Chapter 4
Investigation of TGA (1): Neuropsychology, Neurophysiology and Other Investigations

Abstract This chapter examines the investigation of TGA, particularly the neuropsychological and neurophysiological findings (neuroimaging is considered in Chap. 5). Investigations during the TGA episode have clarified the exact nature of the neuropsychological deficit. EEG may have a role in the differential diagnosis of TGA from transient epileptic amnesia. Clinical investigations undertaken when patients are seen some time after the event are generally normal and probably unnecessary if a definite (criteria-based) clinical diagnosis of pure TGA has been made.

Keywords TGA · Neuropsychology · Neurophysiology

The investigation of TGA may be contemplated as two different scenarios: acutely, during the episode, or interval assessment at some time after the resolution of the attack. The latter has generally been the more common situation, but in recent times the increasing development of acute neurological services, sometimes embedded within emergency room (ER) or accident and emergency (A&E) settings, has enabled acute rather than interval assessment of TGA. This has prompted a change in the way TGA patients are investigated, particularly with respect to neuroimaging (Chap. 5).

4.1 Neuropsychology

There are many different tests available for neuropsychological assessment (e.g. [1, 2]), looking at either single or multiple cognitive domains, and suitable for use in different settings (primary or secondary care, general or specialised clinic) and taking different periods of time to complete (minutes to hours). Those addressing memory function have been most relevant in TGA.

A.J. Larner, *Transient Global Amnesia*,
https://doi.org/10.1007/978-3-030-98939-2_4

Discussion here is largely restricted to definite or pure TGA as defined by the Hodges and Warlow 1990 criteria [3], with only passing reference to possible variant forms of TGA (see Sect. 2.3 for further details of these).

Reports of neuropsychological assessments undertaken during an attack of TGA are relatively uncommon. Indeed, it was not until the 1980s that detailed reports first began to appear (e.g. [4–11] and [12], p.68–78,139–44). Essentially, these showed that pure TGA is characterised by anterograde amnesia (difficulty learning new information) which is often described as severe, dense or profound since new information is lost within minutes, with in addition a retrograde amnesia (loss of previously learned information) extending over very variable time periods in different patients ranging from hours to decades, patchy but showing a temporal gradient. Other domains of cognitive function generally remain intact. Complete recovery except for permanent retrograde amnesia for events that occurred several hours to days before the TGA event is usual.

4.1.1 Neuropsychological Deficits during TGA: Memory

Memory may be conceptualised as a non-uniform, distributed cognitive function within which subdivisions in function may be differentiated (Fig. 2.2): explicit or declarative (episodic, semantic) and implicit on non-declarative. Neuropsychological assessment of each of these memory subdivisions has been undertaken during episodes of TGA.

4.1.1.1 "Working Memory"

"Working memory", or immediate memory, is usually conceptualised as one aspect of attentional mechanisms, rather than mnestic function per se, but since preserved attentional mechanisms are required for any meaningful assessment of memory function the assessment of working memory is an important first step in any neuropsychological evaluation. Acute confusional states (delirium), which enter the differential diagnosis of TGA (Sect. 3.5.1), are characterised by impaired attentional mechanisms.

Working memory is preserved in TGA, as manifested by normal performance on tests in both the verbal (normal forward and backward digit span tests) and nonverbal (block tapping span) domains (e.g. [12], p.70 and [6]).

Quinette et al. [13] examined working memory in more detail, using tests to investigate the various subcomponents in the model of working memory proposed by Baddeley [14]. They showed that the phonological loop and visuospatial sketch pad functions were spared, as were many of the specific executive functions.

4.1.1.2 Anterograde Memory

Characteristically, testing during a TGA attack has shown dense anterograde amnesia, with impairment of new learning ability for material presented either verbally or non-verbally [9, 12].

Verbal material includes recalling a story (e.g. from the Wechsler Memory Scale) or learning word lists. In addition to a low global score on the latter, there may be impairment of the primacy effect but with relative preservation of the recency effect [15].

Non-verbal material includes recall of the Rey–Osterrieth Complex Figure, copying of which is generally good (see Sect. 4.1.2.2). Hodges ([12], p.72) found that none of his subjects could reproduce any elements of the Rey–Osterrieth Complex Figure after a delay of approximately 40 min. Supraspan block tapping test is also a test of non-verbal learning; none of Hodges' patients could learn these sequences, confirming previous findings [4, 5].

Is the observed anterograde amnesia a consequence of failure to acquire, encode or store new information, or is the deficit one of retrieval? This issue may be addressed by investigating whether there is differential performance in tests of recall or recognition. To examine specifically episodic memory, Eustache et al. [16] administered a word-learning task (derived from the Grober and Buschke procedure) to three patients during episodes of TGA. In one patient, there was poor performance on immediate cued recall, a result which suggested an encoding deficit, whereas in the other two patients there was poor performance on delayed recall and recognition, suggesting a storage deficit. Whether this represented heterogeneity within cases of TGA, or different degrees of dysfunction within a common mechanism for encoding and retrieval, was not clear [16, 17], but a later study of two additional patients [18] pointed towards cognitive heterogeneity, one patient having a storage disturbance, whilst the other was unable to learn episodic associations, despite similar neurological features.

A meta-analysis of 25 studies examining the cognitive characteristics of TGA found "an extraordinarily large reduction" of anterograde memory [19].

4.1.1.3 Retrograde Memory

Retrograde amnesia in TGA is of variable duration, ranging from hours to decades, although in most patients it is less than 5 years. The deficit, although patchy, is temporally graded, affecting memory for both personal and public events ([12], p.74–8,81–5, and [6, 8, 9]).

As regards assessment of personal retrograde memory, this is recognised to be difficult to quantify. The Crovitz test of cued autobiographical memory has been reported to show that TGA patients have difficulty in producing personal memories, particularly for the most recent 5 years, and that these accounts are impoverished in terms of detail ([12], p.77–8,83–4, and [6, 9]). Impaired ability to describe detailed life episodes has also been noted using the Autobiographical Memory Interview [20].

In contrast to patients with functional amnesia (Sect. 3.3), TGA patients preferentially use the first person pronoun rather than general pronouns when recounting autobiographical narratives [21].

For assessment of public retrograde memory, various tests may be used, such as the Famous Faces Test (identifying famous people from previous decades) and famous events (dating significant previous events). Such studies indicate a temporal gradient, with poorer performance on more recent material but with more distant memories relatively spared.

A meta-analysis of 25 studies examining the cognitive characteristics of TGA found a milder reduction of retrograde compared to anterograde memory [19]. A permanent retrograde amnesia for events that occurred several hours to days before the TGA event is usual.

4.1.1.4 Semantic Memory

Semantic memory, assessed by category fluency measures, picture naming, and picture–word and picture–picture matching, and reading ability was normal during TGA in two patients assessed by Hodges [22]. More recently, however, Sandikci et al. [23] found impaired semantic fluency in 16 patients during TGA (with typical neuroimaging findings) compared to their function one day later. They suggest their findings support a role for the hippocampus in semantic retrieval.

A possible TGA variant in which transient impairment of semantic memory was present has been described ([24]; see Sect. 2.3.3).

4.1.1.5 Implicit Memory

Implicit memory functions (e.g. for driving; see Sect. 6.4.1) are usually intact in TGA [6]. Indeed, procedural memories for motor and perceptual skills can be acquired during TGA episodes [25, 26], confirming the empirical dissociability of explicit and implicit memory processes. Eustache et al. [15] examined perceptual-verbal procedural memory (mirror reading skill learning task) and lexical–semantic priming (word stem completion task) in a TGA patient and found these abilities to be preserved compared to controls despite the patient's profound explicit memory impairment. Guillery et al. [27] demonstrated semantic priming in three TGA patients, effects which persisted at least 1 day after recovery from TGA, suggesting the possibility of semantic learning without episodic memory.

A possible TGA variant in which procedural memory impairment is present has been described (Sect. 2.3.4).

4.1.1.6 Spatial Memory

Experimental animal studies have suggested that the hippocampus has a function as a cognitive map, underpinning spatial memory [28]. In the light of the focal hippocampal lesions seen on magnetic resonance imaging in TGA patients (see Sect.

5.1.2), Bartsch et al. [29] examined place learning using a virtual Morris water maze in TGA patients with hippocampal lesions. Compared to controls, TGA patients showed a profound impairment of place learning, the deficits in performance correlated with the size of hippocampal lesions and duration of TGA.

More sophisticated tests of hippocampal function have indicated selective and prolonged deficits in allocentric (hippocampus-dependent) spatial navigation in patients following TGA [30] suggesting that damage had occurred within the hippocampus.

4.1.1.7 Metamemory

The term metamemory has been used to describe knowledge about one's memory processes and contents. It has been little studied in TGA compared to other aspects of memory. Neri et al. [31] used the Sehulster Memory Scale [32] to assess metamemory in 20 patients with a previous episode of TGA, finding metamemory evaluations to be more closely related to objective memory function in those with more severe residual retrograde amnesia [31]. Imprecision of metamemory was also reported in TGA patients by Marin-Garcia and Ruiz-Vargas [33].

4.1.2 Neuropsychological Deficits during TGA: Other Cognitive Domains

Cognitive domains other than memory are typically preserved in TGA, such as language, visuospatial function [6] and frontal executive functions [13, 22].

4.1.2.1 Language

All aspects of language tested by Hodges ([12], p.79) were normal.

4.1.2.2 Visuoperceptual and Visuospatial Skills

All aspects of visuoperceptual/visuospatial function tested by Hodges ([12], p.79) were normal. However, reduced ability to copy the Rey–Osterrieth Complex Figure has been observed [8, 9], suggesting to these authors a cognitive deficit separate from and in addition to the amnesia. However, this report would seem to be exceptional.

4.1.2.3 Executive Function

Stillhard et al. [11] found reduced verbal fluency and evidence of colour–word interference in the Stroop test in their patient, suggestive of frontal lobe dysfunction.

A meta-analysis of 25 studies examining the cognitive characteristics of TGA found diminished executive functions, suggesting that non-amnestic cognitive changes may be found in TGA [19].

4.1.3 Neuropsychological Deficits after TGA

Comparison of mnestic function during and a few weeks after TGA usually shows return to normal of both anterograde and retrograde memory [20]. However, testing earlier after the acute episode, for example, after 3 or 4 days, may show persisting impairments in verbal and non-verbal long-term memory and verbal fluency [34], whereas testing at longer time periods may show no difference from controls (e.g. [35, 36]). Cognitive outcomes in the post-acute and longer term following TGA are considered in the Chapter on prognosis (Sect. 6.1 and Sect. 6.3.1, respectively).

Of the various brief ("bedside") cognitive screening instruments which are available (for discussion see [37]), a number have been used by the author in patients who have had attacks of TGA. These have included the Mini-Mental State Examination [38] (MMSE; see Case Study 2.1), the Six-Item Cognitive Impairment Test [39] (6CIT), the Montreal Cognitive Assessment [40] (MoCA; see Case Study 2.1), the AD8 [41, 42], the Mini-Addenbrooke's Cognitive Examination [43] (MACE) and Free-Cog [44] as part of pragmatic diagnostic test accuracy studies [45, 46] of these tests [47–53]. In the majority of cases, these have returned normal scores, the exception being two patients judged to have mild cognitive impairment (aged 73 and 79) independent of their TGA attack (Larner, unpublished observations).

4.2 Neurophysiology

4.2.1 Electroencephalography (EEG)

The suspicion that TGA might be an epileptic phenomenon prompted investigation with standard electroencephalography (EEG) post-event in several of the earliest reports (e.g. [54–57]) and this trend continued; the first report devoted to EEG in TGA was that of Jaffe and Bender of 1966 in which 27 of 51 cases underwent EEG, 5 during the event [58].

Although most reported EEG studies were negative or showed only non-specific changes (e.g. temporal slow waves), occasional reports of spike and wave discharges on interictal recordings appeared, seeming to support an epileptic aetiology for TGA (e.g. [59–62], at least in some cases. However, with hindsight some of these

patients may have had epilepsy rather than TGA, the reports predating publication of TGA diagnostic criteria [3] and characterisation of TEA. Reviews by Pedley (1983) [63], Miller et al. (1987) [64] and Jacome (1989) [65] suggested that some EEG changes reported in TGA were in fact non-specific or represented benign sleep spikes or changes seen in migraine (e.g. [66]). Nevertheless, some authors continued to hold the view that TGA is a form of epilepsy, the electrical changes being too deep for detection by surface EEG recordings (e.g. [67, 68]). Furthermore, recordings made after the TGA episode might not be reflective of the situation during attacks.

4.2.2 EEG during TGA

Reports of EEG recordings during an episode of TGA have been relatively sparse and often a consequence of chance. Generally, as for interictal studies, these have been entirely normal (e.g. [58, 64, 69, 70] and [12], p.65,141; see also Case Study 4.1), although occasional positive findings are reported: Jeong et al. [71] found bitemporal sharp waves accentuated by hyperventilation in a patient with TGA and typical diffusion-weighted magnetic resonance imaging findings (Sect. 5.1.2); EEG changes disappeared with recovery.

Case Study 4.1: EEG during TGA
A 58-year-old lady presented to her local hospital with confusion. She was unable to give a history of what had happened, but her husband reported that she had appeared distressed and was repeatedly asking the same question. She could not remember where she had been on holiday the week before or whether her mother was alive or dead. The episode settled spontaneously after about 6 h. The patient had no subsequent recollection of this period. She was otherwise in good health, with a history of only infrequent migraine. Her general and neurological examinations at presentation were normal. A provisional diagnosis of transient ischaemic attack was made by the local stroke coordinator, but the managing clinician was uncertain as to whether the episode may have been an epileptic seizure, so made arrangements for an outpatient EEG and advised the patient not to drive in the meantime.

About 10 min into the EEG recording, a further similar episode of confusion occurred: the patient was noted to be distressed, did not know where she was or how she had gotten there and repeatedly asked the same questions. The EEG coincident with this episode was normal throughout. Confusion lasted in all about 6 h, without subsequent recall. The patient later admitted to having been very anxious about attending for the EEG.

The patient was subsequently referred to the neurology clinic where, in addition to the above clinical history, collateral history from the husband elicited the fact that the first episode occurred shortly after sexual intercourse. The history was entirely consistent with diagnostic criteria for transient global amnesia (adapted from [70]).

Hence, standard EEG is of little value in the diagnosis of TGA but may have value in the differential diagnosis of attacks of TGA from TEA (Sect. 3.2, Table 2.1 and Table 3.7) if there is doubt on clinical grounds, in which case sleep-deprived EEG may increase the chances of finding changes suggestive of TEA.

More sophisticated quantitative analytic techniques evaluating EEG power spectra (qEEG) may have acute diagnostic [72] and differential diagnostic value versus TEA [73]. Comparing resting-state EEGs obtained both acutely and after recovery from TGA has been reported to show deterioration in network efficiency of the theta band frequency during the attack [74].

4.2.3 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) measures magnetic fields generated by ongoing brain ionic current flows. A couple of studies examining MEG in TGA have appeared [75, 76] but neither provided significant information about underlying changes in brain activity.

4.2.4 Transcranial Magnetic Stimulation (TMS)

Nardone et al. [77] investigated one case of TGA with TMS and found decreased intracortical inhibition (ICI) during the attack.

4.3 Other Investigations

If the clinical diagnosis of "pure" TGA (Sect. 2.2.2) is made, then other investigations are generally unnecessary.

4.3.1 Blood Tests

Standard or routine tests of haematology and blood chemistry seldom, if ever, have any place in the investigation of patients with suspected or confirmed TGA. Occasional reports of abnormal blood tests in TGA have appeared, but generally they constitute anecdotal evidence only. For example, there are occasional reports of TGA occurring in patients with polycythaemia, for example, in association with polycythaemia rubra vera (PRV) [78, 79] and cerebellar haemangioblastoma [80]. In one PRV case [79], multiple recurrences were reported (which may prompt questions about the TGA diagnosis), ceasing with the treatment of

polycythaemia. In the light of these cases, an argument might be made for checking indices such as haematocrit, red cell mass and blood volume and blood viscosity. However, Hodges ([12], p.132) found no significant difference in packed cell volume between TGA patients and TIA controls. Only 1 of 24 TGA patients in the series of Moreno-Lugris et al. [81] had polycythaemia.

Other markers of vascular and/or inflammatory involvement have been examined in TGA patients. For example, hyperfibrinogenaemia, a marker of inflammation, was reported in a patient who developed recurrent episodes of TGA after cardiac surgery, which were manifest only in the upright posture but which resolved promptly when supine [82]. As with other reports of frequently recurrent TGA (Sect. 6.2.1), there must be questions around the diagnosis of TGA here.

Cervera et al. [83] reported a cohort of 1000 patients with antiphospholipid antibody (Hughes') syndrome, of whom 0.7% had "transient amnesia". It has been reported that TGA (and migraine) is more common in Latin American patients with the antiphospholipid syndrome (APS+) than in European APS+ patients [84]. However, it remains to be determined if there is an aetiological relationship with TGA. If there are stigmata of specific vascular diseases (e.g. Sneddon syndrome, scleroderma; Sect. 3.1.4), then checking of relevant autoantibodies might be considered, but not as a routine.

Mazokopakis [85] reported five TGA patients with high serum total homocysteine levels, low serum folate and vitamin B12 and with underlying mutations in the methylenetetrahydrofolate reductase (MTHFR) gene. Hyperhomocysteinaemia, a recognised vascular risk factor, may thus be a risk factor for TGA in some cases. It has been recorded in other case reports ([86, 87] and [88], case1].

A case of TGA with elevation of highly sensitive troponin T levels was reported by Jalanko et al. [89]. This is usually a marker of cardiac ischaemia but may sometimes be seen in acute neurological disorders such as subarachnoid haemorrhage, stroke, TIA, epileptic seizures and traumatic head injury. Eisele et al. [90] found elevated high-sensitivity cardiac troponin I (hs-cTNI) in 17 of 202 TGA patients, but none had clinical or electrocardiographic evidence of myocardial infarction although two had Takotsubo syndrome (see Sect. 3.1.6). Those with elevated hs-cTNI had a significantly greater likelihood of a history of coronary heart disease and a significantly shorter TGA duration at presentation.

Neuron-specific enolase (NSE) may be used as a marker of neuronal cell dysfunction. Lee et al. found NSE to be elevated in 16/48 TGA patients, and these subjects had higher levels of cognitive impairment than those with normal levels [91].

Markers of endocrinological function have sometimes been examined in TGA. There are occasional reports of cases occurring in patients with thyroid dysfunction, for example, as a consequence of autoimmune thyroid disease [92]. A higher rate of thyroid disorders was reported in a retrospective study of 25 TGA patients from Taiwan [93].

Prolactin levels, sometimes used as a serum marker of epileptic seizure, are normal in TGA [94].

A more significant endocrinological marker may be serum cortisol levels in the light of the possible predisposing and precipitating role of stress in TGA (Sect 7.10 and Sect. 8.1 respectively). Schneckenburger et al. [95] compared blood cortisol levels between TGA patients sampled during or shortly after the episode and found significantly higher levels in the ictal group. The results suggested reactivity of the hypothalamic–pituitary–adrenal axis. Griebe et al. [96] found elevated levels of salivary cortisol in TGA patients compared to time-matched delay samples, suggesting enhanced cortisol secretion in TGA patients. However, neither of these studies could determine whether or not these observations were cause or effect of TGA, nor whether they might be of use in the differential diagnosis of acute transient amnesias.

4.3.2 Cerebrospinal Fluid (CSF)

Lumbar puncture for studies of cerebrospinal fluid (CSF) may be indicated if TGA is mistaken for other acute neurological conditions (Sect. 3.5), such as meningitis or encephalitis (looking for markers of infection) or subarachnoid haemorrhage (looking for xanthochromia, blood products), but if the clinical diagnosis of TGA has been made then CSF analysis is not indicated. In view of the acute nature of TGA, it might be interesting to know if markers of neuronal damage, such as the proteins 14–3-3 and s100beta (sometimes looked for in suspected cases of prion disease), are positive in TGA.

It has been reported that biological antioxidant potential (BAP) is elevated in CSF of TGA patients, suggesting that oxidative stress may play a role in the pathogenesis of TGA [97].

4.3.3 Sonography

Sonographic techniques have been used to evaluate both arterial and venous phases of the intra- and extracranial circulation, with the latter producing the most contentious results.

4.3.3.1 Arterial

Extracranial and transcranial arterial echo colour Doppler sonography was undertaken in 75 TGA patients and the same number of age- and gender-matched controls by Baracchini et al. [98]. They found no evidence of significant cervical vessel or intracranial atherosclerosis. There was no difference in resistance index values of the vertebral arteries at rest and during Valsalva manoeuvre and of pulsatility index values of the major intracranial arteries at rest and during Valsalva manoeuvre. Furthermore, no difference in any study item was found between patients assessed

during or soon after the TGA episode. Jovanovic et al. [99] found no significant structural atherosclerotic changes in the cervicocranial arteries on ultrasound of 100 patients with TGA.

4.3.3.2 Venous; Internal Jugular Vein Valve Incompetence

Prompted by Lewis's influential (1998) hypothesis of TGA as a consequence of cerebral venous congestion [100] (see Sect. 9.2.2 for discussion), a number of sonographic studies appeared in the early 2000s examining internal jugular vein blood flow. These detected an increased prevalence of abnormal (retrograde) internal jugular vein blood flow due to jugular vein valve incompetence during a Valsalva manoeuvre in TGA patients compared to TIA patients and normal controls (e.g. [101–103]).

Many subsequent studies addressing this issue have been published (e.g. [99, 104–108]). A meta-analysis of seven case–control studies published in 2012 confirmed the increased incidence of internal jugular vein valve incompetence in TGA patients and also showed that recognised precipitating factors for TGA (Chap. 8) were more common in this group [109]. However, despite internal jugular vein valve incompetence, there may not necessarily be any change in intracranial venous circulation [110]. For example, Baracchini et al. [111] found no difference in blood flow velocity in the deep cerebral veins at rest or during Valsalva manoeuvre in TGA patients or controls, and intracranial venous reflux was not observed. Hence, the relevance of internal jugular vein valve incompetence to the pathogenesis of TGA remains uncertain [112]. Higher rates of compression/stenosis of internal jugular veins and left brachiocephalic vein with transverse sinus hypoplasia have also been recorded in TGA patients [113].

Pragmatically, there seems little indication for undertaking such studies as a routine investigation in patients with single episode pure TGA.

4.4 Summary and Recommendations

TGA is a clinical diagnosis, even when based on widely accepted diagnostic criteria [3]. If a confident clinical diagnosis of pure TGA, based on diagnostic criteria, can be made, then no further investigation may be required (certainly none are mandatory), and management should focus on reassurance.

However, if there is diagnostic uncertainty, for example, if a compelling informant history is not available, then investigations may be required to explore and refine the differential diagnosis. Of these investigations, the precise pattern of neuropsychological deficits may be helpful, although services for acute neuropsychological assessment are not widely available. EEG may be considered if the differential diagnosis with TEA cannot be resolved on clinical grounds. Blood tests

currently have little diagnostic value, although recent investigations of elevated cortisol and troponin raise the possibility that they might be of use.

Overall, the various investigational modalities considered in this chapter have little to recommend them in the acute setting. However, neuroimaging, specifically diffusion-weighted magnetic resonance imaging, has found a place. This, along with other neuroimaging techniques, is considered in the next chapter.

References

1. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York: Oxford University Press; 2012.
2. Tate RL. A compendium of tests, scales, and questionnaires. The practitioner's guide to measuring outcomes after acquired brain impairment. Hove: Psychology Press; 2010.
3. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry. 1990;53:834–43.
4. Caffarra P, Moretti G, Mazzucchi A, Parma M. Neuropsychological testing during a transient global amnesia episode and its follow-up. Acta Neurol Scand. 1981;63:44–50.
5. Gallassi R, Lorusso S, Stracciari A. Neuropsychological findings during a transient global amnesia attack and its follow-up. Ital J Neurol Sci. 1986;7:45–9.
6. Hodges JR, Ward CD. Observations during transient global amnesia. A behavioural and neuropsychological study of five cases. Brain. 1989;112:595–620.
7. Kritchevsky M. Transient global amnesia. In: Squire LR, Butters N, editors. Neuropsychology of memory. 2nd ed. New York: Guilford Press; 1992. p. 147–55.
8. Kritchevsky M, Squire LR. Transient global amnesia: evidence for extensive temporally graded retrograde amnesia. Neurology. 1989;39:213–8.
9. Kritchevsky M, Squire LR, Zouzounis JA. Transient global amnesia: characterization of anterograde and retrograde amnesia. Neurology. 1988;38:213–9.
10. Regard M, Landis T. Transient global amnesia: neuropsychological dysfunction during attack and recovery in two "pure" cases. J Neurol Neurosurg Psychiatry. 1984;47:668–72.
11. 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.
12. Hodges JR. Transient amnesia. Clinical and neuropsychological aspects. London: WB Saunders; 1991.
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. Baddeley AD. Working memory. Oxford: Oxford University Press; 1986.
15. Eustache F, Desgranges B, Petit-Taboué 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.
16. 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.
17. Zeman AZ. Episodic memory in transient global amnesia. J Neurol Neurosurg Psychiatry. 1999;66:135.
18. 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;325:62–6.

19. Jäger 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.
20. 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.
21. Becquet C, Cogez J, Dayan J, et al. Episodic autobiographical memory impairment and differences in pronoun use: study of self-awareness in functional amnesia and transient global amnesia. Front Psychol. 2021;12:624010.
22. Hodges JR. Semantic memory and frontal executive function during transient global amnesia. J Neurol Neurosurg Psychiatry. 1994;57:605–8.
23. Sandikci V, Ebert A, Hoyer C, Platten M, Szabo K. Impaired semantic memory during acute transient global amnesia. J Neuropsychol. 2022;16:149–60.
24. Hodges JR. Transient semantic amnesia: a new syndrome? J Neurol Neurosurg Psychiatry. 1997;63:548–9.
25. Kapur N, Abbott P, Footitt D, Millar J. Long-term perceptual priming in transient global amnesia. Brain Cogn. 1996;31:63–74.
26. Marin-Garcia E, Ruiz-Vargas JM, Kapur N. Mere exposure effect can be elicited in transient global amnesia. J Clin Exp Neuropsychol. 2013;35:1007–14.
27. Guillery B, Desgranges B, Katis S, de la Sayette V, Viader F, Eustache F. Semantic acquisition without memories: evidence from transient global amnesia. Neuroreport. 2001;12:3865–9.
28. O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford: Oxford University Press; 1978.
29. Bartsch T, Schonfeld R, Muller FJ, et al. Focal lesions of human hippocampal CA1 neurons in transient global amnesia impair place memory. Science. 2010;328:1412–5.
30. Schöberl F, Irving S, Pradhan C, et al. Prolonged allocentric navigation deficits indicate hippocampal damage in TGA. Neurology. 2019;92:e234–43.
31. Neri M, Andermarcher E, De Vreese LP, Rubichi S, Sacchet C, Cipolli C. Transient global amnesia: memory and metamemory. Aging (Milano). 1995;7:423–9.
32. Sehulster JR. Structure and pragmatics of a self-theory of memory. Mem Cogn. 1981;9:263–76.
33. Marin-Garcia E, Ruiz-Vargas JM. Memory and metamemory during transient global amnesia: a comparative study about long-term follow up [in Spanish]. Rev Neurol. 2011;53:15–21.
34. Kessler J, Markowitsch HJ, Rudolf J, Heiss WD. Continuing cognitive impairment after isolated transient global amnesia. Int J Neurosci. 2001;106:159–68.
35. Uttner I, Weber S, Freund W, Schmitz B, Ramspott M, Huber R. Transient global amnesia – full recovery without persistent cognitive impairment. Eur Neurol. 2007;58:146–51.
36. Uttner I, Prexl S, Freund W, Unrath A, Bengel D, Huber R. Long-term outcome in transient global amnesia patients with and without focal hyperintensities in the CA1 region of the hippocampus. Eur Neurol. 2012;67:155–60.
37. Larner AJ, editor. Cognitive screening instruments. A practical approach. 2nd ed. London: Springer; 2017.
38. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
39. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. Int J Geriatr Psychiatry. 1999;14:936–40.
40. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
41. Galvin JE, Roe CM, Powlishta KK, et al. The AD8. A brief informant interview to detect dementia. Neurology. 2005;65:559–64.
42. Galvin JE, Roe CM, Xiong C, Morris JE. Validity and reliability of the AD8 informant interview in dementia. Neurology. 2006;67:1942–8.
43. Hsieh S, McGrory S, Leslie F, et al. The Mini-Addenbrooke's Cognitive Examination: a new assessment tool for dementia. Dement Geriatr Cogn Disord. 2015;39:1–11.

44. Burns A, Harrison JR, Symonds C, Morris J. A novel hybrid scale for the assessment of cognitive and executive function: the Free-Cog. Int J Geriatr Psychiatry. 2021;36:566–72.
45. Larner AJ. Dementia in clinical practice: a neurological perspective. Pragmatic studies in the cognitive function clinic. 3rd ed. London: Springer; 2018.
46. Larner AJ. Diagnostic test accuracy studies in dementia. A pragmatic approach. 2nd ed. London: Springer; 2019.
47. Abdel-Aziz K, Larner AJ. Six-item Cognitive Impairment Test (6CIT): pragmatic diagnostic accuracy study for dementia and MCI. Int Psychogeriatr. 2015;27:991–7.
48. Larner AJ. Mini-Addenbrooke's Cognitive Examination: a pragmatic diagnostic accuracy study. Int J Geriatr Psychiatry. 2015;30:547–8.
49. Larner AJ. Implications of changing the Six-item Cognitive Impairment Test cutoff. Int J Geriatr Psychiatry. 2015;30:778–9.
50. Larner AJ. AD8 informant questionnaire for cognitive impairment: pragmatic diagnostic test accuracy study. J Geriatr Psychiatry Neurol. 2015;28:198–202.
51. Larner AJ. Mini-Addenbrooke's Cognitive Examination diagnostic accuracy for dementia: reproducibility study. Int J Geriatr Psychiatry. 2015;30:1103–4.
52. Larner AJ. M-ACE vs. MoCA. A weighted comparison. Int J Geriatr Psychiatry. 2016;31:1089–90.
53. Larner AJ. Free-Cog: pragmatic test accuracy study and comparison with Mini-Addenbrooke's Cognitive Examination. Dement Geriatr Cogn Disord. 2019;47:254–63.
54. Fisher CM, Adams RD. Transient global amnesia. Trans Am Neurol Assoc. 1958;83:143–6.
55. Bender MB. Single episode of confusion with amnesia. Bull NY Acad Med. 1960;36:197–207.
56. Poser CM, Ziegler DK. Temporary amnesia as a manifestation of cerebrovascular insufficiency. Trans Am Neurol Assoc. 1960;85:221–3.
57. Fisher CM, Adams RD. Transient global amnesia. Acta Neurol Scand. 1964;40(Suppl9):1–81.
58. Jaffe R, Bender MB. E.E.G. studies in the syndrome of isolated episodes of confusion with amnesia "transient global amnesia". J Neurol Neurosurg Psychiatry. 1966;29:472–4.
59. Dugan TM, Nordgren RE, O'Leary P. Transient global amnesia associated with bradycardia and temporal lobe spikes. Cortex. 1981;17:633–7.
60. Greene HH, Bennett DR. Transient global amnesia with a previously unreported EEG abnormality. Electroencephalogr Clin Neurophysiol. 1974;36:409–13.
61. Lou H. Repeated episodes of transient global amnesia. Acta Neurol Scand. 1968;44:612–8.
62. Tharp BR. The electroencephalogram in transient global amnesia. Electroencephalogr Clin Neurophysiol. 1969;26:96–9.
63. Pedley TA. Differential diagnosis of episodic symptoms. Epilepsia. 1983;24(Suppl1):S31–44.
64. Miller JW, Yanagihara T, Petersen RC, Klass DW. Transient global amnesia and epilepsy. Electroencephalographic distinction. Arch Neurol. 1987;44:629–33.
65. Jacome DE. EEG features in transient global amnesia. Clin Electroencephalogr. 1989;20:183–92.
66. Dupuis MM, Pierre PH, Gonsette RE. Transient global amnesia and migraine in twin sisters. J Neurol Neurosurg Psychiatry. 1987;50:816–7.
67. Fisher CM. Transient global amnesia. Precipitating activities and other observations. Arch Neurol. 1982;39:605–8.
68. Tharp BR. Transient global amnesia: manifestation of medial temporal lobe epilepsy. Clin Electroencephalogr. 1979;10:54–6.
69. Cole AJ, Gloor P, Kaplan R. Transient global amnesia: the electroencephalogram at onset. Ann Neurol. 1987;22:771–2.
70. Ung KYC, Larner AJ. Transient amnesia: epileptic or global? A differential diagnosis with significant implications for management. Q J Med. 2014;107:915–7.
71. Jeong HS, Moon JS, Baek IC, Lee AY, Kim JM. Transient global amnesia with post-hyperventilation temporal sharp waves—a case report. Seizure. 2010;19:609–11.
72. Imperatori C, Farina B, Todini F, et al. Abnormal EEG power spectra in acute transient global amnesia: a quantitative EEG study. Clin EEG Neurosci. 2019;50:188–95.

73. Lanzone J, Imperatori C, Assenza G, et al. Power spectral differences between transient epileptic and global amnesia: an eLORETA quantitative EEG study. Brain Sci. 2020;10:613.
74. Park YH, Kim JY, Yi S, et al. Transient global amnesia deteriorates the network efficiency of the theta band. PLoS One. 2016;11:e0164884.
75. Mizuno-Matsumoto Y, Ishijima M, Shinosaki K, et al. Transient global amnesia (TGA) in an [sic] MEG study. Brain Topogr. 2001;13:269–74.
76. Stippich C, Kassubek J, Kober H, Soros P, Vieth JB. Time course of focal slow wave activity in transient ischemic attacks and transient global amnesia as measured by magnetoencephalography. Neuroreport. 2000;11:3309–13.
77. Nardone R, Buffone EC, Matullo MF, Tezzon F. Motor cortex excitability in transient global amnesia. J Neurol. 2004;251:42–6.
78. Matias-Guiu J, Masague I, Codina A. Transient global amnesia and high haematocrit levels. J Neurol. 1985;232:383–4.
79. Shuping JR, Rollinson RD, Toole JF. Transient global amnesia. Ann Neurol. 1980;7:281–5.
80. Toledo M, Pujadas F, Purroy F, Alvarez-Sabin J. Polycythaemia as a ready factor of transitory global amnesia [in Spanish]. Neurologia. 2005;20:317–20.
81. Moreno-Lugris XC, Martinez-Alvarez J, Branas F, Martinez-Vazquez F, Cortes-Laino JA. Transient global amnesia. Case-control study of 24 cases [in Spanish]. Rev Neurol. 1996;24:554–7.
82. Sealove BA, Aledort LM, Stacy CB, Halperin JL. Recurrent orthostatic global amnesia in a patient with postoperative hyperfibrinogenemia. J Stroke Cerebrovasc Dis. 2008;17:241–3.
83. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002;46:1019–27.
84. Garcia-Carrasco M, Galarza C, Gomez-Ponce M, et al. Antiphospholipid syndrome in Latin American patients: clinical and immunologic characteristics and comparison with European patients. Lupus. 2007;16:366–73.
85. Mazokopakis EE. Transient global amnesia. Have you considered hyperhomocysteinaemia? Arq Neuropsiquiatr. 2019;77:756–7.
86. Khan R, Hossain M, Nai Q, Yousif AM, Sen S. Hyperhomocysteinaemia association with transient global amnesia: a rare case report. N Am J Med Sci. 2015;7:374–6.
87. Semmler A, Klein A, Moskau S, Linnebank M. Transient global amnesia-like episode in a patient with severe hyperhomocysteinaemia. Eur J Neurol. 2007;14:e5–6.
88. Portaro S, Naro A, Cimino V, et al. Risk factors of transient global amnesia: three case reports. Medicine (Baltimore). 2018;97:e12723.
89. Jalanko M, Forsström F, Lassus J. Cardiac troponin T elevation associated with transient global amnesia: another differential diagnosis of “troponosis”. Eur Heart J Acute Cardiovasc Care. 2015;4:561–4.
90. Eisele P, Baumann S, Noor L, et al. Interaction between the heart and the brain in transient global amnesia. J Neurol. 2019;266:3048–57.
91. Lee DA, Jun KR, Kim HC, Park BS, Park KM. Significance of serum neuron-specific enolase in transient global amnesia. J Clin Neurosci. 2021;89:15–9.
92. Jacobs A, Root J, Van Gorp W. Isolated global amnesia with autoimmune thyroid disease. Neurology. 2006;66:605.
93. Pai MC, Yang SS. Transient global amnesia: a retrospective study of 25 patients. Zhonghua Yi Xue Za Zhi (Taipei). 1999;62:140–5.
94. Matias-Guiu J, Garcia C, Galdos L, Codina A. Prolactin concentrations in serum unchanged in transient global amnesia. Clin Chem. 1985;31:1764.
95. Schneckenburger R, Hainselin M, Viader F, Eustache F, Quinette P. Serum cortisol levels in patients with a transient global amnesia. Rev Neurol (Paris). 2020;176:285–8.
96. Griebe M, Ebert A, Nees F, Katic K, Gerber B, Szabo K. Enhanced cortisol secretion in acute transient global amnesia. Psychoneuroendocrinology. 2019;99:72–9.

97. Kawai T, Sakakibara R, Aiba Y, Tateno F, Ogata T, Sawai S. Increased biological antioxidant potential in the cerebrospinal fluid of transient global amnesia patients. Sci Rep. 2021;11(1):15861.
98. Baracchini C, Farina F, Ballotta E, Meneghetti G, Manara R. No signs of intracranial arterial vasoconstriction in transient global amnesia. J Neuroimaging. 2015;25:92–6.
99. Jovanovic ZB, Pavlovic AM, Vujisic Tesic BP, et al. Comprehensive ultrasound assessment of the craniocervical circulation in transient global amnesia. J Ultrasound Med. 2018;37:479–86.
100. Lewis SL. Aetiology of transient global amnesia. Lancet. 1998;352:397–9.
101. Akkawi NM, Agosti C, Rozzini L, Anzola GP, Padovani A. Transient global amnesia and disturbance of venous flow patterns. Lancet. 2001;357:957.
102. Maalikjy Akkawi N, Agosti C, Anzola GP, et al. Transient global amnesia: a clinical and sonographic study. Eur Neurol. 2003;49:67–71.
103. 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;356:1982–4.
104. Agosti C, Borroni B, Akkawi N, Padovani A. Cerebrovascular risk factors and triggers in transient global amnesia patients with and without jugular valve incompetence: results from a sample of 243 patients. Eur Neurol. 2010;63:291–4.
105. Cejas C, Cisneros LF, Lagos R, Zuk C, Ameriso SF. Internal jugular vein valve incompetence is highly prevalent in transient global amnesia. Stroke. 2010;41:67–71.
106. Himeno T, Kuriyama M, Takemaru M, et al. Vascular risk factors and internal jugular venous flow in transient global amnesia: a study of 165 Japanese patients. J Stroke Cerebrovasc Dis. 2017;26:2272–8.
107. Nedelmann M, Eicke BM, Dieterich M. Increased incidence of jugular valve insufficiency in patients with transient global amnesia. J Neurol. 2005;252:1482–6.
108. 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.
109. Modabbernia A, Taslimi S, Ashrafi M, Modabbernia MJ, Hu HH. Internal jugular vein reflux in patients with transient global amnesia: a meta-analysis of case-control studies. Acta Neurol Belg. 2012;112:237–44.
110. Lochner P, Nedelmann M, Kaps M, Stolz E. Jugular valve incompetence in transient global amnesia. A problem revisited. J Neuroimaging. 2014;24:479–83.
111. Baracchini C, Tonello S, Farina F, et al. Jugular veins in transient global amnesia: innocent bystanders. Stroke. 2012;43:2289–92.
112. Caplan LR. Transient global amnesia and jugular vein incompetence. Stroke. 2010;41:e568.
113. Han K, Chao AC, Chang FC, et al. Obstruction of venous drainage linked to transient global amnesia. PLoS One. 2015;10(7):e0132893.