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SYSTEMATIC REVIEW

Experimental models of vascular dementia and vascular cognitive impairment: a systematic review

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Abstract

Vascular cognitive impairment (VCI) encompasses vascular dementia and is the second most common cause of dementing illness after Alzheimer's disease. The main causes of VCI are: cerebral small vessel disease; multi-infarct dementia; strategic infarct (i.e. located in a functionally-critical brain area); haemorrhage/microbleed; angiopathy (including cerebral amyloid angiopathy); severe hypoperfusion (e.g. cardiac arrhythmia); and hereditary vasculopathy (e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL). In this systematic analysis, we aimed to relate cognitive and neuropathological features of experimental models to clinical VCI. We extracted data from 107 studies covering 16 models. These included: brief global ischaemic insults (in rats, mice or gerbils); chronic global hypoperfusion (rats, mice, gerbils); chronic hypertension (in primates or stroke-prone, spontaneously-hypertensive rats); multiple ischaemic lesions because of intra-vascular emboli (in rodents, rabbits or primates); strategic ischaemic lesions (in rats or minipigs); generalised vasculopathies, because of mutant Notch3, hyperhomocysteinaemia, experimental diabetes mellitus or lack of cerebral vasodilator M_5 receptors (rats or mice). Most cognitive testing showed deficits in working and reference memory. The lesions observed were microinfarcts, diffuse white matter lesions, hippocampal neuronal death, focal ischaemic lesions and micro-haemorrhages. The most-used model was bilateral carotid artery occlusion in rats, leading to chronic hypoperfusion and white matter injury.

Keywords: Binswanger's disease, CADASIL, cognition, lacunar state, small vessel disease.

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Cognition allows past experience and future goals as well as environmental conditions to influence behaviour. Cognitive abilities in humans are considered under a number of broad headings ('domains of cognition') which include: attention, executive function, memory and visuospatial processing. Attention (vigilance, alertness) to environmental stimuli is an essential pre-condition for cognitive activity, and depends on a widely distributed network including frontal cortex, thalamus and brainstem, and the reticular activating system. Self-monitoring, goal setting, and strategic planning are functions of a central executive system, which can be disrupted by lesions to the dorso-lateral prefrontal cortex. The executive system operates in tandem with visual and verbal short-term memory, which localise to different frontal regions. The formation of long-term episodic memories relies on the hippocampus and associated structures in the medial temporal region and limbic connections. Long-term memories are qualitatively different and critically dependent on the anterior temporal lobes. High level visual processing and the ability to execute skilled, goal-directed movements (praxis) may also be disrupted independently, and depend most critically on regions of post-striate cortex and the parietal lobes.

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Abbreviations used: AChAo, anterior choroidal artery occlusion; AD, Alzheimer's disease; APP, amyloid precursor protein; BCCAo, bilateral common carotid artery occlusion; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBF, cerebral blood flow; ET-1, endothelin-1; MBP, myelin basic protein; MCAo, middle cerebral artery occlusion; MWM, Morris water maze; NORT, novel object recognition test; PAT, passive avoidance task; SHRSP, stroke-prone spontaneously hypertensive rat; SVD, small vessel disease; tMCAo, transient MCAo; VCI, vascular cognitive impairment; VO, vessel occlusion.

Vascular cognitive impairment (VCI) is defined as any clinical cognitive disorder of cerebrovascular origin (O'Brien *et al.* 2003; Hachinski *et al.* 2006; Moorhouse and Rockwood 2008). This umbrella concept includes vascular dementia as well as VCI-no dementia (Moorhouse and Rockwood 2008). VCI/vascular dementia is the second most common cause of dementing illness after Alzheimer's disease (AD) with worldwide incidence of $\sim$ 1 in 20 in people aged > 65.

The pattern of cognitive impairments seen in VCI is variable, and may be difficult to distinguish from the progressive cognitive decline which characterizes the earliest stages of AD, usually with episodic memory impairment as the most salient feature (Laukka *et al.* 2004). Indeed, the two pathological lesions often coexist, though large community-based series that include autopsy data, such as the Adult Changes in Thought Study (Sonnen *et al.* 2007), the Honolulu Asia Aging Study (Launer *et al.* 2008) and the Religious Orders Study (Schneider *et al.* 2005), have shown that vascular pathology makes an important and independent contribution to late life cognitive decline. Earlier consensus statements have highlighted the need for valid models of VCI (Hachinski *et al.* 2006).

Scope of this review

The aim of this review is to make a systematic analysis of *in vivo* models of VCI. We will relate cognitive and neuropathological features of experimental models to clinical VCI. Our analysis overlaps with previous reviews of VCI (Sarti and Pantoni 2003; Hachinski *et al.* 2006), lacunar stroke (Bailey *et al.* 2009) and small vessel disease (Hainsworth and Markus 2008). Our earlier systematic review included cognitive aspects of cerebral small vessel disease (Hainsworth and Markus 2008), but was not intended to address the wide spectrum of VCI.

The neuropsychological profile of VCI is characterised by slowing of motor performance and information processing, with impairments in attention, executive function, and memory (O'Brien *et al.* 2003; Hachinski *et al.* 2006; Moorhouse and Rockwood 2008). As VCI shares multiple risk factors with AD including age, the two conditions frequently co-exist in older populations, making differential diagnosis difficult. In contrast to AD, VCI may be more sudden in onset. Executive dysfunction is a more consistent finding in VCI than AD, while the memory impairment that is universally seen in AD, is variable in VCI (Hachinski *et al.* 2006; Moorhouse and Rockwood 2008).

Neuropathological substrates of VCI are numerous (Table 1; Kalaria and Erkinjuntti 2009; O'Brien *et al.* 2003). The most common cause is now understood to be cerebral arteriolosclerosis, or small vessel disease (SVD) (O'Brien *et al.* 2003; Hachinski *et al.* 2006; Kalaria and Erkinjuntti 2009). SVD is seen radiologically as isolated lacunar infarcts and diffuse, ischaemic white matter lesions (leukoaraiosis) in periventricular and deep subcortical white matter. SVD is frequently associated with focal motor deficits and a characteristic 'subcortical' pattern of cognitive decline (i.e. markedly reduced speed of retrieval and processing of information, usually with preserved accuracy). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare, genetic form of SVD, presenting in younger people.

Table 1 Neuropathological causes of clinical VCI

Cerebral small vessel disease: subcortical vascular dementia (including Binswanger's disease, lacunar state)
Large vessel disease: multi-infarct dementia (cortical)
Strategic infarct (e.g. thalamic)
Severe hypoperfusion state
Angiopathy (e.g. CAA)
Haemorrhage/microbleed
Hereditary vasculopathy (e.g. CADASIL)

VCI, vascular cognitive impairment; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

Multi-infarct dementia results from atherosclerotic disease in large arteries (e.g. carotid) with widespread thromboembolic events, primarily in cortical locations. Strategic infarcts cause isolated neuropsychological deficits, of abrupt onset, because of ischaemic insults to cortical areas (e.g. left inferior frontal gyrus) and subcortical regions (e.g. medial dorsal thalamic nuclei) that are critical to specific cognitive abilities. Global failure of cerebral perfusion (severe hypoperfusion state) as a source of cognitive damage can result from loss of heart function, for example, arrhythmia, uncontrolled atrial fibrillation, or complications of cardiopulmonary bypass. Ischaemic damage is maximal in hippocampal neurons and in cortical arterial border zones, including deep white matter. Advances in cardiac care have made this a relatively rare type of VCI. Cerebral amyloid angiopathy (CAA) is associated with VCI and may exist as a feature of AD. CAA is increasingly recognised as a source of multiple, focal haemorrhagic events, ranging in size from microbleeds to extensive lobar haemorrhage.

Cognitive testing in animals

With the exception of CADASIL, which is a 'pure' form of VCI, the majority of human disease states are associated with additional factors with variable effects on cognition (Table 2). Animal models may therefore provide a better medium for examining the effects of vascular damage on cognition. Cognitive domains that can be sampled in animals include: attention/vigilance, information processing speed, problem solving/executive function, learning and memory, working memory. Mapping of animal cognitive domains to the four human cognitive domains is only an approximation, to be approached with caution. For further details on

Table 2 Human disease models of different mechanisms of VCI

Mechanism and disease state	Cognitive profile	Clinical confounds
Global hypoperfusion – chronic		
Low output cardiac failure Large AVM Bilateral carotid stenosis/occlusion Chronic anaemia	No detailed studies; reduced MMSE found in chronic cardiac failure	Aging; neurodegeneration; focal embolic lesions; variable neuroanatomical location
Global hypoperfusion – transient		
Cardiac arrest Carbon monoxide poisoning	Impaired long-term verbal and spatial memory; normal short-term memory	Variable duration; pre-existing chronic hypoperfusion
Focal hypoperfusion		
Small AVM	Depends on lesion size and location	Variable neuroanatomical location
Embolic occlusion		
Focal large vessel stenosis Cardiomyopathy	Few detailed studies, mostly based on MMSE or small test batteries	Depression; anatomical variability
Post-perfusion syndrome (post-cardiopulmonary bypass; multiple emboli)	Cognitive slowing; impaired attention and working memory	Anatomical variability; possibility of more than one mechanism
Hypercoagulable states	Unknown	Variable clinical expression
Hypertensive		
Primary hypertension	Visuospatial deficits; executive dysfunction	Age; hypercholesterolaemia
Secondary hypertension		Renal failure; diabetes
Vasculopathy		
CADASIL	Cognitive slowing; executive dysfunction	None
CAA	Episodic memory disturbance	Lobar haemorrhage; neurodegeneration
Diabetes mellitus types 1 and 2	Cognitive slowing; executive dysfunction	Variable clinical expression; variable neurological involvement

VCI, vascular cognitive impairment; AVM, arteriovenous malformation; MMSE, mini mental state examination; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

cognitive testing in animals, see (Moss and Jonak 2007; Young *et al.* 2009; Saksida and Bussey 2010).

The Morris water maze (MWM) and the Barnes maze (a non-aqueous alternative) are tests of learning and memory in rodents with primarily spatial/visual cues, and aversive motivation. In the majority of studies, these tasks reflect spatial learning and memory, but adaptations can be used to test different aspects of memory function (capacity, consolidation, flexibility). Water maze performance is associated with hippocampal integrity.

Radial arm maze (usually 8-arm) tasks are based on spatial cues and a food reward. They report on reference memory (where the animal learns that one arm is always baited) or working memory (where all arms are baited, and re-entry errors recorded). The working memory task assumes some element of problem solving, resembling executive function.

The novel object recognition test (NORT) assesses (primarily visual) learning. The animal discriminates a novel object from a similar, familiar object after a short delay, typically 15 min (reporting on short-term memory) or a longer interval (e.g. 24 h, long-term memory). The NORT does not require training and has no reward or punishment. The test requires specific cortical areas, and rodents with hippocampal damage can perform normally in the NORT.

Passive avoidance tests (PAT) report on (non-spatial) short-term working memory (5–30 min) or long-term memory (typically 24 h) and are based on learning to avoid an aversive stimulus. For example in a step-down PAT, a rodent on a raised platform learns not to step down onto a metal grid and thus avoid a small electrostatic shock.

Spontaneous alternation in T-maze or Y-maze apparatus is a measure of spatial working memory. Healthy animals released in arm #1 will alternate entries into arm #2 and arm #3, as part of normal exploratory behaviour. Re-entry to a just-visited arm is seen in rodents with frontal cortical lesions. In addition, a variety of rule-shifting tasks have been designed for T-maze models, involving some change in a previously-learned activity. These embody an element of problem solving, and efficiency of acquiring the new rule (speed, error rate) is recorded as a measure of executive function. These tasks are associated with frontal cortical circuits. More lengthy tests of executive function in rodents have been devised (e.g. attentional set-shifting task, Young *et al.* 2009).

More sophisticated cognitive tests have been developed for primates, usually based on neuropsychiatric tests in human subjects (Moss and Jonak 2007). The delayed non-matching to sample task reports on attention, and recognition of novel versus familiar stimuli. The delayed recognition span task is an assay of short-term memory, sensitive to hippocampal damage. The conceptual set-shifting task is designed as a non-human analogue of the Wisconsin card sorting task, to report on executive function.

Methods

Using PubMed, we searched English language publications for the following terms: (brain OR cerebr*) AND (cogniti* OR dement*) AND (Vascular OR cerebrovascular OR stroke OR arteri*) AND (vivo OR rodent OR rat OR mouse OR murine OR rabbit OR gerbil OR hamster OR porcine OR cat OR feline OR dog OR canine OR primate OR monkey OR marmoset OR baboon). Abstracts were viewed and the following exclusion criteria applied: not an animal model; not an *in vivo* model; not an appropriate disease/injury model; review article, without original data (review articles were stored in a separate table and bibliographies sorted); conference abstract or other non-peer-reviewed source. Bibliographies of included papers, and also review articles, were hand-searched and additional hits added. To validate the search strategy back issues of the journals *Stroke* and *Neurobiol. Aging* (1999–2009) were hand-searched.

Data were extracted to a datasheet, including: animal species, numbers used, type of model, general anaesthetic agent used (where appropriate) industrial affiliation of the principal authors, statement of randomised group allocation, blinding of observers, and compliance with animal welfare regulations (Kilkenny *et al.* 2010). Outcome measures were noted under the following categories: cognitive assessment; histopathological data; test of an intervention; other forms of data (e.g. magnetic resonance imaging, brain biochemistry, electrophysiology). All selected papers were reviewed independently by at least two researchers and any differences in interpretation resolved by consensus.

Results

The initial search returned 480 papers. After assessing abstracts and applying exclusion criteria we retained 77 primary sources and 22 review articles (listed in Table S1). From reference lists of primary sources and reviews we added 25 papers. On hand-searching journal back issues four additional papers were found. In a final search (August 4, 2010), one additional paper was added giving a final total of 107 papers (Tables S1–S3).

The following models were excluded as 'not appropriate injury model': trauma (including TBI); subarachnoid haemorrhage; HIV-associated dementia; intra-cerebral injection of excitotoxin (e.g. quisqualate); no brain lesion, for example, retinal injury model; embryonic or neonatal or other immature ischaemia/hypoxia model. Models based on neurodegeneration or neurotoxicity because of injections of amyloid peptides were excluded. Mutant amyloid precursor protein (APP) or other AD-like transgenic strains were excluded from the systematic analysis, but are considered independently below. Effects of middle cerebral artery occlusion (MCAo) and studies on aged animals (i.e. where the 'model' is simply old age) were also omitted from systematic treatment, but are discussed below.

Methodological characteristics of included studies

We analysed four studies using monkeys (Kemper *et al.* 1999, 2001; Moore *et al.* 2002; Sato *et al.* 2009), one using rabbits (Roos and Ericsson 1999), 74 using rats, 19 mice and nine using gerbils. For numbers of animals used, see Table S2. From 2003 onwards, almost all studies included a statement of compliance with animal welfare regulations. Randomisation to groups was stated in 25 studies, and blinding of observers in 22 (Table S2). The neuroprotective agent ketamine was used for general anaesthesia in eight studies, and the mildly neuroprotective barbiturate pentobarbital in 28. In four papers, the primary authors were employed by pharmaceutical companies, though this was not considered a significant bias (Kilkenny *et al.* 2010).

Outline of individual models

Transient global ischaemia

Brief periods of global cerebral ischaemia produce lasting cellular damage and cognitive deficits, see Tables 3 and 4. In rats, brief surgical clamping of both common carotid arteries and both vertebral arteries [4-vessel occlusion (VO), usually for 10–20 min] produced impaired learning and memory, with acute neuronal death in hippocampi, particularly CA1 cells, and apoptotic death of oligodendrocytes in cortex and thalamus 1–2 days later (Pulsinelli and Brierley 1979; Petito *et al.* 1998; Yamaguchi *et al.* 2005). Twenty minutes of 4-VO produced essentially complete CA1 neuronal loss, with maximal impairment of spatial working memory in a radial 8-arm maze task (Chung *et al.* 2002).

In gerbils, the posterior communicating artery is either absent or poorly-developed, leading to an ineffective circle of Willis. Thus, brief global ischaemia is achieved by transient bilateral common carotid occlusion (2-VO; usually 5-min duration). Again the lesion is primarily hippocampal with loss of CA1 neurones, axons and activation of astrocytes. White matter damage – swollen myelin sheaths, degradation of myelin basic protein (MBP) – was seen in striatum and internal capsule at 15 days, often without axonal damage (Mickel *et al.* 1990). Animals showed

Table 3 Cognitive impairment in experimental models

Model	Sensorimotor or other confounding features	Cognitive profile
Global hypoperfusion – chronic		
Rat BCCAo	No major motor deficit. Some optic nerve damage. No/mild hippocampal damage (initially)	Impaired working memory and reference memory (MWM, Radial maze; NORT; TMSAT) (Pappas *et al.* 1996; Ohta *et al.* 1997; Sarti *et al.* 2002; Storozheva *et al.* 2008)
Gerbil bilateral carotid stenosis	Normal locomotor activity	Impaired learning ability at 6–12 weeks (PAT) (Kudo *et al.* 1990, 1993)
Mouse bilateral carotid stenosis	Motor deficits from 3 months (rotarod, hotplate, Posholt forced swim test). Optic nerve damage	Impaired working memory but not reference memory at 30 days; both impaired at 5 months (Radial maze; Barnes maze) (Shibata *et al.* 2007; Nishio *et al.* 2010)
Mouse UCCAo	None seen (normal locomotion)	Impaired memory in NORT but not TMSAT (Yoshizaki *et al.* 2008)
Global hypoperfusion – transient		
Rat 4-VO	Reduced locomotor activity	Impaired working and reference memory (Radial maze; PAT) (Chung *et al.* 2002)
Gerbil 2-VO	No gross abnormalities; increased locomotor activity (Andersen and Sams-Dodd 1998)	Reduced working and reference memory (PAT, TMSAT, MWM) (Wiard *et al.* 1995; Andersen and Sams-Dodd 1998; Carboni *et al.* 2008)
Mouse 2-VO	No effect on motor activity (Matsuoka *et al.* 1995)	Impaired learning (PAT, TMSAT) (Yamamoto *et al.* 2009)
Focal hypoperfusion		
MCAo (rats, mice)	Contra-lateral forepaw dysfunction	Prolonged learning and memory deficits. See text
ET-1 injection	Contra-lateral sensorimotor deficit (Whitehead *et al.* 2005a; Lecrux *et al.* 2008)	Not specifically tested (see Whitehead *et al.* 2005a,b)
Embolic occlusion		
Injected emboli	Impaired paw use (staircase test)	Impaired working and reference memory (TMSAT, Barnes maze) (Rasmussen *et al.* 2006; Rapp *et al.* 2008)
Photo-activated thrombo-emboli	Forelimb dysfunction and incoordination	Impaired learning (MWM) (Alexis *et al.* 1995; Fukatsu *et al.* 2002)
Hypertensive		
Hypertensive monkeys	Some retinopathy	Impaired attention, short-term memory and executive function at 12 months (CSST, DRST) (Kemper *et al.* 2001; Moore *et al.* 2002; Moss and Jonak 2007)
SHRSP	No major neurological deficit prior to stroke event	Impaired learning and memory (TMSAT, PAT) (Yamaguchi *et al.* 1994; Togashi *et al.* 1996; Minami *et al.* 1997; Kimura *et al.* 2000; Ueno *et al.* 2002)
Vasculopathy		
Hyperhomocysteine	Normal motor function (rotarod)	Impaired spatial learning and reference memory but not working memory (MWM, DNMTP) (Bernardo *et al.* 2007; Troen *et al.* 2008)
Notch3 transgenic mice	No impairment reported	None reported
MR5−/− mice	Normal locomotor activity/ coordination	Impaired learning (NORT, TMSAT) (Araya *et al.* 2006; Kitamura *et al.* 2009)
Diabetic rats/mice	Obesity. No visual or motor dysfunction detected	Impaired learning and memory (MWM, PAT) (Kuhad and Chopra 2007; Tsukuda *et al.* 2007; Takeda *et al.* 2010)

BCCAo, bilateral carotid artery occlusion; UCCAo, unilateral common carotid occlusion; VO, vessel occlusion; MCAo, middle cerebral artery occlusion; ET-1, endothelin-1; DNMTP, delayed non-matching to position task; MWM, Morris water maze; NORT, novel object recognition test; PAT, passive avoidance task; TMSAT, T-maze spontaneous alternation test; CSST, conceptual set-shifting task; DRST, delayed recognition span task; SHRSP, stroke-prone spontaneously hypertensive rat.

Table 4 Neuropathology in experimental models

	WML (yes/no)	Focal lesions (yes/no)	Diffuse lesions (yes/no)	References
Global hypoperfusion – chronic				
Rat BCCAo	y	n	y	Wakita *et al.* (1994); Ni *et al.* (1994); etc. (Table S3).
Gerbil bilateral carotid stenosis	y	y	y	Kurumatani *et al.* (1998); Kudo *et al.* (1990, 1993); Hattori *et al.* (1992)
Mouse bilateral carotid stenosis	y	n	y	Nishio *et al.* (2010); Shibata *et al.* (2007, 2004); Miki *et al.* (2009)
UCCAo mice	y	n	y	Yoshizaki *et al.* (2008); Kitagawa *et al.* (2005)
Global hypoperfusion – transient				
Rat 4-VO	y	n	y	Petito *et al.* (1998); Chung *et al.* (2002); Pulsinelli and Brierley (1979); Yamaguchi *et al.* (2005)
Gerbil 2-VO	y	n	y	Mickel *et al.* (1990); Wiard *et al.* (1995); Shughrue and Merchenthaler (2003); Carboni *et al.* (2008)
Mouse 2-VO	y	n	y	Lai *et al.* (2007); Yamamoto *et al.* (2009); Walker and Rosenberg (2010)
Focal hypoperfusion				
MCAo (for comparison)	y	y	n	See text
ET-1 injection rat	y	y	n	Whitehead *et al.* (2005a,b); Lecrux *et al.* (2008)
Embolic occlusion				
Injected emboli	y	y	n	Roos and Ericsson (1999); Rasmussen *et al.* (2006); Rapp *et al.* (2008); Sato *et al.* (2009)
Photo-activated thrombo-emboli	y	y	n	Alexis *et al.* (1995); Dietrich *et al.* (1987); Pratt *et al.* (1998)
Hypertensive				
Hypertensive monkeys	y	y	n	Kemper *et al.* (1999, 2001)
SHRSP	y	y	n	Hainsworth and Markus (2008)
Vasculopathy				
Hyperhomocysteine	NR	n	y	Lee *et al.* (2005); Bernardo *et al.* (2007); Troen *et al.* (2008)
Notch3 transgenic mice	y	n	y	Joutel *et al.* (2010)
MR5–/– mice	y	n	y	Araya *et al.* (2006); Kitamura *et al.* (2009)
Diabetic rats/mice	NR	NR	y	Huber *et al.* (2006); Takeda *et al.* (2010)

BCCAo, bilateral carotid artery occlusion; UCCAo, unilateral common carotid occlusion; VO, vessel occlusion; MCAo, middle cerebral artery occlusion; ET-1, endothelin-1; SHRSP, stroke-prone spontaneously hypertensive rat; WML, white matter lesions; NR, not reported.

chronic impairments in working memory (Andersen and Sams-Dodd 1998; Carboni *et al.* 2008). Impaired spatial memory was seen in the Morris water maze (Wiard *et al.* 1995).

More recently, transient 2-VO (20–30 min) has been employed in mice of the C57BL6 strain, which also have a poorly developed posterior communicating artery (Lai *et al.* 2007; Yamamoto *et al.* 2009; Walker and Rosenberg 2010). Animals showed impaired learning in a passive avoidance test and Y maze, after 5 min 2-VO (Yamamoto *et al.* 2009). Five minutes occlusion reduced hippocampal long-term potentiation. More prolonged occlusion (20 min) was required to produce extensive hippocampal CA1 cell death (Lai *et al.* 2007; Yamamoto *et al.* 2009). Oligodendrocyte death and depletion of MBP were seen in corpus callosum and caudate white matter bundles from 3 to 7 days (Walker and Rosenberg 2010).

Chronic global hypoperfusion

Rat bilateral carotid artery occlusion. This was by far the most common paradigm in our systematic analysis ($n = 43$ papers, Table S2). Surgical ligation of both common carotid arteries in rats produces a chronic, global hypoperfusion state, less severe than 4-VO. Impaired learning and memory were apparent in Morris water maze tasks by ~7 days post-surgery (e.g. Pappas *et al.* 1996; Vicente *et al.* 2009; Wang *et al.* 2010a,b). Impairments in radial arm maze and Y-maze alternation occured later (from ~ 8 weeks; Sarti *et al.* 2002;

Pappas *et al.* 1996), despite substantial recovery of cerebral blood flow (CBF). Cognitive changes resulted primarily from white matter histopathology, with relative sparing of the hippocampus (in contrast with 4-VO) (Wakita *et al.* 1994, 1995; Ohta *et al.* 1997; Farkas *et al.* 2004). Some hippocampal changes appeared from ~ 4 weeks, with increased astrocyte density and cell loss in the CA1 area (Pappas *et al.* 1996; Bennett *et al.* 1998; Farkas *et al.* 2004; Vicente *et al.* 2009). White matter histopathology included demyelination, loss of MBP and microglial activation (Wakita *et al.* 1995, 2003; Ohta *et al.* 1997). Vasculopathy is seen > 12 months after occlusion (increased thickening and fibrosis of capillary walls, De Jong *et al.* 1999; Farkas *et al.* 2007).

White matter lesions and behavioural deficits were ameliorated by cholinergic therapy (Storozheva *et al.* 2008; Wang *et al.* 2010b) and by the phosphodiesterase inhibitor cilostazol (Miyamoto *et al.* 2010). A deficiency of this model is ischaemic damage to the optic nerves. This is avoided in a refinement whereby both internal carotids are ligated, or the common carotid artery ligations are staggered several days apart (Ohta *et al.* 1997; Sarti *et al.* 2002). For a detailed review of the rat bilateral carotid artery occlusion (BCCAo) model, see (Farkas *et al.* 2007).

More severe chronic hypoperfusion is attained either by ligation of both carotids and one vertebral artery (3-VO) (de la Torre *et al.* 1992; Horecky *et al.* 2009), or by ligating one common carotid and the opposite vertebral artery, then 7 days later ligating the other two arteries, that is, chronic 4-VO (Plaschke *et al.* 1999). Animals displayed impaired performance in several cognitive tests (MWM, hole-board test, PAT) but also – unsurprisingly – much-reduced locomotor activity.

Chronic bilateral carotid stenosis – gerbil. Surgical narrowing of both common carotid arteries in gerbils is achieved by use of wire coils. Memory deficit in a passive avoidance test was seen from 6 weeks post-surgery (Kudo *et al.* 1990, 1993). Histologically two types of damage were distinguished. First, focal areas of patchy neuronal loss with gliosis were observed in hippocampus, basal ganglia and cerebral cortex from 1 week (Hattori *et al.* 1992). These discreet necrotic foci (~ 1 mm diameter) were seen in both grey matter and white matter areas. Second, more diffuse white matter injury was seen from 8 weeks of hypoperfusion (Hattori *et al.* 1992; Kurumatani *et al.* 1998). This was characterised by rarefaction of tissue, and gliosis without local ischaemic changes. Abundance of MBP and axonal filaments were decreased (Kurumatani *et al.* 1998).

Chronic bilateral carotid stenosis – mouse. Similar chronic carotid stenosis has recently been characterised in mice (Shibata *et al.* 2004; Nishio *et al.* 2010). After 30 days of chronic hypoperfusion animals showed impaired performance in a working memory task (but not a reference memory task) in the radial 8-arm maze (Shibata *et al.* 2004; Nishio *et al.* 2010) and impaired performance in the Barnes maze (Nishio *et al.* 2010). In a battery of behavioural tests, these animals were essentially neurologically normal (Shibata *et al.* 2007; Nishio *et al.* 2010). Histopathological examination showed microglial and astrocyte proliferation as early as 3 days, with white matter vacuolation in the corpus callosum from around 14 days but no grey matter lesions (Shibata *et al.* 2004, 2007). Loss of myelin basic protein and some apoptotic cells were seen in white matter areas, with minimal damage to the optic tract and hippocampus. The focal necrotic lesions seen in gerbils (above) have not been reported. In chronically hypoperfused mice, some hippocampal hypometabolism was seen on positron emission tomography imaging, and hippocampal atrophy seen histologically after 8 months (Miki *et al.* 2009; Nishio *et al.* 2010). In mice with more-severe stenosis, locomotor damage was observed (Shibata *et al.* 2004; Miki *et al.* 2009; Nishio *et al.* 2010).

Mouse unilateral common carotid occlusion. Modest cerebral hypoperfusion is achieved in C57BL6 mice by surgical occlusion of the right common carotid artery (Yoshizaki *et al.* 2008). Shortly after surgery these mice showed reduced CBF (50–70%) in the ipsilateral hemisphere without change in the contralateral hemisphere, recovering to approximately 80% by 4 weeks (Kitagawa *et al.* 2005; Yoshizaki *et al.* 2008). At 4 weeks novel object recognition was substantially impaired relative to sham-operated mice, though performance in the T maze test and motor activity were normal (Yoshizaki *et al.* 2008). No hippocampal cellular damage was seen at 7 days (Kitagawa *et al.* 2005). Immunohistochemical labelling showed reduced neurofilament density, suggesting loss of axons, and elevation of microglia, in the corpus callosum but not in caudate white matter bundles (Yoshizaki *et al.* 2008).

Focal hypoperfusion models

Stereotaxic endothelin-1 injection. Targeted intra-cerebral injections of the vasoconstrictor endothelin-1 in rats produces a transient local ischaemia (1–2 h) and a focal infarct (Lecrux *et al.* 2008) (Whitehead *et al.* 2005a,b). Animals with a unilateral striatal injection showed the expected neurological deficits, with forelimb asymmetry and impaired motor performance at 14 days (Whitehead *et al.* 2005a,b). Similar strategic infarcts have been produced in internal capsule (Lecrux *et al.* 2008). We found no data on cognitive testing of endothelin-injected rodents.

Middle cerebral artery occlusion. The large literature on MCAo was not included in our systematic analysis. In mice and rats, unilateral MCAo produces a focal ischaemic lesion that includes cortical, caudate and subcortical white matter

territories, with expected contra-lateral sensorimotor deficits (Pantoni *et al.* 1996; Roof *et al.* 2001). Permanent MCAo leads to impaired learning and memory, persisting for many weeks, despite substantial recovery in sensorimotor function (e.g. Smith *et al.* 1997; Yonemori *et al.* 1999). Smaller brain lesions, with milder neurological damage, can be induced with transient MCAo (tMCAo). Errors in a radial arm maze task were seen in rats 3–15 days after tMCAo (90 min) with some recovery evident by 21 days (Sakai *et al.* 1996). Contrasting the effects of MCAo with a purely cortical ischaemic lesion, it appears likely that the cognitive sequelae of MCAo result from subcortical damage (striatum or white matter) (Roof *et al.* 2001). In mice, MCAo produces a range of cognitive changes, depending on gender, strain and duration of ischaemia. Five weeks after tMCAo (60 min) memory acquisition and retention were disrupted (Hattori *et al.* 2000; Bouet *et al.* 2007), although sensorimotor function was by then much recovered (Ferrara *et al.* 2009). Impaired learning in the MWM was seen by some researchers but not others, possibly reflecting differences in brain vasculature between mouse strains (Gibson and Murphy 2004; Bouet *et al.* 2007).

Embolic lesions

Cerebral embolic lesions were induced by intra-vascular injections of suspended cholesterol crystals, agarose or plastic microspheres, or autologous blood clot emboli, in rats (Fukatsu *et al.* 2002; Rasmussen *et al.* 2006; Rapp *et al.* 2008), rabbits (Roos and Ericsson 1999) or monkeys (Sato *et al.* 2009). Scattered small infarcts were seen (Roos and Ericsson 1999; Rapp *et al.* 2008; Sato *et al.* 2009), or a more-extensive territorial infarct (Rasmussen *et al.* 2006). Animals with microinfarcts showed modest impairment in Barnes maze learning (Rapp *et al.* 2008).

Embolic insults can also be initiated by photo-activation of intravascular Rose Bengal dye, leading to local endothelial damage and a shower of thrombo-emboli in the downstream vascular territory (Dietrich *et al.* 1987; Alexis *et al.* 1995; Pratt *et al.* 1998). As above, distinct 'lacunes' (∼ 1 mm diameter) or a well-demarcated territorial infarct were observed. Morris water maze learning was impaired acutely (2 days post-injury) but recovered by 5 weeks (Alexis *et al.* 1995). Lesions were predominantly in the cerebral cortex but also in hippocampus, striatum and subcortical white matter. These were associated with local oedema, reactive astrocytosis and macrophage infiltration, progressing to necrosis and lacune formation. (Dietrich *et al.* 1987; Alexis *et al.* 1995).

The pathogenic mechanism may be similar in rats exposed to whole-brain irradiation with X-rays or γ-rays (Hodges *et al.* 1998; Brown *et al.* 2007). This produced modest changes in cognition ∼ 8 months post-insult. Neuropathological changes were seen with depletion of blood vessels (Brown *et al.* 2007) and necrosis in the fimbria and corpus callosum (Hodges *et al.* 1998).

Hypertensive models

Hypertensive monkeys. Macaque monkeys with surgical narrowing of the thoracic aorta developed chronic hypertension (Kemper *et al.* 1999, 2001; Moore *et al.* 2002). This model is reviewed in detail in (Moss and Jonak 2007). From ∼ 12 months postoperatively the monkeys declined in cognitive function. As well as short-term memory deficit (delayed recognition span task) monkeys showed impairment in attention (delayed non-matching to sample task) and executive function (conceptual set shifting task) (Kemper *et al.* 2001; Moore *et al.* 2002). Impairment in cognitive function correlated with systolic and diastolic blood pressure (Moss and Jonak 2007). Neuropathologically, the most prominent lesions were microinfarcts (< 500 μm diameter) of irregular shape, associated with local gliosis, scattered through grey and white matter in cerebral cortex, brainstem and cerebellum, particularly in forebrain white matter (Kemper *et al.* 1999, 2001; Moore *et al.* 2002; Moss and Jonak 2007). Microinfarcts were smaller than human lacunes and not associated with small vessel disease-like changes in penetrating arteries. These lesions were also clearly different from those in chronically hypertensive rodents, for example, stroke-prone spontaneously hypertensive rat (SHRSP). Cognitive decline and incidence of microinfarcts were progressive over time.

Stroke prone spontaneously hypertensive rats. These rats develop progressive hypertension from age 8–9 weeks, reaching severe hypertension from ∼ 12 weeks, see (Hainsworth and Markus 2008). On a normal diet (without high NaCl loading) stroke events occur from age ∼ 10 months. Cognitive data for these animals were quite sparse (Amenta *et al.* 2003) and of low methodological quality (Table S2). Impaired learning and memory were seen in passive avoidance and Y-maze paradigms (Yamaguchi *et al.* 1994; Togashi *et al.* 1996; Minami *et al.* 1997; Kimura *et al.* 2000; Ueno *et al.* 2002), coincident with increased anxiety in the elevated plus maze (Ueno *et al.* 2002). The histopathology of SHRSP includes chronic vessel changes, with stroke lesions (generally haemorrhagic in nature) of widely-varying size, located in diverse brain regions, predominantly cerebral cortex and basal ganglia (Yamori *et al.* 1976; Hainsworth and Markus 2008).

Models based on vasculopathy

Hyperhomocysteinaemic rodents. Mild-moderate hyperhomocysteinaemia can be induced in rodents by elevated dietary levels of the amino acid homocysteine or its precursor methionine. Mice exposed to elevated dietary methionine for a relatively brief period (10 weeks) developed deficits in learning and memory in the Morris water maze (Troen *et al.* 2008). Spatial memory deficits were also observed in aged APP over-expressing Tg2576 mice, following elevated dietary homocysteine, but with no impairment in a delayed

non-matching to place test of episodic working memory (Bernardo *et al.* 2007). Mild hyperhomocysteinaemia is also observed in mice deficient in homocysteine-metabolising enzymes (Baumbach *et al.* 2002; Mikael *et al.* 2009). Histopathologies include reduced capillary length, reduced microglial abundance and endothelial damage within the hippocampus, but with no detectable neurodegeneration (Lee *et al.* 2005; Troen *et al.* 2008). Wall thickening in cerebral arteries with some modest increase in blood-brain permeability occurs in CBS+/− transgenic mice (Baumbach *et al.* 2002; Kamath *et al.* 2006).

CADASIL Notch3 transgenic mice. Transgenic strains with CADASIL-associated mutations in *Notch3* have shown little cerebral arteriopathy, possibly because of low brain expression of the transgene (Hainsworth and Markus 2008). Recently mice expressing rat Notch3 with CADASIL R169C point mutation have been reported (Joutel *et al.* 2010). Aged mice (18–20 months) showed extensive white matter lesions in corpus callosum, striatum, internal capsule and hippocampus. Lesions were not seen in neocortex. Granular osmiophilic deposits (a hallmark of CADASIL) were seen in vessel myocytes from age 5 months and astrogliosis from 12 months. No changes in blood brain barrier were observed (Joutel *et al.* 2010). Reduced resting CBF (10%) and autoregulatory CBF increase (40%) were seen from age 12 months. No cognitive or neuroimaging data have been reported.

M5R−/− transgenic mice. Muscarinic acetylcholine receptor M5 knockout mice exhibit constitutive vasoconstriction of the cerebral arteries (Yamada *et al.* 2001; Araya *et al.* 2006; Kitamura *et al.* 2009). Reduced CBF was seen in cortex, hippocampus, basal ganglia and thalamic areas (Araya *et al.* 2006). Relative to wild-type littermates, M5R−/− mice showed impaired performance in a Y-maze task, the novel object recognition task and in measures of social interaction (Araya *et al.* 2006; Kitamura *et al.* 2009). Histopathologically, M5R−/− mice had reduced dendritic branching in cortical neurones, and swelling of astrocytes in the cortex and hippocampus (Araya *et al.* 2006; Kitamura *et al.* 2009). Paired pulse facilitation and long-term potentiation, which are electrophysiological measures of glutamate receptor-mediated learning, were impaired (Araya *et al.* 2006). These results were seen in males and ovariectomized females, but not in intact females, suggesting a protective effect of oestrogen activity (Araya *et al.* 2006; Kitamura *et al.* 2009).

Diabetic rats and mice. Chronic experimental diabetes mellitus is observed in rodents following a single intraperitoneal injection of streptazocin (a model of Type 1 diabetes) or in transgenic mice strains such as KK-A^y or ob/ob (Type 2 diabetes) (Huber *et al.* 2006; Kuhad and Chopra 2007; Tsukuda *et al.* 2007; Takeda *et al.* 2010). Impaired spatial (Kuhad and Chopra 2007) and non-spatial (Tsukuda *et al.* 2007) memory were observed. The angiotensin receptor antagonist candesartan, at subhypotensive doses, reversed the cognitive deficit (Tsukuda *et al.* 2007).

Double transgenic mice were obtained by crossing APP23 Alzheimer mice with two diabetic strains (leptin-deficient ob/ob or polygenic Nagoya-Shibata-Yasuda, Takeda *et al.* 2010). As early as 8 weeks of age, learning deficits were seen in double transgenic mice (but not in APP23 or ob/ob single transgenics) that were independent of visual dysfunction or obesity (Takeda *et al.* 2010). In APP23/ob/ob mice, histopathological changes included depletion of hippocampal cholinergic axons and marked astrogliosis, vascular inflammation and amyloid angiopathy. Receptor for advanced glycation end products expression in cerebral vessels was evident from age 3 months with CAA from age 6 months and severe brain atrophy at age 12 months (Takeda *et al.* 2010). No amyloid plaques were seen.

CAA in experimental animal models. Cerebral amyloid disorders, including CAA, are reproduced in a range of transgenic mouse strains, some exhibiting vessel-targeted Aβ deposits with minimal parenchymal plaques (e.g. mice expressing the human 'Dutch' mutant APP, Herzig *et al.* 2006). CAA is also evident in aged dogs and primates (below). While the interaction of amyloid-based brain disease with VCI is clearly of great interest, we have not included the large literature on experimental amyloidopathies in this review. There are recent expert reviews of the vascular effects of amyloidopathy in transgenic animals (Herzig *et al.* 2006; Hamel *et al.* 2008; Kumar-Singh 2009; Wilcock and Colton 2009).

Aged animals. Aged animals (roughly defined as >half normal lifespan) can display cognitive and neuropathological changes resembling human disease. These are evident in rats and mice from age ~ 12 months (Goldman *et al.* 1992; Park *et al.* 2007; Storozheva *et al.* 2008). In aged dogs a 'canine cognitive dysfunction syndrome' is recognised, encompassing decreased attention and activity, sleep disruption, spatial disorientation and incontinence (Cummings *et al.* 1996; Borras *et al.* 1999). Relative to young controls, aged dogs (8–18 years) exhibited worse cognitive scores in object recognition, reversal learning and spatial learning tasks (Head *et al.* 1995; Cummings *et al.* 1996). These were accompanied by vascular lesions including fibrosis and CAA, parenchymal Aβ deposits, widened cerebral ventricles and sulci, and reduced CBF in both grey matter and white matter (Head *et al.* 1995; Cummings *et al.* 1996; Su *et al.* 1998; Borras *et al.* 1999; Torp *et al.* 2000; Tapp *et al.* 2005). In a neuropathological series of 20 aged dogs, the most frequent microscopic findings were vessel wall fibrosis, with focal thickening in both venous and arterial vessels (Borras *et al.* 1999). CAA was common (noted in 65% of cases) in

leptomeningeal and parenchymal arteries and capillaries. Neurofibrillary tangles were not a feature of aged canine brain.

In aged squirrel monkeys (> 13 years), a striking pattern of cortical grey matter CAA, and lesser degree of parenchymal Aβ plaques, was seen (Elfenbein *et al.* 2007). CAA was particularly evident in capillaries. Micro-haemorrhage, fibrinoid exudation and white matter lesions were rare, even in aged animals with severe CAA (Elfenbein *et al.* 2007). In cynomologus macaques, no cognitive differences were seen between 'middle-aged' (10–12 years) and 'aged' animals (15–17 years; Rhyu *et al.* 2010). Aged animals showed improved cognitive performance following a 5 months regime of daily physical exercise, accompanied by a modest increase in vascularity of the motor cortex (Rhyu *et al.* 2010).

Discussion

Comparison of different models: overview

The acute, severely ischaemic rodent models (rat 4-VO, gerbil 2-VO), while producing cognitive loss, cause major hippocampal neuronal death, and also damage to areas critical for neurological function (e.g. optical tract). These models seem quite distant from most clinical VCI. Less extreme ischaemic states, such as rat BCCAo, gerbil or mouse carotid stenosis, or mouse unilateral common carotid occlusion, produce white matter lesions that are relevant to VCI, with much less damage to hippocampi or optic pathways. These models have the advantage of an experimentally-tractable timescale, and the rat BCCAo model is well-established. Drawbacks are the need for expert surgery, and the lack of small vessel changes. Targeted ischaemic lesions to key areas (e.g. selected white matter or cortical areas) is possible with stereotaxic injections [e.g. endothelin-1 (ET-1)], embolization of a chosen territory, or surgical occlusion [e.g. MCAo, anterior choroidal artery occlusion (AChAo)]. These too lack relevant vasculopathy. Chronically-hypertensive primates and rodents (SHRSP) develop some vasculopathy (see our earlier review, Hainsworth and Markus 2008). Here a disadvantage is unpredictability of when and where lesions will occur. With primates, added complications are long experimental duration and inevitably low *n*-numbers. Rodents with experimentally-induced vasculopathy that also exhibit cognitive impairment may be a pragmatic compromise. Examples are the hyperhomocysteinaemic or diabetic rodents, or MR5-null mice listed here. These models exhibited cognitive problems within a relatively-rapid timescale (age ~ 4–6 months) were free from motor deficits, and shared the added advantage of not requiring surgical procedures.

As plotted in Fig. 1, the models retrieved in this review relate to different forms of human VCI (Table 1). Our suggestion for how different models may map onto different forms of human VCI and their neuropathological profiles is given in Fig. 1.

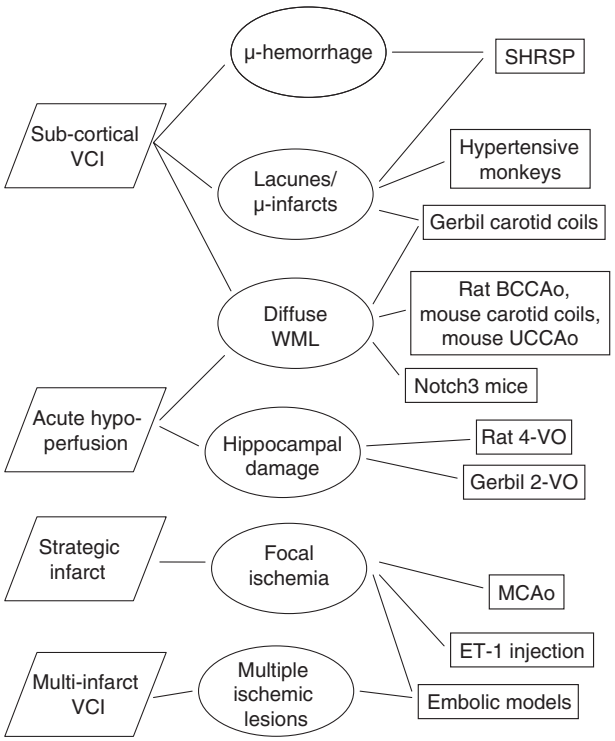

Fig. 1 How do human VCI subtypes relate to neuropathological lesions and animal models? Forms of human VCI, taken from Table 1, are shown in trapezoids. Neuropathological lesions are shown in ellipsoids. Animal models are in rectangles. CADASIL is included within subcortical VCI. Probably all trapezoids could be linked to 'hippocampal damage,' but for clarity these links are omitted.

Models of subcortical VCI

Lacunes and microinfarcts: Focal micro-infarcts are seen in chronically-hypertensive monkeys (Kemper *et al.* 2001) and in gerbils with bilateral carotid stenosis (Hattori *et al.* 1992). Lacune-like lesions can be produced by targeted ischaemia, achieved by stereotaxic injection of a vasoconstrictor (Whitehead *et al.* 2005b; Lecrux *et al.* 2008) or by surgical occlusion of a vessel (e.g. mini-pig AChA occlusion, Tanaka *et al.* 2008). Intravessel embolization in rodents, rabbits or primates can lead to widespread (i.e. not just subcortical) lacunar lesions (Roos and Ericsson 1999; Rapp *et al.* 2008; Sato *et al.* 2009).

Diffuse white matter lesions are seen in a spectrum of chronic hypoperfusion models: rat bilateral carotid occlusion, bilateral carotid narrowing in gerbil or mouse, and mouse unilateral carotid occlusion. These chronic, partial ischaemia states initially exhibit little or no hippocampal pathology, though some hippocampal changes were reported after a timescale of weeks–months.

Microhaemorrhages were not a frequent finding in the models we retrieved. All stroke lesions in SHRSP are in part haemorrhagic and some are small, resembling microhaemorrhages (Yamori *et al.* 1976; Hainsworth and Markus 2008). Vasculopathy that resembles SVD is seen in aged SHRSP (Hainsworth and Markus 2008).

Cognitive changes: The cognitive profiles of all these hypoperfusion models included lasting impairment of learning and memory (Table 3) with essentially normal neurological/sensorimotor function. In milder forms (gerbil or mouse carotid stenosis, mouse unilateral common carotid occlusion), some separation of cognitive deficits is possible (Shibata *et al.* 2007; Yoshizaki *et al.* 2008; Nishio *et al.* 2010). For example, working memory was impaired much earlier than reference memory in mice with chronic carotid stenoses (Shibata *et al.* 2007; Nishio *et al.* 2010). Chronically hypertensive monkeys showed impaired performance in an executive function task (Moss and Jonak 2007).

Some degree of cognitive loss was also observed in hyperhomocysteinaemic mice (Troen *et al.* 2008), MR5−/− mice (Araya *et al.* 2006; Kitamura *et al.* 2009) and APP^{+}ob/ob diabetic mice (Takeda *et al.* 2010). All had some degree of hippocampal damage.

Models of CADASIL

Diffuse white matter damage has recently been seen in aged mice expressing a CADASIL-linked Notch3 mutation, from age ~18 months (Joutel *et al.* 2010). Cognitive sequelae have not been reported. Nevertheless, this promises to be a valuable model of cerebrovascular disease in the absence of hypertension or amyloidopathy.

Models of hypoperfusion state

Severe, global reduction in CBF is reproduced by transient global ischaemia models (rat 4-VO, gerbil or mouse 2-VO). These produce permanent learning and memory deficits, the primary lesion being ischaemic loss of hippocampal CA1 neurones. The degree of impairment, and of motor abnormalities, are highly sensitive to duration of ischaemia.

Models of strategic infarct VCI

Targeted focal ischaemic lesions are produced in rats or mice subjected to MCAo, stereotaxic ET-1 injection, or low-dose photo-activated thrombo-emboli. Cognitive impairment profiles of varying severity are seen, depending on insult magnitude (ET-1 dose, irradiation quantal content or MCAo duration). In all cases, these were accompanied by some motor dysfunction, which adds complexity to experimental testing. In SHRSP, some spontaneous lesions are small, focal and located in strategic areas (striatum, thalamus) but the incidence of these – when, where and in which individual – is highly unpredictable (Hainsworth and Markus 2008). Given rodents' sparse white matter, it may be technically impossible to produce a truly strategic white matter lesion, that impacts on cognition while sparing motor function. Small ischaemic lesions in the internal capsule have been produced by surgical occlusion of the AChA in mini-pigs (Tanaka *et al.* 2008). These strategic lesions resemble lacunar strokes but cognitive changes have not been specifically explored, and lesions in other white matter areas (e.g. frontal subcortical white matter) have not been reported.

Models of multi-infarct VCI

Embolic insults can produce multiple, ischaemic foci (Alexis *et al.* 1995; Rapp *et al.* 2008; Sato *et al.* 2009). These scattered, focal lesions result in impaired learning and memory, with damage in corpus callosum, striatum and (sometimes but not always) hippocampus. Depending on the size of individual lesions, and the vascular territory affected (cortical, subcortical, or both) the resulting injury resembles lacunar state or multi-infarct VCI. More severe embolization leads to a fused, ischaemic lesion, resembling large artery stroke (Rasmussen *et al.* 2006).

Conclusion

Animal models represent a tool for asking how specific vascular changes relate to cognitive impairment, and how different lesion characteristics – histopathological type, volume and location – correlate with degree of cognitive dysfunction (Hachinski *et al.* 2006). They also offer a well-controlled platform for testing interventions, with greater homogeneity of pathophysiology than is available in human studies, better control over diet, medication, timing of disease onset and possible confounding variables. Given the umbrella definition of VCI, there is no one 'optimal VCI model.' We hope that this review will facilitate the selection of the most appropriate animal model for the subtype of VCI under study and the research question addressed.

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Disclosure/conflict of interest

The authors have no conflict of interest.

Supporting information

Additional Supporting information may be found in the online version of this article:

Table S1. Review articles retrieved in the original search.
Table S2. Methodological characteristics of included studies.
Table S3. What was measured?

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