms (and synonyms) 'microinfarct\*', in combination with 'brain or cerebral', and 'autopsy', 'neuropathology', 'MRI', 'imaging', or 'diffusion' were used. To identify relevant animal studies, we used the search terms 'microinfarct\*', 'microemboli', 'ministroke', or 'infarct' and 'brain or cerebral', and 'rodent or mouse', and 'penetrating vessel'. SJvV and GJB selected papers identified through these searches, supplemented with additional papers from personal records, with feedback from the coauthors. Original papers and, where appropriate, high impact reviews were included. The final reference list was generated on the basis of relevance and originality with regard to the topics covered in this Review.

The perilesional and remote effects of cerebral microinfarcts are likely to involve the same pathophysiological processes that occur with larger strokes, but on a smaller scale. For example, cerebral microinfarcts can evoke waves of ischaemic spreading depression that appear several mm from the cerebral microinfarct core, which might contribute to neuronal damage and hypoperfusion.<sup>61</sup> Neuronal dysfunction might also involve diaschisis, whereby death of neurons within the cerebral microinfarct core disables the cortical and subcortical circuits to which they were previously integrated. Maladaptive increases of inhibitory tone in perilesional tissues might also depress neuronal excitation.<sup>76</sup> Additionally, cerebral microinfarcts located within or in close proximity to white matter tracts are likely to disrupt communication between distant brain regions by damaging axonal structure. Impairment of glymphatic drainage might elevate toxic metabolites across the whole brain.<sup>59,74</sup> These potential mechanisms of cerebral microinfarct-induced pathology need to be studied in greater detail using animal models, because the relative importance of each mechanism remains poorly understood.

### Conclusions and future directions

The course of cerebral microinfarct research has largely depended on the relatively complex problem of how to assess their total burden in the brain. Accurate quantification of cerebral microinfarcts is crucial for the identification of their specific effect on brain function, and the pathogenic processes involved in their development. It is thus exciting to note that substantial progress has been made in recent years regarding cerebral microinfarct detection, particularly the publication of pathologically validated structural MRI methods and proposed rating criteria for cortical cerebral microinfarcts (panel 1). Further development of these methods is likely, including the possibility of semi-automated detection methods for cortical cerebral microinfarcts that could be used to analyse large, population-derived 3T MRI datasets. However, current methods can detect only a small fraction of cerebral microinfarcts and therefore a bias exists towards lesions with a particular set of spatial, temporal,

or anatomical characteristics (table). In practice, these limitations imply that all studies of the effects of cerebral microinfarcts have considerable built-in error as a result of miscounting and biased counting of lesions. Moreover, the reliability of visual and emerging computational assessments remains to be assessed (panel 2).

Another area of both notable progress and substantial remaining uncertainty is the extent to which cerebral microinfarcts disrupt the brain tissue in their immediate surrounding, as well as the brain's network structure and function as a whole. Such potential widespread effects of cerebral microinfarcts might allow these numerous, spatially distributed lesions to exert a greater effect on brain function than predicted by their small aggregate volume (which is also likely to be true for other brain lesions in the context of small vessel disease). Because the strongest evidence for widespread effects of cerebral microinfarcts is derived from animal model studies (figure 5), future work needs to translate imaging markers from animals to human beings (panel 2).

Future improvements in cerebral microinfarct detection and measurement of their widespread effects will establish the role of these lesions, not just as markers of microvascular injury and cognitive impairment, but as direct contributors to cognitive decline. Identification of a major causative role for cerebral microinfarcts would lead to the inclusion of these lesions as candidate outcome markers for trials aimed at preventing vascular cognitive impairment. Evidence that suggests the accrual of cerebral microinfarcts has a major causal role in progressive cognitive impairment is needed to bring renewed focus on neuroprotection in ischaemic stroke—a field that has been extensively studied, but has not yielded clinically effective treatments.<sup>78</sup> The potential impact of improvements in the cerebral microinfarct field thus extends beyond simply providing another imaging biomarker of cerebral small vessel disease to the larger goal of guiding future therapeutic approaches.

#### Contributors

SJvV and GJB coordinated the overall process of manuscript production. SJvV, GJB, and SMG were involved in study design. SJvV, AYS, EES, JAS, and JMW performed literature searches, and SJvV and GJB selected relevant papers. SJvV, AYS, EES, SMG, and GJB wrote the manuscript. SJvV and AYS prepared the figures. All authors were involved in critically reading and editing the manuscript. All authors gave final approval for submission.

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