Magnetic Resonance Imaging of Blood-Brain Barrier Permeability in Dementia

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Abstract

Alzheimer's disease (AD) and cerebral small vessel disease (cSVD) are the two main causes of dementia with blood-brain barrier (BBB) breakdown being a common contributor. Recent advances in neuroimaging techniques offer new possibilities to understand how the brain functions in health and disease. This includes methods such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) which allows the detection of subtle regional changes in the BBB integrity. The purpose of this work is to provide a review on the recent DCE-MRI findings of subtle BBB leakage focusing on cSVD and AD, including both clinical and pre-clinical studies. Despite being widely used and well-established, we also highlight some of the DCE-MRI challenges and pitfalls faced in the context of dementia inherent to the subtle nature of BBB impairment.

Introduction

Given its unique metabolic needs, the brain is one of the most highly perfused organs in the body with 400- and 0.4-mile-long vascular network in humans and mice, respectively (Begley and Brightman, 2003; Zlokovic, 2008; Montagne et al., 2017). This represents on average one mile of vessels per three grams of human brain tissue and for mice it is even denser, with one mile of vessels per one gram of brain tissue. All brain capillaries are constantly perfused, and it has been estimated that no neuron is more than 10–20 μm away from a capillary (Tsai et al., 2009), which implies that every neuron has its own capillary and thus demonstrates the critical relationship between the vascular and neuronal

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compartments. Importantly, there is increasing evidence supporting the involvement of brain vascular dysfunction in the early stages of brain disorders such as Alzheimer's disease (AD) (Montagne et al., 2015, 2017, 2020; van de Haar et al., 2016a, 2016b; Nation et al., 2019; Sweeney et al., 2019a) and cerebral small vessel disease (cSVD) (Zhang et al., 2017b; Wardlaw et al., 2019). Furthermore, it was recently discovered that vascular cells express at least 30 of the top 45 AD risk genes using single-nucleus RNA sequencing on human brain samples (Yang et al., 2021), suggesting that the brain vasculature may play a larger role in the pathogenesis of dementia than was originally thought. Vascular dysfunction can take many forms, involving different cell types comprising the neurovascular unit (NVU), and including disruption of the blood-brain barrier (BBB), which plays a vital role in maintaining brain functions. Many neuroimaging and biofluid biomarker studies, as well as neuropathological studies have revealed the importance of BBB breakdown in the development and progression of common dementias, as extensively reviewed elsewhere (Sweeney et al., 2018a, 2018b, 2019b)

The most advanced method for investigating quantitatively and regionally subtle BBB failure in the living human or rodent brain is dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using ~1 kDa paramagnetic gadolinium-based contrast agents (GBCAs). DCE-MRI method has become more and more available, and the field has now moved from the easily measured BBB damage in diseases with large permeability leaks (*e.g.*, brain tumors, multiple sclerosis, or strokes), to more subtle disruption in chronic vascular disease and dementia. The slow accumulation of GBCAs from the intravascular into the extracellular extravascular space of the brain can be measured to determine regional BBB permeability, often referred as the blood-to-brain transfer constant, K_{trans}. The low permeability is in the range of 10^{-4} to 10^{-3} min^{-1}, while permeability in tumors is at least an order of magnitude higher (*i.e.*, 10^{-2} min^{-1}). There are several mathematical models to compute K_{trans} that differ in complexity and assumptions under which they can be applied (Barnes et al., 2016). All the pre- and post-processing steps towards quantifying subtle BBB K_{trans} measurements from DCE-MRI datasets have been summarized elsewhere (Montagne et al., 2016; Raja et al., 2018; Thrippleton et al., 2019; Manning et al., 2021).

In this review, we briefly discuss the role of BBB in health and dementia with a focus on cSVD and AD. Next, we examine the recent DCE-MRI studies performed in both humans and animal models relevant to cSVD and AD pathologies. Finally, we comment on the DCE-MRI challenges and pitfalls from image acquisition to data analysis steps in the context of low-permeability applications.

Blood-Brain Barrier in Health and Dementia

The primary role of the healthy BBB is to keep potentially toxic blood-derived components such as cells and pathogens out of the brain (Zlokovic, 2011; Sweeney et al., 2019b). At the same time, the BBB regulates the transport of molecules in-and-out of the brain and thus controls the chemical composition of the neuronal milieu which is essential for proper neuronal function (Zlokovic, 2011; Zhao et al., 2015; Sweeney et al., 2019b). The BBB comprises several components including endothelial cells, pericytes, basement membrane, astrocyte end feet, neuronal projections and surrounding glial cells, which altogether form

the NVU (Figure 1). Pericytes, embedded within the basement membrane, wrap around endothelial cells that line the BBB, followed by astrocytic end feet encircling them. The BBB links to neurons in a process called neurovascular coupling where alterations in local blood flow occur in response to changes in neuronal activity (Abbott et al., 2010). Other glial and immune cells such as oligodendrocytes, microglia and perivascular macrophages are also in close and sometimes direct contact with the other NVU components allowing for intimate crosstalk (Abbott et al., 2010; Procter et al., 2021). Brain endothelial cells possess a specialized genetic profile which confer the barriers' characteristic properties of limiting paracellular permeability (Pfau et al., 2021). Brain endothelial cells have indeed higher expression of junctional proteins such as adherens junctions (*e.g.*, VE-cadherin), tight junctions (*e.g.*, Occludin, Zonula Occludens-1, Claudin-5) and gap junctions, as detailed elsewhere (Stamatovic et al., 2016). Of note, tight junctions are important in limiting movement of small molecules (<0.8 kDa) across the BBB (Nitta et al., 2003).

In recent years, there is a growing body of evidence for the contribution of BBB breakdown in the development and progression of common dementias such as AD and cSVD (Figure 1), as comprehensively examined elsewhere (Sweeney et al., 2018b, 2019a; Wardlaw et al., 2019). Just to highlight a few, there is neuropathological evidence of BBB disruption in AD and cSVD brains as indicated by loss of pericyte coverage of the brain capillary wall as well as perivascular accumulation of blood-derived fibrin(ogen) (Halliday et al., 2016; McAleese et al., 2019). Strikingly, a large post-mortem study found that four out of five AD patients had signs of vascular pathology (Toledo et al., 2013). There are also biofluid biomarker studies providing further evidence of BBB damage being an important feature of dementia pathophysiology. For instance, increased levels of the most common biofluid marker of BBB breakdown, albumin quotient (Qalb), were found in AD (as reviewed in (Sweeney et al., 2019b)). Additionally, cerebrospinal fluid (CSF) levels of soluble platelet-derived growth factor receptor-β (sPDGFRβ), a marker of damaged pericytes (Montagne et al., 2015; Sweeney et al., 2020), were found increased with normal aging (Montagne et al., 2015) and markedly accelerated as cognition declined (Montagne et al., 2015, 2020; Nation et al., 2019; Ding et al., 2020). Interestingly, CSF sPDGFRβ is significantly elevated in cognitively unimpaired individuals carrying the E4 variant of apolipoprotein E (APOE) *APOE4* (Montagne et al., 2020), the major genetic risk factor for AD, hinting that BBB disruption may be an early marker of cognitive dysfunction and could be considered as a possible driving factor leading to dementia. Besides neuropathological and biofluid biomarkers findings, there are now improved neuroimaging methods such as DCE-MRI which allows for quantifying subtle and local disruption of the BBB in the living human or rodent brain (Raja et al., 2018; Thrippleton et al., 2019). Here, we next summarize the most recent publications using DCE-MRI in the context of cSVD and AD, and applied in both clinical and pre-clinical settings.

DCE-MRI technique

DCE-MRI collects dynamic T1-weighted MRI images that can monitor the change in signal intensity over time. After the collection of some baseline images, a GBCA is injected, this increases the signal intensity proportional to the concentration of the contrast agent. The changes in signal intensity, along with a T1 map (typically measured right before the

DCE scan), are used to calculate a quantitative concentration of contrast agent in the blood plasma (C_p) and in the brain tissue, the extracellular extravascular space (C_t). The transport between these two compartments can then be modeled mathematically to solve for various physiological parameters. The most commonly used model for BBB measurements, the Platlak model, has two parameters that are solved for: K_{trans}, a transfer constant from the blood plasma to the extravascular extracellular space, and V_p, the volume of blood plasma (Figure 2).

There are many different techniques to acquire T1-maps and T1-weighted MRI images. To our knowledge there has not been a thorough analysis of the tradeoffs or superiority of any given technique. The variety of techniques used is likely a significant source of variability across studies, a rigorous comparison and consolidation to recommended techniques would likely benefit the field. For the dynamic T1-weighted images, spoiled gradient echo (SPGR) is by far the most common sequence used, likely because it is the fastest technique. Fast low angle shot (FLASH), SPGR, fast spoiled gradient echo (FSPGR), and gradient echo (GRE) are generally equivalent. Some papers utilized saturation recovery gradient echo sequences or spin echo sequences which are both somewhat slower but can still give high quality DCE images.

There were three main categories of T1-mapping techniques utilized by studies in this review. Variable flip angle (VFA) typically uses a SPGR sequence with identical parameters to the dynamic T1-weighted acquisition. This is repeated generally three to seven times with different flip angles. This is a very fast technique for T1 mapping, and by utilizing the same sequence type and parameters as the dynamic T1-weighted scan, blood inflow effects and artifacts should be similar between the T1 mapping and dynamic sequence. Variable repetition time (VTR) techniques also use multiple image acquisitions but with different repetition times. These are usually a bit slower than VFA, may have different inflow effects across images, but are less sensitive to B1 inhomogeneity which can cause significant errors in VFA techniques. Finally, inversion recovery techniques such as TAPIR, fast T1 mApping sequence with Partial Inversion Recovery, were utilized in a few studies. These are generally a little slower but give high quality T1 maps.

Methods

Search Sources and Selection Criteria

We reviewed the existing literature on DCE-MRI of subtle BBB permeability in aging, cSVD, and AD. The literature available on Pubmed was searched from January 1, 2015 to May 7, 2021. The following combinations of keywords were searched to be in the title, abstract and/or keywords of the article: (Dynamic contrast enhanced MRI) AND (small vessel disease): 30 results; (Dynamic contrast enhanced MRI) AND (Alzheimer's disease): 29 results; (Dynamic contrast enhanced MRI) AND (aging): 47 results; (Dynamic contrast enhanced MRI) AND (dementia): 32 results; (Dynamic contrast enhanced MRI) AND (cognition): 68 results. In total, 206 references were obtained.

Inclusion and Exclusion Criteria

After exclusion of 71 duplicates, a total of 135 references were obtained from the initial Pubmed search. Out of 135 references, 96 were rejected as they were out of scope. From the 39 remaining publications, 23 were clinical, 3 pre-clinical, 5 methodological recommendations, and 8 review articles. In addition, we included 11 recent DCE-MRI publications that fit the scope of our review but did not appear at the initial search. These include 6 clinical studies, 3 pre-clinical studies, and 2 additional reviews. In total, 50 papers were reviewed in this article. See flow diagram in Figure 3. The main findings, sample characteristics, and protocol used in the clinical studies are detailed in Table 1 (cSVD; 11 publications) and Table 2 (normal aging, mild dementia, and AD; 14 publications), while pre-clinical studies are detailed in Table 3 (6 publications).

DCE-MRI in cSVD

Cerebral SVD covers a wide array of pathologies involving the dysfunction of the small vessels of the brain. Clinical manifestations include stroke, cognitive impairment, or gait disturbance. Many studies reported BBB impairment in cSVD patients, particularly in the white matter (WM) (Thrippleton et al., 2019). A growing number of neuroimaging studies have described subtle BBB breakdown in the living cSVD brain using DCE-MRI technique, as summarized in Table 1 and further discussed below.

White matter hyperintensities (WMH) are a common finding in the elderly population and a key feature of cSVD. While their pathogenesis remains yet unclear, BBB leakage is the most accepted hypothesis. In their 2017 article, Li et al. assessed the BBB permeability in a sample of 102 patients with low, medium, or high cSVD burden and found that global BBB permeability was associated with higher WMH burden (Li et al., 2017). The same year, Wardlaw's group also found a relationship between BBB permeability and WMH burden in a cohort of 201 cSVD patients (Wardlaw et al., 2017). Notably, they highlighted the fact that the healthy WM tissue surrounding WMH presented increased BBB permeability, suggesting that BBB disruption could precede further extensions of the WMH lesions. This result was recently confirmed by Kerkhofs et al. who demonstrated that BBB leakage nearing WMH is related to changes in WM diffusivity, an MRI-based diffusion marker of tissue degeneration possibly caused by local BBB damage (Kerkhofs et al., 2021). Furthermore, Wong et al. observed a negative correlation between cerebral blood flow (CBF) and BBB leakage in the tissue surrounding WMH in 27 cSVD patients (Wong et al., 2019).

DCE-based differences in BBB leakage due to normal aging and cSVD may be very subtle as illustrated by the work of Zhang et al. who did not observe a significant difference in BBB leakage rate (Zhang et al., 2017a). However, leakage extent was found to be higher in cSVD patients. Also, Binswanger's disease (BD) belongs to the cSVD spectrum and is characterized by an extensive involvement of WM and impairment of executive functions. Differentiating BD from other cSVD-related conditions is often difficult; hence, Rosenberg et al. aimed to define more specific biomarkers. Among these, WM BBB permeability was found to be increased in BD patients compared to a combined group of patients having multiple infarcts, mixed AD/vascular cognitive impairment (vCI), or leukoaraiosis (Huisa et al., 2015; Rosenberg et al., 2015).

A known consequence of BBB disruption is the increasing occurrence of microbleeds (Wardlaw et al., 2019). Uchida et al. successfully correlated iron accumulation detected by quantitative susceptibility mapping MRI to local BBB leakage in patients with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), emphasizing how alternate imaging techniques could support DCE-MRI findings (Uchida et al., 2020). Another alternate method would be to measure vessel density, diameter, and size from the R2 and R2* relaxation rates upon GBCA injection (Choi et al., 2020)

In a cohort of older subjects at risk for cSVD, Shao et al. compared DCE-MRI to an arterial spin labeling (ASL)-based technique allowing measurement of water permeability across the BBB (Shao et al., 2020). Interestingly, they found only few correlations between K_{trans} and kw, suggesting that the mechanisms regulating the permeability of water or contrast agents across the BBB are likely to be different.

DCE-MRI in the AD-continuum

The vascular contribution to AD pathophysiology is increasingly recognized. As such, BBB breakdown is considered an important player in the development and progression of the most common cause of dementia (Sweeney et al., 2018a, 2018b, 2019b). Thus, it is not surprising to see a growing number of DCE-MRI studies performed in the normal aging to AD spectrum, as reviewed in Table 2 and examined hereafter.

Normal Aging

In 2015, Montagne et al. first showed an age-dependent BBB leakage starting in the hippocampus in a cohort of 24 healthy individuals ranging from 23 to 91 years of age (Montagne et al., 2015), which was further confirmed in a larger cohort of 46 cognitively unimpaired participants (Montagne et al., 2019). Another group also observed that global BBB impairment was correlated with age (Verheggen et al., 2020a) and cognitive decline (Verheggen et al., 2020b) in a sample of 57 healthy elderly individuals. Interestingly, Moon et al. investigated gender-related differences in BBB permeability in a sample of 75 elderly patients (51 females). They showed that while women are better protected than men with regards to age-related BBB disruption thanks to the protective effect of estrogens, they are also more sensitive to late BBB disruption in the occipital cortex, where the estrogen receptor is more expressed (Moon et al., 2021). Another recent DCE study spotted subtle differences between brain regions in a cohort of 35 cognitively normal elderly participants, with the lowest and highest K_{trans} values in the frontal and occipital WM, respectively(Ha et al., 2021). Of note, no differences between left and right hemispheres were detected. Finally, enlarged perivascular spaces (EPVS) are a common finding in normal aging, and highly increased EPVS load is a feature of both cSVD and AD. In a sample of 109 middle-aged to elderly participants, Li et al. found that BBB leakage and EPVS burden were associated in the basal ganglia (Li et al., 2019).

Mild Dementia

Although regional BBB leakage seems to occur during normal aging, Montagne et al. also reported that hippocampal BBB disruption worsened as participants' cognition declined (Montagne et al., 2015, 2019). A following study from the same group observed a local increase of BBB permeability in the medial temporal lobe (MTL) (including the hippocampi and parahippocampal gyri) of 42 patients with mild cognitive impairment (MCI) compared to 20 age-matched cognitively unimpaired controls (Nation et al., 2019). Interestingly, the authors demonstrated that MTL vascular leakage is an independent, early biomarker of cognitive impairment unrelated to amyloid-β (Aβ) and tau pathology, as the positivity for the respective CSF biomarkers $A\beta_{42}$ and phosphorylated tau (pTau) did not affect the results.

Recently, the same authors questioned the relation between *APOE4* genotype and BBB permeability in a cohort of 245 elderly MCI and cognitively unimpaired participants (Montagne et al., 2020). Increased BBB permeability in the MTL was confirmed in MCI and further accelerated in *APOE4* carriers. Interestingly, cognitively unimpaired individuals carrying *APOE4* had substantially higher MTL BBB K_{trans} values compared non-carriers (Montagne et al., 2020), supporting the involvement of BBB dysfunction early in the course of AD.

A study by Li et al. showed that BBB leakage in WMH was significantly higher in vascular MCI individuals, an uncommon condition where the sole cause for cognitive impairment is vascular pathology, when compared to age- and sex-matched healthy controls (Li et al., 2021). Additionally, Freeze et al. investigated the link between BBB leakage, WMH, and processing speed in a cohort of 80 elderly participants, including 34 MCI as well as 14 AD patients (Freeze et al., 2020). The authors found an association between increased BBB permeability in WMH and cognitive impairment suggesting that local BBB breakdown may trigger WM lesions which could then explain the reduction in information processing speed (Freeze et al., 2020).

Alzheimer's Disease

In their AD cohort, Freeze et al. found that BBB disruption throughout the whole brain was associated with cSVD severity, independently of cognitive status (Freeze et al., 2020). The group of Backes recently studied BBB dysfunction in AD using DCE-MRI method. For instance, they confirmed the relationship between BBB disruption and early AD in a cohort of 33 elderly, whom 9 presented MCI and 7 AD diagnosis. Indeed, AD patients showed increased BBB leakage in the whole brain, which worsened with cognitive impairment (van de Haar et al., 2016a). In a follow-up study, the same authors also observed a general decrease in CBF in the gray matter of early AD patients, which correlated with increased BBB leakage in a cohort of 14 MCI/AD and 16 age-matched controls (van de Haar et al., 2016b, 2017).

DCE-MRI in pre-clinical models relevant to dementia

As MRI is becoming more accessible, DCE method is also increasingly applied in a variety of rodent models that are relevant to dementia (see Table 3).

Pericyte Deficiency

Pericytes are a major component of the BBB, especially at the capillary level where the smooth muscle layers are lacking (Procter et al., 2021). Pericytes wrap around endothelial cells that line the BBB, and their dysfunction is thought to play a critical role in aggravating dementia (Sweeney et al., 2019b; Uemura et al., 2020). Analyses of post-mortem brains and CSF samples provided substantial evidence supporting early pericyte loss in AD (Baloyannis and Baloyannis, 2012; Sagare et al., 2013; Sengillo et al., 2013; Miners et al., 2018), mild dementia (Montagne et al., 2015, 2020; Nation et al., 2019), stroke (Yemisci et al., 2009; Hall et al., 2014), and cSVD (Ghosh et al., 2015; Montagne et al., 2018). Using DCE-MRI in a chronic mouse model of pericyte deficiency, Montagne et al. reported a global and age-dependent increase in BBB permeability with the highest K_{trans} values found in WM structures (Montagne et al., 2018). Also, they observed CBF reduction and EPVS in the WM of young pericyte-deficient mice, which are common findings in the aged brain (Montagne et al., 2018). In another model of acute pericyte ablation, the same group reported a substantial circulatory failure with acute BBB disruption and reduced CBF in the cortex and hippocampus, followed by rapid neuronal loss (Nikolakopoulou et al., 2019). These pre-clinical results emphasize the role of pericytes in BBB homeostasis and promote the use of DCE-MRI to detect subtle BBB changes in the living rodent brains.

Amyloid Models

Although several studies found increased BBB permeability to gadolinium contrast agent in rodent models of AD (Montagne et al., 2017), Dickie et al. failed to observe BBB K_{trans} changes in old TgF344-AD rats compared to wildtype controls but did find an increase in water permeability (Dickie et al., 2021). It suggests that old TgF344-AD rats do not develop BBB breakdown with loss of tight junction proteins as one would assume, but rather show an increase in water exchange rate that is facilitated by dedicated water channel, predominantly aquaporin-4 (AQP4) in astrocytes and aquaporin-1 (AQP1) in endothelial and mural cells. Of note, it is important to clarify that Kw and K_{trans} are measuring two very different processes, one being the water exchange rate across the BBB and the other one the BBB permeability to gadolinium contrast (Shao et al., 2020).

As shown in humans carrying *APOE4* (Montagne et al., 2020), the same group found that, compared to *APOE3*, *APOE4* accelerates BBB breakdown, loss of CBF, neuronal loss, and behavioral deficits independently of Aβ using aged *APOE* knock-in mice crossed with *5xFAD* mice (Montagne et al., 2021). Such results support that BBB disruption may occur earlier than anticipated in AD and be an early contributor to the pathogenesis of the disease, thus emphasizing the need for appropriate methods to detect subtle BBB leakage in humans.

Vascular Risk Factors

Several conditions related to lifestyle are associated with BBB disruption. Wang et al. found a sharp increase of BBB K_{trans} measured in the cortex and hippocampus of aged spontaneously hypertensive rats compared with controls (Wang et al., 2018). Similarly, diabetes increased BBB leakage in the cortex, hippocampus, and thalamus of aged rhesus monkeys (Xu et al., 2017). While BBB disruption occurring due to normal aging cannot be

prevented, moderating the lifestyle factors known to affect vessel wall integrity could delay the occurrence of clinical consequences.

DCE-MRI Challenges and Pitfalls in Dementia

The small amounts of leakage that occur in cSVD and AD bring the inherent difficulty of detecting and quantifying very small signal changes in DCE-MRI. This is a significant technical challenge, but steady progress is being made in identifying and mitigating the various challenges. Here we highlight some of the principal challenges that can prevent accurate data. For a more thorough review of the technical challenges, recommended acquisition, and processing steps, see the recent review by (Thrippleton et al., 2019).

Motion

Patient motion is a significant concern over the course of a 10–20-minute DCE acquisition. Even small changes in head position can cause changes in tissue type in a given voxel, particularly at parenchyma-CSF boundaries. These changes show up as gradual increases or decreases in signal intensity. This will bias measured K_{trans} values higher or lower, even causing K_{trans} to have negative values. Figure 4 shows an example of a measured percent signal change over 12 minutes DCE acquisition without any contrast injection, so the expected signal change is zero. Images are shown with and without motion correction co-registration algorithms, and show signal changes up to 25% near CSF boundaries. These changes occur even though there is minimal motion (<0.5 mm of displacement in any direction) but are almost entirely corrected with co-registration. Motion correction with co-registration is recommended for all DCE studies (Thrippleton et al., 2019), and more recent publications have demonstrated errors in fit parameters of >200% in some voxels including many negative K_{trans} values from even low motion that are almost entirely corrected with co-registration (Bernal et al., 2021). We have found co-registration is more effective when a brain mask is applied first, as scalp motion can be independent of brain motion and DCE measurements in the scalp are usually of little interest.

Signal Drift

Small amounts of signal intensity drift over time can be a significant source of error as they can be comparable to the amount of signal intensity change from the contrast agent (Barnes et al., 2016). A frequent cause of signal drift is temperature changes of the MRI hardware and electronics. In animal acquisitions this can be caused by thermal support systems for the animal (particularly blowing warm air into the bore), and care should be taken to achieve a steady temperature and not make adjustments for the entirety of the acquisition. In humans, newer wide bore systems (70 cm bore diameter) are more susceptible to heat transfer from the gradients, and gradient heavy sequences (such as diffusion tensor imaging) can potentially cause heating and signal drift after they are run (as the gradients cool). Signal drift is very system-dependent and therefore it is recommended to acquire some datasets without contrast injection to evaluate any signal drift on the scanner that will be used. If signal drift is a problem on a particular system, it can be monitored and corrected to some extent with constant signal intensity phantom added to the field of view (Barnes et al., 2016; Thrippleton et al., 2019). This is usually a water tube dopped with a small amount of

gadolinium contrast agent. Care should be taken to make sure the phantom is large enough that the signal can be reliably measured, so small movements are not mistaken for signal drift.

Vascular Input Function

The measurement of the vascular input function is a critical step that can have a large effect on the final K_{trans} values. It can be challenging to make accurate measurements for a variety of reasons including: motion artifacts of the flowing blood, small size of vessels causing partial volume errors, inflow of fresh blood that has seen few radiofrequency (RF) pulses and hasn't reached steady state, and insufficient temporal resolution to accurately measure the first pass of the contrast bolus. While each of these can be a source of considerable error, most can be minimized by simple acquisition choices. A coronal acquisition, measuring in the superior sagittal sinus (SSS), and a slow contrast agent injection (greater than the temporal resolution) generally gives good results. The coronal acquisition exposes the blood to many RF pulses ensuring it will reach steady state, as the 2D excitation slab will extend through the neck, and possibly to the heart depending on the angle of the slab (Thrippleton et al., 2019). Measuring in the SSS minimizes the flow speed and associated artifacts compared to arterial measurements. The blood in the SSS has also been exposed to more RF pulses traveling through the brain, so is more likely to achieve steady state. The SSS is also relatively large and stationary so will minimize partial volume errors. The venous measurements have been shown to be very similar to arterial measurements and are largely just shifted by 5–7 seconds (Sourbron et al., 2009; Foottit et al., 2010). For acquisitions with temporal resolution greater than 7 seconds there will be little measurable difference. Finally, injecting the contrast agent over a longer duration will minimize errors in measuring the first pass of a bolus injection (Manning et al., 2021).

Conclusion

DCE-MRI underlined the occurrence of local, subtle, and progressive BBB leakage in aging. One of the plausible causal links to cognitive impairment and dementia is through the passage of blood-derived neurotoxic compounds from the blood to brain tissues, causing progressive damage in strategic regions such as the WM and medial temporal lobe. The integrity of the BBB depends on the cohesion of all its components, especially at the capillary level which represents the largest surface for blood contact. Pericytes are found on the whole vascular tree and are key actors in the regulation of vasomotricity and BBB permeability. *APOE4* genotype leads to faster BBB disruption, which could prevent waste removal and trigger amyloid-related pathologies such as AD. Inter-regional differences, as well as gender-related differences in the development of BBB disruption may lead to a more precise interpretation of the experimental results. Pre-clinical transgenic models, as well as clinical cohorts, have helped to connect vascular aging to cognitive impairment and led to important insights on the physiology and disease processes. However, detecting earlier stages of BBB breakdown is challenging and may require additional technical innovations in DCE-MRI acquisition and processing techniques. Alternate methods evaluating the water permeability of the BBB does not necessarily correlate with DCE-MRI, thus emphasizing

the complexity of the exchanges occurring across the BBB and the need for additional studies to understand these mechanisms.

Acknowledgements

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Highlights

- BBB breakdown is a major driving force in dementia pathology.

- DCE-MRI is the most advanced method to investigate BBB leakage in the living human and rodent brain.

- Many different DCE-MRI techniques and imaging processing methods exist.

- Detecting subtle BBB breakdown using DCE-MRI can be challenging.
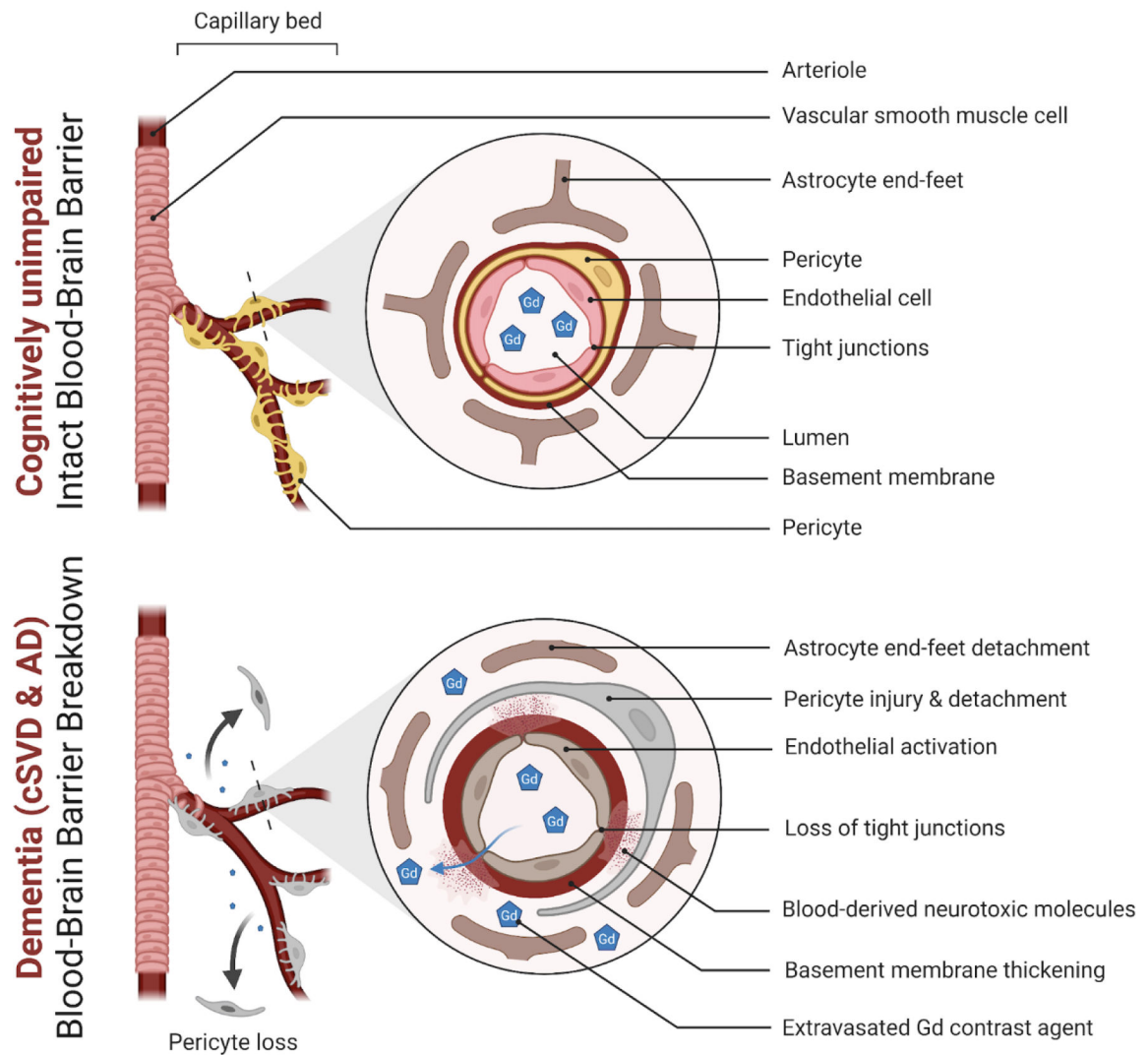
Figure 1. Blood-brain barrier in health and dementia.
A simplified neurovascular unit (NVU) diagram showing a healthy blood-brain barrier
(BBB) with the interactive cellular network at the level of brain capillaries that comprises
endothelial cells, pericytes, basal membrane, and astrocyte end-feet (*top panel*). In dementia,
changes to endothelial cells and pericytes lead to loss of function and BBB breakdown
with loss of tight junction proteins (*bottom panel*). Subtle extravasation of Gadolinium
(Gd) contrast can be detected using dynamic contrast-enhanced magnetic resonance imaging
(DCE-MRI) in both living cerebral small vessel disease (cSVD) and Alzheimer's disease
(AD) participants. Subsequent damage then occurs to the surrounding brain cells such as
astrocytes, neurons, and oligodendrocytes contributing to pathology and cognitive decline
(Figure created using Biorender.com).

Figure 2. DCE-MRI and BBB assessment.
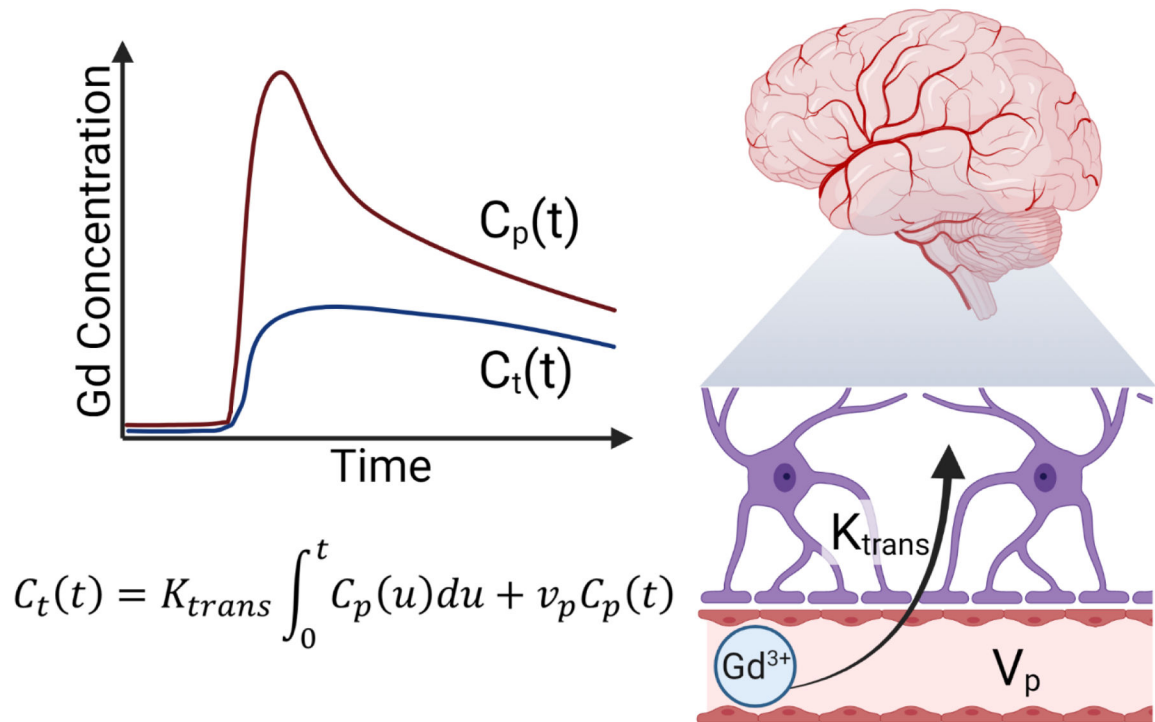DCE-MRI is used to measure BBB integrity by measuring the concentration of gadolinium contrast agent over time in the blood plasma (C_p) and in the brain tissue (C_t). These measured concentrations are then used to calculate the blood-to-brain transfer coefficient (K_{trans}) and the blood volume (v_p) using the Patlak mathematical model (Figure created using Biorender.com).
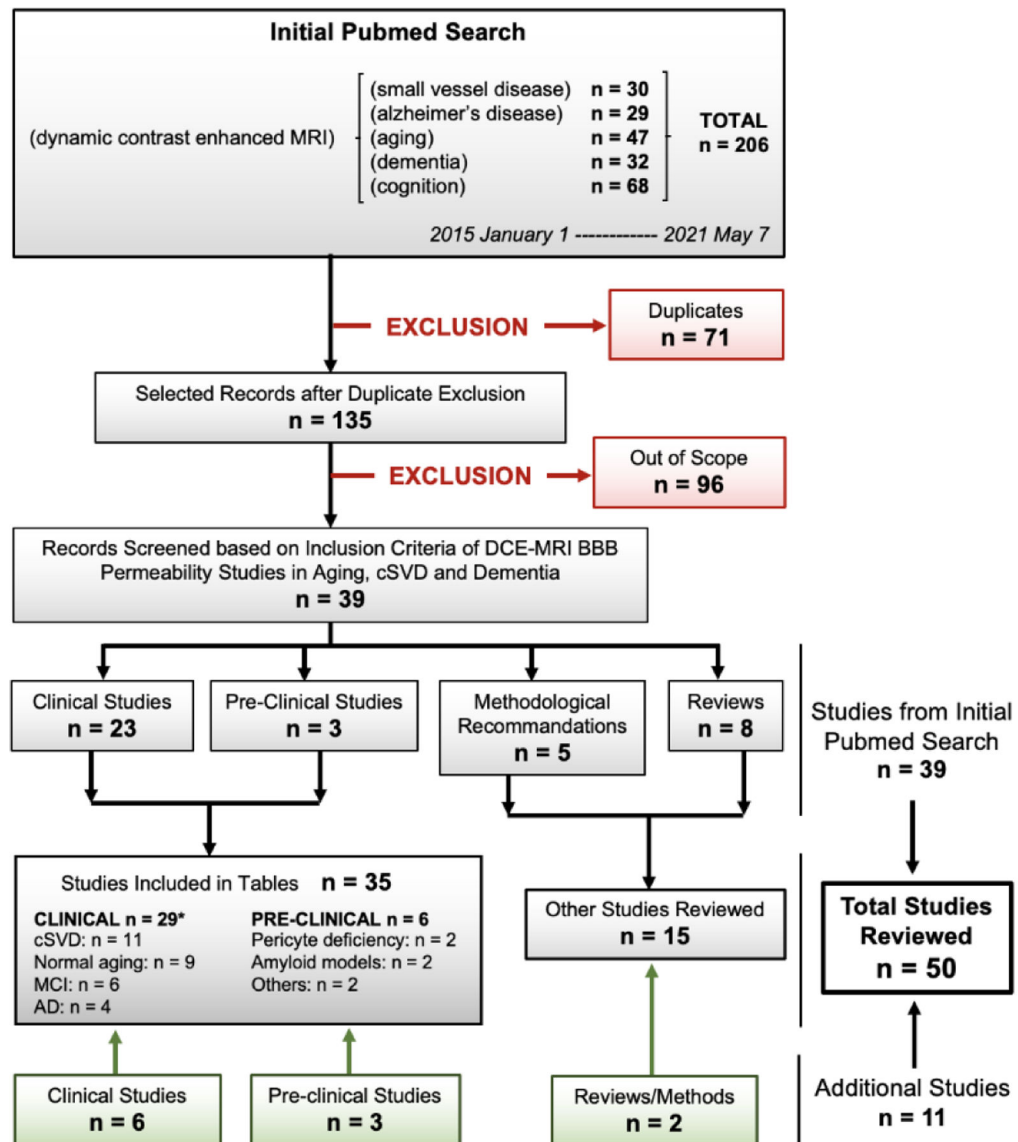
Figure 3. Flow Diagram of literature search.
Recent research articles and reviews (January 1, 2015 - May 7, 2021) focusing on
blood-brain barrier (BBB) permeability measured by dynamic contrast-enhanced magnetic
resonance imaging (DCE-MRI) in normal aging, cerebral small vessel disease (cSVD) or
Alzheimer's disease (AD) were recovered from Pubmed search. In addition to the 39 articles
retrieved from the systematic search, 11 additional articles highly relevant to our focus
were added (*green boxes*), leading to a total of 50 reviewed papers. Research articles were
categorized into three tables: Tables 1 and 2 summarize DCE-MRI studies performed in
cSVD participants (11 publications) and in the AD continuum [including normal aging,
mild cognitive impairment (MCI), and AD participants] (14 publications), respectively;
Table 3 summarizes pre-clinical DCE-MRI studies in animal models relevant to dementia (6
publications). *Some studies have occurrences for several conditions.*
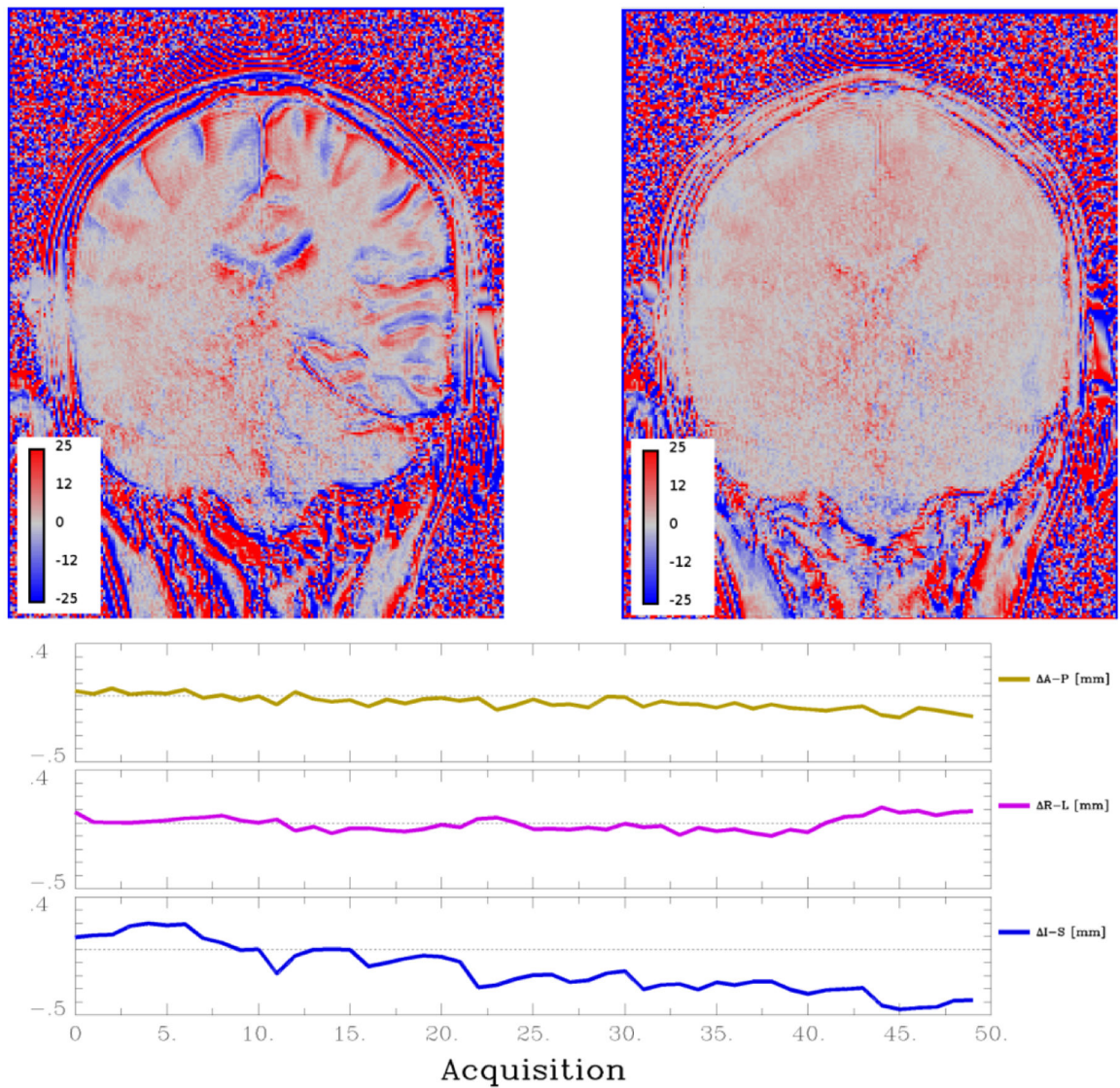
Figure 4. Dynamic contrast-enhanced magnetic resonance imaging and motion correction.
Dynamic contrast-enhanced (DCE) protocol acquisition without contract injection shows
percent signal change calculated from a linear fit over time (*top images*). *Left* image
is the 'without motion correction' and shows signal changes up to 25%, particularly at
cerebrospinal fluid (CSF)-tissue interface, due to small motions of subjects' head. *Right*
image is the same dataset after motion correction, which shows almost all signal change is
eliminated. *Bottom* graphs show calculated brain motion relative to the first image along the
three principal axis (A-P, anterior-posterior; R-L, right-left; I-S, inferior-superior). Even <0.5
mm of motion can induce significant signal changes (Images courtesy of SRB).

Table 1.

Dynamic contrast-enhanced MRI studies in cerebral small vessel disease.

Study	Sample Size (Ct/Pt)	Mean Age (Ct/Pt)	DCE Protocol (FS/PS/TA)	CA/Dose (mmol/kg)	VIF	PK Model	Software	Average BBB K_{trans} (Ct/Pt; $\times 10^{-3}$ min^{-1})				Main Findings
								HC	NAWM	WMH	CGM	
Kerkhofs et al., 2021	NA/43	NA/68	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	NK	NK	NA/0.17[*]	NA/0.18[*]	NA/0.11[*]	BBB leakage in the perilesional zone of WMH is related to WM degeneration
Shao et al., 2020	NA/16	NA/68	3T/VFA-SPGR/16min	Dotarem (0.1)	Carotid artery	Patlak	Rocketship	NA/0.76	NA/0.61	NK	NA/0.68	Patterns of BBB permeability for water (Kw) and Gd tracer (K_{trans}) are different
Uchida et al., 2020	21/21	46/51	3T/VFA-SPGR/5min	Dotarem (0.1)	CCA	Patlak	In-house scripts (MATLAB)	0.78/0.89	NK	NK	NK	Iron leakage is associated with increased BBB permeability
Wong et al., 2019	NA/27	NA/69	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	NK	NK	NA/0.19[*]	NA/0.20[*]	NK	Association between BBB impairment, WMH, and hypoperfusion
Li et al., 2018	31/68	NA/70	3T/VFA-SPGR/NK	Gadolinium (0.1)	SSS	Patlak	nordicICE	NK	0.01/0.03	0.03/0.05	0.09/0.14	BBB leakage is associated with cSVD burden
Li et al., 2017	NA/102	NA/70	3T/VFA-SPGR/NK	Gadolinium (0.1)	SSS	Patlak	nordicICE	NK	0.01/0.03	0.03/0.05	0.09/0.14	BBB leakage is associated with cSVD burden
Wardlaw et al., 2017	NA/201	NA/67	1.5T/VFA-SPGR/24min	Dotarem (0.1)	SSS	Linear mixed model	SAS 9.3	NK	NK	NK	NK	BBB leakage in NAWM nearing WMH predicts cognitive decline
Zhang et al., 2017	40/80	69/70	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	NK	NK	0.58[*]/0.53[*]	0.48[*]/0.47[*]	0.82[*]/0.79[*]	BBB leakage is associated with cSVD
Heye et al., 2016	NA/201	NA/66	1.5T/VFA-SPGR/24min	Dotarem (0.1)	SSS	Patlak	In-house scripts (MATLAB)	NK	NA/0.30	NA/0.40	NK	Patlak model is suited for evaluating subtle BBB leakage, but signal drift is limiting
Huisa et al., 2015	12/22	61/67	1.5T-3T/TAPIR/2028min	Magnevist (NK)	SSS	Patlak	In-house scripts (MATLAB)	NK	NK	NK	NK	BBB permeability aeras fluctuates in Binswanger's disease
Rosenberg et al., 2015	NA/25	NA/66	1.5T/TAPIR/NK	Magnevist (NK)	NK	Patlak	NK	NK	NA/1.87[*]	NK	NK	BBB permeability is a predictor of Binswanger's disease

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Abbreviations: BBB: Blood-Brain Barrier; CA: Contrast Agent; CCA: Common Carotid Artery; CGM: Cortical Gray Matter; cSVD: Cerebral Small Vessel Disease; Ct: Controls; DT-SRGRE: Dual-time SRGRE; FS: Field Strength; Gd: Gadolinium; HC: Hippocampus; Ki & K_{trans}: Blood-to-Brain Transfer Constant; Kw: Blood-to-Brain Water Exchange Rate; NAWM: Normal Appearing White Matter; NA: Not Applicable; NK: Not Known; PK: Pharmacokinetic; PS: Pulse Sequence; Pt: Patients; SPGR: Spoiled Gradient; SRGRE: Saturation Recovery Gradient Echo; SSS: Superior Sagittal Sinus; TA: Time Acquisition; TAPIR: fast T1 mApping sequence with Partial Inversion Recovery; VFA: Variable Flip Angle; VIF: Vascular Input Function; WMH: White Matter Hyperintensities.

*
Denote Ki -> K_{trans} conversion using Ki = K_{trans}/[1-hematocrit] with hematocrit = 0.45.

Table 2.

Dynamic contrast-enhanced MRI studies in Alzheimer's disease-continuum.

Study	Sample Size (Ct/Pt)	Mean Age (Ct/Pt)	DCE Protocol (FS/PS/TA)	CA/Dose (mmol/kg)	VIF	PK Model	Software	Average BBB K_{trans} (Ct/Pt; $\times 10^{-3}$ min^{-1})				Main Findings
								HC	NAWM	WMH	CGM	
Ha et al., 2021	34/NA	65/NA	3T/VFA-SPGR/10min	Gadovist (0.1)	SSS	Patlak	nordicICE	0.56/NA	0.33/NA	NK	NK	Regional BBB K_{trans} differences exist in cognitively normal elderly adults
Moon et al., 2021	75/NA	67/NA	3T/GRE/10min	Gadovist (1.0)	SSS	Patlak	nordicICE	NK	NK	NK	NK	Females are protected from early BBB breakdown in cortex
Montagne et al., 2020	206#/NA	69/NA	3T/VFA-SPGR/16min	Dotarem (0.05)	ICA	Patlak	Rocketship	1.38/NA	1.90/NA	NK	1.43/NA	Increased BBB permeability in the MTL of cognitively unimpaired APOE4 carriers
Normal aging												
Verheggen et al., 2020a	57/NA	66/NA	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	NK	0.61E-3 */NA	NK	0.50E-3 */NA	Increased BBB permeability with aging
Verheggen et al., 2020b	57/NA	66/NA	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	0.94E-3 */NA	0.61E-3 */NA	NK	0.50E-3 */NA	BBB leakage is associated with memory decline in normal aging
Li et al., 2019	109/NA	70/NA	3T/VFA-SPGR/NK	Gadolinium (0.1)	SSS	Patlak	nordicICE	NK	0.03/NA	NK	NK	Increased BBB permeability correlates with BGEPVS
Montagne et al., 2019	46/NA	69/NA	3T/VFA-SPGR/16min	Multihance (0.05) / Dotarem (0.05)	CCA	Patlak	Rocketship	1.12/NA	NK	NK	NK	Increased hippocampal BBB permeability with normal aging
Montagne et al., 2015	24/NA	63/NA	3T/VFA-SPGR/16min	Multihance (0.05)	CCA	Patlak	Rocketship	1.18/NA	2.06/NA	NK	1.26/NA	BBB breakdown starts in HC
MCI												
Li et al., 2021	21/26	67/71	3T/VFA-SPGR/NK	Gadolinium (0.1)	SSS	Patlak	nordicICE	NK	0.02/0.03	0.03/0.06	0.09/0.16	Increased BBB permeability in WMH is linked to CI

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Study	Sample Size (Ct/Pt)	Mean Age (Ct/Pt)	DCE Protocol (FS/PS/TA)	CA/Dose (mmol/kg)	VIF	PK Model	Software	Average BBB K_{trans} (Ct/Pt; ×10⁻³ min⁻¹)				Main Findings
								HC	NAWM	WMH	CGM	
Freeze et al.,2020	32/34	72/69	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	0.40E-3 */ 0.16E-3 *	0.67E-3 */ 1.03E-3 *	0.69E-3 */ 0.72E-3 *	0.54E-3 */ 0.47E-3 *	Increased BBB permeability in WMH is linked to CI
Montagne et al., 2020	206/39	69/72	3T/VFA-3D-VIBE/16min	Dotarem (0.05)	CCA	Patlak	Rocketship	1.38/1.69	1.90/2.13	NK	1.43/1.42	Accelerated BBB breakdown in the MTL of *APOE4* carriers
Montagne et al., 2019	40/12	74/75	3T/VFA-SPGR/16min	Multihance (0.05) / Dotarem (0.05)	CCA	Patlak	Rocketship	1.36/1.70	NK	NK	NK	Increased hippocampal BBB permeability in MCI
Nation et al., 2019	42/20	74/73	3T/VFA-SPGR/16min	Multihance (0.05) / Dotarem (0.05)	CCA	Patlak	Rocketship	1.38/1.67	2.23/2.39	NK	1.32/1.35	Increased hippocampal BBB permeability in MCI independent of amyloid and tau pathology
Montagne et al., 2015	18/21	73/72	3T/VFA-SPGR/16min	Multihance (0.05)	CCA	Patlak	Rocketship	1.28/1.64	2.19/2.30	NK	1.29/1.38	BBB breakdown starts in HC and may contribute to CI
AD												
Freeze et al., 2020	32/14	72/72	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	0.40E-3 */ 0.25E-3 *	0.67E-3 */ 0.44E-3 *	0.69E-3 */ 0.56E-3 *	0.54E-3 */ 0.41E-3 *	Increased BBB permeability is related to cSVD severity in AD patients
Van de Haar et al., 2017	17/7	76/74	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	NK	0.04 */ 0.04 *‡	NK	4.00E-3 */ 0.057 *‡	Global BBB leakage in patients with early AD that is associated with cognitive decline
Van de Haar et al., 2016a	17/7	76/74	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	NK	0.04/0.04 ‡	0.03/0.06 ‡	4.00E-3/0.05 ‡	Brain-wide increased BBB permeability in AD patients is associated with CI
Van de Haar et al., 2016b	16/7	76/75	3T/DT-SRGRE/25min	Gadovist (0.1)	SSS	Patlak	In-house scripts (MATLAB)	NK	NK	NK	0.18/0.27 ‡	AD patients show increased BBB permeability in cortex

Abbreviations: AD: Alzheimer's Disease; APOE4: Apolipoprotein E4; BG-EPVS: Enlarged Perivascular Spaces in the Basal Ganglia; BBB: Blood-Brain Barrier; CA: Contrast Agent; CCA: Common Carotid Artery; CDR: Clinical Dementia Rating; CGM: Cortical Gray Matter; CI: Cognitive Impairment; cSVD: Cerebral Small Vessel Disease; Ct: Controls; DT-SRGRE: Dual-time SRGRE; FS: Field Strength; FSPGR: Fast SPGR; GRE: Gradient Echo; HC: Hippocampus; ICA: Internal Carotid Artery; Ki & Ktrans: Blood-to-Brain Transfer Constant; MCI: Mild Cognitive Impairment; MTL: Median Temporal Lobe; NAWM: Normal Appearing White Matter; NA: Not Applicable; NK: Not Known; PK: Pharmacokinetic; PS: Pulse Sequence; Pt: patients; sPDGFRβ: Soluble Platelet-Derived Growth Factor Receptor β; SPGR: Spoiled Gradient; SRGRE: Saturation Recovery Gradient Echo; SSS: Superior Sagittal Sinus; TA: Time Acquisition; VFA: Variable Flip Angle; VIBE: Volumetric Interpolated Breath-Hold; VIF: Vascular Input Function; WMH: White Matter Hyperintensities.

*
Denote Ki -> Ktrans conversion using Ki = Ktrans/[1-hematocrit] with hematocrit = 0.45;

#
Denotes all cognitively normal (CDR=0) participants;

†
MCI and AD groups combined.

Table 3.

Dynamic contrast-enhanced MRI *studies in animal models relevant to dementia.*

Study	Model (species)	Sample Size (Ct/Tg)	Age (months)	DCE Protocol (FS/PS/TA)	CA/Dose (mmol/kg)	VIF	PK Model	Software	Average BBB K_{trans} (Ct/Tg; $\times 10^{-3}$ min^{-1})				Main Findings
									HC	CTX	THAL	CC	
Pericyte deficiency													
Nikolakopoulou et al., 2019	Pericyte-Cre-DTR (mouse)	5/6	2–3	7T/VFA-FLASH/15min	Magnevist (0.5)	CCA	Patlak	Rocketship	0.59[#]/1.13[#]	0.68[#]/1.23[#]	NK	NK	Increased BBB permeability after pericyte ablation
Montagne et al., 2018	*Pdgfrb^{F7/F7}* (mouse)	5–7/5–7	1–1.5, 3–4, 9–12	7T/VTR-FLASH/35min	Magnevist (0.5)	CCA	Patlak	Rocketship	NK	NK	NK	0.60/0.86, 0.58/1.05, 0.70/1.22	Increased BBB permeability in pericyte-depleted WM regions
Dickie et al., 2021	TgF344-AD (rat)	16/13, 5/7, 7/8	13, 18, 21	7T/VFA-SPGR/10min	Dotarem (0.5)	SSS	Patlak	R	NK	NK	NK	NK	AD genotype did not lead to K_{trans} changes, but higher water permeability (Kw) was observed
Amyloid models													
Montagne et al., 2021	5xFAD; TR-APOE3/4 (mouse)	12-14 FAD–/13-16 FAD+	18–24	7T/VFA-FLASH/25min	Gd-DTPA (BioPAL) (0.5)	CCA	Patlak	Rocketship	0.68/0.98[$]	0.69/0.91[$]	NK	NK	Increased BBB permeability in *APOE4* AD mice, independent of amyloid pathology
Wang et al., 2018	SHR (rat)	5/5	17	7T/Spin Echo/35min	Magnevist (0.2)	NK	Extended Tofts	DCE@urLAB	8.40/31.60	5.20/30.20	NK	NK	Increased BBB permeability and Aβ accumulation in HC and CTX of SHR rats
Others													
Xu et al., 2017	Diabetes (rhesus monkey)	6/5	13 years	3T/SRGRE/10 min	MultiHance (0.1)	SSS	Extended Tofts	DCE@urLAB	3.32/7.91	3.27/8.11	3.30/7.47	NK	Increased BBB permeability in diabetic monkeys

Abbreviations: Aβ: Amyloid-beta; AD: Alzheimer's Disease; APOE4: Apolipoprotein E4; BBB: Blood-Brain Barrier; CA: Contrast Agent; CCA: Common Carotid Artery; cSVD: Cerebral Small Vessel Disease; Ct: Controls; CTX: Cortex; DTR: Diphtheria Toxin Receptor; DT-SRGRE: Dual-time SRGRE; FAD: Familial Alzheimer's Disease; FLASH: Fast Low Angle Shot; FS: Field Strength; HC: Hippocampus; Ki & K$_{trans}$: Blood-to-Brain Transfer Constant; Kw: Blood-to-Brain Water Exchange Rate; NK: Not Known; Pdgfrb: Platelet-Derived Growth Factor Receptor b; PK: Pharmacokinetic; PS: Pulse Sequence; SHR: Spontaneously Hypertensive Rat; SPGR: Spoiled Gradient; SRGRE: Saturation Recovery Gradient Echo; SSS: Superior Sagittal Sinus; TA: Time Acquisition; Tg: Transgenic Animals; TR: Targeted Replacement; THAL: Thalamus; VFA: Variable Flip Angle; VIF: Vascular Input Function; VTR: Variable Time Repetition.

#BBB K$_{trans}$ values from 15 days post Diphtheria Toxin treatment;

$BBB K$_{trans}$ values from TR-APOE4;5xFAD (Tg) vs TR-APOE3;5xFAD (Ct) mice.