Amnesic disorders

Hans J Markowitsch, Angelica Staniloiu

Memory disturbances frequently occur after brain damage, but can be associated with psychiatric illnesses as well. Amnesia—the most severe form of memory impairment—has several variants, including anterograde and retrograde amnesia, material-specific and modality-specific amnesia, and transient global amnesia. We searched databases to obtain an overview of amnesia research from the past 5 years. Research into amnesia has increased exponentially, probably because of the availability of modern brain-imaging techniques. In line with the view that memory is not a unity but is organised into several systems, amnesia is described as a multifaceted disease with a frequently poor prognosis.

Lancet 2012; 380: 1429–40

Published Online
April 13, 2012
htttp://dx.doi.org/10.1016/S0140-6736(11)61304-4

Physiological Psychology, University of Bielefeld, Bielefeld, Germany (Prof H J Markowitsch PhD, A Staniloiu MD)**; Alfried Krupp Institute for Advanced Study, Greifswald, Germany** (H J Markowitsch)**; Centre for Addiction and Mental Health, Toronto, ON, Canada** (A Staniloiu)**; and University of Toronto, ON, Canada** (A Staniloiu)

Correspondence to:
Prof Hans J Markowitsch, Physiological Psychology, University of Bielefeld, Postfach 10 01 31, 33501 Bielefeld, Germany
hjmarkowitsch@uni-bielefeld.de

Introduction

The term amnesia is mainly used in two ways. First, it is generally used to describe any severe memory impairment or deficit, irrespective of the cause. Second, it is used in line with the traditional view that amnesia is a memory impairment that occurs in the absence of other substantial cognitive impairments, and is restricted to specific disorders. These disorders—referred to as either amnesic or amnestic disorders according to different international classifications—have as a core feature a memory impairment that is not due to dementia or delirium and represents a decline from a previously attained functional level. This decline in function differentiates them from infantile amnesia or neurodevelopmental disorders.

In this Review, we outline the classification of memory systems and summarise relevant aspects of what causes amnesic disorders, their neurobiology, epidemiology, diagnosis, and management. We discuss neuroimaging and genetic studies and emphasise the need for methodological rigour with respect to memory-testing paradigms.

Memory systems and memory processes

Although the term amnesia was used rather loosely until the 1980s[1]—often to describe total memory loss—we now know that memory impairment in amnesic disorders is likely to be restricted to specific kinds of memory. This view is supported by the existence of several distinct memory systems, each with different neuroanatomical substrates. In addition to the division into short-term and long-term memory, the work of Tulving,[2–4] especially, led to a content-based classification of long-term memory into five systems (figure), which are hierarchically organised according to their assumed ontogenetic and phylogenetic development (appendix).

A distinction is made between episodic-autobiographical memory (EAM—eg, remembering your dinner from the previous night) and semantic autobiographical memory (eg, memory or knowledge of your date of birth). Semantic autobiographical memory might be impaired in dissociative amnesia, but is usually preserved in other amnesic disorders; to know a fact is assumed to need less contextual and associational information than to remember a personal event.

The inability to store new information long-term is named anterograde amnesia and the inability to recall stored information is termed retrograde amnesia. Retrograde memory impairment usually follows Ribot's law of regression[5]—ie, recent memories are more affected than earlier ones. Isolated retrograde amnesia is reported to occur after neurological or psychological incidents. Some investigators argue that even with clear evidence of pathological changes within the brain, psychological factors substantially contribute to persistence of retrograde EAM impairment.[6]

EAM serves both retrospective and prospective functions. The ability to remember to do a future action in response to a prespecified cue (prospective memory) might be impaired in amnesic disorders as a result of disruptions to EAM, semantic memory, or executive functions.[7]

Memory processing is implicit (subconscious) or explicit (conscious). Implicit processing is typically coupled with procedural and priming memory systems and explicit memory is generally associated with perceptual and semantic memory and EAM. EAM is state-dependent; optimum retrieval of memories occurs when the environmental and mood conditions match those that were present when the memory was encoded. Panel 1 shows various kinds of amnesia (see appendix for the psychological processes associated with memory).

Neuroanatomy and neurobiology of memory

The debate about whether the brain contains functionally specialised regions or acts Gestalt-like[1] (as a whole) took on a new dimension with the advent of functional

Search strategy and selection criteria

This Review is based on material identified through searches of PubMed, Medline, and Scopus for original research or review articles from 2005 to early 2011 written in English, German, and French, with a combination of the words "amnesia", "memory", "memory impairments", "memory disturbances", "genetics", and "treatment". We based selection of material on its quality, originality, and relevance to the subject. We also cited a few book chapters and older seminal articles on the topic.

See Online for appendix

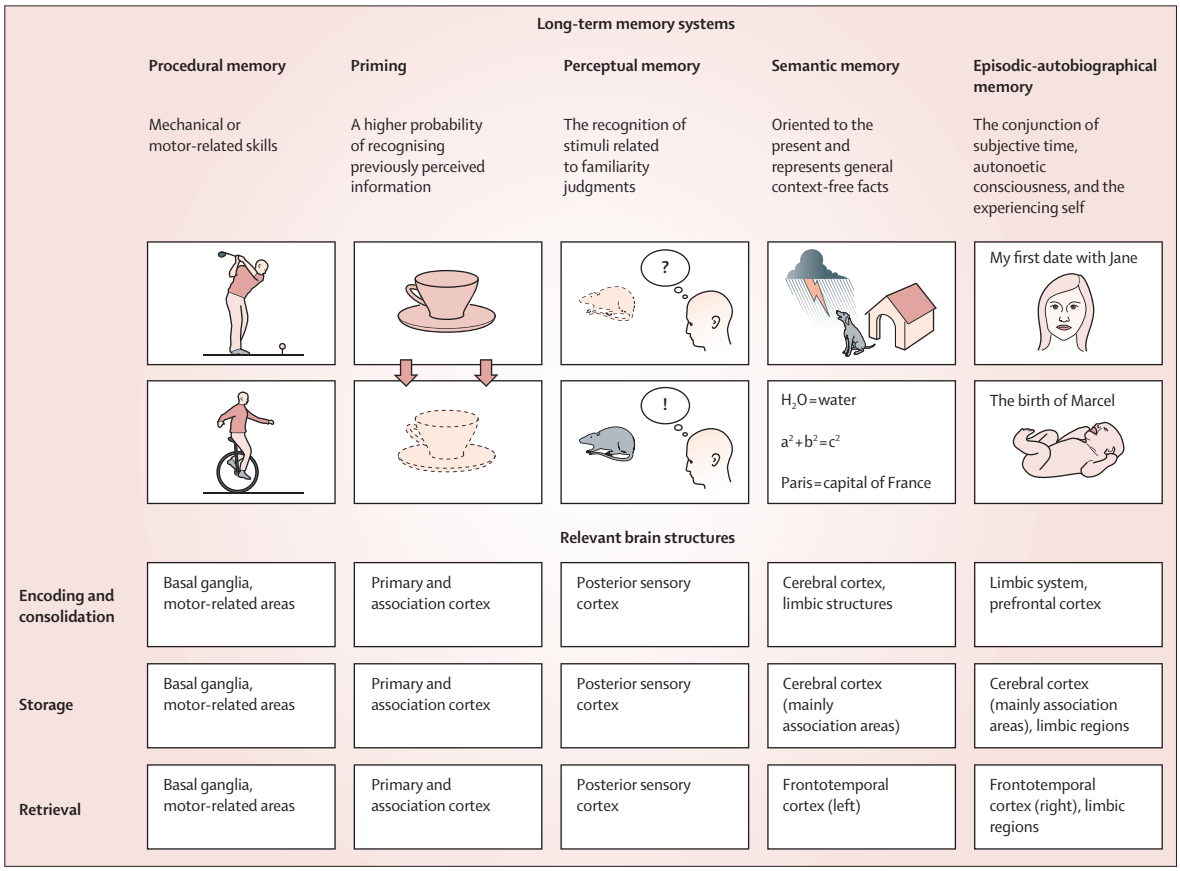

Figure: **The five long-term memory systems and their presumed brain bases**

imaging, which sometimes points towards a high degree of cortical specialisation.[8] Amnesias arise after damage to bottleneck structures through which information has to pass before it is stored long-term,[9] but can also take place after widespread cortical damage (panel 2; see appendix for a schematic of the two main circuits implicated in memory binding and long-term storage). Panel 3 presents brain regions whose (bilateral) damage is most frequently implicated in amnesia.

Some amnesic disorders occur without evidence of substantial brain damage on conventional structural imaging. These disorders include those that are aetiologically linked to psychosocial mechanisms, such as dissociative or psychogenic amnesias or mnestic block syndrome,[10] and amnesic disorders with an unknown cause (functional amnesias; see panel 1).[11] After research by HJM,[11] and colleagues, was reported, several studies identified changes in brain function affecting regions with crucial roles in memory processing in amnesic disorders that do not show evidence of structural brain damage.[10,12,13] Investigators have analysed data obtained with glucose PET from 14 patients at rest with dissociative amnesia and severe retrograde EAM impairments and reported hypometabolism in the right temporofrontal regions, especially in the inferolateral prefrontal cortex.[10]

Processing in various memory systems is associated with similar mechanisms and molecular steps across many species, especially during encoding, consolidation, and storage. Several types of synaptic plasticity subserve memory formation, such as long-term potentiation and depression, synaptogenesis, and synapse remodelling. The cellular and molecular mechanisms underlying long-term memory acquisition consist of various signalling pathways, gene transcription, protein synthesis, and synaptic morphological changes.[14,15] Long-term storage of memories might need active self-sustaining molecular mechanisms (eg, a functional prion protein).[16]

Environmentally driven changes in long-term memory formation and synaptic plasticity might arise as a result of changes in gene transcription and protein synthesis via epigenetic mechanisms (DNA methylation, post-translational histone chemical modifications, or micro RNAs).[16,17] Some epigenetic modifications might be reversible via pharmacological manipulation.[17]

International classifications of amnesic disorders

The International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10)[18] and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR)[19]

classify amnesic disorders on the basis of their strong aetiological link to general medical disorders, the direct effects of psychoactive substances in the patient's body persisting beyond the intoxication or withdrawal period, or psychological factors. Although the terms dissociative, psychogenic, and functional amnesia are often used interchangeably, differences exist between them (panel 1).

Several medical disorders can lead to amnesic disorders (panel 2). In most cases, EAM is solely or predominantly affected. A new form of substance-induced memory impairment is emerging that has therapeutic aims—namely, to weaken traumatic memories by hampering their consolidation or post-retrieval reconsolidation.[20] Electroconvulsive therapy has received much attention with respect to the extent and persistence of retrograde memory loss that it can cause.[21] Most research with objective measures showed that EAM loss in patients who had undergone electro-convulsive therapy was short-term, but in a prospective, naturalistic, non-randomised study, some patients still had EAM impairments after 6 months.[22]

Brain damage of the limbic system and amnesia

Data for amnesia come from case reports and group studies. These group studies frequently combine patients whose amnesia has different causes, but who presumably have the same main locus of brain damage. Three main forms of amnesia have been classically described on the basis of the locus of brain damage: hippocampal or medial temporal lobe (MTL) amnesia, diencephalic amnesia, and basal forebrain amnesia. Despite some differences (table 1), they share many features. Various portions of the limbic system can easily be arranged in a Gestalt-like way, which is supported by findings that severe amnesia can result from brain damage at the intersection between the MTL and the diencephalon. Using diffusion tensor imaging, Papanicolaou and colleagues[23] provided evidence that bilateral damage to fornix—the fibre bundle projecting from the hippocampal formation (HF; part of the MTL) to the mammillary bodies (part of the diencephalon)—was underlying a case of severe amnesia.

The amygdaloid complex—a region whose contribution to amnesic disorders has been debated—is situated within the MTL and, concomitantly, is part of the basolateral limbic circuit with connections to diencephalon and basal forebrain. The amygdala is implicated in emotional tagging of EAM.[24] Activation of right amygdala was recorded during retrieval of old emotional EAM[25] and association of faces with emotional judgments (social memory).[26] Hurlemann[15] emphasised that both hypermnesia and periemotional amnesia (diminished memories of neutral events during simultaneously enhanced encoding of an aversive event) are amygdala-dependent, varying as a function of noradrenergic-glucocorticoid input to the amygdala. Rutishauser and colleagues[27] reported that single-unit

***Panel 1:* Variants of amnesia and forms of associated diseases or behavioural disorders**

Global amnesia
An outdated diagnosis that implies total memory loss (it is outdated because in most amnesiacs implicit processing via the procedural and priming systems is usually preserved)

Anterograde amnesia
Inability to acquire, store, or retrieve new information long-term and consciously after a memory-impairing incident

Retrograde amnesia
Inability to consciously re-activate information that was stored long ago

Partial amnesia (lacunar amnesia)
Memory loss restricted to particular kinds of information or life epochs

Material-specific amnesia
Naming impairment with respect to objects or materials

Autobiographical amnesia
Inability to recall events (and to a minor degree personal knowledge) from own life

Semantic amnesia
Inability to reactivate general facts, or (less often) linguistic expressions (as in semantic dementia)

Topographical amnesia
Disturbance of memory for locations and space

Reduplicative paramnesia
Disturbed sense of familiarity; the patient is convinced that a person, place, or object exists twice (repeatedly); usually caused by organic brain damage (ie, neurologically based)

Capgras (delusion) syndrome
Disturbed sense of familiarity; the patient assumes that a close friend or relative has been replaced by an impostor, or double; usually no hallucinatory symptoms, but subsumed under psychiatric diseases

Infantile/childhood amnesia
Inability to consciously retrieve events from the first 3–4 years of life (probably caused by insufficiently developed brain, self, and language and by the existence of state-dependent memory retrieval)

Developmental amnesia
Episodic-autobiographical amnesia with preserved semantic memory after hypoxic-ischaemic events sustained usually within the first year of life

Korsakoff's syndrome/amnesia
A symptom agglomerate with severe anterograde amnesia, variable retrograde amnesia, confabulations, and a disorientation with respect to time and place; intelligence and short-term memory are frequently preserved; usually caused by severe and long-term alcohol misuse, but mainly a disorder of malnutrition with a distinct pattern of mainly medial diencephalic brain degeneration

Pseudodementia
Amnesia-like symptoms might be apparent, but the primary cause of the disorder is based on a depressive illness

Mnestic block syndrome
Memory block, caused by psychological factors such as severe stress or psychological trauma

(Continues on next page)

(Continued from previous page)

Dissociative amnesia
Psychiatric disorder characterised by an inability to recall personal information that is underlain by the psychological mechanism of dissociation

Dissociative fugue
Form of dissociative amnesia that is characterised by the patient leaving their place of living (their home)

Dissociative identity disorder (multiple personality disorder)
Existence of two or more personalities or personality states; amnesia for everyday events is a common feature and personalities are usually amnesic towards each other

Ganser syndrome
Dissociative disorder solely defined when a patient gives approximate answers to questions; its original description also included hysterical semitrance, amnesia, and hallucinations

Psychogenic amnesia
Broad term that refers to amnesic disorders that are linked to psychological factors; it makes no a-priori assumption about the nature of the associated psychological mechanisms

Functional amnesia
Amnesia usually without evidence of brain damage on conventional structural imaging, and of an unsure cause

Posthypnotic amnesia
Inability to recall events that occurred during hypnosis

Transient global amnesia
Massive anterograde and partial retrograde amnesia, usually of elderly people (>60 years), lasting less than 24 h; it is thought to be benign and is usually triggered by physical or psychological stress factors

Transient epileptic amnesia
Recurrent, transient episodes of isolated memory loss usually lasting less than 1 h; a subtype of temporal lobe epilepsy

Amnestic mild cognitive impairment
Subtype of mild cognitive impairment characterised by a decline in memory beyond age-correlated benign forgetfulness and with a higher likelihood of progression to Alzheimer's disease than other forms of mild cognitive impairment

Post-traumatic amnesia
Term used in publications about traumatic brain injury; sometimes it describes the phase after the resolution of delirium that is characterised mainly by memory impairments; sometimes the term overlaps with delirium, encompassing a period from injury until recovery of full consciousness and memory

Feigned amnesia
Feigned memory impairments or intentional exaggeration of existing memory impairments, possibly motivated by external incentives (in the case of malingering) or the intrapsychic need to assume the sick role (such as in factitious disorder)

activity in hippocampus and amygdala correlated positively with successful recollection of previously perceived stimuli. EAM impairments might accompany Urbach-Wiethe disease, a genetic disorder associated with bilateral amygdala calcifications.[28]

Evidence that the MTL—particularly the HF—played a major part in memory first appeared in about 1900;[1] however, no-one focused on MTL's association with memory until 1957 when Scoville and Milner reported patients with bilateral MTL surgery secondary to intractable epilepsy.[29] Within this series, the case of one patient—known as HM—became famous. HM was operated on in 1953 and died in 2008. At the time of surgery he had normal intelligence and memory function. After surgery he lost his ability to consciously form new, stable long-term memories, although his preoperative semantic and procedural memories remained largely intact. Initial descriptions suggested that he could retrieve most of his old autobiographical events. Later studies revealed that he could still acquire information that was processed at the levels of conditioning, priming, and procedural memory. Imaging that was undertaken almost four decades after surgery revealed that HM had undergone bilateral removal of the amygdala, parahippocampal-entorhinal cortex, and anterior hippocampus.

Since the first reports of HM's memory deficits, HF (including hippocampus proper, dentate gyrus, and subiculum) was thought to be the major hub for transmission of information from short-term to long-term storage, and this view received support from subsequent work in people and animals. Pathological changes to HF were thought to underlie amnesic disorders caused by MTL epilepsy, viral infections, hypoxia, or carbon monoxide poisoning.[30] However, investigators have questioned how selective patients' brain damage is after they have had these disorders.[31,32] For example, herpes simplex encephalitis might lead to degeneration of the anterior and medial temporal lobes and orbitofrontal cortex.[32]

HF atrophy generally accompanies early Alzheimer's disease, but was also noted in non-demented elderly people.[33] For the past few years, researchers have attempted to differentiate, within the HF, activations during encoding from activations during retrieval[32] and different forms of memory (semantic memory, EAM, and spatial memory).[32] Studies reporting that patients with damage to the HF find it difficult to imagine new experiences[34] or re-experience old EAMs ignited much interest;[35] however, subsequent investigations into imagination of future experiences in patients with HF damage did not yield uniform results, perhaps because there were differences in the extent and onset of the damage, selectivity of lesions, and testing methods.[36]

Several studies of patients with MTL amnesia or diencephalic amnesia have focused on the possibility that recollection and familiarity processes are neuroanatomically separate. Recollection is the process needed to recall associative elements of knowledge and specific contextual details of a previous event so that the past can be re-experienced or relived. The feeling of familiarity is based on the matching of processes between retrieval cues and memory representations, in the absence of recollective experience. Shortcomings of studies attempting to

discover which brain regions are implicated in specific processes include the small number of study patients and the low selectivity of their lesions.

Gilboa and colleagues' article,[37] reportedly on hippocampal contributions to recollection, stemmed from findings from two patients—one with "bilateral fornix and septal nuclei lesions" and mild "cortical and hippocampal atrophy" (the hippocampus is in fact a component of the cerebral cortex), and the other with traumatic brain injury with widespread limbic and neocortical damage of all cortical lobes. Despite the low number of cases and the non-selectivity of the brain damage, the investigators still concluded that the "extended hippocampal system is required to support recollection".[37]

In a thoughtful theoretical analysis based on quantitative modelling, Shimamura[38] concluded that retrieval of EAM is a whole-brain experience in which the hippocampus proper can be viewed as sitting at the top of a hierarchy of MTL structures, all of which are dependent on further sensory and emotional information processing regions. This view is the same as the one proposed in figure 3 of HJM's report of psychogenic amnesia.[39] Differing theories exist about whether the retrieval of old autobiographical memories occurs independently from MTL structures such as the HF, or whether these structures are engaged in addition to neocortical networks. The standard model[40] assumes that newly consolidated information becomes independent of the hippocampus after some time, whereas the multiple-trace model[41] assumes that hippocampal regions remain engaged during retrieval for the duration of that person's life. Winocur and colleagues[42] formulated a compromise by suggesting that less integrated, schematic versions of original EAMs become independent of the hippocampus, whereas those with contextual details remain dependent on the hippocampus.

A special variant of MTL amnesia is developmental amnesia, which is thought to be caused by selective damage to hippocampi due to neuronal loss (usually leading to at least a 30–40% reduction in bilateral volume of hippocampi compared with controls). It might follow episodes of ischaemic hypoxia, occurring perinatally or in childhood. Children with developmental amnesia can acquire and retrieve facts, but their acquisition and retrieval of EAMs is greatly impaired. These findings emphasise that HF is a key structure in the formation of lasting EAMs.

Studies of young adults with developmental amnesia have explored the ability of these patients to imagine the future[43,44] and differences between recognition/familiarity versus recall/recollection.[45–47] With respect to imagination of future episodes, only one[43] of the two studies[43,44] identified deficits, despite similar hippocampal volume reductions (50%). This finding warrants the need for additional investigations into the contribution of residual hippocampal tissue in the imagination of future events compared with the contribution of other structures. Besides hippocampal abnormalities, older studies of developmental amnesia described some changes to the putamen, thalamus, and right retrosplenial cortex.[45] With respect to recognition/familiarity versus recall, a disproportionally high impairment in free recall was consistently reported,[46,47] which is a result not always[48] described in hippocampal damage of adult onset. Patients with developmental amnesia seem therefore to have deficit patterns that partly overlap with those of patients who acquired their hippocampal abnormalities in adulthood, suggesting that hippocampal damage might lead to specific variations in phenotype, dependent on the onset of the damage.

The prototype of diencephalic amnesia is Wernicke-Korsakoff's syndrome, which is characterised by both anterograde and retrograde impairments of EAM, and occasionally by impairments of semantic memory, and confabulations.[49,50] The syndrome typically occurs in individuals with chronic alcohol misuse and concurrent

***Panel 2:* Medical, substance-related, psychiatric, and iatrogenic causes of amnesic disorders**

Medical
- Head injury (closed or penetrating)
- Stroke (ischaemic or haemorrhagic)
- Aneurysmal bleeding (subarachnoid haemorrhage) or aneurysm surgery
- Medial temporal lobe epilepsy
- Intracranial tumour
- Limbic encephalitis due to infections (herpes simplex virus 1 and 2, herpes zoster virus, and human herpes virus 6 in transplant recipients), of paraneoplastic origin, or associated with autoimmune diseases (eg, systemic lupus erythematosus, voltage-gated potassium channel antibody-associated encephalitis, or encephalitis associated with antibodies against N-methyl-D-aspartate receptor)
- Neurosyphilis
- Vitamin deficiencies (vitamin B1 deficiency)
- Transient global amnesia
- Transient epileptic amnesia

Substance-related
- Chronic alcohol misuse/vitamin B1 deficiency (Korsakoff's syndrome)
- Drug misuse: anxiolytics (benzodiazepines), sedative-hypnotics (barbiturates, zolpidem)
- Anticholinergics

Psychiatric
- Dissociative amnesia
- Dissociative fugue
- Dissociative identity disorder (multiple personality disorder)
- Dissociative trance disorder

Iatrogenic
- Drug side-effects—eg, of anticholinergic drugs including antidepressants (tricyclic and tetracyclic antidepressants), antipsychotics, or antiparkinsonian agents with anticholinergic properties (eg, benzatropine), and anaesthetics
- Surgical procedures on brain
- Electroconvulsive therapy

***Panel 3:* Brain regions whose (bilateral) damage is followed by characteristic memory disturbances**

Medial temporal lobe (especially hippocampal formation and surrounding structures)
Encoding and consolidation of EAM and semantic memory into the long-term store; spatiotemporal integration

Amygdaloid complex
Assessment of biological and social significance; emotional tagging of memories, especially of episodic-autobiographical memory

Prefrontal cortex
Short-term memory (dorsolateral prefrontal cortex); encoding and recall of episodic and semantic information (especially effortful recall)

Orbitofrontal cortex; basal forebrain
Encoding and emotional connections to information; control and suppression of confabulatory tendencies

Limbic thalamic nuclei; fornix; mammillary bodies
Binding and association processes for transfer into long-term storage; consciousness

Pulvinar
Processing, especially of language-related information, attention, and semantic memory

Cingulate gyrus
Processing of components of memory related to attention and wilful acts

Retrosplenial cortex; precuneus
Imagination; representation of memories; familiarity

Lateral parietal cortex (especially left)
Short-term memory; mediation of mnemonic processing by attention

Basal ganglia
Procedural memory processing

	MTL	D	BF
Abilities of conscious reflection and self-awareness	+	+/–	–/+
Tendencies of disinhibition and perseveration	–	+/–	–/+
Anosognosia	–	–/+	+
Initial loss of the sense of time (chronotaraxis)	–	–/+	–
Disproportional impairment of recall as opposed to recognition	–	–	+
Tendency to confabulate	–	–/+	+
Deficits in tasks needing executive functions	–	+/–	+
Emotional instability and mood disorders	–	–/+	+
Difficulties with attention and concentration	–	–	+

Damage to the region is (+) associated; (–) not associated; (+/–) often associated; or (–/+) occasionally associated with this characteristic.

***Table 1:* Characteristics of amnesias related to medial temporal lobe (MTL), diencephalic (D), and basal forebrain (BF) damage**

thiamine deficiency, or with other disorders associated with thiamine deficiency.[49] Because patients with chronic alcoholism might also display EAM impairments and deficits in working memory, metamemory, and executive functions,[51] there might be a continuum between symptoms of alcoholism and Korsakoff's syndrome.[51] Brain abnormalities in patients with Korsakoff's syndrome might seem to be more widespread (including the middle cingulate gyrus) when measured by changes in brain glucose metabolism[51] than when assessed by post-mortem analyses. Post-mortem findings mainly point to the degeneration of midline diencephalic structures, but do not confirm whether, in addition to the usually affected mammillary bodies, degeneration occurs in the mediodorsal thalamic nucleus (or just its medial, magnocellular portion) or the parataenial nuclei situated medially to the mediodorsal nucleus.

Studies of patients with more selective bilateral mediodorsal or anterior thalamic nuclear damage have pointed to the association of these parataenial nuclei with memory.[52] Furthermore, several reports have provided evidence that bilateral damage to the mammillary bodies or the mammillothalamic tract (or even to the tegmental nuclei of Gudden with bidirectional connections with the mammillary nuclei) is sufficient to cause amnesia.[53] Earlier predictions linking different aspects of memory processing (familiarity versus recollection) to the anterior or mediodorsal thalamus were not confirmed.[52] However, investigators have now proposed that mammillothalamic or anterior nuclei damage probably leads to deficits in recollection, whereas damage to the ventral amygdalofugal pathway or mediodorsal nucleus affects familiarity processing.[54] Thalamic damage is most common after stroke. Four arterial branches vascularise different thalamic regions and can be affected either in combination or individually, leading to distinct symptoms[55] (appendix).

The basal forebrain is composed of three major nuclear complexes made up of neurons containing acetylcholine (and γ-aminobutyric acid): basal nucleus of Meynert, diagonal band of Broca, and septal nuclei. These nuclei project to the HF and other cortical areas. The (medial) septal region is connected to the amygdaloid complex. The amygdaloid complex enhances the emotional relevance of information while the septal nuclei are thought to exert an opposite, dampening effect. Basal forebrain amnesia can occur after rupture and surgery of aneurysms of the anterior communicating artery and tumours. Clinical differences between basal forebrain amnesia and MTL or diencephalic amnesia mainly arise because of the location of the basal forebrain nuclei in the penumbra of the ventral prefrontal cortex. In basal forebrain amnesia, executive dysfunctions are common, and recall—requiring active effort—is more impaired than recognition of information.[56] If the damage extends to upper portions of the frontal lobes, source amnesia (failure to remember where information came from) might occur.[57] Damage to basal forebrain associated with aneurysms of anterior communicating arteries can lead to enhanced vulnerability to provoked confabulations and false recognition in procedural memory (table 1).[58]

White-matter damage and amnesia as a disconnection syndrome

The occurrence of amnesia after fibre tract damage was first reported some time ago.[1] Several fibre bundles are of special interest in memory processing because they interconnect relevant bottleneck structures[9,59,60] (see appendix). The fornix connects all three major regions that are important for memory consolidation and transfer into long-term memory (MTL, diencephalon, and basal forebrain). In a study of 38 patients who had undergone colloid cyst removal, significant negative correlations were reported between fornix volume and recall in standardised memory tests.[61] Fibres passing through the internal and external capsules (especially thalamocortical connections) and temporal stem (especially the uncinate fascicle connecting prefrontal, amygdalar, and temporal areas) provide important links that complete the network of limbic and paralimbic regions (prefrontal and temporal lobes, and diencephalon), and their damage can lead to memory deficits.[62]

Mesulam[63] and others reported the existence of large-scale networks for mnemonic processing. Functional neuroimaging enabled the characterisation of large-scale brain systems, such as the default mode network, which has functions in prospection and EAM.[64] Abnormal default mode network activity was reported in amnestic mild cognitive impairment and early Alzheimer's disease.[64]

White matter ensures proper flow of information in brain networks. Structural imaging techniques, such as diffusion tensor imaging and magnetisation transfer ratio measurement, improved the ability to estimate the integrity of white matter in memory-impairing disorders. Investigators using magnetisation transfer imaging in a patient with functional amnesia recorded subtle changes in white matter in the right prefrontal area.[65] White-matter damage occurs in several illnesses, such as multiple sclerosis (in which memory difficulties are common). Sepulcre and colleagues[66] identified damage to many fibre tracts, especially those running through the temporal stem and internal capsule, in a large sample of patients with multiple sclerosis. White-matter damage is common in patients who have had a stroke. Stroke is the only cause of amnesia that can affect all memory-processing structures of the limbic system.[67]

Traumatic brain injuries resulting in diffuse (multifocal) axonal injury might also lead to disturbances in anterograde and retrograde memory.[6] One topic of continuing interest is the relation between traumatic brain injury, in particular (concussive) mild head injury, and psychogenic or functional amnesia.[11,65] To what extent the rupture of fine connections between synapses and dendrites might cause widespread cerebral dysfunction is unresolved, and whether the traumatic experience itself can lead to a psychological shock disorder, which then might result in severe and persistent amnesia and other cognitive disturbances, is also unknown.[13] Incidentally, brain concussions at various locations along the skull can lead to amnesia that is mainly retrograde.[6]

Amnesias with mixed psychological and physiological causes

Transient global amnesia happens suddenly, usually in adults older than 60 years, and is triggered by physiological or psychological factors.[68] Its course is benign because it (typically) disappears within a day. Slight memory deficits might, however, persist for months, especially if patients continue to have anxiety or depression.[69] Transient global amnesia affects mostly anterograde memories, but can partly affect retrograde memories as well.[70] The cause of transient global amnesia is still elusive, although hypotheses have suggested that small thrombi in deep cerebral veins[71] or internal jugular vein valve incompetence[72] might be to blame. Bartsch and Deuschl[70] emphasised that the vulnerability of the cornu ammonis (CA1) neurons of the hippocampus to metabolic stress is pivotal in the pathophysiological cascade underlying transient global amnesia. The transient global amnesia recurrence rate is substantial (6–10% per year).[70]

Differential diagnoses of transient global amnesia include the recurrent shorter-lasting episodes of transient epileptic amnesia, which can occur on awakening in individuals of middle and old age (mean age of 57 years). Patients with transient epileptic amnesia often complain of persistent interepisodic memory deficits. Although objective measures on standard tests of anterograde memory can be normal, accelerated long-term forgetting for days to weeks and deficits of remote EAM were documented.[73]

Functional, psychogenic, or dissociative amnesias might be associated with psychological factors co-occurring with a (minor) physical injury. They are generally diagnosed in people aged 20–40 years and characterised by retrograde EAM impairments. Occasionally, anterograde amnesia in the absence of retrograde EAM impairment might take place.[13]

The mechanism of dissociation underlies dissociative amnesia,[19] which is linked to psychological stress in various cultures.[13] Psychogenic amnesia consists of disorders with various psychological mechanisms.[13] Not all functional amnesias are diagnosed with a definite background of psychological factors.[13]

Epidemiology and genetics

Epidemiological data are available for only specific amnesic disorders. The incidence of transient global amnesia is 3–8 per 100 000 people per year.[70] Head trauma is the most probable cause of amnesic disorders that are due to a general medical disorder. Although decreases in the incidence of thiamine-related disorders were reported in several countries after fortification of bread with thiamine, an increase in the incidence of Korsakoff's syndrome was described in some European countries.[49] For dissociative

amnesia, a 12 month prevalence of 1·8% was reported in a US community of 658 adults.[74]

The genetic underpinnings of human amnesia are still unknown. Studies of the genetics of Korsakoff's syndrome and transient global amnesia yielded no conclusive results.[49,75] Although EAM impairments could be regarded as an intermediate phenotype[76] in amnesic disorders, which might be proximal to their underlying genetic risk, data about how genetics affect EAM are inconclusive. Several researchers state that about 50% of the inter-individual variability in memory ability is attributable to genetic factors;[76] this assertion is, however, based on results of behavioural genetic twin studies[77] that did not use EAM testing paradigms in accordance with the present definition of EAM.[3]

Work in animals prompted several hypothesis-driven behavioural and imaging genetic studies that investigated the association between memory performance in different populations and variants of several candidate genes.[76] Several researchers have done genome-wide association studies[78] to try to find associations between variations of different genes (table 2) and episodic memory performance.[76,79,80] However, apart from one minor exception,[81] most studies that reported to have investigated an association between one of the described gene variants and episodic memory did not use EAM testing paradigms that were congruent with EAM's definition.[76,79,80,82]

Because EAM is a complex neurocognitive system, it is probably affected by genes, environment, and their interplay. Technological improvements and the use of methodological rigour with respect to EAM testing paradigms might help us to better understand EAM's genetic foundation.

Assessment of amnesic disorders

Assessment of amnesic disorders includes anamnesis and medical, laboratory, and occupational-therapy evaluations (see appendix for a flow diagram on assessment strategies). Neuropsychological testing is invaluable to objectively establish the nature and severity of the memory impairment, to quantify longitudinal changes, and to distinguish between amnesias of different causes and feigned amnesia. Cognitive disturbances due to infarct or closed head injury can change over time. Furthermore, studies sometimes report discrepancies between subjective complaints and objective measurement[21] or suggest exaggeration or reduced effort.[56]

Various approaches attempt to differentiate feigned from true amnesia. Many are based on testing with concealed levels of difficulty and use effort measures,

	Product	Presumed function in memory
WWC1	KIBRA (a scaffolding protein, highly expressed in hippocampus/temporal lobe)	Long-term memory acquisition and storage; interaction with protein kinase Cζ/Mζ; recall
CLSTN2	Calsyntenin-2 (a synaptic protein)	Interactive effect with KIBRA
PDYN	Prodynorphin (endogenous opioid, precursor of dynorphins)	Memory acquisition
COMT	Catechol O-methyltransferase (enzyme implicated in the catabolism of monoamines [dopamine and noradrenaline])	Encoding; arousal-mediated consolidation
PRNP	Prion protein	Long-term memory formation and maintenance
CPEB3	Cytoplasmic polyadenylation element-binding protein 3	Memory formation and maintenance
GRM3	Metabotropic glutamate receptor 3	Memory formation
CHRNA7	Neuronal acetylcholine receptor subunit alpha-7	Learning and memory
HTR2A	5-hydroxytryptamine receptor 2A	Modulation of serotonin transmission; memory formation
Genes of the protein kinase A enzyme family	Protein kinase A enzymes	Late-phase of long-term potentiation; memory consolidation
Genes of the protein kinase C enzyme family	Protein kinase C enzymes	Maintenance of long-term memories (protein kinase Cξ/Mξ)
BDNF (valine66 to methionine polymorphism)	Brain-derived neurotrophic factor (a neurotrophin)	Regulation of synaptic plasticity (long-term potentiation and long-term depression); encoding and retrieval
SLC6A4 (5-HTTLPR [serotonin-transporter-linked polymorphic region])	Sodium-dependent serotonin transporter	Serotonin re-uptake; encoding and consolidation
APOE (ε allele combinations)	Apolipoprotein E	Lipid transport protein implicated in maintenance and repair of neuronal cells; regulation of deposition and formation of amyloid plaques and neurofibrillary tangles
CETP (SNP at codon 405 [isoleucine to valine V405])	Cholesteryl ester transfer protein	CNS cholesterol homoeostasis
CTNNBL1	Beta-catenin-like protein 1 (brain-expressed)	Memory encoding and consolidation

SNP=single nucleotide polymorphism.

Table 2: **Genes proposed to be associated with episodic-autobiographical memory or episodic memory performance**

recognition (forced-choice paradigms), or calculation abilities[83,84] (see figure 1 of Yochim and colleagues[85]). The idea is to provide the potential feigner with a substantial amount of simple information and to convey the impression of a difficult memory task, when in reality it is not difficult (healthy people perform at the upper limit).[84] Results from psychological experiments show that we are easily able to recognise an enormous number of pictures and are typically much better at item recognition than at item (free) recall. Furthermore, we perform during free recall in a typical pattern—namely, in a learning curve with a primacy and a recency effect. However, feigners might show atypical or inconsistent performance on systematic testing. Structured inventories can aid with detection of malingering in forensic or litigation cases.[84] Functional neuroimaging can be used to investigate neural correlates of false memories and feigning.[86] Results are still divergent, and designs that are more ecologically valid are being tested.[87]

In amnesic disorders, the acquisition of a multidimensional profile is advisable. Usually, left-hemispheric damage mainly leads to verbal memory impairments, whereas right-hemispheric damage affects non-verbal memory deficits. Short-term memory is only rarely affected.

The patient's intelligence should always be measured or at least estimated. Because low levels of attention and concentration can impair the acquisition of new information, their measurement is essential. Differentiation between memory measures of free recall (active information generation), cued recall, and recognition is important. Patients, especially those with frontal lobe damage, might show a discrepancy between recognition and free recall.[56] Tests to assess patients with amnesia and criteria for assessment of retrograde EAM impairments are described in the appendix.

Prognosis and treatment of amnesic disorders

A few amnesic disorders (such as transient global amnesia) have good prognosis, others partly improve, and for some disorders—especially those with complete bilateral damage to MTL, diencephalon, or basal forebrain—prognosis remains poor. Traditionally, most cases of dissociative amnesia were reported to resolve spontaneously; however, reports have since suggested that chronic forms exist.[10,13]

Parenteral thiamine given routinely to patients at risk decreases their likelihood of developing Wernicke-Korsakoff's syndrome.[49] Memory impairments related to electroconvulsive therapy might be reduced by unilateral electrode placement, titration of the electrical current according to the patient's seizure threshold,[21,22] and ultrabrief pulses.[88]

Pharmacological treatment data for amnesic disorders are scarce and come from studies with small numbers of cases that often do not have a placebo-control group. An open-label, non-randomised study of 11 patients with basal forebrain amnesia after aneurysm rupture noted verbal memory improvements after a 12 week trial of 5–10 mg donepezil per day.[89]

A few placebo-controlled studies suggested that cholinesterase inhibitors could be used to address chronic post-traumatic memory impairments in patients with traumatic brain injury.[90,91] No controlled studies addressed the psychopharmacological (or psychotherapeutic) treatment of dissociative amnesia.[12] Studies have looked at novel drugs (histone deacetylase inhibitors)[17] and somatic (brain stimulation) interventions that might aid memory improvement.[92]

Thus, no evidence-based psychopharmacological or somatic treatments are known to be definitively effective at reversing memory impairments or deficits in amnesic disorders. The increase in group studies and rapid advances in the biological understanding of memory give hope to the development of effective psychopharmacological and somatic interventions for amnesic disorders.

Ideally, rehabilitation should address cognitive, emotional, and psychosocial functioning and prospective memory.[93] Generally, it consists of training strategies aiming to establish previous levels of functioning and compensatory strategies. Implicit training strategies with procedural and priming tasks have been successfully used for patients with severe forms of amnesia.[94] Emphasis is laid on errorless learning procedures[95] and semantic strategies.[96] Success with implicit and errorless learning is not that common and cannot be generalised.

Supportive psychotherapy can enhance rehabilitation outcomes for patients with preserved insight. Besides computer-aided training,[97] virtual-reality environments are used for memory training,[98] and even non-invasive cortical stimulation has been applied.[99] Reliance on external memory aids and support from modern computer-based equipment is increasing.

Evidence-based data for memory rehabilitation are scarce.[100] Cicerone and colleagues[100] reviewed class Ia studies that provided evidence that visual imagery is better than standard memory training; the same was true for self-instructed training, at least for patients with mild memory impairment. The use of portable pagers was also effective.

However, a detailed review on cognition-based interventions in older people, including memory training and transfer of training effects, stated that "immediate and delayed verbal recall improved significantly through training compared to a no-treatment control condition, but the improvements did not exceed the improvement in the active control condition".[101]

Future directions

Amnesia in the strict sense—ie, a total and exclusive loss of the ability to store new information consciously and long term, or to retrieve long-term stored information consciously—is rarely found. In fact, proposals were made

by the DSM-V neurocognitive disorders work group to replace the DSM-IV-TR category of delirium, dementia, amnestic and other geriatric cognitive disorders with a new category called neurocognitive disorders. Longitudinal studies of (dissociative) amnesia might be needed to quantify possible cognitive deteriorations over time.[102] The identification of neural correlates of various amnesias and predictors for effective rehabilitation might benefit from combined use of functional and structural imaging. An understanding of the (epi)genetics of memory processes might help with the design of novel treatments for amnesias in the future.

Contributors

HJM and AS contributed equally to the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

Our research was funded by the University of Bielefeld and grants from the Cluster of Excellence "Cognitive Interaction Technology (CITEC)", EU (NEST programme; "Eyewitness Memory"; FP6-043460), German Research Council (Br 2894/1, 3), and Alfried-Krupp Stiftung, Greifswald.

References

1 Markowitsch HJ. Intellectual functions and the brain: an historical perspective. Toronto: Hogrefe & Huber Publishers, 1992.

2 Tulving E. Episodic memory: from mind to brain. *Annu Rev Psychol* 2002; **53:** 1–25.

3 Tulving E. Episodic memory and autonoesis: uniquely human? In: Terrace H, Metcalfe J, eds. The missing link in cognition: origins of self-reflective consciousness. New York: Oxford University Press, 2005: 3–56.

4 Markowitsch HJ. Anterograde memory. In: Goldenberg G, Miller BL, eds. Handbook of clinical neurology, vol. 88: neuropsychology and behavioral neurology. Amsterdam: Elsevier, 2008: 155–83.

5 Ribot T. Diseases of memory. New York: D Appleton & Company, 1882.

6 Kopelman MD. Retrograde memory loss. In: Goldenberg G, Miller BL, eds. Handbook of clinical neurology, vol. 88: neuropsychology and behavioral neurology. Amsterdam: Elsevier, 2008: 185–202.

7 Eustache F, Desgranges B. MNESIS: Towards the integration of current multisystem models of memory. *Neuropsychol Rev* 2008; **18:** 53–69.

8 Kanwisher N. Functional specificity in the human brain: A window into the functional architecture of the mind. *Proc Natl Acad Sci USA* 2010; **107:** 11163–70.

9 Brand M, Markowitsch HJ. The principle of bottleneck structures. In: Kluwe RH, Lüer G, Rösler F, eds. Principles of learning and memory. Basel: Birkhäuser, 2003: 171–84.

10 Brand M, Eggers C, Reinhold N, et al. Functional brain imaging in 14 patients with dissociative amnesia reveals right inferolateral prefrontal hypometabolism. *Psychiatry Res* 2009; **174:** 32–39.

11 Markowitsch HJ. Functional retrograde amnesia–mnestic block syndrome. *Cortex* 2002; **38:** 651–54.

12 Markowitsch HJ, Kessler J, Weber-Luxenburger G, Van der Ven C, Heiss WD. Neuroimaging and behavioral correlates of recovery from 'mnestic block syndrome' and other cognitive deteriorations. *Neuropsychiatry Neuropsychol Behav Neurol* 2000; **13:** 60–66.

13 Staniloiu A, Markowitsch HJ. Searching for the anatomy of dissociative amnesia. *J Psychol* 2010; **218:** 96–108.

14 Gold PE. Protein synthesis inhibition and memory: Formation *vs* amnesia. *Neurobiol Learn Mem* 2008; **89:** 201–11.

15 Hurlemann R. Noradrenergic-glucocorticoid mechanisms in emotion-induced amnesia: from adaptation to disease. *Psychopharmacology* 2008; **197:** 13–23.

16 Kandel ER. The biology of memory: a forty-year perspective. *J Neurosci* 2009; **29:** 12748–56.

17 Zhang T-Y, Meaney MJ. Epigenetics and the environmental regulation of the genome and its function. *Annu Rev Psychol* 2010; **61:** 419–66.

18 WHO: The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines. Geneva: WHO, 1992.

19 American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th edn, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Publishing, 2000.

20 Brunet A, Orr SP, Tremblay J, et al. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *J Psychiatr Res* 2008; **42:** 503–06.

21 Fraser LM, O'Caroll RE, Ebmeier KP. The effect of electroconvulsive therapy on autobiographic memory: a systematic review. *J ECT* 2008; **24:** 10–17.

22 Sackeim HA, Prudic J, Fuller R, et al. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 2007; **32:** 244–54.

23 Papanicolaou AC, Hasan KM, Boake C, Eluvathingal TJ, Kramer L. Disruption of limbic pathways in a case of profound amnesia. *Neurocase* 2007; **13:** 226–28.

24 Markowitsch HJ, Staniloiu A. Amygdala in action: relaying biological and social significance to autobiographical memory. *Neuropsychologia* 2011; **49:** 718–33.

25 Buchanan TW, Tranel D, Adolphs R. Emotional autobiographical memories in amnesic patients with medial temporal lobe damage. *J Neurosci* 2005; **25:** 3151–60.

26 Somerville LH, Wig GS, Whalen PJ, Kelley WM. Dissociable medial temporal lobe contributions to social memory. *J Cogn Neurosci* 2006; **18:** 1253–65.

27 Rutishauser U, Schuman EM, Mamelak AN. Activity of human hippocampal and amygdala neurons during retrieval of declarative memories. *Proc Natl Acad Sci USA* 2008; **105:** 329–34.

28 Hurlemann R, Wagner M, Hawellek B, et al. Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach-Wiethe disease. *Neuropsychologia* 2007; **45:** 877–84.

29 Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neur Neurosurg Psychiatry* 1957; **20:** 11–21.

30 Bird CM, Shallice T, Cipolotti L. Fractionation of memory in medial temporal lobe amnesia. *Neuropsychologia* 2007; **45:** 1160–71.

31 Schon K, Quiroz YT, Hasselmo ME, Stern CE. Greater working memory load results in greater medial temporal activity at retrieval. *Cereb Cortex* 2009; **19:** 2561–71.

32 Greenberg DL, Keane MM, Ryan L, Verfaellie M. Impaired category fluency in medial temporal lobe amnesia: the role of episodic memory. *J Neurosci* 2009; **29:** 10900–08.

33 Knoops AJG, van der Graaf Y, Appelman APA, et al. Visual rating of the hippocampus in non-demented elders: does it measure hippocampal atrophy or other indices of brain atrophy? The SMART-MR study. *Hippocampus* 2009; **19:** 1115–22.

34 Hassabis D, Kumaran D, Vann SD, Maguire EA. Patients with hippocampal amnesia cannot imagine new experiences. *Proc Natl Acad Sci USA* 2007; **104:** 1726–31.

35 Steinvorth S, Levine B, Corkin S. Medial temporal lobe structures are needed to re-experience remote autobiographical memories: evidence from H.M. and W.R. *Neuropsychologia* 2005; **43:** 479–96.

36 Squire LR, van der Horst AS, McDuff SGR, et al. Role of the hippocampus in remembering the past and imagining the future. *Proc Natl Acad Sci USA* 2010; **107:** 19044–48.

37 Gilboa A, Winocur G, Rosenbaum RS, et al. Hippocampal contributions to recollection in retrograde and anterograde amnesia. *Hippocampus* 2006; **16:** 966–80.

38 Shimamura AP. Hierarchical relational binding in the medial temporal lobe: the strong get stronger. *Hippocampus* 2010; **20:** 1206–16.

39 Markowitsch HJ. Psychogenic amnesia. *Neuroimage* 2003; **20** (suppl 1)**:** S132–38.

40 Squire LR, Bayley PJ. The neuroscience of remote memory. *Curr Opin Neurobiol* 2007; **17:** 185–96.

41 Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr Opin Neurobiol* 2006; **16:** 179–90.

42 Winocur G, Moscovitch M, Bontempi B. Memory formation and long-term retention in humans and animals: convergence towards a transformation account of hippocampal-neocortical interactions. *Neuropsychologia* 2010; **48:** 2339–56.

43 Kwan D, Carson N, Addis DR, Rosenbaum RS. Deficits in past remembering extend to future imagining in a case of developmental amnesia. *Neuropsychologia* 2010; **48:** 3179–86.

44 Maguire EA, Vargha-Khadem F, Hassabis D. Imaging fictitious and future experiences: evidence from developmental amnesia. *Neuropsychologia* 2010; **48:** 3187–92.

45 Vargha-Khadem F, Salmond CH, Watkins KE, et al. Developmental amnesia: effect of age at injury. *Proc Natl Acad Sci USA* 2003; **100:** 10055–60.

46 Brandt KR, Gardiner JM, Vargha-Khadem F, Baddeley AD, Mishkin M. Impairment of recollection but not familiarity in a case of developmental amnesia. *Neurocase* 2008; **15:** 60–65.

47 Adlam A-LR, Malloy M, Mishkin M, Vargha-Khadem F. Dissociation between recognition and recall in developmental amnesia. *Neuropsychologia* 2009; **47:** 2207–10.

48 Jeneson A, Kirwan BC, Hopkins RO, Wixted JT, Squire LR. Recognition memory and the hippocampus: a test of the hippocampal contribution to recollection and familiarity. *Learn Mem* 2010; **17:** 63–70.

49 Zahr NM, Kaufman KL, Harper CG. Clinical and pathological features of alcohol-related brain damage. *Nat Rev Neurol* 2011; **7:** 284–94.

50 Borsutzky S, Fujiwara E, Brand M, Markowitsch HJ. Confabulations in alcoholic Korsakoff patients. *Neuropsychologia* 2008; **46:** 3133–43.

51 Pitel AL, Beaunieux H, Witkowski T, et al. Episodic and working memory deficits in alcoholic Korsakoff patients: the continuity theory revisited. *Alcohol Clin Exp Res* 2008; **32**: 1229–41.

52 Cipolotti L, Husain M, Crinion J, et al. The role of the thalamus in amnesia: a tractography, high-resolution MRI and neuropsychological study. *Neuropsychologia* 2008; **46:** 2745–58.

53 Vann SD. Re-evaluating the role of the mammillary bodies in memory. *Neuropsychologia* 2010; **48:** 2316–27.

54 Carlesimo GA, Lombardi MG, Caltagirone C. Vascular thalamic amnesia: a reappraisal. *Neuropsychologia* 2011; **49:** 777–89.

55 Perren F, Clarke S, Bogousslavsky J. The syndrome of combined polar and paramedian thalamic infarction. *Arch Neurol* 2005; **62:** 1212–16.

56 Jetter J, Poser U, Freeman RB Jr, Markowitsch HJ. A verbal long term memory deficit in frontal lobe damaged patients. *Cortex* 1986; **22:** 229–42.

57 Lakhan SE. Neuropsychological generation of source amnesia: an episodic memory disorder of the frontal brain. *J Med Biol Sci* 2006; **1:** 1–13.

58 Borsutzky S, Fujiwara E, Brand M, Markowitsch HJ. Susceptibility to false memories in patients with ACoA aneurysm. *Neuropsychologia* 2010; **48:** 2811–23.

59 Kier EL, Staib LH, Davis LM, Bronen RA. MR Imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. *AJNR Am J Neuroradiol* 2004; **25:** 677–91.

60 Schmahmann JD, Smith EE, Eichler FS, Filley CM. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. *Ann N Y Acad Sci* 2008; **1142:** 266–309.

61 Tsivilis D, Vann SD, Denby C, et al. A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nat Neurosci* 2008; **11:** 834–42.

62 Gerber DJ, Weintraub AH, Cusick CP, Ricci PE, Whiteneck GG. Magnetic resonance imaging of traumatic brain injury: relationship of T2 SE and T2*GE to clinical severity and outcome. *Brain Inj* 2004; **18:** 1083–97.

63 Mesulam M-M. Behavioral neuroanatomy: large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specialization. In: Mesulam M-M, ed. Principals of behavioral neurology. New York: Oxford University Press, 2000: 1–120.

64 Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008; **1124:** 1–38.

65 Tramoni E, Aubert-Khalfa S, Guye M, et al. Hypo-retrieval and hyper-suppression mechanisms in functional amnesia. *Neuropsychologia* 2009; **47:** 611–24.

66 Sepulcre J, Masdeu JC, Sastre-Garriga J, et al. Mapping the brain pathways of declarative verbal memory: evidence from white matter lesions in the living human brain. *Neuroimage* 2008; **42:** 1237–43.

67 Lim C, Alexander MP. Stroke and episodic memory disorders. *Neuropsychologia* 2009; **47:** 3045–58.

68 Markowitsch HJ, ed. Transient global amnesia and related disorders. Toronto: Hogrefe & Huber Publishers, 1990.

69 Noël A, Quinette P, Dayan J, et al. Influence of patients' emotional state on the recovery processes after a transient global amnesia. *Cortex* 2011; **47:** 981–91.

70 Bartsch T, Deuschl G. Transient global amnesia: functional anatomy and clinical implications. *Lancet Neurol* 2010; **9:** 205–14.

71 Solheim O, Skeidsvoll T. Transient global amnesia may be caused by cerebral vein thrombosis. *Med Hypotheses* 2005; **65:** 1142–49.

72 Cejas C, Fernandez Cisneros L, Lagos R, Zuk C, Ameriso SF. Internal jugular vein valve incompetence is highly prevalent in transient global amnesia. *Stroke* 2010; **41:** 67–71.

73 Butler CR, Graham KS, Hodges JR, et al. The syndrome of transient epileptic amnesia. *Ann Neurol* 2007; **61:** 587–98.

74 Johnson JG, Cohen P, Kasen S, Brook JS. Dissociative disorders among adults in the community, impaired functioning, and axis I and II comorbidity. *J Psychiatr Res* 2006; **40:** 131–40.

75 Segers-van Rijn J, de Bruijn SF. Transient global amnesia: a genetic disorder? *Eur Neurol* 2010; **63:** 186–87.

76 Rasch B, Papassotiropoulos A, de Quervain DF. Imaging genetics of cognitive functions: focus on episodic memory. *Neuroimage* 2010; **53:** 870–77.

77 McClearn GE, Johansson B, Berg S, et al. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science* 1997; **276:** 1560–63.

78 Papassotiropoulos A, Stefanova E, Vogler C, et al. A genome-wide survey and functional brain imaging study identify CTNNBL1 as a memory-related gene. *Mol Psychiatry* 2011; published online Nov 22. DOI:10.1038/mp.2011.148.

79 Papassotiropoulos A, Stephan DA, Huentelman MJ, et al. Common *Kibra* alleles are associated with human memory performance. *Science* 2006; **314:** 475–78.

80 Preuschhof C, Heekeren HR, Li SC, et al. KIBRA and CLSTN2 polymorphisms exert interactive effects on human episodic memory. *Neuropsychologia* 2010; **48:** 402–08.

81 Lemogne C, Bergouignan L, Boni C, et al. Genetics and personality affect visual perspective in autobiographical memory. *Conscious Cogn* 2009; **18:** 823–30.

82 Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. *Neurobiol Aging* 2011; **32:** 63–74.

83 Taylor LA, Kreutzer JG, West DD. Evaluation of malingering cut-off scores for the Rey 15-item test: a brain injury case study series. *Brain Inj* 2003; **17:** 295–308.

84 Greiffenstein MF, Greve KW, Bianchini KJ, Baker WJ. Test of memory malingering and word memory test: a new comparison of failure concordance rates. *Arch Clin Neuropsychol* 2008; **23:** 801–07.

85 Yochim BP, Kane KD, Horning S, Pepin R. Malingering or expected deficits? A case of herpes simplex encephalitis. *Neurocase* 2010; **16:** 451–60.

86 Abe N, Okuda J, Suzuki M, et al. Neural correlates of true memory, false memory, and deception. *Cereb Cortex* 2008; **18:** 2811–19.

87 Mohamed FB, Faro SH, Gordon NJ, et al. Brain mapping of deception and truth telling about an ecologically valid situation: functional MR imaging and polygraph—initial experience. *Radiology* 2006; **238:** 679–88.

88 Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul* 2008; **1:** 71–83.

89 Benke T, Köylü B, Delazer M, Trinka E, Kemmler G. Cholinergic treatment of amnesia following basal forebrain lesion due to aneurysm rupture – an open-label pilot study. *Eur J Neurol* 2005; **12:** 791–96.

90 Writer BW, Schillerstrom JE. Psychopharmacological treatment for cognitive impairment in survivors of traumatic brain injury: a critical review. *J Neuropsychiatr Clin Neurosci* 2009; **21:** 362–70.

91 Silver JM, Koumaras B, Meng X, et al. Long-term effects of rivastigmine capsules in patients with traumatic brain injury. *Brain Injury* 2009; **23:** 123–32.

92 Laxton AW, Tang-Wai DF, McAndrews MP, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol* 2010; **68:** 521–34.

93 Cheng H, Tian Y, Hu P, Wang J, Wang K. Time-based prospective memory impairment in patients with thalamic stroke. *Behav Neurosci* 2010; **124:** 152–58.

94 Dewar B-K, Patterson K, Wilson BA, Graham KS. Re-acquisition of person knowledge in semantic memory disorders. *Neuropsychol Rehab* 2009; **19:** 383–421.

95 Laffan AJ, Metzler-Baddeley C, Walker I, et al. Making errorless learning more active: self-generation in an error free learning context is superior to standard errorless learning of face–name associations in people with Alzheimer's disease. *Neuropsychol Rehab* 2010; **20:** 197–211.

96 Moses SN, Ostreicher ML, Rosenbaum RS, Ryan JD. Successful transverse patterning in amnesia using semantic knowledge. *Hippocampus* 2008; **18:** 121–24.

97 Gaggioli A, Meneghini A, Morganti F, Alcaniz M, Riva G. A strategy for computer-assisted mental practice in stroke rehabilitation. *Neurorehabil Neural Repair* 2006; **20:** 503–07.

98 Crosbie JH, Lennon S, Basford JR, McDonough SM. Virtual reality in stroke rehabilitation: still more virtual than real. *Disabil Rehabil* 2007; **29:** 1139–46; discussion 1147–52.

99 Floel A, Cohen LG. Contribution of noninvasive cortical stimulation to the study of memory functions. *Brain Res Rev* 2007; **53:** 250–59.

100 Cicerone KD, Dahlberg C, Malex JF, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch Phys Med Rehabil* 2005; **86:** 1681–92.

101 Martin M, Clare L, Altgassen AM, et al. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev* 2011; **1:** CD006220.

102 Yaffe K, Vittinghoff E, Lindquist K, et al. Posttraumatic stress disorder and risk of dementia among US veterans. *Arch Gen Psychiatr* 2010; **67:** 608–13.