Transient global amnesia: functional anatomy and clinical implications

Thorsten Bartsch, Günther Deuschl

More than 50 years after its initial description, transient global amnesia (TGA) remains one of the most enigmatic syndromes in clinical neurology. Recent MRI data suggest that a transient perturbation of hippocampal function is the functional correlate of TGA because focal diffusion lesions can be selectively detected in the CA1 field of the hippocampal cornu ammonis. Although various factors, such as migraine, focal ischaemia, venous flow abnormalities, and epileptic phenomena, have been suggested to be involved in the pathophysiology of TGA, the factors triggering the emergence of these lesions are still elusive. Recent data suggest that the vulnerability of CA1 neurons to metabolic stress plays a pivotal part in the pathophysiological cascade, leading to an impairment of hippocampal function during TGA. In this Review, we discuss clinical aspects, new imaging findings, and recent clinical–epidemiological data with regard to the phenotype, functional anatomy, and putative cellular mechanisms of TGA.

Lancet Neurol 2010; 9: 205–14

Department of Neurology, University Hospital Schleswig-Holstein, University of Kiel, Kiel, Germany
(T Bartsch MD, G Deuschl MD)

Correspondence to:
Thorsten Bartsch, Department of Neurology, University Hospital Schleswig-Holstein, Schittenhelmstrasse 10, 24105 Kiel, Germany
t.bartsch@neurologie.uni-kiel.de

Introduction

The syndrome of transient global amnesia (TGA) was described independently in two case series by Bender[1] and by Guyotat and Courjon[2] in 1956. However, in 1882 and 1909, Ribot[3] and Benon[4] had already described transient amnestic states suggestive of a TGA.[5] In 1964, Fisher and Adams[6] published a large case series and introduced the term as used today. Since then, the clinical characteristics of TGA have been well described, although the exact aetiology and pathophysiology of this disorder are still not completely understood.[7]

TGA is defined by a sudden onset of an anterograde and retrograde amnesia that lasts up to 24 h. The clinical and neuropsychological aspects of this syndrome have been characterised in recent studies, and several aetiological factors, such as migraine-related mechanisms, focal ischaemia, venous flow abnormalities, and epileptic phenomena, have been suggested to be involved in the pathophysiology.[8–10] Data from neuropsychological studies that characterise the memory impairment of patients with acute TGA show a profound reduction of anterograde and a milder reduction of retrograde episodic memory, including executive functions and recognition.[7,11–17] Thus, given the memory impairment in TGA, an involvement of temporal lobe structures including the hippocampus has long been suggested.[18]

Although the core amnestic syndrome usually lasts substantially less than 24 h, mild subclinical neuropsychological deficits with concomitant vegetative symptoms can last for days after the episode.[7,11,13,17,19] Some studies indicate that a subclinical impairment of memory functions might persist for months after the acute episode.[11,20–23] A recent meta-analysis including 25 studies, however, could not find differences in the long-term cognitive performance between patients and healthy controls.[17]

Recent high-resolution imaging data suggest an involvement of memory circuits in the mesiotemporal region, as hyperintense MRI lesions can be detected in the hippocampal formation in TGA.[7,10,24–28] An analysis of the functional anatomy of these lesions shows a selective distribution within the CA1 subfield of the hippocampal cornu ammonis.[7,24] Further imaging findings have implicated cellular mechanisms in the development of these lesions, suggesting that the selective vulnerability of CA1 neurons to metabolic stress plays a crucial part in the pathophysiological cascade that leads to a transient perturbation of memory pathways in TGA.

In this Review, we summarise clinically relevant aspects and give practical recommendations for the diagnosis and imaging of patients with acute TGA. We describe recent imaging findings and epidemiological studies and we present a pathophysiological framework of TGA.

Epidemiology

Most systematic epidemiological studies show that the incidence of TGA ranges between 3 and 8 per 100 000 people per year.[29–32] 75% of attacks occur in people aged between 50 and 70 years, and occurrence in patients younger than 40 years of age is rare. The rate of recurrence of a second or a third episode varies across studies; a recent thorough meta-analysis described the rate of annual recurrence to be between 6% and 10%.[31]

The nature of precipitating events directly before a TGA has been widely studied. Events frequently described include sudden immersion in cold or hot water, physical exertion, emotional or psychological stress, pain, medical procedures, sexual intercourse, and Valsalva-associated manoeuvres,[7,8,32–34] and such events have been observed in 50–90% of documented attacks (figure 1). Data from epidemiological studies suggest that certain personality traits might be relevant in the aetiology of TGA. In their large case series, Quinette and colleagues[31] found an increased frequency of patients who had psychological or emotional instability. Pantoni and colleagues[33,35,36] found a higher occurrence of a personal or family history of psychiatric disorders or phobic traits in comparison with patients who have had a transient ischaemic attack or healthy controls. By use of a multivariate analysis of 142 patients with TGA, Quinette and colleagues[31] classified 63 patients into three groups according to their precipitating events and clinical characteristics: in men,

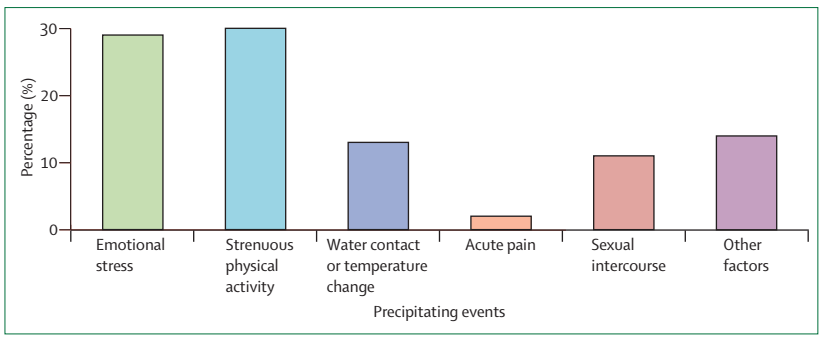

Figure 1: **Frequency of various precipitating events directly before the onset of an acute TGA**
Data from 631 TGA episodes pooled from published papers showing the frequency of various precipitating events directly before the onset of an acute TGA.[7,31] For reasons of comparability, we used the classification of events as outlined by Quinette and colleagues.[31] This classification does not account for multiple overlapping factors, such as Valsalva-associated manoeuvres, that might occur under various conditions. Other factors include those that cannot be clearly classified or are not discernible. Data from Bartsch and colleagues[7] and Quinette and colleagues.[31]

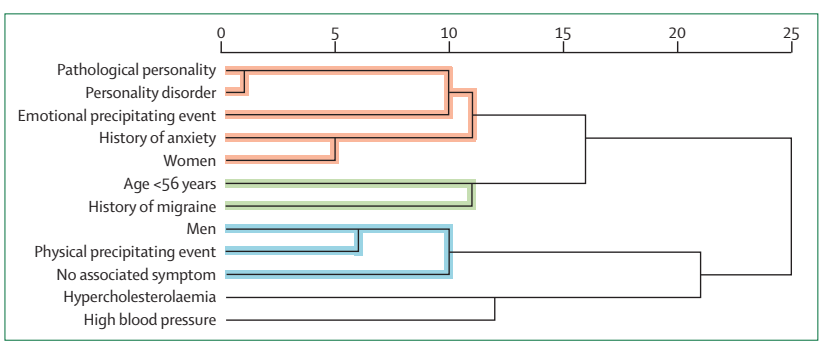

Figure 2: **Clinical and epidemiological characteristics of patients with TGA**
Hierarchical cluster analysis of 63 patients with TGA into three different classes of patients according to their clinical and epidemiological characteristics (highlighted in orange, green, and blue). In men, the TGA episode occurred more frequently after a strenuous physical event, whereas, in women, TGA was more closely associated with emotional distress, such as arousal, stress, or anxiety. In patients younger than 56 years, TGA was associated with a past history of migraine.[31] The classification of a pathological personality refers to the personality disorder, anxious depressive profile, and emotional instability items as assessed by the Minnesota Multiphasic Personality Inventory.[31] Dendrogramm modified according to the classification by Quinette and colleagues.[31] Calculation of distance (0–25) based on the measure of similarity (Yule's Q) and the cluster algorithm (average linkage). Reprinted from Quinette and colleagues,[31] with permission from Oxford University Press.

the TGA episode occurred more frequently after a strenuous physical event, whereas, in women, TGA was more closely associated with an emotional event, such as arousal, stress, or anxiety. In patients younger than 56 years of age, TGA was associated with a past history of migraine (figure 2).[31,37]

In summary, these results indicate that the occurrence of TGA might be associated with events involving a stress response, an allostatic overload, changes in bodily homeostasis, and emotional state, particularly in susceptible individuals.[19,38]

Diagnostic criteria and differential diagnosis

The diagnosis of TGA is primarily a clinical one and can be made if the following diagnostic criteria by Caplan[37] and Hodges[18] are fulfilled: (i) presence of an anterograde amnesia that is witnessed by an observer, (ii) no clouding of consciousness or loss of personal identity, (iii) cognitive impairment limited to amnesia, (iv) no focal neurological or epileptic signs, (v) no recent history of head trauma or seizures, and (vi) resolution of symptoms within 24 h (panel 1). A temporally graded retrograde amnesia is consistently present during the acute attack in patients with acute TGA, although this feature is not included in the present diagnostic criteria. Mild vegetative symptoms such as headache, nausea, and dizziness might be present during the acute phase. A further diagnostic assessment should be done if vascular risk factors are present, if no reliable witness account is available, or if the symptomatology is ambiguous. The diagnosis of TGA can be positively supported by MRI (figure 3).

There is a limited, but important, range of differential diagnoses that might clinically mimic a TGA (panel 2). A transient ischaemic attack in the vascular distribution of the posterior cerebral artery might show the clinical presentation of an amnestic syndrome.[39] Similarly, an infarction in the territory of the anterior choroidal artery might result in amnestic deficits. The body of the hippocampus is mainly supplied by the posterior cerebral artery, which branches into the proximal posterior cerebral artery, the anterior, middle, and posterior hippocampal artery, and finally into the longitudinal terminal segments of the hippocampal arteries. The head of the hippocampus is supplied by the anterior choroidal artery branching from the internal carotidal artery.[39] Strategic insults in the medial thalamus in the supply territory of the thalamoperforate arteries can result in a diencephalic amnesia.[40] If a stroke is suspected, particularly when additional focal neurological signs can be found, the patient should be evaluated for stroke risk factors and investigated with MRI and/or CT, and receive electrocardiography, blood test, ultrasound of the cranial vessels, and cardiac check-up. Patients with TGA should have an electroencephalogram (EEG) to rule out post-ictal disorders or non-convulsive status epilepticus. Temporal lobe or complex partial seizures might present as transient epileptic amnesia, particularly when repetitive and witnessed episodes of transient amnesia occur (panel 3).[41] TGA is not associated with an altered consciousness, loss of personal identity, or stereotypical movements. EEG during acute TGA does not show abnormalities suggestive of epileptiform activity. Seizures in the course of hypoglycaemia or hypoglycaemia itself can result in an amnestic deficit and might be considered as a differential diagnosis if the patient is young and diabetic. A precipitating head trauma might result in post-traumatic amnesia, and an acute-onset or residual conditions of a herpetic or a limbic encephalitis might also present with an amnestic syndrome, although these are usually accompanied with confusion and focal neurological signs.

Intoxications with drugs that affect the CNS, such as hypnotics, benzodiazepines, opioids, or antidepressants, might be considered as they can mimic an acute amnestic syndrome, although patients typically show an altered state of consciousness with slowness, drowsiness, or sleepiness (panel 4). Obtaining a drug history is

mandatory in these patients. Psychiatric disorders can also be considered as a differential diagnosis, such as dissociative episodes, psychogenic fugues, or an acute episode of depression, including side-effects of psychiatric pharmacotherapy such as an anticholinergic or serotonergic syndrome.[43] Functional amnesias are mostly characterised by a prominent retrograde amnesia.[44]

Pathophysiological mechanisms

Since its description, several pathophysiological mechanisms, such as migraine-related mechanisms, hypoxic–ischaemic events, venous flow abnormalities, psychological mechanisms, and epilepsy-related activity, have been suggested to be associated with the pathophysiology of TGA.[9] As many patients report Valsalva-associated manoeuvres before the onset of TGA, recent studies have investigated the possibility of an increased venous pressure leading to a hippocampal venous congestion with subsequent ischaemia.[8,45] A high rate of retrograde flow patterns in the jugular vein during the Valsalva manoeuvre in combination with a high rate of insufficient jugular vein valves in patients with TGA was described compared with controls.[8,45–50] Chung and colleagues[50] showed that, by use of time-of-flight MRI in ten patients with TGA, compression of the brachiocephalic vein leads to a retrograde intracranial venous flow in half the patients. The retrograde flow was found only in the left side. Akkawi and colleagues[51] found a predominant right-sided internal jugular vein incompetence. Combining ultrasonography and magnetic resonance venography in patients with TGA with and without a preceding Valsalva manoeuvre, a correlation between intracranial venous drainage patterns and jugular valve insufficiency was not found, arguing against a direct association between jugular flow and TGA.[48,52] Furthermore, it seems difficult to link the discrete and focal hippocampal lesions found in TGA with a global increase in intracranial venous pressure.

TGA-related mechanisms and stroke

Given the abrupt onset of TGA and imaging findings, stroke-like mechanisms in terms of a haemodynamic or thromboembolic aetiology have been suggested to be involved in the aetiology of TGA.[27,53–55] However, data from several systematic case-control studies that compared patients with TGA and patients with transient ischaemic attacks did not find an association between the frequency of stroke risk factors and TGA, although an increased risk for TGA was associated with a history of migraine.[30,36,54,56–59] Nevertheless, one meta-analysis confirmed that there is no association between vascular risk factors and TGA, including migraine.[31] Compared with patients with a transient ischaemic attack, patients with TGA have a better prognosis with regard to further cerebrovascular events.[1,29,30,32,56,57,60,61] Accordingly, further imaging assessments in patients with TGA do not show abnormalities in intracranial magentic resonance angiography and in perfusion-weighted imaging during acute episodes, thus making the possibility of an arterial ischaemia less likely.[7,62,63] However, a study that combined duplex sonography and MRI reported an increased intima-media thickness in the common carotid arteries and a high occurrence of carotid plaques in patients with TGA in whom hippocampal diffusion lesions could be found, suggesting a high prevalence of artherosclerosis in these patients.[54] Enzinger and colleagues[59] evaluated MRI correlates of cerebral small-vessel disease in patients with TGA with and without concomitant hippocampal lesions seen on diffusion-weighted imaging (DWI), but could not find an increased rate of microangiopathic white matter hyperintensities and lacunar lesions or an increased frequency of cerebrovascular risk factors. Furthermore, hippocampal infarcts caused by arterial ischaemia in the posterior cerebral artery show a different phenotype compared with

Panel 1: Diagnostic criteria for transient global amnesia by Caplan[37] and Hodges[18]

- Presence of an anterograde amnesia, which is witnessed by an observer
- No clouding of consciousness or loss of personal identity
- Cognitive impairment limited to amnesia
- No focal neurological or epileptic signs
- No recent history of head trauma or seizures
- Resolution of symptoms within 24 h
- Mild vegetative symptoms (headache, nausea, dizziness) might be present during the acute phase

Panel 2: Considerations in the differential diagnosis of acute amnestic syndromes

- Ischaemia in the posterior cerebral circulation
- Intoxication, adverse drug side-effects
- Complex focal seizures, transient epileptic amnesia, post-ictal conditions
- Psychogenic fugue, dissociative disorders
- Post-traumatic amnesia
- Hypoglycaemia

Panel 3: Diagnostic criteria of transient epileptic amnesia[41,42]

- History of recurrent witnessed episodes of transient amnesia
- Cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
- Evidence for a diagnosis of epilepsy based on one or more of the following:
  - Epileptiform abnormalities on electroencephalography
  - The concurrent onset of other clinical features of epilepsy (eg, lip-smacking, olfactory hallucinations)
  - Clear response to anticonvulsant therapy

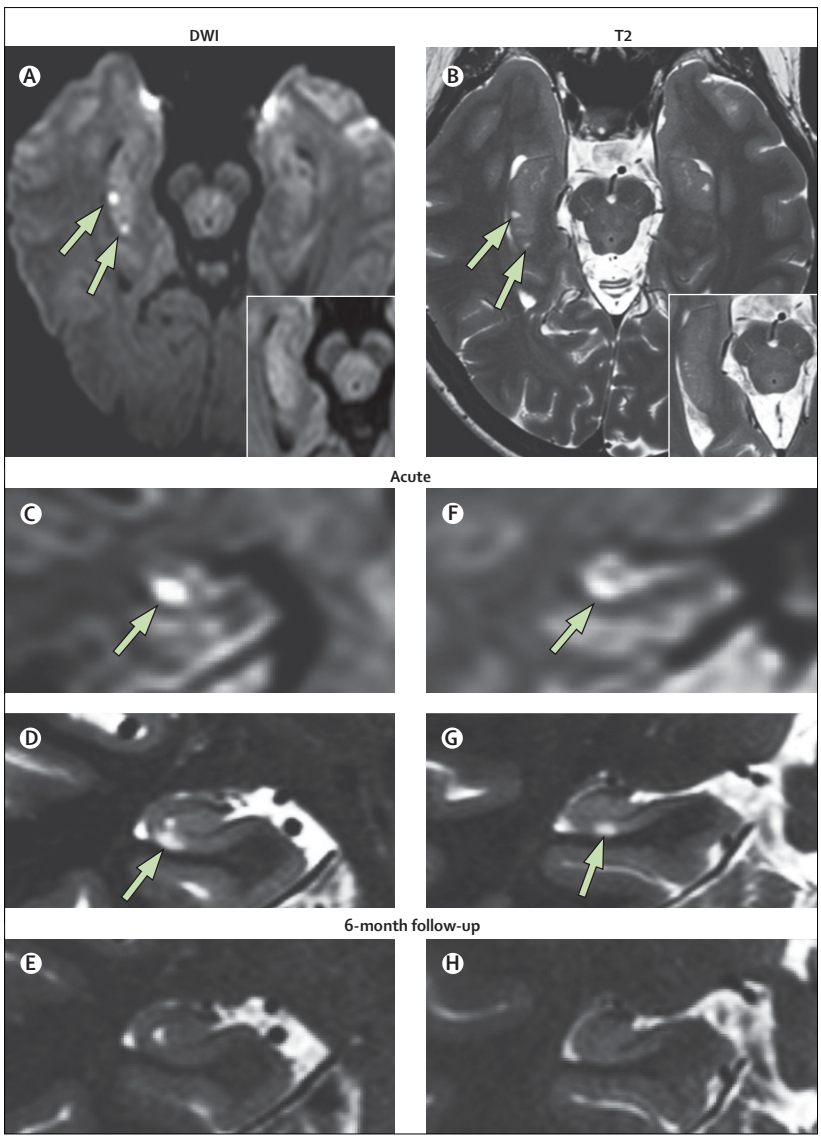

Figure 3: **MRI findings in TGA**
Representative 3T MRI of a patient with TGA with typical lesions (arrows) shown on DWI (A) and corresponding lesions seen on T2-weighted images (B). Note the two unilateral lesions in the lateral hippocampus. Small insets in A and B show a 6-month follow-up scan. Insets C and F show magnified DWI lesions in the coronal plane, with corresponding lesions seen on T2-weighted scans (D and G), indicating lesions in the CA1 field of the cornu ammonis. Insets E and H show a 6-month follow-up coronal T2 image, with a complete resolution of lesions. For reasons of identification of identical slices, slice thickness of follow-up images was 1 mm. Images courtesy of Olav Jansen, Department of Neuroradiology, University Hospital, Kiel, Germany. DWI=diffusion-weighted imaging.

hippocampal lesions caused by TGA with regard to lesion size and distribution.[39]

TGA and migraine-related mechanisms

Pathophysiological mechanisms linking migraine and migraine with aura with TGA have been widely discussed, as several studies have reported a higher incidence of a history of migraine in patients with TGA than in healthy controls.[31,58,64] However, patients rarely had an active migraine in the months before TGA or migrainous

Panel 4: **Practical guide for the bedside diagnostic evaluation of acute transient global amnesia**

Signs supportive of diagnosis

- Are there strenuous physical activities or strong emotional events preceding the onset of symptoms?
- Are symptoms limited to loss of memory (eg, three-word test/word list, recall of recent events)?
- Does the patient repetitively ask the same questions?
- Is the patient cooperative, able to follow your requests, and able to correctly name things?

Signs not supportive of diagnosis

- Are there indications of a hypoglycaemia, trauma, seizure, or recent changes in medication?
- Is there evidence of further neurological signs?
- Is the patient agitated, sleepy, or drowsy?
- Can the patient recall details and the temporal course of the acute episode?
- Is there a sole retrograde amnesia?
- Are there repetitive amnestic episodes (>3 per year)?

features during the acute TGA, indicating that an acute TGA is not a reflection of an episode of acute migraine with or without aura. The occurrence of headaches during the acute TGA episode is not associated with a history of migraine.[31] A study of 63 patients identified a past history of migraine as a risk factor in patients with TGA who were younger than 56 years of age.[31]

A key pathophysiological mechanism in migraine is cortical spreading depression that mirrors a glutamate-mediated transient neuronal and glial depolarisation, which is followed by a long-lasting suppression of neuronal activity. Cortical spreading depression propagates across the cortex with a speed of 3–5 mm/min and is accompanied by a short-lasting hyperperfusion followed by a hypoperfusion. Experimental and clinical findings strongly suggest that cortical spreading depression is the neurophysiological correlate of migraine with aura.[65] This event can also be elicited in the hippocampus, where it propagates across the cortical surface and modulates excitability of CA1 neurons and alters the distribution of excitatory transmitter receptors, including glutamate.[66,67] Furthermore, cortical spreading depression is accompanied by a decrease in the apparent diffusion coefficient, indicating decreased cellular diffusion.[68] Importantly, as seen in the rodent hippocampus, cortical spreading depression might lead to hypoxic states in the CA1 field with subsequent cellular damage to CA1 neurons.[69]

Cortical spreading depression-related mechanisms in the hippocampus might thus affect CA1 neuronal function and impair structural integrity. In addition to the general vulnerability of CA1 neurons, these events might be a neurophysiological trigger that elicits cellular metabolic changes, resulting in TGA.[64,70] However, compared with neocortical tissue, the threshold for

eliciting a cortical spreading depression in the hippocampus is substantially higher and, during an acute TGA, patients do not typically show symptoms suggestive for acute migraine attack or migraine with aura. In human beings, a cortical spreading depression in the hippocampus has not yet been shown. Parenchymal diffusion changes in the neocortex during migraine with aura as visualised by MRI show a different temporal course and distribution than those seen with the hippocampal lesions found in TGA.[71]

Pathophysiological mechanisms of hippocampal dysfunction

The CA1 sector of the hippocampal cornu ammonis shows a selective vulnerability to metabolic and oxidative stress caused by hypoxaemia, β-amyloid-induced neurotoxicity, and ischaemia mediated by glutamate overload and calcium influx.[72,73] The exact mechanisms underlying this region-specific vulnerability and glutamate toxicity, however, are not well understood, but could include genomic-determined differences in the tolerability to glutamate and distribution of glutamate receptors, as well as an increase in excitatory synaptic transmission.[74,75]

Several studies have described emotional, physical, and behavioural stress situations preceding the onset of TGA (figure 1).[18,30,31,33,34,36,38,57] In this context, recent data from studies that investigated stress responses in the hippocampus of animals show that acute emotional and behavioural stress impairs long-term potentiation and enhances long-term depression in CA1 neurons, leading to a disruption of hippocampus-dependent memory.[76] Acute stress might thus modulate CA1 synaptic mechanisms involved in learning and memory.[76–78] The enhanced glutamatergic transmission and increased calcium influx in CA1 neurons in response to stress is mediated by increased levels of corticotropin-releasing hormone, neurosteroids, β-adrenoceptor agonists, and corticosterone acting via CA1 mineralocorticoid and glucocorticoid receptors.[79] This potentiated calcium exposure might be a risk factor for CA1 neurons with regard to an increased metabolic vulnerability and thus potentially impairing their structural integrity.[79] These mechanisms might also be involved in the pathophysiological cascade, and could selectively affect hippocampal CA1 neurons with a subsequent perturbation of memory pathways, which might result in acute TGA (figure 4). The particular susceptibility of the hippocampus with regard to behavioural stress might also have a role in memory deficits in disorders such as post-traumatic stress syndrome and depression. More data are needed to understand the pathophysiological role of the CA1 hippocampal involvement in patients with TGA, and the nature of the trigger eliciting the lesions.

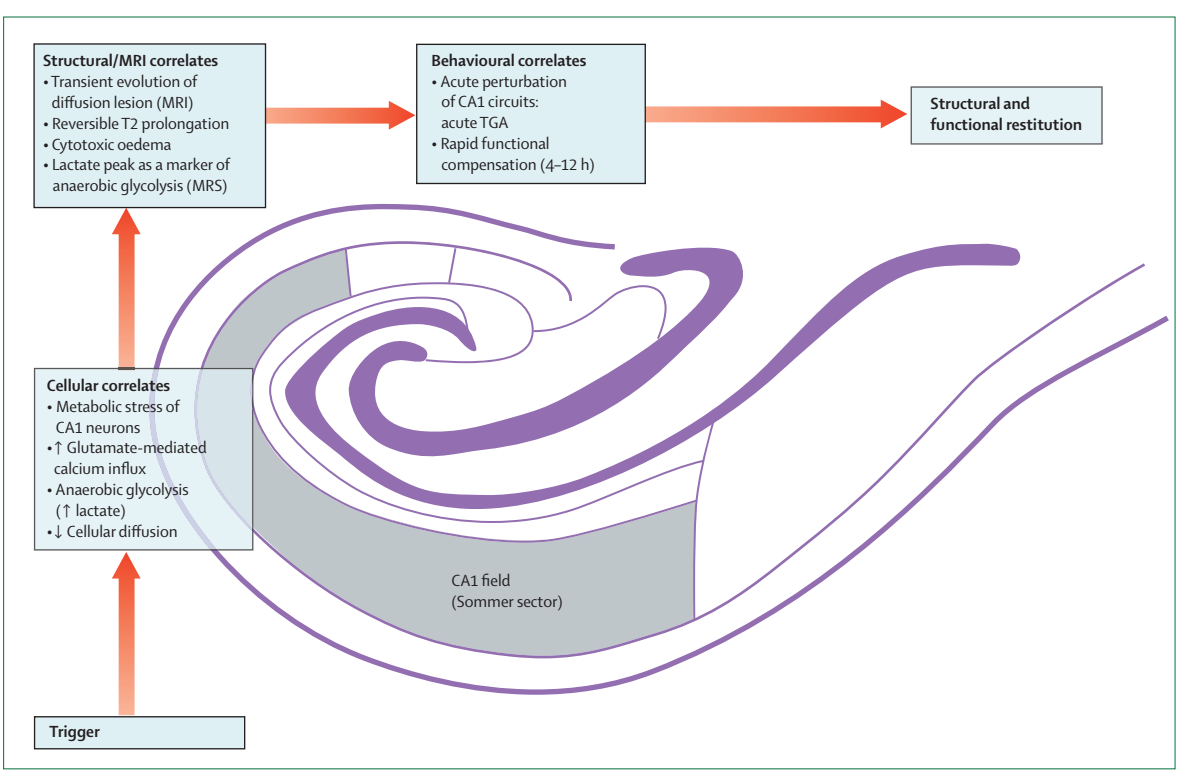

Figure 4: **Pathophysiological framework of TGA**
Schematic model highlighting the cellular mechanisms and pathophysiological cascade in the CA1 field of the cornu ammonis involved in the emergence of hippocampal TGA lesions. This model does not account for the spectrum and nature of triggers in inducing the pathophysiological cascade. Please see text for details. MRS=magnetic resonance spectroscopy. TGA=transient global amnesia.

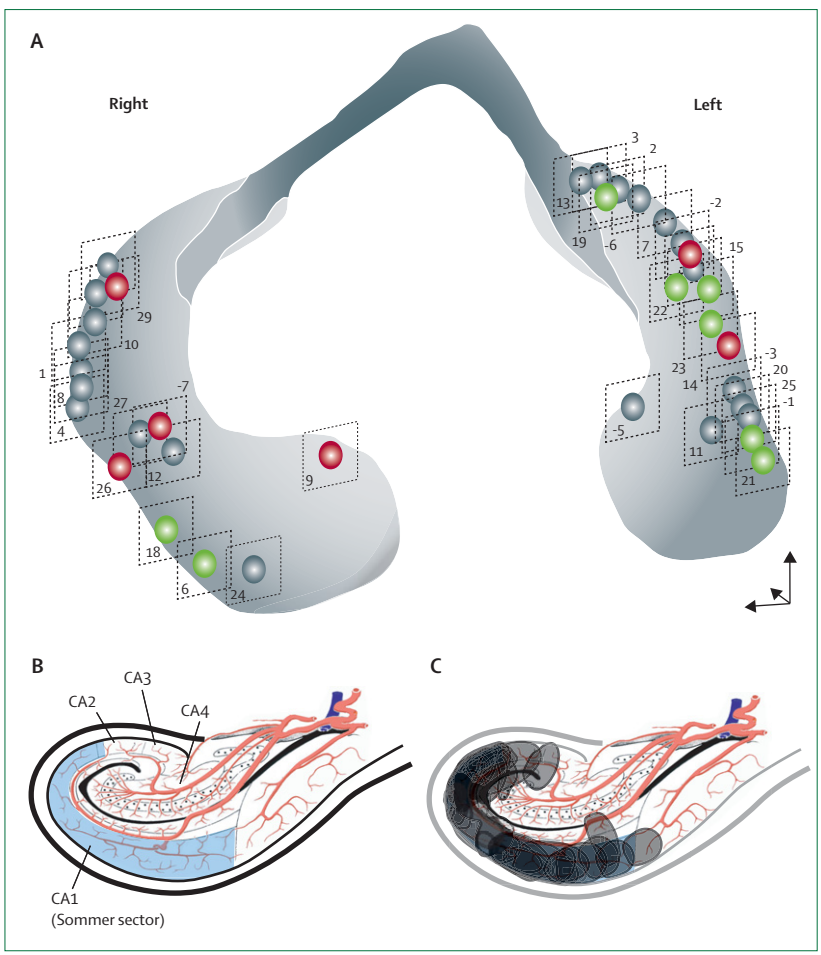

Figure 5: **Model of the hippocampus showing the distribution of the MRI lesions found in patients with TGA**
(A) Green spots indicate lesions in areas that cause impaired verbal memory and red spots indicate lesions in areas that cause nonverbal memory deficits. Grey spots indicate areas of normal memory testing (patients tested >24 h after acute TGA).[7] (B) Anatomical template showing the different subfields of the hippocampal cornu ammonis as described by Lorento de No.[7,116] (C) Distribution of diffusion-weighted imaging/T2 lesions within the cornu ammonis: the lesions are confined to the CA1 subfield.[7] Reprinted from Bartsch and colleagues,[7] with permission from Oxford University Press.

Neuroimaging

PET and SPECT

Quantitative imaging of changes of regional cerebral glucose, oxygen metabolism, or cerebrovascular blood flow in TGA have been studied by use of PET and single photon emission computed tomography (SPECT). In some studies, mesiotemporal flow changes have been described.[80–93] However, most studies have also noted concomitant decreased or increased changes in cerebral blood flow in other anatomical structures, such as unilateral or bilateral thalamic, prefrontal, frontal, amygdalian, striatal, cerebellar, occipital, precentral, and postcentral areas.[15,27,80,81,84,85,87,90,92,94–100] In some studies, either no mesiotemporal changes, no cerebral changes, or a global hypoperfusion were detected.[88,101–103] In summary, the imaging data derived from PET and SPECT studies are difficult to compare and interpret. Most changes normalised on follow-up examination. The variabilities in PET and SPECT are probably associated with differences in the study designs, such as the imaging protocol and resolution, and the latency of scanning, frequently done days or weeks after the acute TGA and thus not covering the initial pathophysiological event.[92] A correlation between SPECT and MRI in the time window of 24–73 h after onset has been found in a study including only six patients. In five patients, a predominant hypoperfusion in the cerebellar vermis was observed in combination with punctuate DWI lesions in the hippocampus,[104] whereas in another patient a bilateral hypoperfusion in the temporal lobes was detected by use of SPECT.[55] Functional MRI was used in two patients during an acute TGA to assess memory function and cerebral activation patterns. In both patients, there was reduced or no activation in temporal lobe structures during encoding of visual scenes or recognition of old scenes, thus reflecting the functional impairment of temporal lobe structures.[105,106]

MRI

Use of structural imaging with MRI has detected abnormalities in memory-relevant structures of the mesiotemporal region. Early results have been inconsistent and controversial about the type and location of signal abnormalities described in some patients.[54,62,107–115] Recent data from studies that used high-resolution MRI have shown that focal hyperintense lesions correlating to restricted diffusion in the lateral hippocampus can now be reliably detected (figure 3 and figure 5).[7,10,24–28] The detection rate of these lesions can be improved by up to 85% with optimised MRI parameters and by acknowledging the time course of the lesion (panel 5).

A detailed analysis of the location of hippocampal lesion shows that almost all lesions can be selectively found in the area corresponding to the CA1 sector (Sommer sector) of the hippocampal cornu ammonis.[7,24] Lesions seen on DWI can also be detected by use of T2-weighted images. The size of focal hyperintense lesions ranges from 1 to 5 mm. Single or multiple lesions in the T2-weighted images show an oedema-like configuration and are usually clearly distinguishable from the sharply configurated residual cavities of the vestigial hippocampal sulcus. Recent neuroimaging data have shown that the level of detection of hippocampal DWI lesions in patients with TGA is dependent on the time of imaging. The maximum level of detection occurs within 48–72 h after onset of symptoms, so early imaging might not detect these lesions.[24,112] The identification of lesions is dependent on the sensitivity of the magnetic resonance scanner.[24,28] The evolution of hippocampal lesions was studied by measuring the time course of the apparent diffusion coefficient of hippocampal DWI lesions in patients with TGA by use of serial 3T MRI.[10,28] The acute phase of TGA

typically lasts no longer than 12 h. The lesions can be seen to develop over 24–48 h by use of DWI and can be detected for up to 7–10 days after the TGA. Correspondingly, apparent diffusion coefficient values show a minimum value between 24 h and 72 h and normalise around day 10.[10] By use of serial MRI, weak DWI lesions could retrospectively be detected in those patients scanned within a very early time window (<6 h after onset of symptoms).[10,24] In a substantial number of patients, however, there are no discernible DWI lesions despite typical symptomatology. This suggests a threshold-dependent phenomenon of the pathophysiological mechanisms, leading to functional deficits in CA1 but not to signal changes detectable with MRI. However, in patients without discernible hippocampal lesions, a different aetiology leading to the amnestic syndrome cannot be ruled out. Impairments in diffusion indicate cytotoxic oedema in affected tissue, and these impairments can be observed in other disorders such as encephalitis, multiple sclerosis, and epilepsy and thus are not specific for ischaemic events. Although the course of diffusion changes in TGA does mimic the temporal evolution of ischaemic lesions, structural sequelae in CA1 detectable with high-resolution MRI have not been observed so far (figure 3).[7,117]

A recent retrospective, post-hoc study that used structural MRI reported an increased prevalence of hippocampal cavities corresponding to the vestigial hippocampal sulcus in patients with TGA compared with controls.[118] This higher load of pre-existing cavities might further contribute to the vulnerability of hippocampal CA1 neurons to metabolic or vascular stress.

In addition to DWI, which provides information about the structural integrity of brain tissue, magnetic resonance spectroscopy enables assessment of in vivo metabolic changes of cerebral structures. Complementary imaging studies combining MRI and focal magnetic resonance spectroscopy of CA1 DWI/T2 lesions revealed a distinct lactate peak.[26] As a marker of anaerobic glycolysis, lactate thus indicates acute metabolic stress of CA1 neurons in TGA.[26] The lactate peak was confined to the DWI lesion and could not be detected in peri-focal tissue, suggesting that the metabolic changes in CA1 neurons that indicate metabolic stress are indeed highly focal and not suggestive of a globally altered metabolic status in the hippocampus.

The evolution of hippocampal CA1 lesions in the course of TGA strongly suggests a transient perturbation of hippocampal or mesiotemporal memory circuits. Clinical and experimental data show that hippocampal CA1 neurons are crucially involved in the process of memory consolidation, constituting a relay function in direct and polysynaptic intrahippocampal circuits. On a cellular network level, CA1 neurons of the cornu ammonis receive information input from the parahippocampal postrhinal and medial entorhinal cortex (layer III) via the perforant pathways and via Schaffer collaterals from CA3 neurons. Postsynaptic output from CA1 neurons projects via the subiculum to deep layers of the entorhinal cortex, so that lesions in CA1 affect the output relay function of the hippocampus.[119]

Panel 5: Practical recommendations for imaging in transient global amnesia[10,28]

- MRI, preferentially on a 3T unit
- Time window of imaging: 24–72 h after onset
- DWI/apparent diffusion coefficient transverse oblique plane parallel to the hippocampus and coronal perpendicular to the hippocampus
- T2 transverse and coronal orientation as for DWI
- 3-mm (DWI) or 2-mm (T2) slice thickness to minimise partial volume-averaging effect
- High *b* value (*b*=2000–3000 s/mm²)

DWI=diffusion-weighted imaging.

Conclusions and clinical implications

Recent neuroimaging findings suggest that a transient perturbation of hippocampal function is the correlate of TGA, as focal lesions can be reliably detected in the CA1 field of the cornu ammonis by use of DWI. The maximum level of detection of these lesions is 24–72 h after onset of symptoms. Although the diagnosis of TGA is primarily a clinical one, neuroimaging in TGA can positively support the diagnosis. Further investigations, including imaging, can be recommended if cerebrovascular risk factors are present, the patient is younger than 50 years, or the symptomatology is ambiguous. If a patient has repetitive amnestic episodes, EEG is mandatory to exclude a transient epileptic amnesia. Epidemiological data suggest that the recurrence rate of TGA is low, but a few patients could have a second episode. To date, data from MRI has not found evidence for structural sequelae of these hippocampal lesions, and recent neuropsychological findings have also not found evidence for clinically relevant chronic neuropsychological deficits. Neuroimaging data suggest that the vulnerability of hippocampal CA1 neurons has a pivotal role in the pathophysiological cascade leading

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "amnesia", "transient global amnesia", "TGA", "hippocampus", and "CA1" between January, 1990, and August, 2009. Only papers published in English were reviewed. The references from identified papers and the authors' own files were also searched for relevant publications. The final reference list was chosen on the basis of relevance to the topics covered in this Review (eg, their originality, contribution to hippocampal and TGA anatomy and physiology, pathophysiology, diagnosis or treatment).

to an impairment of hippocampal function during TGA.

Future research should focus on elucidating pathophysiological correlates of the acute phase, particularly on deciphering which trigger induces the pathophysiological cascade that affects CA1 neurons. TGA could be used in future neuropsychological studies as a natural lesion model of a perturbation of hippocampal CA1 neurons. Understanding the pathophysiological mechanisms in TGA could facilitate insights in other neurological disorders that affect the hippocampus, such as stroke, encephalitis, and Alzheimer's disease.

Contributors

TB prepared the draft of this Review. GD edited the Review.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments

We thank Karsten Alfke and Olav Jansen for helpful input and support. This work was supported by a grant from the Deutsche Forschungsgemeinschaft (SFB 654) and the Faculty of Medicine, University of Kiel, Germany.

References

1 Bender MB. Syndrome of isolated episode of confusion with amnesia. *J Hillside Hosp* 1956; 5: 212–15.
2 Guyotat M, Courjon J. Les ictus amnésiques. *J Med Lyon* 1956; 37: 697–701.
3 Ribot T. Diseases of memory. New York: Appleton, 1882.
4 Benon R. Les ictus amnésiques dans les démences 'organiques'. *Ann Méd Psychol* 1909; **67:** 207–19.
5 Pearce JM, Bogousslavsky J. 'Les ictus amnesiques' and transient global amnesia. *Eur Neurol* 2009; **62:** 188–92.
6 Fisher CM, Adams RD. Transient global amnesia. *Acta Neurol Scand Suppl* 1964; **40** (suppl 9): 1–83.
7 Bartsch T, Alfke K, Stingele R, et al. Selective affection of hippocampal CA-1 neurons in patients with transient global amnesia without long-term sequelae. *Brain* 2006; **129:** 2874–84.
8 Lewis SL. Aetiology of transient global amnesia. *Lancet* 1998; **352:** 397–99.
9 Sander K, Sander D. New insights into transient global amnesia: recent imaging and clinical findings. *Lancet Neurol* 2005; **4:** 437–44.
10 Bartsch T, Alfke K, Deuschl G, Jansen O. Evolution of hippocampal CA-1 diffusion lesions in transient global amnesia. *Ann Neurol* 2007; **62:** 475–80.
11 Hodges JR, Ward CD. Observations during transient global amnesia. A behavioural and neuropsychological study of five cases. *Brain* 1989; **112:** 595–620.
12 Eustache F, Desgranges B, Laville P, et al. Episodic memory in transient global amnesia: encoding, storage, or retrieval deficit? *J Neurol Neurosurg Psychiatry* 1999; **66:** 148–54.
13 Quinette P, Guillery B, Desgranges B, de la Sayette V, Viader F, Eustache F. Working memory and executive functions in transient global amnesia. *Brain* 2003; **126:** 1917–34.
14 Guillery-Girard B, Desgranges B, Urban C, Piolino P, de la Sayette V, Eustache F. The dynamic time course of memory recovery in transient global amnesia. *J Neurol Neurosurg Psychiatry* 2004; **75:** 1532–40.
15 Zeman AZ. Episodic memory in transient global amnesia. *J Neurol Neurosurg Psychiatry* 1999; **66:** 135.
16 Jager T, Szabo K, Griebe M, Bazner H, Moller J, Hennerici MG. Selective disruption of hippocampus-mediated recognition memory processes after episodes of transient global amnesia. *Neuropsychologia* 2009; **47:** 70–76.
17 Jager T, Bazner H, Kliegel M, Szabo K, Hennerici MG. The transience and nature of cognitive impairments in transient global amnesia: a meta-analysis. *J Clin Exp Neuropsychol* 2009; **31:** 8–19.
18 Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *J Neurol Neurosurg Psychiatry* 1990; **53:** 834–43.
19 Kessler J, Markowitsch HJ, Rudolf J, Heiss WD. Continuing cognitive impairment after isolated transient global amnesia. *Int J Neurosci* 2001; **106:** 159–68.
20 Hodges JR, Oxbury SM. Persistent memory impairment following transient global amnesia. *J Clin Exp Neuropsychol* 1990; **12:** 904–20.
21 Gallassi R, Stracciari A, Morreale A, Lorusso S, Rebucci GG, Lugaresi E. Transient global amnesia: neuropsychological findings after single and multiple attacks. *Eur Neurol* 1993; **33:** 294–98.
22 Borroni B, Agosti C, Brambilla C, et al. Is transient global amnesia a risk factor for amnestic mild cognitive impairment? *J Neurol* 2004; **251:** 1125–27.
23 Guillery-Girard B, Quinette P, Desgranges B, et al. Long-term memory following transient global amnesia: an investigation of episodic and semantic memory. *Acta Neurol Scand* 2006; **114:** 329–33.
24 Sedlaczek O, Hirsch JG, Grips E, et al. Detection of delayed focal MR changes in the lateral hippocampus in transient global amnesia. *Neurology* 2004; **62:** 2165–70.
25 Lee HY, Kim JH, Weon YC, et al. Diffusion-weighted imaging in transient global amnesia exposes the CA1 region of the hippocampus. *Neuroradiology* 2007; **49:** 481–87.
26 Bartsch T, Alfke K, Wolff S, Rohr A, Jansen O, Deuschl G. Focal MR spectroscopy of hippocampal CA-1 lesions in transient global amnesia. *Neurology* 2008; **70:** 1030–35.
27 Yang Y, Kim S, Kim JH. Ischemic evidence of transient global amnesia: location of the lesion in the hippocampus. *J Clin Neurol* 2008; **4:** 59–66.
28 Weon YC, Kim JH, Lee JS, Kim SY. Optimal diffusion-weighted imaging protocol for lesion detection in transient global amnesia. *AJNR Am J Neuroradiol* 2008; **29:** 1324–28.
29 Miller JW, Petersen RC, Metter EJ, Millikan CH, Yanagihara T. Transient global amnesia: clinical characteristics and prognosis. *Neurology* 1987; **37:** 733–37.
30 Hodges JR, Warlow CP. The aetiology of transient global amnesia. A case-control study of 114 cases with prospective follow-up. *Brain* 1990; **113:** 639–57.
31 Quinette P, Guillery-Girard B, Dayan J, et al. What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases. *Brain* 2006; **129:** 1640–58.
32 Berli R, Hutter A, Waespe W, Bachli EB. Transient global amnesia—not so rare after all. *Swiss Med Wkly* 2009; **139:** 288–92.
33 Inzitari D, Pantoni L, Lamassa M, Pallanti S, Pracucci G, Marini P. Emotional arousal and phobia in transient global amnesia. *Arch Neurol* 1997; **54:** 866–73.
34 Rosler A, Mras GJ, Frese A, Albert I, Schnorpfeil F. Precipitating factors of transient global amnesia. *J Neurol* 1999; **246:** 53–54.
35 Pantoni L, Lamassa M, Inzitari D. Transient global amnesia: a review emphasizing pathogenic aspects. *Acta Neurol Scand* 2000; **102:** 275–83.
36 Pantoni L, Bertini E, Lamassa M, Pracucci G, Inzitari D. Clinical features, risk factors, and prognosis in transient global amnesia: a follow-up study. *Eur J Neurol* 2005; **12:** 350–56.
37 Caplan L. Transient global amnesia. In: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of Clinical Neurology. Amsterdam: Elsevier, 1985: 205–18.
38 Merriam AE, Wyszynski B, Betzler T. Emotional arousal-induced transient global amnesia. A clue to the neural transcription of emotion? *Psychosomatics* 1992; **33:** 109–13.
39 Szabo K, Forster A, Jager T, et al. Hippocampal lesion patterns in acute posterior cerebral artery stroke: clinical and MRI findings. *Stroke* 2009; **40:** 2042–45.
40 Graff-Radford NR, Tranel D, Van Hoesen GW, Brandt JP. Diencephalic amnesia. *Brain* 1990; **113:** 1–25.
41 Butler CR, Graham KS, Hodges JR, Kapur N, Wardlaw JM, Zeman AZ. The syndrome of transient epileptic amnesia. *Ann Neurol* 2007; **61:** 587–98.
42 Zeman AZ, Boniface SJ, Hodges JR. Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. *J Neurol Neurosurg Psychiatry* 1998; **64:** 435–43.
43 Kopelman MD, Panayiotopoulos CP, Lewis P. Transient epileptic amnesia differentiated from psychogenic "fugue": neuropsychological, EEG, and PET findings. *J Neurol Neurosurg Psychiatry* 1994; **57:** 1002–04.

44 Kritchevsky M, Zouzounis J, Squire LR. Transient global amnesia and functional retrograde amnesia: contrasting examples of episodic memory loss. *Philos Trans R Soc Lond B Biol Sci* 1997; **352:** 1747–54.

45 Akkawi NM, Agosti C, Rozzini L, Anzola GP, Padovani A. Transient global amnesia and disturbance of venous flow patterns. *Lancet* 2001; **357:** 957.

46 Sander D, Winbeck K, Etgen T, Knapp R, Klingelhofer J, Conrad B. Disturbance of venous flow patterns in patients with transient global amnesia. *Lancet* 2000; **356:** 1982–84.

47 Akkawi NM, Agosti C, Anzola GP, et al. Transient global amnesia: a clinical and sonographic study. *Eur Neurol* 2003; **49:** 67–71.

48 Schreiber SJ, Doepp F, Klingebiel R, Valdueza JM. Internal jugular vein valve incompetence and intracranial venous anatomy in transient global amnesia. *J Neurol Neurosurg Psychiatry* 2005; **76:** 509–13.

49 Nedelmann M, Eicke BM, Dieterich M. Increased incidence of jugular valve insufficiency in patients with transient global amnesia. *J Neurol* 2005; **252:** 1482–86.

50 Chung CP, Hsu HY, Chao AC, Chang FC, Sheng WY, Hu HH. Detection of intracranial venous reflux in patients of transient global amnesia. *Neurology* 2006; **66:** 1873–77.

51 Akkawi NM, Agosti C, Borroni B, Padovani A. Detection of intracranial venous reflux in patients of transient global amnesia. *Neurology* 2007; **68:** 163.

52 Bettermann K. Transient global amnesia: the continuing quest for a source. *Arch Neurol* 2006; **63:** 1336–38.

53 Felix MM, Castro LH, Maia AC Jr, da Rocha AJ. Evidence of acute ischemic tissue change in transient global amnesia in magnetic resonance imaging: case report and literature review. *J Neuroimaging* 2005; **15:** 203–05.

54 Winbeck K, Etgen T, von Einsiedel HG, Rottinger M, Sander D. DWI in transient global amnesia and TIA: proposal for an ischaemic origin of TGA. *J Neurol Neurosurg Psychiatry* 2005; **76:** 438–41.

55 Di Filippo M, Calabresi P. Ischemic bilateral hippocampal dysfunction during transient global amnesia. *Neurology* 2007; **69:** 493.

56 Melo TP, Ferro JM, Ferro H. Transient global amnesia. A case control study. *Brain* 1992; **115:** 261–70.

57 Zorzon M, Antonutti L, Mase G, Biasutti E, Vitrani B, Cazzato G. Transient global amnesia and transient ischemic attack. Natural history, vascular risk factors, and associated conditions. *Stroke* 1995; **26:** 1536–42.

58 Schmidtke K, Ehmsen L. Transient global amnesia and migraine. A case control study. *Eur Neurol* 1998; **40:** 9–14.

59 Enzinger C, Thimary F, Kapeller P, et al. Transient global amnesia: diffusion-weighted imaging lesions and cerebrovascular disease. *Stroke* 2008; **39:** 2219–25.

60 Gandolfo C, Caponnetto C, Conti M, Dagnino N, Del Sette M, Primavera A. Prognosis of transient global amnesia: a long-term follow-up study. *Eur Neurol* 1992; **32:** 52–57.

61 Guidotti M, Anzalone N, Morabito A, Landi G. A case-control study of transient global amnesia. *J Neurol Neurosurg Psychiatry* 1989; **52:** 320–23.

62 Budson AE, Schlaug G, Briemberg HR. Perfusion- and diffusion-weighted magnetic resonance imaging in transient global amnesia. *Neurology* 1999; **53:** 239–40.

63 Toledo M, Pujadas F, Grive E, Alvarez-Sabin J, Quintana M, Rovira A. Lack of evidence for arterial ischemia in transient global amnesia. *Stroke* 2008; **39:** 476–79.

64 Olesen J, Jorgensen MB. Leao's spreading depression in the hippocampus explains transient global amnesia. A hypothesis. *Acta Neurol Scand* 1986; **73:** 219–20.

65 Bergerot A, Holland PR, Akerman S, et al. Animal models of migraine: looking at the component parts of a complex disorder. *Eur J Neurosci* 2006; **24:** 1517–34.

66 Wernsmann B, Pape HC, Speckmann EJ, Gorji A. Effect of cortical spreading depression on synaptic transmission of rat hippocampal tissues. *Eur J Neurosci* 2006; **23:** 1103–10.

67 Haghir H, Kovac S, Speckmann EJ, Zilles K, Gorji A. Patterns of neurotransmitter receptor distributions following cortical spreading depression. *Neuroscience* 2009; **163:** 1340–52.

68 Bradley DP, Smith JM, Smith MI, et al. Cortical spreading depression in the feline brain following sustained and transient stimuli studied using diffusion-weighted imaging. *J Physiol* 2002; **544:** 39–56.

69 Pomper JK, Haack S, Petzold GC, et al. Repetitive spreading depression-like events result in cell damage in juvenile hippocampal slice cultures maintained in normoxia. *J Neurophysiol* 2006; **95:** 355–68.

70 Gorji A. Spreading depression: a review of the clinical relevance. *Brain Res Brain Res Rev* 2001; **38:** 33–60.

71 Schwedt TJ, Dodick DW. Advanced neuroimaging of migraine. *Lancet Neurol* 2009; **8:** 560–68.

72 Calabresi P, Centonze D, Pisani A, Cupini L, Bernardi G. Synaptic plasticity in the ischaemic brain. *Lancet Neurol* 2003; **2:** 622–29.

73 Kosuge Y, Imai T, Kawaguchi M, Kihara T, Ishige K, Ito Y. Subregion-specific vulnerability to endoplasmic reticulum stress-induced neurotoxicity in rat hippocampal neurons. *Neurochem Int* 2008; **52:** 1204–11.

74 Ikegaya Y, Matsuki N. Regionally selective neurotoxicity of NMDA and colchicine is independent of hippocampal neural circuitry. *Neuroscience* 2002; **113:** 253–56.

75 Quintana P, Stefano A, Hakkoum D, Muller D. Glutamate receptor changes associated with transient anoxia/hypoglycaemia in hippocampal slice cultures. *Eur J Neurosci* 2006; **23:** 975–83.

76 Howland JG, Wang YT. Synaptic plasticity in learning and memory: stress effects in the hippocampus. *Prog Brain Res* 2008; **169:** 145–58.

77 Kim JJ, Foy MR, Thompson RF. Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. *Proc Natl Acad Sci USA* 1996; **93:** 4750–53.

78 Yang CH, Huang CC, Hsu KS. Behavioral stress enhances hippocampal CA1 long-term depression through the blockade of the glutamate uptake. *J Neurosci* 2005; **25:** 4288–93.

79 Joels M. Stress, the hippocampus, and epilepsy. *Epilepsia* 2009; **50:** 586–97.

80 Stillhard G, Landis T, Schiess R, Regard M, Sialer G. Bitemporal hypoperfusion in transient global amnesia: 99m-Tc-HM-PAO SPECT and neuropsychological findings during and after an attack. *J Neurol Neurosurg Psychiatry* 1990; **53:** 339–42.

81 Goldenberg G, Podreka I, Pfaffelmeyer N, Wessely P, Deecke L. Thalamic ischemia in transient global amnesia: a SPECT study. *Neurology* 1991; **41:** 1748–52.

82 Tanabe H, Hashikawa K, Nakagawa Y, et al. Memory loss due to transient hypoperfusion in the medial temporal lobes including hippocampus. *Acta Neurol Scand* 1991; **84:** 22–27.

83 Heiss WD, Pawlik G, Holthoff V, Kessler J, Szelies B. PET correlates of normal and impaired memory functions. *Cerebrovasc Brain Metab Rev* 1992; **4:** 1–27.

84 Evans J, Wilson B, Wraight EP, Hodges JR. Neuropsychological and SPECT scan findings during and after transient global amnesia: evidence for the differential impairment of remote episodic memory. *J Neurol Neurosurg Psychiatry* 1993; **56:** 1227–30.

85 Lin KN, Liu RS, Yeh TP, Wang SJ, Liu HC. Posterior ischemia during an attack of transient global amnesia. *Stroke* 1993; **24:** 1093–95.

86 Baron JC, Petit-Taboue MC, Le Doze F, Desgranges B, Ravenel N, Marchal G. Right frontal cortex hypometabolism in transient global amnesia. A PET study. *Brain* 1994; **117:** 545–52.

87 Jung HH, Baumgartner RW, Burgunder JM, Wielepp JP, Lourens S. Reversible hyperperfusion of the right medial temporal lobe in transient global amnesia. *J Neurol Neurosurg Psychiatry* 1996; **61:** 654–55.

88 Eustache F, Desgranges B, Petit-Taboue MC, et al. Transient global amnesia: implicit/explicit memory dissociation and PET assessment of brain perfusion and oxygen metabolism in the acute stage. *J Neurol Neurosurg Psychiatry* 1997; **63:** 357–67.

89 Schmidtke K, Reinhardt M, Krause T. Cerebral perfusion during transient global amnesia: findings with HMPAO SPECT. *J Nucl Med* 1998; **39:** 155–59.

90 Jovin TG, Vitti RA, McCluskey LF. Evolution of temporal lobe hypoperfusion in transient global amnesia: a serial single photon emission computed tomography study. *J Neuroimaging* 2000; **10:** 238–41.

91 Warren JD, Chatterton B, Thompson PD. A SPECT study of the anatomy of transient global amnesia. *J Clin Neurosci* 2000; **7:** 57–59.

92 Eustache F, Desgranges B, Aupee AM, Guillery B, Baron JC. Functional neuroanatomy of amnesia: positron emission tomography studies. *Microsc Res Tech* 2000; **51:** 94–100.

93 Guillery B, Desgranges B, de la Sayette V, Landeau B, Eustache F, Baron JC. Transient global amnesia: concomitant episodic memory and positron emission tomography assessment in two additional patients. *Neurosci Lett* 2002; **325:** 62–66.

94 Laloux P, Brichant C, Cauwe F, Decoster P. Technetium-99m HM-PAO single photon emission computed tomography imaging in transient global amnesia. *Arch Neurol* 1992; **49:** 543–46.

95 Matsuda H, Higashi S, Tsuji S, et al. High resolution Tc-99m HMPAO SPECT in a patient with transient global amnesia. *Clin Nucl Med* 1993; **18:** 46–49.

96 Kazui H, Tanabe H. Hippocampus and memory disturbance: study on cases of transient global amnesia with dysfunction in the medial temporal lobe. *No To Shinkei* 1995; **47:** 421–28 (in Japanese).

97 Sakashita Y, Kanai M, Sugimoto T, Taki S, Takamori M. Changes in cerebral blood flow and vasoreactivity in response to acetazolamide in patients with transient global amnesia. *J Neurol Neurosurg Psychiatry* 1997; **63:** 605–10.

98 Takeuchi R, Yonekura Y, Matsuda H, et al. Resting and acetazolamide-challenged technetium-99m-ECD SPECT in transient global amnesia. *J Nucl Med* 1998; **39:** 1360–62.

99 Pai MC, Yang SS. Transient global amnesia: a retrospective study of 25 patients. *Zhonghua Yi Xue Za Zhi (Taipei)* 1999; **62:** 140–45.

100 Nardone R, Buffone EC, Matullo MF, Tezzon F. Motor cortex excitability in transient global amnesia. *J Neurol* 2004; **251:** 42–46.

101 Fujii K, Sadoshima S, Ishitsuka T, et al. Regional cerebral blood flow and metabolism in patients with transient global amnesia: a positron emission tomography study. *J Neurol Neurosurg Psychiatry* 1989; **52:** 622–30.

102 Chung YA, Jeong J, Yang DW, et al. A Tc-99m SPECT study of regional cerebral blood flow in patients with transient global amnesia. *Neuroimage* 2009; **47:** 50–55.

103 Yamane Y, Ishii K, Shimizu K, et al. Global cerebral hypoperfusion in a patient with transient global amnesia. *J Comput Assist Tomogr* 2008; **32:** 415–17.

104 Yang Y, Kim JS, Kim S, Kim YK, Kwak YT, Han IW. Cerebellar hypoperfusion during transient global amnesia: an MRI and oculographic study. *J Clin Neurol* 2009; **5:** 74–80.

105 LaBar KS, Gitelman DR, Parrish TB, Mesulam MM. Functional changes in temporal lobe activity during transient global amnesia. *Neurology* 2002; **58:** 638–41.

106 Westmacott R, Silver FL, McAndrews MP. Understanding medial temporal activation in memory tasks: evidence from fMRI of encoding and recognition in a case of transient global amnesia. *Hippocampus* 2008; **18:** 317–25.

107 Woolfenden AR, O'Brien MW, Schwartzberg RE, Norbash AM, Tong DC. Diffusion-weighted MRI in transient global amnesia precipitated by cerebral angiography. *Stroke* 1997; **28:** 2311–14.

108 Ay H, Furie KL, Yamada K, Koroshetz WJ. Diffusion-weighted MRI characterizes the ischemic lesion in transient global amnesia. *Neurology* 1998; **51:** 901–03.

109 Gass A, Gaa J, Hirsch J, Schwartz A, Hennerici MG. Lack of evidence of acute ischemic tissue change in transient global amnesia on single-shot echo-planar diffusion-weighted MRI. *Stroke* 1999; **30:** 2070–72.

110 Ay H, Buonanno FS, Rordorf G, et al. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology* 1999; **52:** 1784–92.

111 Schaefer PW. Diffusion-weighted imaging as a problem-solving tool in the evaluation of patients with acute strokelike syndromes. *Top Magn Reson Imaging* 2000; **11:** 300–09.

112 Huber R, Aschoff AJ, Ludolph AC, Riepe MW. Transient global amnesia. Evidence against vascular ischemic etiology from diffusion weighted imaging. *J Neurol* 2002; **249:** 1520–24.

113 Matsui M, Imamura T, Sakamoto S, Ishii K, Kazui H, Mori E. Transient global amnesia: increased signal intensity in the right hippocampus on diffusion-weighted magnetic resonance imaging. *Neuroradiology* 2002; **44:** 235–38.

114 Kappeller P, Horner S, Melisch B, et al. Transient global amnesia with hippocampal ischemic lesions—a report of 2 cases. *Cerebrovasc Dis* 2003; **16** (suppl 4)**:** 2.

115 Greer DM, Schaefer PW, Schwamm LH. Unilateral temporal lobe stroke causing ischemic transient global amnesia: role for diffusion-weighted imaging in the initial evaluation. *J Neuroimaging* 2001; **11:** 317–19.

116 Lorente de N'o R. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. *J Psychol Neurol* 1934; **46:** 113–77.

117 Cianfoni A, Tartaglione T, Gaudino S, et al. Hippocampal magnetic resonance imaging abnormalities in transient global amnesia. *Arch Neurol* 2005; **62:** 1468–69.

118 Nakada T, Kwee IL, Fujii Y, Knight RT. High-field, T2 reversed MRI of the hippocampus in transient global amnesia. *Neurology* 2005; **64:** 1170–74.

119 Squire LR, Stark CE, Clark RE. The medial temporal lobe. *Annu Rev Neurosci* 2004; **27:** 279–306.