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Neuroimaging of Small Vessel Disease in Late-Life Depression

Nadim S. Farhat,

Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh,
Pittsburgh, PA, USA

Robert Theiss,

School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Tales Santini

Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh,
Pittsburgh, PA, USA

Tamer S. Ibrahim

Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh,
Pittsburgh, PA, USA

Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Department of Radiology, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Howard J. Aizenstein

Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh,
Pittsburgh, PA, USA

Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Cerebral small vessel disease is associated with late-life depression, cognitive impairment, executive dysfunction, distress, and loss of life for older adults. Late-life depression is becoming a substantial public health burden, and a considerable number of older adults presenting to primary care have significant clinical depression. Even though white matter hyperintensities are linked with small vessel disease, white matter hyperintensities are nonspecific to small vessel disease and can co-occur with other brain diseases. Advanced neuroimaging techniques at the ultrahigh field magnetic resonance imaging are enabling improved characterization, identification of cerebral small vessel disease and are elucidating some of the mechanisms that associate small vessel disease with late-life depression.

Keywords

Cerebral small vessel disease; Late-life depression; Ultrahigh field; Magnetic resonance imaging; Cerebral microvascular mechanisms; Tic-tac-toe radiofrequency head coil

Introduction

Most older adults have neuroradiologic evidence of cerebral small vessel disease (SVD) [1]. Although many older adults carry the burden of SVD without clinical manifestations, population studies have clearly shown that a high burden of small vessel disease is associated with cognitive, physical, and mood dysfunction [2–4]. Specifically, small vessel disease has been linked to the thinning of the cerebral cortex, gray matter atrophy [5], greater cerebral blood flow decline [6, 7], increased white matter hyperintensity volume [8–11], and worsening cognition [8, 9, 11, 12]. It is also shown that small vessel disease is strongly associated with late-life depression (LLD) [13]. Depression is a leading cause of morbidity and mortality in the elderly [14–19]. Better understanding triggers for late-life depression like small vessel disease will facilitate both prevention strategies and treatment plans. However, the progress in understanding the role of small vessel disease and how it contributes to late-life depression has been stymied in part by a lack of specificity when it comes to the imaging and classification of white matter hyperintensities (WMH). White matter hyperintensities are currently identified using MRI imaging and are a hallmark of small vessel disease [13, 20–25]. White matter hyperintensities represent components of edema, gliosis, ischemia, and inflammation. There is an established longitudinal association between white matter hyperintensities and late-life depression; specifically, the progression of small vessel disease as based on imaging is associated with persistent depression [26, 27].

Furthermore, depression can cause many complications in the growing elderly population, and at times, it is poorly responsive to treatment [26, 27]. Characterizing the pathophysiologic subcomponents responsible for white matter hyperintensity progression in late-life depression through advanced neuroimaging techniques is of great importance, as it will allow for an understanding of how depression develops over time. The neuroimaging characterization of small vessel disease will, in turn, shape decision making about what to do about this growing public health problem moving forward [28].

Magnetic resonance imaging (MRI) neuroimaging plays an essential role in exploring and understanding small vessel disease (SVD) and its association with late-life depression (LLD). MRI is noninvasive, without ionizing radiation, and due to the low risk associated with this imaging technique, it is ideal for longitudinal studies. Lately, ultrahigh field (UHF

7 T) MRI has been extensively used in MRI neuroimaging research. This significant development in MRI coupled with the advances in computer hardware and medical imaging analysis paradigms are enhancing the visualization, analysis, and help in better understanding LLD and its association with SVD. Despite these recent advances in the available neuroimaging techniques for SVD and LLD, these techniques are mostly applied for research purposes and are under heavy development, and we expect that they will mature to be used in clinics in the next few years.

The potential clinical applications of these UHF MRI neuroimaging techniques cover diagnosis, individualized treatment options, and treatment monitoring. The MRI neuroimaging techniques available to investigate SVD and LLD are numerous and multimodal. Therefore, we will focus our discussion on three main topics: (1) introduction to

UHF MRI, (2) the advances in the neuroimaging of small vessel disease structural imaging with ultrahigh field MRI, (3) novel methods in assessing microvascular mechanism in small vessel disease, and (4) neuroimaging connectomes for late-life depression and small vessel disease.

UHF MRI

Human MRI UHF is impacting the neuroimaging field with its higher image resolution, higher signal-to-noise ratio (SNR) and enhanced soft tissue contrast. 7 Tesla (T) MRI has reached a level of maturity that can meet the demand of clinical settings, being recently cleared by the Food and Drug Administration [29] for clinical use. At the time of writing this article, there are 70 human 7 T scanners installed worldwide [30]. These new MRI scanners are usually installed with optimized head coils designs [31], better gradients, and powerful computing engines. In this section, we will explain what the advantages of 7 T MRI are and discuss some of the main challenges of scanning at 7 T.

Benefits of Ultrahigh Field MR

There are three main benefits of increasing the magnetic field in MRI; a higher signal-to-noise ratio (SNR), which can be used to either increase spatial resolution or to perform faster scans with higher acceleration factors, increased susceptibility effects, which increases blood oxygenation level dependent (BOLD) contrast, and longer T1 and shorter T2/T2* relaxation times, which enhances contrast in certain applications.

MRI SNR increases with magnetic field strength [32]. Consequently, this increase in SNR means that scans to be collected at higher spatial resolution (more voxels per volume unit) without an increase in acquisition time. As an example: Table 1 shows that the MPRAGE at 7 T collects almost twice the amount of the voxels per volume with a comparable acquisition time of 3 T MPRAGE.

The other benefits are a higher contrast-to-noise ratio (CNR) and an enhanced T2* effect (relaxation time due to magnetic susceptibility effects) which grows with the magnetic field and leads to more significant variability of relaxation times between several tissues which can be exploited in differentiating between structures. Moreover, this higher CNR contrast enables more accurate quantification susceptibility maps (QSM) of the iron deposit in the brain [33].

T1 relaxation time is longer with the magnetic field [34]; this effect is exploited to increase the CNR in time of flight (TOF) magnetic resonance angiography (MRA). This gain in CNR is utilized to detect smaller arteries [35]. Lastly, UHF has a higher sensitivity to blood oxygenation level dependent (BOLD) contrast [36]. The increased BOLD contrast has a significant effect on enhancing functional MRI spatial resolution, CNR, and temporal resolution of (fMRI) [37].

Radio Frequency Transmit Nonuniformity and Specific Absorption Rate

In MRI, the transmit radiofrequency (RF) coil produces the RF transverse magnetic field responsible for the spin excitation (B1+). The B1+ field distribution becomes more

inhomogeneous with the increase of the magnetic field. The inhomogeneity of the B1+ field is an unwanted consequence that causes the appearance of inhomogeneities in the images or low contrast in certain parts of the brain, especially in high flip angle sequences like the fluid-attenuated inverse recovery (FLAIR) [38]. Parallel transmissions using several RF transmit coils and pulses sequences that are insensitive to the RF inhomogeneity (e.g., adiabatic pulses) [39] might alleviate the RF Tx field inhomogeneity. However, in certain instances, solving the RF transmit inhomogeneity issues might cause RF heating effects. Moreover, the B1+ field distribution changes with different head shapes (loads); therefore, these transmit fields change for each subject [40, 41].

Load Insensitive Head Coil Design and Full Head Coverage Parallel Transmission

The tic-tac-toe (TTT) RF system for 7 T head MRI is composed by a 16-channel transmit array (4 TTT elements located around the head) and a 32-channel receive insert, for optimal receiving performance. The TTT transmit array has been shown to produce a homogenous spin excitation at 7 T frequencies [42] and superior subject insensitiveness (low variations of the RF performance with different head shapes) [43]. It also presents lower global and local (SAR) when compared with other transmit coil designs [42, 43], increasing patient safety and minimizing the risks of temperature increase and tissue damage.

Future of UHF

Several centers are exploring neuroimaging at UHF MRI at 9.4, 10.5, 11.2, and 20 T [30]. The current state of the art in 7 T is to optimize sensitivity, spatiotemporal resolution, and encoding speed [44] and to improve B₀ homogeneity to address susceptibility artifacts [45].

Neuroimaging of Small Vessel Disease Structural Imaging with Ultrahigh Field MRI

The neuroimaging standards of SVD designate a set of distinct neuroimaging features in the brain. These features are acute small subcortical infarct, lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (PvS), cerebral microbleeds (CMBs), and atrophy [46]. Although these distinct SVD features were regarded as different types of tissue changes, there is increasing evidence that these features are associated and might be caused by the diffuse nature of the small vessel pathological changes. 7 T UHF has a huge impact on the imaging of PvS, CMB, lacunes, and cortical microinfarcts. Therefore, in the following section of the book chapter, we will focus our review on how 7 T UHF impacted PvS, CMB, lacunes, and cortical microinfarcts.

Lacunes and PvS at 7 T

Lacunes—Lacunes are small cavities filled with fluid and have a diameter between 3 and 15 mm. Lacunes often form as a result of acute small subcortical infarcts or hemorrhages of a nearby perforating arteriole. On MRI, their shapes are usually round or oval with a hyperintense rim. These lacunes cavities have hyperintense signals in T2 sequences similar to the cerebral spinal fluid signal. On the other hand, the lacunes signal is hypointense in T2-FLAIR. While the presence of some lacunes is mostly asymptomatic, large amounts of lacunes are correlated with dementia, cognitive impairment, gait disturbance, and increased risk of stroke [47–49].

Enlarged Perivascular Spaces (PvS)—Perivascular spaces are cerebrospinal fluid (CSF) filled cavities areas surrounding cerebral arteries or veins, and they extend from the subarachnoid space [50]. Perivascular spaces (PvS) are usually <5 mm and have an irregular shape [20]. Since PvS are filled with CSF, they are hyperintense in T2 and hypointense in T2-FLAIR. These spaces tend to enlarge with age. Despite being considered, as a normal aging phenomenon, PvS are increasingly thought to be associated with the occurrence of cerebral small vessel disease. Additionally, studies have shown that PvS presence could be a risk factor for antidepressant resistance [51].

UHF 7 T MRI Role in Distinguishing Between Lacunes and Perivascular Spaces

UHF 7 T MRI plays a major role in distinguishing between lacunes and PvS. At low resolution on imaging such as 1.5 and 3 T, PvS can look the same as lacunes. Both pathologies are filled with liquid, and therefore, they have hyperintense signal in T2. Consequently, larger PvS might have been confused with lacunes in several studies looking at small vessel changes [52]. The hyperintense rim surrounding the hypointense “hole” on FLAIR, which is thought to be a distinguishing feature of lacunes from PvS, can be absent in some cases. The colocalization of PvS with extensive WMH areas may mimic the hyperintense rim of lacunes, subsequently causing misidentification. The importance of distinguishing between lacunar infarct and PvS cannot be overstated [53], as they are the result of different cerebral pathologies and lead to distinct clinical outcomes. The superior capability of 7 T in detecting PvS has been noted in the literature and offers a solution to the current problem [54]. The resolving power of 7 T UHF can better detect the small vessels in the PvS, which leads to a better characterization of PvS when compared to lacunar infarcts [55]. When comparing 7 and 1.5 T (7 and 1.5 T) [56], 7 T was more sensitive to PvS than 1.5 and 3 T (Fig. 1).

Cerebral Microbleeds (CMB)

Cerebral microbleeds (CMBs) are small (typically 2–5 mm in diameter), ovoid hypointense signals on T2*. Susceptibility-based sequences are sensitive to microbleeds [46]. CMBs correlate with neurodegenerative brain diseases, including the small vessel disease seen in late-life depression [57, 58]. The increase in the magnetic field at 7 T makes CMBs more prominent than the surrounding tissue. Several studies have confirmed that 7 T is more reliable than 1.5 T at detecting CMBs, which lead researchers to investigate CMBs at 7 T as an imaging marker for SVD [59–61]. For example, in another study, the confidence in detecting microbleeds in vivo is slightly higher at 7 T compared to 3 T. However, increased susceptibility effects at 7 T also increases the number of artifacts on imaging. The susceptibility artifacts make detecting microbleeds near other structures challenging and will have to be addressed for better results in the future [62].

Cortical Microinfarcts

Cortical microinfarcts (CMI) were first observed in autopsy reports [63] in a mixed aging population. CMIs are found in the brains of non-demented elderly, Alzheimer disease, and vascular dementia patients [64]. There is an increased interest in studying CMI and their relations to small vessel disease (SVD). Cortical microinfarcts are sometimes visible in 3 T

scanning [65], yet most of the time, they go undetected in the routine examination due to their size 0.2–2.9 mm [66]. While CMIs are relatively small, CMIs have an effect volume 12 times the volume of their core [67]. This affected volume causes disorganization in the adjacent axons, which might induce clinical deficits seen in the aging population [68]. Several studies reported that CMIs are more visible and easier to detect in both ex vivo and in vivo [69, 70] at 7 T MRI. There have even been new guidelines established for the detection and characterization of CMIs following these findings, which illustrates the potential of 7 T in helping to pick up small changes in the microvasculature and influence care [71].

Neuroimaging of Microvascular Mechanism in Small Vessel Disease

In the section above, “Neuroimaging of small vessel disease structural imaging with ultrahigh field MRI,” we had discussed the neuroimaging methods investigating SVD that assess parenchymal and cortical structural damage, these methods in addition to WHM evaluation reflect damage in the later stage of the small vessel disease. With the technical advancement, the SVD research is heading toward detecting changes that happen earlier than overt disease on structural imaging. In addition to being a diffuse disease and a whole-brain disease [72], there is an accumulation of evidence that suggests the intrinsic aspect of small vessel disease. The changes appear to start at the endothelial level which leads later on to disorders in the cerebral microvasculature, to fibrinoid necrosis, and then to perivascular tissue injury [73]; this new understanding of the pathophysiology of small vessel disease created a need to detect features at an earlier stage of SVD that are associated with the microvessels health. Subsequently, the following section will review the advancement of neuroimaging of small vessel disease in terms of cerebral microvascular changes (venules and arterioles), tissue pulsatility, and blood–brain barrier.

Small Arteries Imaging

MRA and TOF visualize large cerebral arteries such as middle cerebral artery (MCA) and the circle of Willis. Even with the administration of contrast, clinical MRI scanners are not able to visualize accurately perforating arteries at the lower magnetic field (1.5 and 3 T) [46, 74]. The visualization of perforating arteries and the consequences of their pathology can elucidate some of the SVD mechanism [75]. Ultrahigh field (7 T and more) has a higher contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) clinical scanners. The imaging at UHF enables the visualization of some of the intracranial perforating arteries without the administration of contrast; several studies reported 0.3–0.2 mm³ resolution for MRA [35]. Recent studies reported the visualization of lenticulostriate arteries in the basal ganglia (BPA) and the thalamus (TPA) [76, 77]. Although great progress has been made in the visualization of small arteries, MRA is still limited in the visualization of smaller arteries that are distal to the circle of Willis. The state of art research is to increase the contrast of 7 T UHF to detect small arteries either by the use of extrinsic contrast agents [78] or the use of blood flow as an intrinsic contrast agent [79].

Small Veins Imaging

An early cerebral microvascular study observed that arterioles become more tortuous in some of SVD earlier states [80]. The visualization of the venous side of the cerebral microvascular pathology was not possible without contrast; therefore, the alterations of the venules due to small vessel disease were rarely investigated and thus poorly understood [81]. The increase in susceptibility ($T2^*$) at the Ultrahigh field (7 T) MR imaging enables the visualization of venous microcirculation [82, 83]. SWI enhances the contrast of deoxyhemoglobin compared to the brain parenchyma, therefore, enables the visualization of venules without a contrast agent. This contrast enhancement leads to the development of methods to quantify venules in multiple sclerosis [84] sickle cell anemia, [85] CADASIL [86] and Alzheimer's disease (AD) [87]. In addition to arterioles pathology, venules pathology such as occluded venules may be a contributing factor to small vessel disease [88] and venule tortuosity is a potential indicator of venule pathology, and the tortuosity computation is done at 7 T without contrast [81]. More tortuous venules are more common with aging and mostly distributed near regions of white matter hyperintensities [89, 90]. The venule tortuosity is believed to be the result of inflammation changes and is associated with white matter hyperintensities in the brain parenchyma and could predate radiologically overt white matter hyperintensities [81] (Fig. 2).

Arterial Pulsatility Index

In the past few years, there is an increasing amount of research papers that are showing an association between intracranial pulsatility and cerebral vessel disease. The increase in the intracranial pulsatility could be a contributing mechanism in small vessel disease [91]. Arterial pulsatility index is shown higher in more severe small vessel disease cases [92]. Most of these studies were done using transcranial Doppler Ultrasound and lower field MRI and investigated larger arteries such as the middle cerebral arteries [93]. Small perforating arteries have small diameters $<300\ \mu\text{m}$ [94, 95] and they are challenging to visualize in the current techniques let alone measuring their flow and pulsatility. Building on the relative increase in the $T2^*$ contrast of the arterial blood, cardiac gated 7 T MRI 2D phase-contrast method can measure the pulsatility and blood flow in small artery with good precision and repeatability [96]. This method measured a higher pulsatility in patients with lacunar infarct and intracerebral hemorrhages on both the basal ganglia and semioval centers [97]. Most of the studies in the MRI cerebral artery pulsatility are cross-sectional and have a limited number of patients. They need to be adjusted to several confounding factors such as age. Nonetheless, with the increase in centers using 7 T and development of automatic methods to segment arteries and estimating pulsatility index, small arterioles pulsatility index could help in unraveling poorly understood mechanisms in small vessel disease.

Cerebral Reactivity

Cerebral reactivity measurements might estimate the small vessel disease burden directly. The reactivity measures the response of microvasculature to the administration of acetazolamide and by manipulations of the air breathed by the subject (CO_2 challenge) breath-holding, and neuronal activation (high-frequency visual tasks). A reduced reactivity is a sign of exhausted autoregulation and impaired adaptation of microvasculature which can

be a consequence of the loss of smooth muscle cells, vessel walls stiffness [98], or poor functioning of the pericytes [99].

As a consequence of the impaired autoregulation ischemia of the brain is more frequent [100]. The MRI methods to estimate cerebral reactivity are BOLD, arterial spin labels, phase-contrast MRI. BOLD MRI [101], which measures the increase of blood oxygenation and the neurovascular coupling, is the most popular method used in estimating the cerebral reactivity measures [102]. Though the interpretation of BOLD signal alterations and their relation to cerebral reactivity can be complex, it is the most widely used method for cerebral reactivity assessment. In a recent paper, the authors indicated that spontaneous low-frequency fluctuations (0.02–0.04 Hz) without gaseous challenge are a measure of cerebral reactivity [103]. As mentioned above, the increase in the magnetic field increases the BOLD signal contrast. Therefore, the cerebral reactivity measurement using BOLD signal is expected to have higher sensitivity at 7 T [104].

Blood-Brain Barrier

The integrity of the blood–brain barrier (BBB) is imaged with dynamic contrast-enhanced (DCE) MRI [105], this has demonstrated BBB breakdown associated with tumor infiltration. DCE MRI has recently been explored as a marker of blood–brain barrier breakdown in small vessel disease as well as in conditions such as diabetes and Alzheimer’s disease. BBB acts as a regulator for material transfer to and out of the cerebrum, Also BBB maintains homeostasis of the brain cell environment. In addition to the breakdown of the BBB with tumor infiltration, the BBB may leak more with advancing age [76] and is leakier in white matter hyperintensities in small vessel disease [106]. In a recent case report using ultrahigh field MRI, it was observed that microbleeds were formed in the areas of BBB disruption [107].

Mechanical Assessment of Cerebral Tissue

Age and disease alter brain tissue mechanical properties [108, 109]. Elastography methods are imaging-based techniques that can estimate the elastic property of biological tissue [110]. The elastography techniques can use the endogenous small vessel pulsatility to estimate the displacement (<1 mm) in the brain tissue [111] or apply exogenous force to estimate stiffness. Magnetic resonance elastography (MRE) uses an exogenous force to estimate brain tissue stiffness. This exogenous force induces mechanical waves that travel perpendicular to the direction of the applied force. The wave speeds are measured using magnetic resonance elastography (MRE). MRE can be sensitive to tissue alterations [112]. Thus, MRE has the potential to assess tissue alterations in SVD at an early stage. The MRE is finding its way into the UHF field, and it is expected to be added as a routine research sequence [113].

Neuroimaging Connectomes for Late-Life Depression and Small Vessel Disease

Connectomes are defined as the structural and functional mapping of neural connections between different brain regions to understand the organization of the human brain [114].

This functional and structural organization of networks can be analyzed using MRI and has benefited from the advances of the ultrahigh field imaging [30].

Structural Networks

Diffusion-weighted imaging (DWI) may detect the weakened white matter integrity on a microstructure scale, in normal-appearing white matter [115]. Therefore, it can be used as an indicator of small vessel disease. Diffusion tensor imaging (DTI) and graph theory [116, 117] measures the white matter integrity of the whole-brain structural networks. In SVD, metrics such as path length (connecting two brain regions) and efficiency are used to investigate how the burden of SVD affects the brain. For example, an increase in path length between two brain regions means the information is routed through the long way. Thus, DTI-based connectomes can be used as an indicator of the severity of the disease [118].

Functional Networks

Neuronal activity at rest (under no cognitive command) induces spontaneous fluctuation throughout the brain; this fluctuation can be temporally correlated in different brain regions without direct fiber connectivity. This synchronized activity is called resting states; it was observed in BOLD fMRI [119]. Resting states fMRI (rs-fMRI) is analyzed using distinct computational methods (seed-based correlations [120], independent component analysis [121] and graph theory [122]) to extract resting brain networks. The resting brain networks provide information about the intrinsic organization of the brain networks, and the alteration of these networks can be indicative of a pathogenic brain process that affects mental health like major depression disorder [123], schizophrenia [124, 125] and cognition like attention-deficit/hyperactivity disorder [126, 127]. Similar to the structural connectomes, functional connectomes shows a disrupted organization of the functional brain networks in late-life depression [128] and small vessel disease [129].

Connectomes in the Clinics

The evidence is growing that the connectomes are a potential clinical tool that can map and characterize brain networks in healthy aging population as opposed to an aging population with small vessel disease. However, a considerable effort is required to validate the reliability, reproducibility, specificity, and sensitivity of SVD connectomes, if they are going to be used as a clinical tool and marker for the small vessel diseases.

Conclusion

In this chapter, we have highlighted how UHF MRI can enhance the imaging of small vessel disease (SVD). The advances rely on improvements in the basic MR coil design, which allow for uniform high SNR. We reviewed how the UHF MRI allows for improved identification of small microbleeds and microinfarcts, as well as improved characterization of the small arteries and veins. Small vessel disease is strongly associated with a variety of neuropsychiatric syndromes in late-life, including late-life depression. Advanced imaging techniques, such as those described in this chapter, can help identify mechanisms relating SVD to depression. Moreover, they may help identify targets for prevention and treatment.

References

1. De Leeuw FE, De Groot JC, Achten E, Oudkerk M, Ramos LMP, Heijboer R, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam scan study. *J Neurol Neurosurg Psychiatry*. 2001;70(1):9–14. [PubMed: 11118240]
2. Kuo H-K, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol Ser A Biol Sci Med Sci*. 2004;59(8):M818–26. <http://www.ncbi.nlm.nih.gov/pubmed/15345732>.
3. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. *J Neurol Neurosurg Psychiatry*. 2007;79(6):619–24. <http://jnnp.bmj.com/cgi/doi/10.1136/jnnp.2007.124651>. [PubMed: 17717021]
4. Silbert LC, Nelson C, Howieson DB, Moore MM, Kaye JA. Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. *Neurology*. 2008;71(2): 108–13. <http://www.neurology.org/cgi/doi/10.1212/01.wnl.0000316799.86917.37>. [PubMed: 18606964]
5. Steffens DC, Tupler LA, Ranga K, Krishnan R. Magnetic resonance imaging signal hypointensity and iron content of putamen nuclei in elderly depressed patients. *Psychiatry Res Neuroimaging*. 1998;83(2):95–103. <https://linkinghub.elsevier.com/retrieve/pii/S0925492798000328>.
6. Sabayan B, Westendorp RG, Grond J van der, Stott DJ, Sattar N, van Osch MJP, et al. Markers of endothelial dysfunction and cerebral blood flow in older adults. *Neurobiol Aging*. 2014;35(2):373–7. <https://linkinghub.elsevier.com/retrieve/pii/S0197458013003540>. [PubMed: 24054993]
7. Beason-Held LL, Moghekar A, Zonderman AB, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke*. 2007;38(6):1766–73. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.106.477109>. [PubMed: 17510458]
8. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77(5):461–8. <http://www.neurology.org/cgi/doi/10.1212/WNL.0b013e318227b227>. [PubMed: 21810696]
9. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, et al. Cardiac index is associated with brain aging. *Circulation*. 2010;122(7):690–7. <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.109.905091>. [PubMed: 20679552]
10. Vidal J-S, Sigurdsson S, Jonsdottir MK, Eiriksdottir G, Thorgeirsson G, Kjartansson O, et al. Coronary artery calcium, brain function and structure. *Stroke*. 2010;41(5):891–7. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.110.579581>. [PubMed: 20360538]
11. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology*. 1998;51(4):986–93. <http://www.neurology.org/cgi/doi/10.1212/WNL.51.4.986>. [PubMed: 9781518]
12. Strassburger TL, Lee H-C, Daly EM, Szczepanik J, Krasuski JS, Mentis MJ, et al. Interactive effects of age and hypertension on volumes of brain structures. *Stroke*. 1997;28(7):1410–7. <https://www.ahajournals.org/doi/10.1161/01.STR.28.7.1410>. [PubMed: 9227693]
13. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963–74. <http://www.nature.com/articles/mp201320>. [PubMed: 23439482]
14. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci*. 2003;58(3):249–65. <http://www.ncbi.nlm.nih.gov/pubmed/12634292>. [PubMed: 12634292]
15. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365(9475):1961–70. <https://linkinghub.elsevier.com/retrieve/pii/S0140673605666652>. [PubMed: 15936426]
16. Gallegos-Carrillo K, Garcia-Pena C, Mudgal J, Romero X, Durán-Arenas L, Salmerón J. Role of depressive symptoms and comorbid chronic disease on health-related quality of life among community-dwelling older adults. *J Psychosom Res*. 2009;66(2): 127–35. <https://linkinghub.elsevier.com/retrieve/pii/S0022399908003632>. [PubMed: 19154855]
17. Lebowitz BD, Pearson JL, Schneider LS, Reynolds CF, Alexopoulos GS, Bruce ML, et al. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA*. 1997;278(14):1186–90. <http://www.ncbi.nlm.nih.gov/pubmed/9326481>. [PubMed: 9326481]

18. Vu NQ, Aizenstein HJ. Depression in the elderly. *Curr Opin Neurol*. 2013;26(6):656–61. <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00019052-201312000-00011>. [PubMed: 24184971]
19. Suzuki A, Kondo T, Mihara K, Yasui-Furukori N, Otani K, Furukori H, et al. Association between Taq I A dopamine D2 receptor polymorphism and therapeutic response to bromperidol: a preliminary report. *Eur Arch Psychiatry Clin Neurosci*. 2001;251(2):57–9. <http://link.springer.com/10.1007/s004060170053>. [PubMed: 11407439]
20. Sheline YI, Pieper CF, Barch DM, Welsh-Boehmer K, McKinsty RC, MacFall JR, et al. Support for the vascular depression hypothesis in late-life depression. *Arch Gen Psychiatry*. 2010;67(3):277 <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archgenpsychiatry.2009.204>. [PubMed: 20194828]
21. Sheline YI, Price JL, Vaishnavi SN, Mintun MA, Barch DM, Epstein AA, et al. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry*. 2008;165(4):524–32. <http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.2007.07010175>. [PubMed: 18281408]
22. Gouw AA, van der Flier WM, Fazekas F, van Straaten ECW, Pantoni L, Poggesi A, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period. *Stroke*. 2008;39(5):1414–20. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.107.498535>. [PubMed: 18323505]
23. Quarantelli M, Lanzillo R, Del Vecchio W, Mollica C, Prinster A, Iadicicco L, et al. Modifications of brain tissue volumes in facioscapulohumeral dystrophy. *Neuroimage*. 2006;32(3):1237–42. <https://linkinghub.elsevier.com/retrieve/pii/S105381190600526X>. [PubMed: 16806975]
24. Tupler LA, Krishnan KRR, McDonald WM, Dombeck CB, D'Souza S, Steffens DC. Anatomic location and laterality of MRI signal hyperintensities in late-life depression. *J Psychosom Res*. 2002;53(2):665–76. <https://linkinghub.elsevier.com/retrieve/pii/S0022399902004257>. [PubMed: 12169341]
25. Nebes RD, Vora IJ, Meltzer CC, Fukui MB, Williams RL, Kamboh MI, et al. Relationship of deep white matter hyperintensities and apolipoprotein e genotype to depressive symptoms in older adults without clinical depression. *Am J Psychiatry*. 2001;158(6):878–84. <http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.158.6.878>. [PubMed: 11384894]
26. Taylor WD, Steffens DC, MacFall JR, McQuoid DR, Payne ME, Provenzale JM, et al. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry*. 2003;60(11):1090 <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.60.11.1090>. [PubMed: 14609884]
27. Khalaf A, Edelman K, Tudorascu D, Andreescu C, Reynolds CF, Aizenstein H. White matter hyperintensity accumulation during treatment of late-life depression. *Neuropsychopharmacology*. 2015;40(13):3027–35. <http://www.nature.com/articles/npp2015158>. [PubMed: 26058663]
28. Aizenstein HJ, Khalaf A, Walker SE, Andreescu C. Magnetic resonance imaging predictors of treatment response in late-life depression. *J Geriatr Psychiatry Neurol*. 2014;27(1):24–32. [PubMed: 24381231]
29. Ochs RA. FDA approval of Magnetom Terra. 2017 https://www.accessdata.fda.gov/cdrh_docs/pdf17/K170840.pdf.
30. Polimeni JR, Uluda K. Neuroimaging with ultra-high field MRI: present and future. *Neuroimage*. 2018;168(February):1–6. [PubMed: 29410013]
31. Ibrahim T, Hue Y, Gilbert R, Boada F. Tic Tac Toe: highly-coupled, load insensitive Tx/Rx array and a quadrature coil without lumped capacitors. Proceedings of the 16th scientific meeting, international society for magnetic resonance in medicine, Toronto, January 2008. p. 438 <https://cds.ismrm.org/ismrm-2008/files/00438.pdf>.
32. Pohmann R, Speck O, Scheffler K. Signal-to-noise ratio and MR tissue parameters in human brain imaging at 3, 7, and 9.4 tesla using current receive coil arrays. *Magn Reson Med*. 2016;75(2):801–9. <http://doi.wiley.com/10.1002/mrm.25677>. [PubMed: 25820458]
33. Peters AM, Brookes MJ, Hoogenraad FG, Gowland PA, Francis ST, Morris PG, et al. T2* measurements in human brain at 1.5, 3 and 7 T. *Magn Reson Imaging*. 2007;25(6):748–53. <https://linkinghub.elsevier.com/retrieve/pii/S0730725X07001701>. [PubMed: 17459640]

34. Rooney WD, Johnson G, Li X, Cohen ER, Kim S-G, Ugurbil K, et al. Magnetic field and tissue dependencies of human brain longitudinal $1\text{H}_2\text{O}$ relaxation in vivo. *Magn Reson Med*. 2007;57(2): 308–18. <http://doi.wiley.com/10.1002/mrm.21122>. [PubMed: 17260370]
35. Park C-A, Kang C-K, Kim Y-B, Cho Z-H. Advances in MR angiography with 7 T MRI: From microvascular imaging to functional angiography. *Neuroimage*. 2018;168(January 2017):269–78. 10.1016/j.neuroimage.2017.01.019. [PubMed: 28089903]
36. van der Zwaag W, Francis S, Head K, Peters A, Gowland P, Morris P, et al. fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. *Neuroimage*. 2009;47(4):1425–34. 10.1016/j.neuroimage.2009.05.015. [PubMed: 19446641]
37. Yacoub E, Shmuel A, Pfeuffer J, Van De Moortele P-F, Adriany G, Andersen P, et al. Imaging brain function in humans at 7 Tesla. *Magn Reson Med*. 2001;45(4):588–94. <http://doi.wiley.com/10.1002/mrm.1080>. [PubMed: 11283986]
38. Zwanenburg JJM, Hendrikse J, Visser F, Takahara T, Luijten PR. Fluid attenuated inversion recovery (FLAIR) MRI at 7.0 Tesla: comparison with 1.5 and 3.0 Tesla. *Eur Radiol*. 2010;20(4): 915–22. [PubMed: 19802613]
39. van Kalleveen IML, Koning W, Boer VO, Luijten PR, Zwanenburg JJM, Klomp DWJ. Adiabatic turbo spin echo in human applications at 7 T. *Magn Reson Med*. 2012;68(2):580–7. <http://doi.wiley.com/10.1002/mrm.23264>. [PubMed: 22213273]
40. Ibrahim TS, Abduljalil AM, Baertlein BA, Jin JM, Chen J, Prock T, et al. B1 field homogeneity and SAR calculations for the birdcage coil. *Phys Med Biol*. 2001;46:609–19. [PubMed: 11229737]
41. Ibrahim TS, Abduljalil AM, Baertlein BA, Lee R, Robitaille P-M-L. Analysis of B 1 field profiles and SAR values for multi-strut transverse electromagnetic RF coils in high field MRI applications. *Phys Med Biol*. 2001;46(10):2545–55. <http://stacks.iop.org/0031-9155/46/i=10/a=303?key=crossref.47bbda7bd3ed5b0905ee30465694aa42>. [PubMed: 11686274]
42. Santini T, Zhao Y, Wood S, Krishnamurthy N, Kim J, Farhat N, et al. In-vivo and numerical analysis of the eigenmodes produced by a multi-level Tic-Tac-Toe head transmit array for 7 Tesla MRI. Lundberg P, editor. *PLoS One*. 2018;13(11):e0206127 <http://dx.plos.org/10.1371/journal.pone.0206127>. [PubMed: 30481187]
43. Krishnamurthy N, Santini T, Wood S, Kim J, Zhao T, Aizenstein HJ, et al. Computational and experimental evaluation of the Tic-Tac-Toe RF coil for 7 Tesla MRI. Orzada S, editor. *PLoS One*. 2019;14(1):e0209663 <http://dx.plos.org/10.1371/journal.pone.0209663>. [PubMed: 30629618]
44. Winkler SA, Schmitt F, Landes H, de Bever J, Wade T, Alejski A, et al. Gradient and shim technologies for ultra high field MRI. *Neuroimage*. 2018;168:59–70. <https://linkinghub.elsevier.com/retrieve/pii/S1053811916306498>. [PubMed: 27915120]
45. Stockmann JP, Wald LL. In vivo B 0 field shimming methods for MRI at 7 T. *Neuroimage*. 2018;168:71–87. <https://linkinghub.elsevier.com/retrieve/pii/S1053811917304822>. [PubMed: 28602943]
46. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–38. [PubMed: 23867200]
47. Vermeer SE, Longstreth WT, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6(7):611–9. <https://linkinghub.elsevier.com/retrieve/pii/S1474442207701709>. [PubMed: 17582361]
48. Snowdon DA. Brain infarction and the clinical expression of alzheimer disease-reply. *J Am Med Assoc*. 1997;278(2):114 <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1997.03550020046024>.
49. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348(13):1215–22. <http://www.nejm.org/doi/abs/10.1056/NEJMoa022066>. [PubMed: 12660385]
50. Schrag M, McAuley G, Pomakian J, Jiffry A, Tung S, Mueller C, et al. Correlation of hypointensities in susceptibility-weighted images to tissue histology in dementia patients with cerebral amyloid angiopathy: a postmortem MRI study. *Acta Neuropathol*. 2010;119(3):291–302. <http://link.springer.com/10.1007/s00401-009-0615-z>. [PubMed: 19937043]

51. Patankar TF, Baldwin R, Mitra D, Jeffries S, Sutcliffe C, Burns A, et al. Virchow–Robin space dilatation may predict resistance to antidepressant monotherapy in elderly patients with depression. *J Affect Disord.* 2007;97(1–3):265–70. <https://linkinghub.elsevier.com/retrieve/pii/S0165032706002916>. [PubMed: 16919335]
52. Potter GM, Marlborough FJ, Wardlaw JM. Wide variation in definition, detection, and description of lacunar lesions on imaging. *Stroke.* 2011;42(2):359–66. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.110.594754>. [PubMed: 21193752]
53. Benjamin P, Trippier S, Lawrence AJ, Lambert C, Zeestraten E, Williams OA, et al. Lacunar infarcts, but not perivascular spaces, are predictors of cognitive decline in cerebral small-vessel disease. *Stroke.* 2018;49(3):586–93. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.117.017526>. [PubMed: 29438074]
54. Madai VI, von Samson-Himmelstjerna FC, Bauer M, Stengl KL, Mutke MA, Tovar-Martinez E, et al. Ultrahigh-field MRI in human ischemic Stroke—a 7 Tesla study. Herholz K, editor. *PLoS One.* 2012;7(5):e37631 <http://dx.plos.org/10.1371/journal.pone.0037631>. [PubMed: 22701525]
55. Zong X, Park SH, Shen D, Lin W. Visualization of perivascular spaces in the human brain at 7 T: sequence optimization and morphology characterization. *Neuroimage.* 2016;125:895–902. <https://linkinghub.elsevier.com/retrieve/pii/S1053811915010022>. [PubMed: 26520772]
56. Bouvy WH, Zwanenburg JJM, Reinink R, Wisse LEM, Luijten PR, Kappelle LJ, et al. Perivascular spaces on 7 Tesla brain MRI are related to markers of small vessel disease but not to age or cardiovascular risk factors. *J Cereb Blood Flow Metab.* 2016;36(10):1708–17. <http://journals.sagepub.com/doi/10.1177/0271678X16648970>. [PubMed: 27154503]
57. De Cocker LJ, Lindenholz A, Zwanenburg JJ, van der Kolk AG, Zwartbol M, Luijten PR, et al. Clinical vascular imaging in the brain at 7 T. *Neuroimage.* 2018;168(November 2016):452–8. 10.1016/j.neuroimage.2016.11.044. [PubMed: 27867089]
58. Shoamanesh A, Preis SR, Beiser AS, Vasan RS, Benjamin EJ, Kase CS, et al. Inflammatory biomarkers, cerebral microbleeds, and small vessel disease: Framingham heart study. *Neurology.* 2015;84(8):825–32. <http://www.neurology.org/cgi/doi/10.1212/WNL.0000000000001279>. [PubMed: 25632086]
59. Theysohn JM, Kraff O, Maderwald S, Barth M, Ladd SC, Forsting M, et al. 7 tesla MRI of microbleeds and white matter lesions as seen in vascular dementia. *J Magn Reson Imaging.* 2011;33(4):782–91. <http://www.ncbi.nlm.nih.gov/pubmed/21448941>. [PubMed: 21448941]
60. Stehling C, Wersching H, Kloska SP, Kirchhof P, Ring J, Nassenstein I, et al. Detection of asymptomatic cerebral microbleeds. *Acad Radiol.* 2008;15(7):895–900. <https://linkinghub.elsevier.com/retrieve/pii/S1076633208000469>. [PubMed: 18572126]
61. Nandigam RNK, Viswanathan A, Delgado P, Skehan ME, Smith EE, Rosand J, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. *Am J Neuroradiol.* 2009;30(2):338–43. <http://www.ajnr.org/lookup/doi/10.3174/ajnr.A1355>. [PubMed: 19001544]
62. de Bresser J, Brundel M, Conijn MM, van Dillen JJ, Geerlings MI, Viergever MA, et al. Visual cerebral microbleed detection on 7 T MR imaging: reliability and effects of image processing. *Am J Neuroradiol.* 2013;34(6):E61–4. <http://www.ajnr.org/lookup/doi/10.3174/ajnr.A2960>. [PubMed: 22345502]
63. White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross GW, et al. Cerebrovascular pathology and dementia in autopsied honolulu-asia aging study participants. *Ann N Y Acad Sci.* 2002;977(1):9–23. <http://doi.wiley.com/10.1111/j.1749-6632.2002.tb04794.x>. [PubMed: 12480729]
64. Brundel M, de Bresser J, van Dillen JJ, Kappelle LJ, Biessels GJ. Cerebral microinfarcts: a systematic review of neuropathological studies. *J Cereb Blood Flow Metab.* 2012;32(3):425–36. <http://journals.sagepub.com/doi/10.1038/jcbfm.2011.200>. [PubMed: 22234334]
65. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822–38. <https://linkinghub.elsevier.com/retrieve/pii/S1474442213701248>. [PubMed: 23867200]

66. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *Lancet Neurol.* 2012;11(3):272–82. <https://linkinghub.elsevier.com/retrieve/pii/S1474442211703076>. [PubMed: 22341035]
67. Summers PM, Hartmann DA, Hui ES, Nie X, Deardorff RL, McKinnon ET, et al. Functional deficits induced by cortical microinfarcts. *J Cereb Blood Flow Metab.* 2017;37(11):3599–614. <http://journals.sagepub.com/doi/10.1177/0271678X16685573>. [PubMed: 28090802]
68. Coban H, Tung S, Yoo B, Vinters HV, Hinman JD. Molecular disorganization of axons adjacent to human cortical microinfarcts. *Front Neurol.* 2017;8 <http://journal.frontiersin.org/article/10.3389/fneur.2017.00405/full>. [PubMed: 28163694]
69. van Veluw SJ, Zwanenburg JJM, Engelen-Lee J, Spliet WGM, Hendrikse J, Luijten PR, et al. In vivo detection of cerebral cortical microinfarcts with high-resolution 7 T MRI. *J Cereb Blood Flow Metab.* 2013;33(3):322–9. <http://journals.sagepub.com/doi/10.1038/jcbfm.2012.196>. [PubMed: 23250109]
70. van Veluw SJ, Zwanenburg JJ, Rozemuller AJ, Luijten PR, Spliet WG, Biessels GJ. The spectrum of MR detectable cortical microinfarcts: a classification study with 7-Tesla postmortem MRI and histopathology. *J Cereb Blood Flow Metab.* 2015;35(4):676–83. <http://journals.sagepub.com/doi/10.1038/jcbfm.2014.258>. [PubMed: 25605293]
71. van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol.* 2017;16(9):730–40. [10.1016/S1474-4422\(17\)30196-5](https://doi.org/10.1016/S1474-4422(17)30196-5). [PubMed: 28716371]
72. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. *BMJ.* 2016;1(3):83–92. <http://svn.bmj.com/cgi/doi/10.1136/svn-2016-000035>.
73. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol.* 2013;12(5):483–97. <https://linkinghub.elsevier.com/retrieve/pii/S1474442213700607>. [PubMed: 23602162]
74. Heverhagen JT, Bourekas E, Sammet S, Knopp MV, Schmalbrock P. Time-of-flight magnetic resonance angiography at 7 Tesla. *Invest Radiol.* 2008;43(8):568–73. <https://insights.ovid.com/crossref?an=00004424-200808000-00004>. [PubMed: 18648256]
75. Pantoni L Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* 2010;9(7):689–701. <https://linkinghub.elsevier.com/retrieve/pii/S1474442210701046>. [PubMed: 20610345]
76. Cho Z-H, Kang C-K, Han J-Y, Kim S-H, Kim K-N, Hong S-M, et al. Observation of the lenticulostriate arteries in the human brain in vivo using 7.0T MR Angiography. *Stroke.* 2008;39(5):1604–6. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.107.508002>. [PubMed: 18340096]
77. Kang C-K, Park C-A, Kim K-N, Hong S-M, Park C-W, Kim Y-B, et al. Non-invasive visualization of basilar artery perforators with 7 T MR angiography. *J Magn Reson Imaging.* 2010;32(3):544–50. <http://doi.wiley.com/10.1002/jmri.22250>. [PubMed: 20815051]
78. Hartevelde AA, De Cocker LJJ, Dieleman N, van der Kolk AG, Zwanenburg JJM, Robe PA, et al. High-resolution postcontrast time-of-flight MR angiography of intracranial perforators at 7.0 Tesla. Paul F, editor. *PLoS One.* 2015;10(3):e0121051 <https://dx.plos.org/10.1371/journal.pone.0121051>. [PubMed: 25774881]
79. Cho Z-H, Kang C-K, Park C-A, Hong S-M, Kim S-H, Oh S-T, et al. Microvascular functional MR angiography with ultra-high-field 7 t MRI: comparison with BOLD fMRI. *Int J Imaging Syst Technol.* 2012;22(1):18–22. <http://doi.wiley.com/10.1002/ima.22008>.
80. Moody DM, Brown WR, Challa VR, Ghazi-Birry HS, Reboussin DM. Cerebral microvascular alterations in aging, leukoaraiosis, and Alzheimer's disease. *Ann N Y Acad Sci.* 1997;826(1 Cerebrovascul):103–16. <http://doi.wiley.com/10.1111/j.1749-6632.1997.tb48464.x>. [PubMed: 9329684]
81. Shaaban CE, Aizenstein HJ, Jorgensen DR, MacCloud RL, Meckes NA, Erickson KI, et al. In vivo imaging of venous side cerebral small-vessel disease in older adults: an MRI method at 7 T. *Am J Neuroradiol.* 2017;38(10):1923–8. <http://www.ajnr.org/lookup/doi/10.3174/ajnr.A5327>. [PubMed: 28775055]

82. Mittal S, Wu Z, Neelavalli J, Haacke EM. Susceptibility-weighted imaging: technical aspects and clinical applications, Part 2. *Am J Neuroradiol*. 2009;30(2):232–52. <http://www.ajnr.org/lookup/doi/10.3174/ajnr.A1461>. [PubMed: 19131406]
83. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng Y-CN. Susceptibility-weighted imaging: technical aspects and clinical applications, Part 1. *Am J Neuroradiol*. 2009;30(1):19–30. <http://www.ajnr.org/lookup/doi/10.3174/ajnr.A1400>. [PubMed: 19039041]
84. Sinnecker T, Bozin I, Dörr J, Pfueller CF, Harms L, Niendorf T, et al. Periventricular venous density in multiple sclerosis is inversely associated with T2 lesion count: a 7 Tesla MRI study. *Mult Scler J*. 2013;19(3):316–25. <http://journals.sagepub.com/doi/10.1177/1352458512451941>.
85. Novelli EM, Elizabeth Sarles C, Jay Aizenstein H, Ibrahim TS, Butters MA, Connelly Ritter A, et al. Brain venular pattern by 7 T MRI correlates with memory and haemoglobin in sickle cell anaemia. *Psychiatry Res Neuroimaging*. 2015;233(1):18–22. <https://linkinghub.elsevier.com/retrieve/pii/S0925492715000931>.
86. De Guio F, Vignaud A, Ropele S, Dueling M, Duchesnay E, Chabriat H, et al. Loss of venous integrity in cerebral small vessel disease. *Stroke*. 2014;45(7):2124–6. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.114.005726>. [PubMed: 24867926]
87. Kuijff HJ, Bouvy WH, Zwanenburg JJM, Razoux Schultz TB, Viergever MA, Vincken KL, et al. Quantification of deep medullary veins at 7 T brain MRI. *Eur Radiol*. 2016;26(10):3412–8. <http://link.springer.com/10.1007/s00330-016-4220-y>. [PubMed: 26883328]
88. Hartmann DA, Hyacinth HI, Liao F-F, Shih AY. Does pathology of small venules contribute to cerebral microinfarcts and dementia? *J Neurochem*. 2018;144(5):517–26. <http://doi.wiley.com/10.1111/jnc.14228>. [PubMed: 28950410]
89. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*. 1993;43(9):1683–9. <http://www.ncbi.nlm.nih.gov/pubmed/8414012>. [PubMed: 8414012]
90. Moody DM, Brown WR, Challa VR, Anderson RL. Periventricular venous collagenosis: association with leukoaraiosis. *Radiology*. 1995;194(2):469–76. <http://pubs.rsna.org/doi/10.1148/radiology.194.2.7824728>. [PubMed: 7824728]
91. Webb AJS, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis. *Stroke*. 2012;43(10):2631–6. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.112.655837>. [PubMed: 22923446]
92. Shi Y, Thrippleton MJ, Marshall I, Wardlaw JM. Intracranial pulsatility in patients with cerebral small vessel disease: a systematic review. *Clin Sci*. 2018;132(1):157–71. <http://www.clinsci.org/cgi/doi/10.1042/CS20171280>. [PubMed: 29229867]
93. Blair GW, Hernandez MV, Thrippleton MJ, Doubal FN, Wardlaw JM. Advanced neuroimaging of cerebral small vessel disease. *Curr Treat Options Cardiovasc Med*. 2017;19(7):56 <http://link.springer.com/10.1007/s11936-017-0555-1>. [PubMed: 28620783]
94. Furuta A, Ishii N, Nishihara Y, Horie A. Medullary arteries in aging and dementia. *Stroke*. 1991;22(4):442–6. <https://www.ahajournals.org/doi/10.1161/01.STR.22.4.442>. [PubMed: 2024272]
95. Miao Q, Paloneva T, Tuominen S, Pöyhönen M, Tuisku S, Viitanen M, et al. Fibrosis and stenosis of the long penetrating cerebral arteries: the cause of the white matter pathology in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Brain Pathol*. 2006;14(4):358–64. <http://doi.wiley.com/10.1111/j.1750-3639.2004.tb00078.x>.
96. Geurts L, Biessels GJ, Luijten P, Zwanenburg J. Better and faster velocity pulsatility assessment in cerebral white matter perforating arteries with 7 T quantitative flow MRI through improved slice profile, acquisition scheme, and postprocessing. *Magn Reson Med*. 2018;79(3):1473–82. <http://doi.wiley.com/10.1002/mrm.26821>. [PubMed: 28699211]
97. Geurts LJ, Zwanenburg JJM, Klijn CJM, Luijten PR, Biessels GJ. Higher pulsatility in cerebral perforating arteries in patients with small vessel disease related stroke, a 7 T MRI study. *Stroke*. 2019;50(1):62–8. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.118.022516>.
98. Zwanenburg JJM, van Osch MJP. Targeting cerebral small vessel disease with MRI. *Stroke*. 2017;48(11):3175–82. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.117.016996>. [PubMed: 28970280]

99. Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*. 2014;508(7494):55–60. <http://www.nature.com/articles/nature13165>. [PubMed: 24670647]
100. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol Circ Physiol*. 2017;312(1):H1–20. <http://www.physiology.org/doi/10.1152/ajpheart.00581.2016>.
101. Ogawa S, Lee T-M, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*. 1990;14(1):68–78. <http://doi.wiley.com/10.1002/mrm.1910140108>. [PubMed: 2161986]
102. Blair GW, Doubal FN, Thrippleton MJ, Marshall I, Wardlaw JM. Magnetic resonance imaging for assessment of cerebrovascular reactivity in cerebral small vessel disease: a systematic review. *J Cereb Blood Flow Metab*. 2016;36(5):833–41. <http://journals.sagepub.com/doi/10.1177/0271678X16631756>. [PubMed: 26884471]
103. Liu P, Li Y, Pinho M, Park DC, Welch BG, Lu H. Cerebrovascular reactivity mapping without gas challenges. *Neuroimage*. 2017;146:320–6. <https://linkinghub.elsevier.com/retrieve/pii/S1053811916306723>. [PubMed: 27888058]
104. Huber L, Ivanov D, Krieger SN, Streicher MN, Mildner T, Poser BA, et al. Slab-selective, BOLD-corrected VASO at 7 tesla provides measures of cerebral blood volume reactivity with high signal-to-noise ratio. *Magn Reson Med*. 2014;72(1):137–48. <http://doi.wiley.com/10.1002/mrm.24916>. [PubMed: 23963641]
105. Heye AK, Culling RD, Valdés Hernández MDC, Thrippleton MJ, Wardlaw JM. Assessment of blood–brain barrier disruption using dynamic contrast-enhanced MRI: a systematic review. *NeuroImage Clin*. 2014;6:262–74. <https://linkinghub.elsevier.com/retrieve/pii/S2213158214001387>. [PubMed: 25379439]
106. Wardlaw JM, Makin SJ, Valdés Hernández MC, Armitage PA, Heye AK, Chappell FM, et al. Blood-brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort study. *Alzheimer's Dement*. 2017;13(6):634–43. <https://linkinghub.elsevier.com/retrieve/pii/S1552526016300401>.
107. van Nieuwenhuizen KM, Hendrikse J, Klijn CJM. New microbleed after blood–brain barrier leakage in intracerebral haemorrhage. *BMJ Case Rep*. 2017;bcr-2016–218794. <http://casereports.bmj.com/lookup/doi/10.1136/bcr-2016-218794>.
108. Hiscox LV, Johnson CL, Barnhill E, McGarry MDJ, Huston J, van Beek EJ, et al. Magnetic resonance elastography (MRE) of the human brain: technique, findings and clinical applications. *Phys Med Biol*. 2016;61(24):R401–37. <http://stacks.iop.org/0031-9155/61/i=24/a=R401?key=crossref.ecc79a2b0aeac0f13673535f9385f27a>. [PubMed: 27845941]
109. Sack I, Beierbach B, Wuerfel J, Klatt D, Hamhaber U, Papazoglou S, et al. The impact of aging and gender on brain viscoelasticity. *Neuroimage*. 2009;46(3):652–7. <https://linkinghub.elsevier.com/retrieve/pii/S1053811909002237>. [PubMed: 19281851]
110. Sarvazyan AP, Skovoroda AR, Emelianov SY, Fowlkes JB, Pipe JG, Adler RS, et al. Biophysical bases of elasticity imaging. In 1995 p. 223–40. http://link.springer.com/10.1007/978-1-4615-1943-0_23.
111. Desmidt T, Brizard B, Dujardin P-A, Ternifi R, Réménieras J-P, Patat F, et al. Brain tissue pulsatility is increased in midlife depression: a comparative study using ultrasound tissue pulsatility imaging. *Neuropsychopharmacology*. 2017;42(13):2575–82. <http://www.nature.com/articles/npp2017113>. [PubMed: 28585568]
112. Johnson CL, Telzer EH. Magnetic resonance elastography for examining developmental changes in the mechanical properties of the brain. *Dev Cogn Neurosci*. 2018;33:176–81. <https://linkinghub.elsevier.com/retrieve/pii/S1878929317300373>. [PubMed: 29239832]
113. Fehlnner A, Hirsch S, Weygandt M, Christophel T, Barnhill E, Kadobianskyi M, et al. Increasing the spatial resolution and sensitivity of magnetic resonance elastography by correcting for subject motion and susceptibility-induced image distortions. *J Magn Reson Imaging*. 2017;46(1):134–41. <http://doi.wiley.com/10.1002/jmri.25516>. [PubMed: 27764537]

114. Toga AW, Clark KA, Thompson PM, Shattuck DW, Van Horn JD. Mapping the human connectome. *Neurosurgery*. 2012;71(1):1–5. <https://academic.oup.com/neurosurgery/article-lookup/doi/10.1227/NEU.0b013e318258e9ff>. [PubMed: 22705717]
115. Schmidt R, Ropele S, Ferro J, Madureira S, Verdelho A, Petrovic K, et al. Diffusion-weighted imaging and cognition in the leukoariosis and disability in the elderly study. *Stroke*. 2010;41(5). <https://www.ahajournals.org/doi/10.1161/STROKEAHA.109.576629>.
116. Tuladhar AM, van Dijk E, Zwiers MP, van Norden AGW, de Laat KF, Shumskaya E, et al. Structural network connectivity and cognition in cerebral small vessel disease. *Hum Brain Mapp*. 2016;37(1):300–10. <http://doi.wiley.com/10.1002/hbm.23032>. [PubMed: 26466741]
117. Tuladhar AM, Lawrence A, Norris DG, Barrick TR, Markus HS, de Leeuw F-E. Disruption of rich club organisation in cerebral small vessel disease. *Hum Brain Mapp*. 2017;38(4):1751–66. <http://doi.wiley.com/10.1002/hbm.23479>. [PubMed: 27935154]
118. Lawrence AJ, Tozer DJ, Stamatakis EA, Markus HS. A comparison of functional and tractography based networks in cerebral small vessel disease. *NeuroImage Clin*. 2018;18(February):425–32. 10.1016/j.nicl.2018.02.013. [PubMed: 29541576]
119. Biswal B, Zerrin Yetkin F, Houghton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magn Reson Med*. 1995;34(4):537–41. <http://doi.wiley.com/10.1002/mrm.1910340409>. [PubMed: 8524021]
120. Cole. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Front Syst Neurosci*. 2010; <http://journal.frontiersin.org/article/10.3389/fnsys.2010.00008/abstract>.
121. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci*. 2009;106(31):13040–5. <http://www.pnas.org/cgi/doi/10.1073/pnas.0905267106>. [PubMed: 19620724]
122. Fornito A, Zalesky A, Bullmore ET. *Fundamentals of brain network analysis*. Elsevier; 2016 <https://linkinghub.elsevier.com/retrieve/pii/C2012006036X>.
123. Craddock RC, Holtzheimer PE, Hu XP, Mayberg HS. Disease state prediction from resting state functional connectivity. *Magn Reson Med*. 2009;62(6):1619–28. <http://doi.wiley.com/10.1002/mrm.22159>. [PubMed: 19859933]
124. Venkataraman A, Kubicki M, Westin C-F, Golland P. Robust feature selection in resting-state fMRI connectivity based on population studies. In: 2010 IEEE computer society conference on computer vision and pattern recognition—workshops. IEEE; 2010 p. 63–70. <http://ieeexplore.ieee.org/document/5543446/>. [PubMed: 21660131]
125. Yu Y, Shen H, Zhang H, Zeng L-L, Xue Z, Hu D. Functional connectivity-based signatures of schizophrenia revealed by multiclass pattern analysis of resting-state fMRI from schizophrenic patients and their healthy siblings. *Biomed Eng Online*. 2013;12(1):10 <http://biomedical-engineering-online.biomedcentral.com/articles/10.1186/1475-925X-12-10>. [PubMed: 23390976]
126. Eloyan A, Muschelli J, Nebel MB, Liu H, Han F, Zhao T, et al. Automated diagnoses of attention deficit hyperactive disorder using magnetic resonance imaging. *Front Syst Neurosci*. 2012;6 <http://journal.frontiersin.org/article/10.3389/fnsys.2012.00061/abstract>.
127. Dai D, Wang J, Hua J, He H. Classification of ADHD children through multimodal magnetic resonance imaging. *Front Syst Neurosci*. 2012;6 <http://journal.frontiersin.org/article/10.3389/fnsys.2012.00063/abstract>.
128. Li W, Douglas Ward B, Liu X, Chen G, Jones JL, Antuono PG, et al. Disrupted small world topology and modular organisation of functional networks in late-life depression with and without amnesic mild cognitive impairment. *J Neurol Neurosurg Psychiatry*. 2015;86(10):1097–105. <http://jnnp.bmj.com/lookup/doi/10.1136/jnnp-2014-309180>. [PubMed: 25433036]
129. Reijmer YD, Fotiadis P, Piantoni G, Boulouis G, Kelly KE, Gurol ME, et al. Small vessel disease and cognitive impairment: the relevance of central network connections. *Hum Brain Mapp*. 2016;37(7):2446–54. <http://doi.wiley.com/10.1002/hbm.23186>. [PubMed: 27004840]
130. Brinker T, Stopa E, Morrison J, Klinge P. A new look at cerebrospinal fluid circulation. *Fluids Barriers CNS*. 2014;11 (1):10 <http://fluidsbarrierscns.biomedcentral.com/articles/10.1186/2045-8118-11-10>. [PubMed: 24817998]

131. Moody DM, Bell MA, Challa VR. Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: an anatomic study. *Am J Neuroradiol.* 1990;11:431–9. <https://cds.ismrm.org/ismrm-2008/files/00438.pdf>. [PubMed: 2112304]

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Fig. 1.

This figure compares 7 T versus 3 T T2 turbo spin echo (TSE) resolution comparison of perivascular spaces appearances (PvS). The blue and yellow boxes show the PvS well-defined features at 7 T; the green and red boxes show PvS at 3 T. The top arrow shows PvS at 3 T; the bottom arrow shows PvS at 7 T. Note the black dot inside the PvS is a vessel and a distinctive feature of PvS that is most visible at 7 T. The bottom of the figure shows a diagram of a longitudinal view of PvS spaces and the morphology of perivascular spaces. PvS are delineated by basal membranes of glia, pia, and endothelium; the PvS depicts the space surrounding vessels penetrating into the parenchyma. These vessels penetrating the PvS are clearly seen in the 7 T image. The diagram is adapted from Ref. [130] under the Common Attribution 2.0 Generic License

Fig. 2.

High resolution in vivo gradient echo (GRE) whole-brain acquisitions at 7 T, showing details of the brain structure and a comparison with histology. The images were acquired with the tic-tac-toe RF system [42, 43] and with the following GRE sequence parameters: TR = 1960, TE = 14, in-plane resolution $0.21 \times 0.21 \text{ mm}^2$, slice thickness of 1.5 mm, and 64 slices (114.9 mm) in total (20% gap between slices). In (a), selected slices showing the whole-brain acquisition; in (b), zoomed image showing the medullary draining veins throughout the deep white matter acquired without acceleration (18 min acquisitions); in (c), similar zoomed images acquired with acceleration factor (GRAPPA) 2 (9 min acquisition); in (d), the zoomed image in the cortical region, showing cortical microvessels (black arrows), without acceleration in the acquisition; in (e), similar slice showing the cortical regions and cortical microvessels (black arrows), acquired with GRAPPA 2; in (f), figure adapted from Ref. [130], showing similar vasculature structure in the histopathology images of the cortical region. The received profile of the MRI images (a–e) was corrected using the SPM12 software package

Table 1

This table shows typical pulse sequences used for small vessel disease MRI imaging. The “Purpose” column describes the marker for SVD targeted by the sequence. The second column lists the typical resolutions used in clinics. The third column lists the typical resolutions in SVD research in 3 T MRI. The fourth column lists the typical resolutions in SVD research in 7 T MRI

Sequences	Purpose	Clinical brain MRI The thickness in-plane Resolution	3 T Research brain MRI The slice thickness and in-plane resolution	7 T research brain The slice thickness and in-plane resolution
T1-Weighted/MPRAGE	Brain Atrophy distinguishing between Lacunes and perivascular spaces	3–5 mm 1 mm × 1 mm	MPRAGE 1 mm Isotropic (5 min acquisition)	MPRAGE 0.75 isotropic (5 min acquisition) 0.55 mm isotropic (8 min acquisition)
Diffusion-weighted imaging (DWI)	Acute ischemic stroke	3–5 mm 2 mm × 2 mm	3–5 mm × 2 mm × 2 mm	1.5 mm isotropic
T2-Weighted	Brain structures perivascular spaces white matter hyperintensities	3–5 mm 2 mm × 2 mm	1 mm isotropic	0.6 mm isotropic
Fluid-attenuated inversion recovery (FLAIR)	White matter hyperintensities differentiate Lacunes from PVS	3–5 mm 1 mm × 1 mm	1.6 mm × 0.8 mm × 0.8 mm	1.5 × 0.75 mm × 0.75 mm
T2* GRE/susceptibility-weighted imaging	Microbleeds/hemorrhage	3–5 mm 1 mm × 1 mm	SWI 1 mm × 1 mm × 1 mm	SWI 0.75 mm × 0.35 mm × 0.35 mm
Magnetic resonance angiography	Mainly stenosis visualization for large vessels, such as middle cerebral artery and internal carotid	1 mm isotropic with contrast and reconstruction		0.38 mm isotropic no contrast