Cognitive Recovery after Stroke: Memory

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Abstract

Memory impairment occurs in over a third of patients after symptomatic stroke. Memory deficits rarely occur in isolation but are an important component of the post-stroke cognitive syndrome because of the strong relationship with the risk of post-stroke dementia. In this review, we summarise available data on impairment of episodic memory, with a particular emphasis on the natural history of memory impairment after stroke and the factors influencing trajectory informed by an updated systematic review. We next discuss the pathophysiology of memory impairment and mechanisms of both decline and recovery of function. We then turn to the practical issue of measurement of memory deficits after stroke, emerging biomarkers and therapeutic approaches. Our review identifies critical gaps, particularly in studies of the natural history that properly map the long-term trajectory of memory and the associations with factors that modulate prognosis. Few studies have used advanced neuroimaging and this, in conjunction with other biomarker approaches, has the potential to provide a much richer understanding of the mechanisms at play and promising therapeutic avenues.

Keywords: memory; cognitive impairment; rehabilitation

Non-standard Abbreviations and Acronyms

ACE-III	Addenbrooke's Cognitive Examination, 3rd edition
AHA	American Heart Association
ApoE	Apolipoprotein E
ATN	Amyloid, tau, neurodegeneration
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CA (1-4)	Cornu Ammonis
DM	Diabetes mellitus
EAN	European Academy of Neurology
ESO	European Stroke Organisation
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
HVLT	Hopkins Verbal Learning Test
MMSE	Minimental State Examination
MoCA	Montreal Cognitive Assessment
PET	Positron emission tomography
SVD	Small vessel disease
VCI	Vascular Cognitive Impairment

Introduction

Cognitive impairment is prevalent in stroke. Dementia develops in 1 in 10 after a first ever event, and approximately 1 in 3 after a recurrent stroke[1,2], with memory impairment a cornerstone of the dementia syndrome. Milder cognitive deficits, including deficits of memory, are present in approximately a further 40%. These observations are reflected by the high frequency with which subjective memory deficits are reported by stroke survivors (43% in a UK Stroke Survivor Survey), with memory difficulty identified by patients and families as a major cause of unmet need[3] and difficulty with daily functioning[4].

Episodic memory describes the conscious recollection of previously encountered events. In episodic memory, information is encoded along spatial and temporal planes enabling recall or recognition over minutes to years, generating an experience of mental time travel[5]. It is distinct from other types of declarative memory such as semantic memory (knowledge of the world crystallized over many years) and working memory in which information is held and manipulated over shorter periods of time (often seconds). Working memory is considered alongside other executive functions in a separate review of this series.

Episodic memory is supported by networks in the brain that are widely distributed, including core networks that are embedded in the medial temporal lobe involved in memory encoding, storage and retrieval[6,7]. Episodic memory networks are distinct from those underpinning working memory. This distributed architecture makes episodic memory deficits after stroke likely since lesions in a broad range of locations can cause network disruption. In addition, since stroke is predominantly a disease of older people (mean age of onset ~74 years), it often occurs in the context of pre-existing Alzheimer's disease (AD) pathology in which early involvement of memory systems is common. Memory impairment in the short-term after stroke therefore depends largely on the effect of the stroke lesion, and pre-existing neurodegenerative and vascular disease, on memory systems. In the longer term, the balance between mechanisms of recovery and the accrual of further pathology will determine whether early deficits improve or deteriorate further.

In this focussed update, we review episodic memory function after stroke, with a particular emphasis on its natural history (**Figure 1**) informed by an updated systematic review of studies examining memory trajectory after stroke. We also consider the evidence for factors associated with memory impairment and recovery, and the likely underlying mechanisms. Finally, we briefly review emerging areas including advanced imaging, genetics and precision medicine treatments and trials in memory rehabilitation.

Memory impairment after stroke and associated factors

Prevalence and natural history

The majority of cognitively impaired patients post-stroke have deficits in multiple cognitive domains. Impairment in memory affects around a 25-30% of patients acutely with lower prevalence (9-15%) when measured in the chronic phase (> 6 months)[8]. Regarding cognitive trajectory, longitudinal studies show that incident stroke accelerates global cognitive decline[9] but there is considerable variation in the pattern of change over time. Overall, the early post-stroke period (up to 1-year) appears to be characterized by cognitive recovery[10,11], although early transient impairments and delirium remain risk markers for later dementia[12].

Data on the natural history of deficits within specific cognitive domains, evaluated longitudinally, are sparse making it challenging to obtain a clear overview. As for other domains, episodic memory deficits in the early post-stroke period predict memory function later, consistent with a pattern of incomplete recovery[8,13]. A systematic review (in 2016) of six studies specifically on memory trajectory after stroke found conflicting results with decline (n=2), stability (n=3), and improvement (n=1) reported[10]. We therefore performed an updated review of the natural history and associated risk factors to include studies published since 2016 (**Supplemental Methods**[14-27]). This identified 8 studies published since the previous review (n=262 total, mean age 51-69 years) with verbal episodic memory assessments and a wide range of follow-up times (3 months to 8.2 years, **Table 1**). Apolipoprotein E (ApoE) genotype is the major genetic risk factor for Alzheimer's disease, and homozygosity for ApoE-ε4 is associated with dementia after stroke[28]. Consequently, some studies included subgroup analyses according to ApoE status. Studies reported improvement in verbal episodic memory (n=2, n=1 subgroup analysis of ApoE ε4 carriers)[19-21], no change (n=2, n=1 subgroup analysis of ApoE ε4 non-carriers) [14,21,22] and decline in both stroke patients and controls with no difference in rate of decline (n=1)[16]. Others reported improvement in non-verbal memory[21] (n=3, n=1 subgroup analysis in ApoE ε4 non-carriers). Although these findings were conflicting, a meta-analysis of pooled individual patient data from nine studies (STROKOG consortium) indicated a "turning point" at one year after stroke with significant improvement in memory function from baseline until one year followed by rapid decline[11]. Variations in follow-up time may therefore contribute to mixed results across studies, including a shift from more restricted post-stroke to more general vascular dementia mechanisms with increasing time.

Factors associated with memory impairment after stroke

Available data suggest that the risk factors for post-stroke memory impairment show substantial overlap with those for post-stroke dementia. This can be conceptualized as a

balance between cerebral vulnerability and reserve, with accrual of small vessel disease (SVD) and neurodegeneration relatively more important than the effects of an incident stroke in the longer term[29]. Increasing age is associated with memory impairment after stroke,[19,30] and with post-stroke dementia[1]. Female sex has been found to be a risk factor,[1,31] but the effect attenuates after adjustment for age.[17] Education is protective with lower prevalence of memory deficits early[32] and in the long-term (>5-years) after stroke[22] consistent with the concept of "cognitive reserve".[33,34] Greater social support is also protective[35]. Post-stroke memory function appears similar across ethno-racial groups[30] although the risk of post-stroke dementia is higher in blacks and ethno-racial differences may influence relationships between vascular risk factors and post-stroke memory.[36] Regarding vascular factors, diabetes mellitus (DM), previous stroke, stroke severity and congestive heart failure predict memory impairment early after stroke, as seen in post-stroke dementia.[11,17] ApoE ε4 carriers show more impaired verbal memory than non-carriers early after stroke,[21,27,37] along with reduced entorhinal cortex volumes.[21] Pre-stroke cognitive function, inferred from the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-see later) is associated with long-term memory impairment[32].

Factors associated with longitudinal memory trajectory

There are few data on the factors associated with specific trajectory patterns (recovery, stability, decline) of memory function after stroke. Among the 14 studies included in the original and updated systematic reviews, 7 examined risk factors in relation to memory trajectory.[16,17,21,22,24,26,27] Some studies reported older age to be associated with faster decline in memory post-stroke with short-term improvement more likely in younger people.[16,17] However, in the REGARDS study, older age was associated with more rapid decline in executive function but not memory[16]. The effect of sex differences is uncertain, with faster pre-stroke decline reported in women in a population-based study[30] and faster post-stroke long-term memory decline in men[26]. Vascular risk factors including atrial fibrillation, DM, hyperlipidemia, hypertension, smoking status, and previous stroke were examined in few studies,[15-17] none of which found associations with memory trajectory. One study examined the effect of baseline stroke severity but found no association[17]. Premorbid cognitive impairment (IQCODE) was associated with longitudinal decline in memory over a 6-year follow up period, with more severe premorbid cognitive impairment predicting greater declines in visual episodic memory[22].

Little data has combined brain imaging markers with longitudinal evaluation of episodic memory: a single included study examined temporal lobe atrophy, finding an association with memory decline in ApoE-ε4 carriers[21]. No studies examined imaging markers of SVD

(although SVD is associated with recovery of executive function[38,39]) or lesion factors such as lesion location and the extent of damage to specific anatomical systems. Studies of ApoE genotype and long-term trajectory show mixed results. One study found improvement between 3-months and 1-year post stroke in both carriers and non-carriers: ε4 carriers demonstrated improvement in verbal episodic memory, whereas non-carriers showed improvement in non-verbal memory[21]. Other studies reported no difference between groups[17,24] or even greater decline in non-carriers[26].

Pathophysiology

Memory impairment after stroke reflects the summation of a variety of mechanisms which influence the risk of immediate post-stroke impairment but also its trajectory over time. In the context of a robust brain (as is usually the case in young stroke), the impact of the stroke lesion will often be the primary determinant of impairment. In those with frail brains, co-existent Alzheimer-type pathology or SVD may limit recovery or make long-term decline likely.

Direct injury to memory systems

The network of regions that supports episodic memory is relatively well established from animal experiments and lesional studies in humans (**Figure 2**).[7,40] Direct injury to the hippocampal formation can occur in posterior cerebral artery territory stroke. Median thalamic infarction is a widely recognized cause of episodic memory impairment, primarily through damage to the mammillothalamic tract.[41] Stroke affecting other structures including the internal capsule and deep white matter and basal forebrain, predominantly of the left hemisphere, may also cause memory impairment[42,43].

The hippocampus and medial thalamus are examples of regions where the extended hippocampal network funnels through a structure that is easily recognizable by imaging. However, case series of infarcts in these and other “strategic infarct” locations may under-estimate the frequency of direct injury to episodic memory networks. In a cohort of patients with first ever ischaemic stroke collected in the STRATEGIC study, memory impairment was found in 4/5 patients with left posterior cerebral artery territory infarcts that explicitly spared the hippocampal formation. The common anatomical factor in amnestic patients was interruption of the parahippocampal cingulum (**Figure 3**), a white matter pathway shown by diffusion MRI studies to be associated with memory in healthy adult volunteers.[44]

Secondary injury and degeneration

The concept of secondary injury encompasses mechanisms whereby injury extends beyond the initial ischaemic core (area of necrosis) through pathological events spreading to adjacent tissue or triggering change in remote locations. Candidate mechanisms include programmed cell death (apoptosis), injury from inflammation[45] and secondary injury from aberrant electrical activity and excitotoxicity. Atrophy remote from the site of injury is a putative marker. The CANVAS (Cognition And Neocortical Volume After Stroke) Study has shown that whole brain atrophy proceeds at a faster rate in survivors of first ever stroke than in stroke-free participants of similar age[46]. The rate of hippocampal atrophy specifically was not significantly greater than in controls. However, others have found greater volume loss in the ipsilateral hippocampus after stroke,[47] suggesting that secondary injury occurs. Microstructural alterations in the ipsilateral hippocampus also occur after young onset stroke[48], when concomitant degenerative changes are less likely to be a factor. Hippocampal subfield volumes correlate with verbal memory performance after stroke[49] and pathology studies reveal neuronal volume loss, which correlates with memory scores during life, consistent with secondary injury.[50]

Given its role in cross-network integration, secondary changes in the thalamus could propagate across multiple networks and cognitive domains. In animal models of stroke, remote thalamic changes include activation of microglia, suggesting that inflammation may contribute to secondary injury.[51] Inflammation may also be promoted by systemic illness after stroke. Enhanced blood brain barrier permeability facilitates the entry of systemic factors to the brain, which may have an impact on inflammation within the brain. This may explain why post-stroke complications including “hypoxic-ischemic episodes” are associated with an increased risk of post-stroke dementia and why infection is a risk factor for dementia in community cohorts.[1,52] However, we did not identify any studies in our systematic review that examined memory function after stroke in relation to these non-brain factors.

Mechanisms of Plasticity and Recovery

Several studies (as reviewed above) show cognitive recovery in a substantial proportion of patients, at least in the first 12-18 months after stroke.[19-21,27,53] Mechanisms of recovery of function are, however, relatively understudied. A recent longitudinal study showed that fornix microstructural integrity of the fornix and greater grey matter volume within the cholinergic basal forebrain nuclei, but not cortical grey matter volumes, were associated with improvement in memory performance over time (**Figure 4**)[54]. Interestingly, the pattern of associations was similar for episodic, short-term and working memory, suggesting a common infrastructure that supports adaptation to injury across cognitive domains. A role for

the cholinergic system in neural adaptation is also supported by studies in early Alzheimer's disease.[55]

Recruitment of homologous contralateral or "multiple demand" cortical regions has been investigated in relation to motor and language recovery,[56] but there is less evidence for recruitment of undamaged cortex to support episodic memory. One weakness of the study implicating cholinergic systems was the absence of serial imaging, necessary to identify alterations in grey matter morphology consistent with neural plasticity. Future studies should look for evidence of changes in cortical structure and function associated with recovery, possibly linking these to neurotransmitter and subcortical systems that could facilitate plasticity following stroke.

Concomitant Brain Pathologies

The likelihood of pre-existing brain pathology increases with age of stroke onset. Alzheimer's pathology, is of particular importance in memory decline, and individuals with co-existent Alzheimer's pathology will be at increased risk of post-stroke memory impairment and decline over the longer term. Similarly, individuals with progressive SVD would be expected to show ongoing cognitive decline after stroke. Neurodegeneration and SVD may also enhance direct injury resulting from the stroke lesion as suggested by studies showing dementia to be a risk factor not only for stroke but also for more severe stroke[2]. DM is also associated with more severe stroke possibly through associations with SVD although neuropathological studies show no excess risk of Alzheimer's pathology[57]. Concomitant pathology potentially influences secondary injury and mechanisms of plasticity after stroke. For example, cognitive decline appears accelerated early after stroke in ApoE-ε4 carriers[28] and global cognitive recovery is reduced where there is a high SVD burden[38,39] or DM.[39]

Measurement of Memory Function after Stroke

The choice of test often depends on factors including case-mix and setting, resources and the aim of testing. There is a trade-off between obtaining more detailed data and recruitment and retention of participants, particularly older or more impaired individuals. In clinical practice and large pragmatic studies, brief screening tests may be used. The Mini-Mental State Examination (MMSE)[58] is insensitive to milder deficits and although focused on domains commonly affected in Alzheimer's Disease, the 3-word recall task has a substantial ceiling effect. The Montreal Cognitive Assessment (MoCA)[58] detects milder deficits but the more difficult 5-word recall task has a floor effect, which can be partly mitigated by separately recording immediate and cued recall responses. The Addenbrooke's Cognitive Examination-III (ACE-III) memory tasks[58] may be less subject to floor and ceiling effects but the test is longer and not widely used outside the UK and Australasia.

Heterogeneity in choice of memory tests is recognised as a barrier to pooling and comparing data from individual studies. The Vascular Cognitive Impairment Harmonisation Standards included a 60-minute protocol for more detailed assessment with neuropsychological tests recommended based on psychometrics, global reach, feasibility, validity, absence of floor/ceiling effects and availability of norms[59]. For verbal episodic memory, the Hopkins Verbal Learning Test (HVLT) or California Verbal Learning Tests were proposed. The HLVT has been validated for use post-stroke in the UK[58] and Korea[60]. Only one of the 14 studies included in the updated systematic review used the HVLT, with 12 different tests employed in the 11 studies published from 2010, suggesting that heterogeneity remains a problem. Alternative list-learning tests were used in 4 other studies, including the Rey Auditory Verbal Learning Test and the Seoul Verbal Learning Test. The HVLT and California Verbal Learning Test were preferred over these tests in the VCI Harmonization Standards because of the presence of multiple parallel versions for repeated testing, and assessment of interference and cueing effects, respectively[59]. Recent guidelines from the American Heart Association (AHA) and European Stroke Organisation/European Academy of Neurology (ESO/EAN) do not suggest specific memory tests but note that any cognitive assessment must consider cultural and educational factors, patient anxiety and specific stroke impairments. Testing of memory in the presence of aphasia is problematic although some recently developed stroke specific cognitive screens (e.g. Oxford Cognitive Screen) have been designed that minimize the verbal loading of tasks.[61]

For repeated testing necessary to establish longitudinal cognitive trajectory, sensitivity to change over time and practice effects should be considered, together with the effects of selection and attrition biases that favour under-estimation of deterioration over time. Practice effects have been quantified for short screening tests including the MMSE and MoCA and are relatively small such that these tests appear able to detect meaningful change over time after stroke. Data on practice effects or sensitivity to change specifically in the memory subtest scores are sparse.

Biomarkers and Emerging Areas

Imaging

Accurate prognostication and development of new therapies for post-stroke memory impairment are critical areas for future development. Emerging lesion mapping approaches offer the possibility of mapping injury from stroke in a way that reflects the underlying neuroanatomy, especially in terms of connectional anatomy which was not available from traditional T1 and T2-weighted magnetic resonance imaging (MRI). Establishing large reference datasets also provides the opportunity to predict prognosis based on analysis of

large numbers of similar lesions[62]. However, to provide insights into the mechanisms of memory impairment or recovery these approaches need to adopt more precise cognitive measures that match the anatomical resolution of the imaging methods as measures of verbal or visual memory – or recollection versus familiarity – show strong double dissociations in their anatomical substrates. A persisting limitation to date has been the use of general or composite cognitive scores that depend on multiple cognitive processes, and in turn are likely to relate to a wide range of anatomical networks and regions.

Non-invasive evaluation of inflammatory processes remains a challenge for human neuroimaging, but new methods are emerging. Analysis approaches to diffusion MRI data are increasingly identifying measures that evaluate aspects of microstructure tightly linked to inflammation[63]. Positron emission tomography (PET) imaging with ligands to the translocator protein has already provided some insight on the possible role of microglial activation and newer ligands are emerging. PET can also provide insight into accumulation of abnormal proteins in neurodegeneration.

Blood and cerebrospinal fluid biomarkers

Studies of fluid biomarkers in dementia have been expanding rapidly. The National Institute on Aging and Alzheimer's Association Alzheimer's Disease and Related Dementias (ADRD) have proposed a research framework that focuses on the diagnosis of Alzheimer's disease with biomarkers *in vivo*.[64] Biomarkers are grouped using the so-called ATN classification (A: β-amyloid deposition; T-pathologic tau; N-neurodegeneration). Although none have yet entered routine clinical use, ATN biomarkers are being evaluated in real-world settings including memory clinics. Importantly, A and T blood biomarkers are now available, greatly increasing the feasibility of studies in acute stroke. It could be hypothesized that the presence of ATN markers suggestive of Alzheimer-type pathology might predict increased risk of dementia after stroke, memory deficits and future decline and less potential for recovery. A wide range of other blood biomarkers including inflammatory mediators and growth factors also remain to be investigated[65]. As for all biomarkers, to be clinically useful, they must have predictive value over and above standard clinical variables including cognitive assessment.

Genetics

As noted above, ApoE genotype is associated with impaired verbal episodic memory[21,27,37] after stroke but further studies are needed on how it influences post-stroke memory trajectory. Other risk genes, notably those coding for cholesterol transport and microglial and immune function, can be captured in polygenic risk scoring systems now available commercially which improve on risk prediction using ApoE genotype alone[66]. These

polygenic scoring systems have not been tested in the post-stroke setting but could identify those with increased likelihood of co-existent Alzheimer's disease and therefore of memory impairment and cognitive decline. Other candidate genes include brain derived neurotrophic factor[67] which has been implicated in Alzheimer's disease and cognitive function in older populations.

Current Practice and Emerging Treatments

Although cognitive assessment is recommended after stroke in order to identify deficits and individualise care, the management of cognitive impairment varies across countries and regions. Impairments occur across all cognitive domains so screening should cover a broad range of domains to avoid missing key deficits important in rehabilitation and discharge planning. There is consensus, as stated in both AHA and ESO/EAN guidelines, that multidisciplinary assessment and management is required and that allied health professionals play a key role. The recent ESO/EAN guidelines did not identify any randomized trials of cognitive rehabilitation or training with a sample size of at least 50 participants and a follow-up to at least 6 months. Some smaller studies with short-term follow-up have shown short-term improvement in cognition with training or rehabilitation interventions including specifically in memory.[68,69] Multicomponent interventions may be beneficial but evidence for long-term benefit is lacking[70]. Emerging evidence suggest a possible role for virtual reality therapies but evidence of benefit from serious games accessed via computers and mobile devices is conflicting. There is therefore a need for methodologically robust trials to assess the benefit of cognitive rehabilitation for cognition in general and on specific cognitive domains. Such trials need to incorporate appropriate control groups especially given the natural history of recovery in many patients, have sufficiently long-term follow-up to assess retention of any benefit and transfer to cognitive tasks not specifically targeted in the training. Outcome measures must be designed in collaboration with patients and carers such that they are meaningful. Some previous trials have reported small improvements in cognition after intervention, but clinical relevance is uncertain. Finally, the timing of treatment must be considered. In physical rehabilitation, very early intervention may be harmful and there may be an optimal window in which interventions are likely to be effective.

Neurostimulation and Precision Approaches

Neurostimulation approaches have been trialled in memory impairment related to early dementia but have not been used to date after stroke. Consistent with the idea of recruitment of domain-general cortex, stimulation of the anterior cingulate region with transcranial magnetic stimulation enhances language learning in volunteers. Evidence of the involvement

of the cholinergic system in memory recovery raises the possibility that this system is a potential target for treatment, possibly as an adjunct to cognitive rehabilitation.[54]

Inflammation

Evidence of importance of secondary injury raises the question of whether these mechanisms represent a potential target for treatment to ameliorate decline and improve prognosis for memory. Experiments in rodent models suggest that minocycline reduces secondary injury and ameliorates functional deficits, including behavioural measures. Translation of these results to a human trial has not, to our knowledge, been attempted. The MINERVA trial will test this hypothesis in a group of patients with severe SVD but not in a wider post-stroke cohort[71]. A remaining question – which intervention studies will help to address – is whether inflammation is a causal factor in memory decline or alternatively may be a bystander phenomenon or even enhance recovery.

Gaps and Recommendations

This review has identified areas in which further studies are required (**Table 2**). Detailed data on the natural history of memory function after stroke remains sparse and in general based on unrepresentative cohorts. This gap – along with the absence of cognitive measures, including assessment of memory in many stroke intervention studies – has been recognised as a major barrier to design of trials targeting cognitive recovery and rehabilitation[72]. There is little information on how vascular risk factors and brain imaging specifically impact memory domain impairment and recovery or on the role of systemic factors known to be risk factors for dementia and global cognitive decline. State-of-the-art neuroimaging and the advent of fluid biomarkers invite studies exploring mechanisms which may aid in the development of new treatments.

Conclusions

Both mild and more severe memory impairment is common after stroke. However, understanding of the trajectory of memory impairment overt time after stroke is limited. The early post-stroke phase appears to be characterised in general by recovery, but early impairment indicates cognitive fragility and increased risk of later dementia. The mechanisms of impairment and recovery are incompletely understood but involve pre-existing or later accrual of neurodegeneration and SVD, and the direct and secondary effects of the stroke lesion, likely combined with systemic effects. The advent of novel neuroimaging and fluid biomarkers bring the opportunity for better understanding to which should be added the assembly of carefully phenotyped and representative cohort studies.

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Supplemental Material

Supplemental Methods

Figure S1

Table S1

Table 1. Studies included in updated systematic review and studies with memory tests in Tang et al. 2018.

Study	Design	Age, mean/SD	Female, %	N	Risk Factors Tested Against Cognitive Functions	Memory Measures	Follow-ups, n	Intervals	Trajectory
Recent meta-analysis:									
Lo et al. 2022[11]	STROKOG Consortium	66.3/11.1	38	1488	-	Various, harmonized by study authors	1-10	median 1-5.14 years	< 1 year ↕ > 1 year ↕
Studies included in updated systematic review (2016-current):									
Erdal et al. 2021[14]	Stroke cohort	52.2/7	26	23	-	Adapted RAVLT WMS-R-VM	1	within 6.4 months	↔
Levine et al. 2018[16]	Community cohort (REGARDS)	67.9/8.3	50	694	Age, education, race, sex, region, hypertension, DM, hyperlipidemia, exercise, smoking	WLR	10	6 monthly, mean 8.2 years	↕
Lim et al. 2017[17]	Stroke cohort (Bundang VCI)	69.1/9.7	41	375	AF, age, ApoE4, DM, sex, education, hypertension, stroke history, stroke severity, premorbid dysfunction, MTLA, WML	SVLT	7	within 91.8 months	↕
Olabarrieta-Landa et al. 2021[18]	Community cohort	51.6/12.2	48	50	-	ROCF VMC	3	at 3, 6, 12 months	↕
Sagnier et al. 2017[19]	Stroke cohort (BBS)	64/13	29	212	Age, sex	MoCA	2	at 3, 12 months	↕
Taskiran-Sag et al. 2020[20]	Stroke cohort	54.1/3.1	14	14	-	ECRT	1	within 116-135 days	↕
Werden et al. 2019[21]	Stroke cohort (CANVAS)	66.9	25	40	ApoE4, MTLA	HVLT-R ROCF	2	at 3, 12 months	↕
Zhao et al. 2021[22]	Stroke cohort	60.9/9.6	29	244	Age, baseline MoCA, DM, education, hyperlipidemia, hypertension, premorbid dysfunction, previous vascular events, race, sex, smoke, stroke severity	SRT WLR WMS-R-PR WMS-R-VR	5	at 3-6 months, 1, 3-4, 5, 6 years	↔

Studies with memory tests included in Tang et al. 2018:									
Comijs et al. 2009[23]	Community cohort (LASA)	72.1	48.5	50	-	RAVLT	3	within 6 years	
Dik et al. 2000[24]	Community cohort (LASA)	74.6/6.7	30.2	53	ApoE4	RAVLT	1	at 3 years	
Kohler et al. 2012[25]	Community cohort (AgeCoDe)	79.7/3.6	65.5	3214	-	CERAD-DR	3	every 18 months	
Levine et al. 2013[15]	Community cohort (SALSA)	72/8	56.3	151	Hypertension, sex	WLR	> 3	annually	
Reitz et al. 2006[26]	Community cohort	76.2/6	69.6	97	ApoE4, sex	BSRT	3	every 18 months	
Wagle et al. 2010[27]	Stroke cohort	75.9/10.9	46.2	104	AF, age, angina, ApoE4, DM, education, hyperlipidemia, hypertension, premorbid dysfunction, previous vascular events, sex, smoking, stroke severity	RBANS-DM	1	at 12-15 months	

AF, atrial fibrillation; AgeCoDe, Ageing, Cognition and Dementia in Primary Care Patients; BBS, Bulgarian Poststroke Study; BRT, Benton Recognition Test; BSRT, Buschke Selective Reminding Test; Bundang VCI, Bundang Vascular Cognitive Impairment; CANVAS, Cognition and Neocortical Volume After Stroke; CASPER, Cognition and Affect After Stroke: Prospective Evaluation of Risks Bulgarian; CERAD-DR, Consortium to Establish a Register for Alzheimer's Disease Delayed Recall; COAST, Cognitive Outcome After Stroke; DM, diabetes mellitus; ECRT, Enhanced Cued Recall Test; EpiUSA, Epidemiologic Study of the Risk of Dementia After Stroke; HVLT-R, Hopkins Verbal Learning Test-Revised; LASA, Longitudinal Aging Study Amsterdam; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RAVLT, Rey Auditory Verbal Learning Test; RBANS-DM, Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory; RBANS-DM, Repeatable Battery of Neuropsychological Status Delayed Memory; REGARDS, Reasons for Geographic and Racial Differences in Stroke; ROCF, Rey-Osterrieth Complex Figure Test; SALSA, Sacramento Area Latino Study on Aging; SIS, Six-Item Screener; SRT, Story Recall Test; SSS, Sydney Stroke Study, WML, white matter lesion.

Table 2. Gaps and Recommendations for Future Studies

Subject	Gaps and research questions
Natural history of memory impairment	What is the post-stroke trajectory of memory impairment in representative samples with careful attention to selection and attrition bias? What are the reasons for heterogeneity in existing studies?
Delayed onset memory impairment	What is the trajectory of memory function in the longer-term in those without early impairment?
Clinical Factors	How do clinical factors influence memory trajectory and do associations differ over time after stroke? Do vascular risk factors, and pre-stroke cognitive function predict memory changes differently from change in other cognitive domains? What is the role of systemic factors (e.g., infection, hypotension, hypoxia) frailty and multi-morbidity?
Brain imaging	How do imaging markers such as SVD, temporal lobe atrophy, cortical microinfarcts modulate the relationship between stroke and memory impairment and recovery? Can novel structural imaging techniques give insight into mechanisms? Can MRI be used to define potential for recovery and map plasticity over time? Can PET studies tease apart the contributions of inflammation and neurodegeneration in those with memory impairment?
Genetic factors	Do polygenic risk scores for Alzheimer's disease predict memory decline after stroke over and above ApoE genotype? Are there other important genetic factors?
Fluid biomarkers	Can fluid biomarkers (ATN framework) predict memory decline after stroke? Do these biomarkers act differently over time? Are other classes of biomarker useful (e.g. inflammatory mediators or growth factors)?
Treatments	What is the role of cognitive rehabilitation/cognitive training? Can specific memory interventions produce long-term and meaningful benefit to patients? If so, does the benefit only occur in certain groups (e.g., without underlying neurodegeneration)

Figure Legends

Figure 1. Memory Trajectory after Stroke

Pre-stroke factors, lesion characteristics and pathological events after acute injury all influence memory trajectory after stroke. Trajectory varies between individuals (person A and person B). The potential to modify trajectory with rehabilitation approaches, and the impact of some factors such as post-stroke inflammation, remains unknown. (SVD=small vessel disease).

Figure 2. Regions that support human episodic memory.

The extended hippocampal system supports recollection. The fornix is a bidirectional white matter pathway that links the hippocampus with the mammillary bodies, basal forebrain, thalamus and frontal lobe. ATN, anterior thalamic nucleus. *Reproduced from Aggleton et al. Brain 2016: 139; 1877-1890.*[40]

Figure 3. Disconnection of left-sided parahippocampal connections and verbal recall impairment after stroke.

Top: score for each of the five left posterior cerebral artery patients on tests of verbal recall and visual recognition. Bottom: sagittal sections of a standard MNI brain template (co-ordinates x = -20 and x= -24 mm). Each infarct is shown in red; the left parahippocampal cingulum (PHC), defined by the Johns Hopkins University atlas is shown in green; the overlap in yellow. Verbal recall scores were lowest in the individual with most marked overlap of the PHC (far left). FCSRT = Free and Cued Selective Reminding Test. (Participant 3 was unable to perform FCSRT verbal recall).

Figure 4. Regions involved in recovery of memory after stroke

White matter microstructure of the fornix (blue) and grey matter volume in the cholinergic nuclei of the basal forebrain (red to yellow) were positively associated with change in memory performance from 3 to 12 months after stroke. These regions were not affected by stroke lesions (a representative infarct outline is shown in blue). The Nucleus Basalis of Meynert sends projections to the neocortex (shown schematically in green). The results suggest that these projections are involved in facilitating recovery.

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