Chapter 5
Investigation of TGA (2): Neuroimaging

Abstract This chapter examines the investigation of TGA using neuroimaging techniques, (neuropsychological and neurophysiological investigations are considered in Chap. 4). Diffusion-weighted magnetic resonance imaging may show focal areas of signal change within the hippocampus, often in the CA1 subfield, in the first few days after the TGA episode. These changes may contribute to the diagnosis of TGA, although they are not currently included in diagnostic criteria and their pathogenesis remains uncertain. More sophisticated neuroimaging techniques may contribute to further understanding of the pathophysiology of TGA.

Keywords TGA · Neuroimaging

The investigation of TGA may be contemplated as two different scenarios: the more common occurrence is when the patient presents to medical attention at some time after the resolution of the attack of TGA and the much less common situation when the patient is seen during the attack itself. If a confident clinical diagnosis of pure TGA, based on diagnostic criteria, can be made, then no further investigation may be required, and management should then focus on reassurance.

Of the various investigations available, many different neuroimaging modalities, both structural and functional, have been applied to patients with TGA, including X-ray computed tomography (CT), magnetic resonance (MR) imaging, single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Of these, diffusion-weighted magnetic resonance imaging has proved to be the most diagnostically informative, often showing transient abnormalities confined to the hippocampus.

A.J. Larner, *Transient Global Amnesia*,
https://doi.org/10.1007/978-3-030-98939-2_5

5.1 Structural Neuroimaging

5.1.1 Computed Tomography (CT)

Historically, computed tomography (CT) was the first neuroimaging modality to be widely used in TGA, beginning in the 1970s and 1980s (note that prior to this time the term "brain scanning" often referred to isotope scans, for example, using technetium pertechnetate [1]).

Although some early studies reported a high prevalence of CT abnormalities, including infarction in specific vascular territories, these series may have been contaminated by non-TGA cases, prior to the definition of diagnostic criteria in 1990 [2]. In his review published in 1985, Caplan reviewed the reported CT changes in TGA and concluded that there were insufficient data to reach general conclusions [3]. Hodges and Warlow detected small deep white matter and basal ganglia lacunar infarcts and periventricular lucencies in around 10% of their cases, but these changes were thought to be incidental, since they did not involve memory eloquent brain structures [2]. Hence, in his monograph, Hodges concluded that CT scanning in TGA was nearly always normal ([4], p.31).

Various CT lesions have been reported on occasion in TGA patients, including cerebrovascular disease (infarction, haemorrhage; Tables 3.4 and 3.5) and mass lesions (Table 7.4). Although in some cases these might be instances of "symptomatic TGA" (Sect. 2.2.2 and 2.2.3), more likely the changes seen are incidental to TGA, albeit they may have implications for patient management independent of the TGA episode.

5.1.2 Magnetic Resonance (MR) Imaging

The increased resolution of magnetic resonance (MR) imaging compared to CT might have been anticipated to generate many more neuroimaging findings in TGA cases (including incidental changes, as in other MR imaging applications in neurology [5]). Although some negative studies were reported initially (e.g. [6, 7]), the particular value of diffusion-weighted imaging MR sequences (MR-DWI) soon became apparent, showing focal areas of high signal, or hyperintensity, within the medial temporal lobe and specifically within the hippocampal formation (e.g. [8–24]). Several large series of TGA patients examined with MR-DWI have subsequently been reported (e.g. [25–30]), and, at time of writing, one systematic review and meta-analysis has been presented including 22 original articles with 1732 participants [31], plus one other systematic review [32].

These studies have established MR-DWI as the neuroimaging modality of choice, if available and required, in TGA diagnosis (Fig. 5.1). A number of conclusions may be drawn from these various studies with respect to issues such as clinical phenotype, lesion location and size, and optimal timing and technical MR imaging factors.

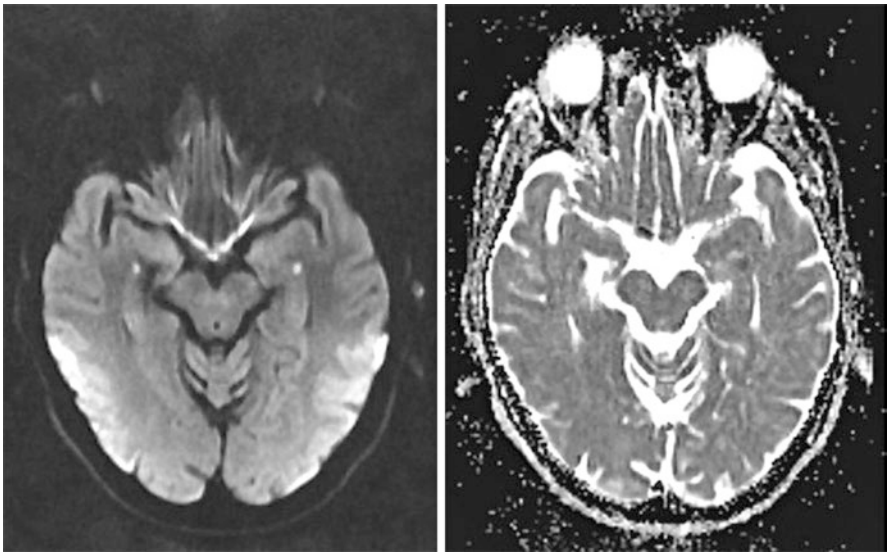

Fig. 5.1 MR brain imaging in TGA: diffusion-weighted imaging (left) and apparent diffusion coefficient map (right), 48 h after onset of TGA, showing respectively bilateral medial temporal lobe high signal and restricted diffusion (adapted from [22] with permission)

5.1.2.1 Clinical Phenotype Vs. MR-DWI Changes

TGA patients with MR-DWI lesions (DWI+) have been reported to show similar clinical characteristics to those without imaging changes (DWI−), with no significant differences in age, sex, vascular risk factors, precipitating factors or clinical presentation between the DWI+ and DWI− groups [25, 26, 33].

A small study ($n = 27$) found that patients with recurrent (i.e. a second attack of) TGA had a significantly higher association with reversible MR-DWI abnormality [34] (see Sect. 6.2.2).

5.1.2.2 Lesion Location, Number and Size

Bartsch et al. reported that most MR-DWI lesions in TGA patients were found in the CA1 (or Sommer) sector of the hippocampus (following the nomenclature of hippocampal anatomy derived from Rafael Lorente de Nó [35]), changes which gradually resolved between 3 and 10 days post-event [10, 11]. Lee et al. noted that MR-DWI lesions associated with TGA were localised exclusively to the lateral portion of the hippocampus, corresponding to the CA1 region [36]. Other studies also found the majority of TGA patients showed typical MR-DWI lesions in the CA1 region [37, 38]. However, hippocampal regions other than CA1 may be involved. For example, Kim et al. found that 23, 36 and 8 patients (= 29%, 47% and 10%) exhibited a single lesion in the hippocampal head, body and tail, respectively [27].

The systematic review of Lim et al. found figures of 12.6%, 64.4% and 23% for head, body and tail, respectively [31].

Whilst it may be the case that "[t]ypically lesions outside CA1 or outside the hippocampus are not detected in TGA" ([39], p.746), extrahippocampal hyperintense lesions have also been described in association with the typical TGA clinical phenotype on occasion [40], for example, in the splenium of the corpus callosum [9] or the cerebellum (junction of superior cerebellum and vermis) [41]. Ganeshan et al. found acute MR-DWI lesions in cortical regions other than the hippocampus in 11% of their series of TGA patients (n = 126), all presenting with typical TGA without any additional symptoms [42]. In a case series and literature review, Piffer et al. reported 26 patients with typical clinical TGA and extrahippocampal punctate diffuse lesions on MR imaging. These extrahippocampal lesions may occur with or without the typical hippocampal lesions. A classification taking these changes into account has been suggested [43]. It is possible that some of the "TGA–stroke" patients previously reported (Table 3.4) in fact have acute extrahippocampal lesions, indicative of acute focal metabolic stress but not necessarily of ischaemic origin.

Hippocampal lesions are usually single but may be multiple and may be unilateral or bilateral. Lim et al. reported the incidence of left, right and bilateral lesions to be 42%, 37% and 25%, respectively [31]. Lesion size ranged from 1 to 15.1 mm, mean 2.8–10.2 mm [31].

5.1.2.3 Timing of MR-DWI Changes

Higher MR-DWI lesion detection rates occurring after rather than during the hyperacute event have been noted by many authors (e.g. [19, 21]). Ahn et al. performed MR-DWI in 203 TGA episodes and found hippocampal lesions (= DWI+) in 16. The median time interval from amnesia to imaging was significantly longer in the DWI+ group (9 h) than in the DWI- group (5 h), indicating that MR-DWI had a low diagnostic yield (this term was not defined in the text, hence is presumably used qualitatively) if performed early in the course of TGA [25]. Ryoo et al. found an increase in the lesion detection rate with time lapse after symptom onset (0–6 h: 34%; 6–12 h: 62%; 12–24 h: 67%; day 3: 75%) [28]. Higashida et al. found that detection rate increased linearly 24 h after onset, reached a plateau by 84 h and then decreased rapidly [26]. These findings were confirmed in the systematic review by Lim et al. [31] who reported a higher diagnostic yield when DWI was performed between 24 and 96 h after symptom onset than before 24 h or after 96 h.

These data may therefore explain in part the negative findings of some of the early MR studies: Gass et al. performed DWI in the active phase in two patients and 1–8 h after cessation of symptoms in six patients [6], whilst in the series of Huber the average imaging delay was 18 h [7].

Lesions gradually resolve and disappear between 3 and 10 days post-event [10, 11, 44]. Follow-up MR imaging studies of TGA using very high field strength (7 T) showed no visible sequelae [45].

5.1.2.4 MR Field Strength, Slice Thickness and T_2-Weighting

Higher lesion detection rates have been noted in some studies dependent upon certain technical MR imaging factors, such as the use of higher MR field strength [28, 46], thinner slice thickness [29, 47] and higher resolution imaging [47]. Lim et al., in their systematic review, found no difference in diagnostic yield using 3 T vs 1.5 T field strength but higher yield using slice thickness ≤3 mm vs. >3 mm [31]. Considering the size range of punctate lesions, down to 1 mm and with a mean of 2.8 mm in some studies (Sect. 5.1.2.2), then clearly slice thickness of >3 mm could miss these changes. No added benefit was observed using T_2-weighted MR imaging [31] (see also Sect. 5.1.2.7).

5.1.2.5 Diagnostic Value of MR-DWI Changes

Lim et al. calculated the diagnostic yield of MR imaging as the ratio of the number of patients with small hyperintense MR-DWI lesions suggestive of TGA to the total number of patients with TGA [31], a ratio which equates to test sensitivity (i.e. ratio of true positives to sum of true positives and false negatives [48]). The pooled diagnostic yield thus defined was 39%, although there was marked heterogeneity between studies included in this systematic review (range 0–92%). Whilst this overall sensitivity is low, suggesting that there are many false negatives, yield may be improved by factors such as optimal timing of imaging (24–96 h post-TGA) and MR slice thickness (≤3 mm) [31].

Wong et al. attempted to quantitate the sensitivity of MR-DWI in TGA as a function of time from symptom onset by means of a systematic review encompassing 23 papers and 1688 patients. Pooled sensitivity was reported to be 15.6% between 0 and 12 h from symptom onset, 23.1% at 0–24 h, 72.8% at 12–24 h, 68.8% at 24–36 h, 72.4% at 36–48 h, 82.8% at 46–60 h, 66.9% at 60–72 h and 72.0% at 72–96 h [32].

Dot-like hippocampal lesions, including punctate CA1 hippocampal hyperintensities, may be seen in other clinical circumstances, such as ischaemia, encephalitis, status epilepticus [49, 50], acute headache (with features different from migraine) [51] and even incidentally [52]. Förster et al. claimed that it is not possible on neuroimaging grounds alone to differentiate isolated hippocampal infarction from TGA [50]. Hence, any suggestion that MR-DWI changes are specific to TGA is incorrect, in that false-positive instances are possible, which will reduce specificity (and positive predictive value, since false-positives feature in the denominators of both these metrics [48].) The current evidence suggests that CA1 lesions are neither necessary nor sufficient for a diagnosis of TGA.

To my knowledge, a dedicated diagnostic test accuracy study of MR-DWI changes in TGA has yet to be reported. Such a study would ideally, as per other pragmatic diagnostic test accuracy studies in cognitive disorders [53], have to image all patients presenting with suspected TGA according to a predetermined imaging protocol, with diagnosis of TGA made on clinical (criterial) grounds, blind to the

neuroimaging findings. Such a study would likely include patients with other conditions falling within the differential diagnosis of TGA (Chap. 3). Meantime, pending such a study or studies, the recommendation that MR-DWI may be used in the appropriate clinical setting to support the diagnosis of TGA [30] stands, allowing for the possibility of both false-negative and false-positive findings on neuroimaging. (The current widely used diagnostic criteria for TGA are exclusively clinical and do not require imaging findings [2]; Sect. 2.2.2).

5.1.2.6 Pathogenesis of MR-DWI Changes

What is the pathogenesis of the punctate lesions seen on MR-DWI in TGA patients? Many early studies interpreted the appearances as indicative of ischaemia (e.g. [10, 11, 15, 23]), but their time course is not that of a classic ischaemic lesion nor do they resemble venous congestion or infarcts.

As discussed (Sect. 5.1.2.5), the typical MR-DWI appearances seen in TGA are not specific for ischaemia, although very occasional cases of acute stroke may mimic the phenotype of TGA (Sect. 3.1.2; Table 3.4). Certainly, the CA1 region of the hippocampus is known to be particularly vulnerable to hypoxia and selective injury may be associated with amnesia (e.g. [54–56]). Other investigational modalities (MRS; Sect. 5.2.4) suggest that some form of acute metabolic stress occurs [57], but the exact pathogenesis currently remains uncertain (see Sect. 9.7.5 and 9.7.6 for further discussion).

Although finding MR-DWI changes may be helpful in differential diagnosis (Chap. 3) in the appropriate clinical circumstances [30], the suggestion that these changes indicate that TGA is a disease process localised or in some way restricted to CA1 may be challenged, both empirically and conceptually. Empirically, CA1 lesions may not be seen in some TGA cases, and extrahippocampal lesions without CA1 involvement may occur (Sect. 5.1.2.2); moreover, the imaging changes become increasingly apparent with time after the clinical event (Sect. 5.1.2.3) suggesting they are downstream events. Conceptually, damage to a specific area associated with a specific functional consequence does not necessarily indicate that that particular location is responsible for that particular function. Whilst the method of lesion observation may assist in clinico-anatomical or clinico-radiological correlation, the observed lesion may have simply interrupted fibres of passage, abolished tonic "permissive" inputs or interfered with blood supply to tissue elsewhere (transient diaschisis) ([58], p.15–16).

Thus, to describe TGA as a "natural lesion model of hippocampal CA1 neurons" ([39], p.737) appears to be an oversimplification, and data interpretation which "critically relies on the selectivity of CA1 lesions" ([39], p.745) must be vulnerable to critique. Attempts to model TGA pathogenesis should rightly be predicated on hippocampal anatomy but need to take account of more than simply CA1 (Sect. 9.7).

5.1.2.7 Other MR Findings

A study using high-resolution T2-reversed MR imaging in 15 patients who had recovered from TGA found hippocampal cavities in all patients, bilateral in eight, of frequency and size greater than in normal controls [59]. The rounded shape of these cavities was said to resemble the appearances seen in specimens of hypoxia-related hippocampal CA1 necrosis, prompting the view that the changes seen in TGA patients might represent neuronal loss within the hippocampal CA1 area, an observation which might have prognostic implications. However, Bartsch et al. [10] argued that these cavities were in the hippocampal sulcus, outside the CA1 region. Uttner et al. found no difference in cognitive performance in TGA patients with and without hippocampal cavities or in comparison to healthy controls (tested a median of >3 years post-TGA), although they confirmed the increased incidence of hippocampal cavities in TGA patients [60], as did Park et al. [33].

Functional MR imaging has also been used to assess patients with TGA (Sect. 5.2.6).

5.1.3 Voxel-Based Morphometry (VBM) and Diffusion Tensor Imaging (DTI)

Advanced structural imaging techniques such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) are research tools which permit assessment of indices such as cortical thickness and structural connectivity. DTI can be used to assess white matter microstructure in terms of its fractional anisotropy and mean diffusivity.

VBM showed significant differences in limbic structures including the hippocampus between patients with TGA and controls, changes which were thought possibly to contribute to the vulnerability of memory pathways [33].

Using DTI, Moon et al. initially reported evidence suggesting disrupted neuronal integrity of cingulum bundle fibres in TGA [61] but subsequently reported no disruptions in the structural connectivity of the memory pathway in patients with recurrent TGA, suggesting no effect of recurrent events on brain microstructure [62].

Park et al. undertook DTI in recovered TGA patients and found no global differences with healthy controls and no differences in fractional anisotropy and mean diffusivity but did find reorganisation of network hubs [63]. These findings suggested the possibility that developmentally defined alterations in brain networks might predispose to TGA. Hodel et al. used DTI to show decreased structural connectivity in the limbic system in TGA patients with associated lower cortical thickness, at both acute (mean 44 h post-onset) and recovery (mean 35 days) stages [64]. Regional changes in cortical thickness and cortical volumes in TGA patients were also reported by Kim et al. [65]

Wang et al. found reduced fractional anisotropy in the hippocampus 3 months after recovery from TGA, but not at 2 weeks, suggesting the possibility of microstructural changes in hippocampus [66].

Lee et al. performed volumetric analysis and structural covariance network analysis in TGA patients and found no significant differences with healthy controls in global structural covariance network. However, the subgroup of patients with recurrent TGA did show significant alterations in this network, as well as in an intrahippocampal circuit which was also affected in single episode TGA patients. The authors suggested that these changes in connectivity could be relevant to TGA pathogenesis [67]. The same group of investigators also reported significant differences in functional networks in several brain regions according to TGA recurrence [68].

5.2 Functional Neuroimaging

5.2.1 Single-Photon Emission Computed Tomography (SPECT)

Of the various functional imaging modalities, single-photon emission computed tomography using 99mTechnetium hexamethylpropylene amine oxime (99mTc HMPAO-SPECT) to assess cerebral perfusion has generally been the most widely available resource and hence the most likely to be deployed in cases of TGA. The low spatial resolution of SPECT imaging compares unfavourably to MR imaging.

SPECT studies have generally shown decreased perfusion, in temporal lobe(s), frontal regions and parietotemporal regions, during attacks of TGA, with recovered perfusion seen in delayed imaging (e.g. [69–78]).

However, reports have also appeared of thalamic hypoperfusion [74, 75, 79–81] and global cerebral hypoperfusion [82]. Other reports have presented findings of hyperperfusion, of medial temporal lobe [83] and right parahippocampal gyrus ([84], case 1).

Lampl et al. found that SPECT remained abnormal at 3 and 12 months in three patients with recurrent TGA, whereas perfusion abnormalities resolved in patients with a first episode of TGA [73], observations which may be relevant to the prognosis of TGA (Sect. 6.2).

SPECT with 99mTc-ethyl cysteinate dimer (ECD) has also shown significant hypoperfusion acutely in left hippocampus, left thalamus and bilateral cerebellum, with restoration of perfusion in follow-up scans [85].

Examining MR and SPECT imaging in a series of TGA patients, Park et al. found that those with more anterior MR-DWI changes (especially hippocampal head) had associated SPECT hypoperfusion in the anterior frontal and temporal areas, whereas those with posterior MR-DWI changes (especially hippocampal tail)

were associated with SPECT hypoperfusion in the posterior temporal, parietal, occipital and cerebellar areas, consistent with two parallel pathways between hippocampus and neocortex [86]. This observation, if corroborated, might explain some of the heterogeneity previously observed in SPECT imaging in TGA.

SPECT imaging in TGA has been superseded by MR imaging for a number of reasons: the low resolution and non-diagnostic nature of SPECT images and the now near ubiquity of access to acute MR imaging.

5.2.2 Positron Emission Tomography (PET)

Positron emission tomography (PET) may be used to assess cerebral blood flow and metabolism. The earliest PET studies in TGA were those of Oghino et al. [87] and Fujii et al. [88], undertaken several days to weeks after the attack.

A case study of a patient in the "acute (early recovery)" phase of TGA found a matched reduction in cerebral blood flow and oxygen consumption over the entire right lateral frontal cortex with an associated, less significant, reduction in ipsilateral thalamic and lentiform nucleus metabolism, but with sparing of the hippocampal area. Changes had resolved by the time of a follow-up scan 3 months later [89]. Further PET studies from this research group included a 59-year-old woman whose imaging showed reduced cerebral metabolic rate for oxygen and oxygen extraction fraction over the left cortical convexity, with metabolic rate particularly reduced in the left frontal and temporal regions, as well as over the left lenticular nucleus, but the hippocampal area appeared unremarkable. Findings were thought to indicate flow-metabolism uncoupling [90]. Two further patients examined with PET during TGA attacks showed significant changes in the amygdala (right or left) and left posterior hippocampus [91]. The findings suggested vascular disturbance during TGA attacks. Gonzalez-Martinez et al. reported left hippocampal hypometabolism following a tracer injection 2 h after onset of TGA [92].

PET studies conducted after TGA episodes have suggested better preservation of cerebral blood flow and oxygen metabolism compared with TIA patients [88]. Jia et al. reported "low metabolism in local areas related to memory in 2 of 3 patients" examined with PET at "different periods during recovery" [93].

5.2.3 CT Perfusion (CTP) Imaging

CT perfusion (CTP) imaging may be used for the early diagnosis of acute ischaemic stroke and TIA. In a single-centre study of CTP in 30 TGA patients, all had normal findings with respect to the hippocampi [94].

5.2.4 MR Spectroscopy (MRS)

Proton MR spectroscopy (1H-MRS) is a form of functional imaging which permits analysis of metabolites such as creatine (Cr), lactate, N-acetyl aspartate (NAA; a neuronal marker) and myoinositol (a marker of glial cells). One single patient study showed no changes in these markers [95]. However, Bartsch et al. performed focal MR spectroscopy of hippocampal CA1 lesions. In 4 of 7 TGA patients studied, the typical MR-DWI changes in the CA1 sector of the hippocampus were seen. MRS of diffusion lesions showed a lactate peak, a marker of anaerobic glycolysis, in three of four patients, but not in patients without a diffusion lesion. The NAA/Cr ratio was normal, suggesting no neuronal loss. The changes were thought to indicate acute metabolic stress of CA1 neurones [57].

5.2.5 Perfusion-Weighted MR Imaging

Perfusion-weighted MR imaging (dynamic susceptibility contrast perfusion-weighted MRI) may be used to assess cerebral perfusion in TGA, although this has more usually been assessed using SPECT and PET imaging (Sect. 5.2.1 and 5.2.2 respectively). No perfusion alterations were observed by visual inspection of perfusion-weighted MR imaging in five TGA patients, but group differences were found versus controls, with lower blood flow values bilaterally in the hippocampus, in the left thalamus and globus pallidus, as well as bilaterally in the putamen and the left caudate nucleus [96].

Shimizu et al. investigated TGA patients with conventional MR imaging as well as neurite orientation dispersion and density imaging (NODDI) and arterial spin labelling (ASL). They found no obvious microstructural or perfusion abnormalities in the hippocampus in DWI+ TGA patients, suggesting that neither destructive damage nor perfusion abnormalities were related to diffusion-restricted lesions [97]. Kim et al. found no differences in cerebral blood flow between single episode and recurrent TGA using MR-ASL [98].

5.2.6 Functional MRI (fMRI)

LaBar et al. used functional MRI (fMRI) to assess the integrity of temporal lobe activity during and after an episode of TGA using a visual scene encoding task. The findings were of deficits in a temporo-limbic circuit which recovered with time. During the amnesic state, the precentral gyrus and posterior parietal cortex were utilised more than after recovery from TGA. The authors suggested that frontoparietal areas recruited during the amnesic state may indicate a compensatory strategy using visuospatial or working memory capabilities. A reduction in responses in

extrastriate cortex with repeated testing suggested the possibility of intact visual priming in TGA [99].

A similar fMRI study reported by Westmacott et al. showed no medial temporal activation associated with encoding of new scenes or recognition of old scenes during the amnesic period. However, there was strong hippocampal activation during attempted recognition despite unsuccessful retrieval. These changes had normalised at 3-month follow-up [100].

Peer et al. used resting-state fMRI in the acute phase of TGA in 12 patients to demonstrate a significant reduction in the functional connectivity of the episodic memory network, not just the hippocampus, which was reversible on recovery [101].

Zidda et al. showed reduced functional connectivity in executive network and hippocampus using fMRI in acute TGA compared to controls and recovered TGA patients, the latter two groups showing no significant differences [102].

Kim et al. [68] reported transiently greater functional connectivity in the salience network in TGA patients undergoing resting-state fMRI and lower functional connectivity in the default mode network, with preserved connectivity in the central executive network. The changes normalised by 3 months post-event.

5.3 Summary and Recommendations

Since TGA is a clinical diagnosis, no specific neuroimaging investigations are indicated. However, if there is diagnostic uncertainty, then investigations may be required to explore and refine the differential diagnosis. Neuroimaging may be required if there is a clinical suspicion of stroke. Of these investigations, diffusion-weighted magnetic resonance imaging is currently the most helpful. Focal punctate areas of signal change may be seen in the hippocampus, most often in the CA1 region, with the detection rate increasing between 1 and 4 days post-TGA and when using thin slice imaging. Whether or not these imaging changes leave long-term sequelae that might impact the prognosis of TGA, examined in the next chapter, remains uncertain, although some intriguing evidence to suggest altered network connectivity in recurrent TGA has emerged.

References

1. Riddoch D, Drolc Z. The value of brain scanning. Postgrad Med J. 1972;48:231–5.
2. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry. 1990;53:834–43.
3. Caplan LB. [sic]. Transient global amnesia. In: Frederiks JAM, editor. Handbook of clinical neurology. Volume 1 (45). Clinical neuropsychology. Amsterdam: Elsevier Science Publishers; 1985. p. 205–18.
4. Hodges JR. Transient amnesia. Clinical and neuropsychological aspects. London: WB Saunders; 1991.

5. Morris Z, Whiteley WN, Longstreth WT, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2009;339:547–50.
6. 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;30:2070–2.
7. Huber R, Aschoff AJ, Ludolph AC, Riepe MW. Transient global amnesia. Evidence against vascular ischemic etiology from diffusion weighted imaging. J Neurol. 2002;249:1520–4.
8. Alberici E, Pichiecchio A, Caverzasi E, et al. Transient global amnesia: hippocampal magnetic resonance imaging abnormalities. Funct Neurol. 2008;23:149–52.
9. Ay H, Furie KL, Yamada K, Koroshetz WJ. Diffusion-weighted MRI characterizes the ischemic lesion in transient global amnesia. Neurology. 1998;51:901–3.
10. 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.
11. 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.
12. 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.
13. Cianfoni A, Tartaglione T, Gaudino S, et al. Hippocampal magnetic resonance imaging abnormalities in transient global amnesia. Arch Neurol. 2005;62:1468–9.
14. Enzinger C, Thimary F, Kapeller P, et al. Transient global amnesia: diffusion-weighted imaging lesions and cerebrovascular disease. Stroke. 2008;39:2219–25.
15. Felix MM, Castro LH, Maia AC Jr, da Rocha AJ. Evidence of acute ischaemic tissue change in transient global amnesia in magnetic resonance imaging: case report and literature review. J Neuroimaging. 2005;15:203–5.
16. Fernandez A, Rincon F, Mazer SP, Elkind MS. Magnetic resonance imaging changes in a patient with migraine attack and transient global amnesia after cardiac catheterization. CNS Spectr. 2005;10:980–3.
17. Inamura T, Nakazaki K, Yasuda O, et al. A lesion diagnosed by MRI in a case of transient global amnesia [in Japanese]. No To Shinkei. 2002;54:419–22.
18. 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;44:235–8.
19. 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.
20. Strupp M, Brüning R, Wu RH, Deimling M, Reiser M, Brandt T. Diffusion-weighted MRI in transient global amnesia: elevated signal intensity in the left mesial temporal lobe in 7 out of 10 patients. Ann Neurol. 1998;43:164–70.
21. 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;29:1324–8.
22. Wilkinson T, Geranmayeh F, Dassan P, Janssen JC. Neuroimaging in transient global amnesia. Pract Neurol. 2013;13:56–7.
23. Winbeck K, Etgen T, von Einsiedel HG, Röttinger 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.
24. Woolfenden AR, O'Brien MW, Schwartzberg RE, Norbash AM, Tong DC. Diffusion-weighted MRI in transient global amnesia precipitated by cerebral angiography. Stroke. 1997;28:2311–4.
25. Ahn S, Kim W, Lee YS, et al. Transient global amnesia: seven years of experience with diffusion-weighted imaging in an emergency department. Eur Neurol. 2011;65:123–8.
26. Higashida K, Okazaki S, Todo K, et al. A multicenter study of transient global amnesia for the better detection of magnetic resonance imaging abnormalities. Eur J Neurol. 2020;27:2117–24.

27. Kim J, Kwon Y, Yang Y, et al. Clinical experience of modified diffusion-weighted imaging protocol for lesion detection in transient global amnesia: an 8-year large-scale clinical study. J Neuroimaging. 2014;24:331–7.
28. Ryoo I, Kim JH, Kim S, Choi BS, Jung C, Hwang SI. Lesion detectability on diffusion-weighted imaging in transient global amnesia: the influence of imaging timing and magnetic field strength. Neuroradiology. 2012;54:329–34.
29. Scheel M, Malkowsky C, Klingebiel R, Schreiber SJ, Bohner G. Magnetic resonance imaging in transient global amnesia: lessons learned from 198 cases. Clin Neuroradiol. 2012;22:335–40.
30. Szabo K, Hoyer C, Caplan LR, et al. Diffusion-weighted MRI in transient global amnesia and its diagnostic implications. Neurology. 2020;95:e206–12.
31. Lim SJ, Kim M, Suh CH, Kim SY, Shim WH, Kim SJ. Diagnostic yield of diffusion-weighted brain magnetic resonance imaging in patients with transient global amnesia: a systematic review and meta-analysis. Korean J Radiol. 2021;22:1680–9.
32. Wong ML, Silva LO, Gerberi DJ, Edlow JA, Dubosh NM. Sensitivity of diffusion-weighted magnetic resonance imaging in transient global amnesia as a function of time from onset. Acad Emerg Med. 2021; https://doi.org/10.1111/acem.14390. Online ahead of print
33. Park KM, Han YH, Kim TH, et al. Pre-existing structural abnormalities of the limbic system in transient global amnesia. J Clin Neurosci. 2015;22:843–7.
34. Auyeung M, Tsoi TH, Cheung CM, et al. Association of diffusion weighted imaging abnormalities and recurrence in transient global amnesia. J Clin Neurosci. 2011;18:531–4.
35. Lorente de Nó 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.
36. Lee HY, Kim JH, Weon YC, et al. Diffusion-weighted imaging in transient global amnesia exposes the CA1 region of the hippocampus. Neuroradiology. 2007;49:481–7.
37. Döhring J, Schmuck A, Bartsch T. Stress-related factors in the emergence of transient global amnesia with hippocampal lesions. Front Behav Neurosci. 2014;8:287.
38. 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.
39. Hanert A, Pedersen A, Bartsch T. Transient hippocampal CA1 lesions in humans impair pattern separation performance. Hippocampus. 2019;29:736–47.
40. Tarazona LR, Martinez EL, Llopis CM. Transient global amnesia with extra-hippocampal lesion and a normal cardiovascular study. Can J Neurol Sci. 2021;24:1–2. https://doi.org/10.1017/cjn.2021.116. Online ahead of print
41. Morena J, Kamdar HA, Adeli A. Cerebellar ischemia presenting as transient global amnesia. Cogn Behav Neurol. 2021;34:319–22.
42. Ganeshan R, Betz M, Scheitz JF, et al. Frequency of silent brain infarction in transient global amnesia. J Neurol. 2022;269:1422–6.
43. Piffer S, Nannoni S, Maulucci F et al. The transient global amnesia-hippocampal punctate diffusion lesion spectrum: atypical clinical and radiological presentations. A case series and systematic review. 2021; submitted.
44. Ueno H, Naka H, Ohshita T, Wakabayashi S, Matsumoto M. Serial changes in delayed focal hippocampal lesions in patients with transient global amnesia. Hiroshima J Med Sci. 2010;59:77–81.
45. Paech D, Kuder TA, Roßmanith C, et al. What remains after transient global amnesia (TGA)? An ultra-high field 7T magnetic resonance imaging study of the hippocampus. Eur J Neurol. 2020;27:406–9.
46. Lee SY, Kim WJ, Suh SH, Oh SH, Lee KY. Higher lesion detection by 3.0T MRI in patient with transient global amnesia. Yonsei Med J. 2009;50:211–4.
47. Choi BS, Kim JH, Jung C, Kim SY. High-resolution diffusion-weighted imaging increases lesion detectability in patients with transient global amnesia. AJNR Am J Neuroradiol. 2012;33:1771–4.

48. Larner AJ. The 2x2 matrix. Contingency, confusion and the metrics of binary classification. London: Springer; 2021.
49. Bartsch T, Döhring J, Reuter S, et al. Selective neuronal vulnerability of human hippocampal CA1 neurons: lesion evolution, temporal course, and pattern of hippocampal damage in diffusion-weighted MR imaging. J Cereb Blood Flow Metab. 2015;35:1836–45.
50. Förster A, Al-Zghloul M, Wenz H, Böhme J, Groden C, Neumaler-Probst E. Isolated punctuate hippocampal infarction and transient global amnesia are indistinguishable by means of MRI. Int J Stroke. 2017;12:292–6.
51. Park JH, Oh CG, Kim SH, Lee S, Jang J. Hippocampal lesions of diffusion weighted magnetic resonance image in patients with headache without symptoms of transient global amnesia. Dement Neurocogn Disord. 2017;16:87–90.
52. Jeong M, Jin J, Kim JH, Moon Y, Choi JW, Kim HY. Incidental hippocampal hyperintensity on diffusion-weighted MRI: individual susceptibility to transient global amnesia. Neurologist. 2017;22:103–6.
53. Larner AJ. Diagnostic test accuracy studies in dementia. A pragmatic approach. 2nd ed. London: Springer; 2019.
54. Bartsch T, Döhring J, Rohr A, Jansen O, Deuschl G. CA1 neurons in the human hippocampus are critical for autobiographical memory, mental time travel, and autonoetic consciousness. Proc Natl Acad Sci U S A. 2011;108:17562–7.
55. Kartsounis LD, Rudge P, Stevens JM. Bilateral lesions of CA1 and CA2 fields of the hippocampus are sufficient to cause a severe amnesic syndrome in humans. J Neurol Neurosurg Psychiatry. 1995;59:95–8.
56. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci. 1986;6:2950–67.
57. 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;70:1030–5.
58. Carpenter RHS. Neurophysiology. 3rd ed. London: Arnold; 1996.
59. Nakada T, Kwee IL, Fujii Y, Knight RT. High-field, T2 reversed MRI of the hippocampus in transient global amnesia. Neurology. 2005;64:1170–4.
60. Uttner I, Weber S, Freund W, et al. Hippocampal cavities are not associated with cognitive impairment in transient global amnesia. Eur J Neurol. 2011;18:882–7.
61. Moon Y, Oh J, Kwon KJ, Han SH. Transient global amnesia: only in already disrupted neuronal integrity of memory network? J Neurol Sci. 2016;368:187–90.
62. Moon Y, Moon WJ, Han SH. The structural connectivity of the recurrent transient global amnesia. Acta Neurol Scand. 2016;134:160–4.
63. Park KM, Lee BI, Kim SE. Is transient global amnesia a network disease? Eur Neurol. 2018;80:345–54.
64. Hodel J, Leclerc X, Zuber M, et al. Structural connectivity and cortical thickness alterations in transient global amnesia. AJNR Am J Neuroradiol. 2020;41:798–803.
65. Kim HC, Lee BI, Kim SE, Park KM. Cortical morphology in patients with transient global amnesia. Brain Behav. 2017;7:e00872.
66. Wang X, Zhang R, Wei W, et al. Long-term sequelae of hippocampal lesions in patients with transient global amnesia: a multiparametric MRI study. J Magn Reson Imaging. 2018;47:1350–8.
67. Lee DA, Lee S, Kim DW, Lee H, Park KM. Effective connectivity alteration according to recurrence in transient global amnesia. Neuroradiology. 2021;63:1441–9.
68. Kim GH, Kim BR, Chun MY, Park KD, Lim SM, Jeong JH. Aberrantly higher functional connectivity in the salience network is associated with transient global amnesia. Sci Rep. 2021;11:20598.
69. Bucuk M, Muzur A, Willheim K, Jurjevic A, Tomic Z, Tuskan ML. Make love to forget: two cases of transient global amnesia triggered by sexual intercourse. Coll Anthropol. 2004;28:899–905.

70. 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.
71. 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.
72. 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;49:543–6.
73. Lampl Y, Sadeh M, Lorberboym M. Transient global amnesia—not always a benign process. Acta Neurol Scand. 2004;110:75–9.
74. Sakashita Y, Sugimoto T, Taki S, Matsuda H. Abnormal cerebral blood flow following transient global amnesia. J Neurol Neurosurg Psychiatry. 1993;56:1327.
75. Schmidtke K, Reinhardt M, Krause T. Cerebral hypoperfusion during transient global amnesia: findings with HMPAO SPECT. J Nucl Med. 1998;39:155–9.
76. 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.
77. 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;84:22–7. [Erratum Acta Neurol Scand. 1991;84:463]
78. Warren JD, Chatterton B, Thompson PD. A SPECT study of the anatomy of transient global amnesia. J Clin Neurosci. 2000;7:57–9.
79. Goldenberg G. Transient global amnesia. In: Baddeley AD, Wilson BA, Watts FN, editors. Handbook of memory disorders. Chichester: John Wiley; 1995. p. 113–4.
80. Goldenberg G, Podreka I, Pfaffelmeyer N, Wessely P, Deecke L. Thalamic ischemia in transient global amnesia: a SPECT study. Neurology. 1991;41:1748–52.
81. Nardone R, Buffone EC, Matullo MF, Tezzon F. Motor cortex excitability in transient global amnesia. J Neurol. 2004;251:42–6.
82. Yamane Y, Ishii K, Shimizu K, et al. Global cerebral hypoperfusion in a patient with transient global amnesia. J Comput Assist Tomogr. 2008;32:415–7.
83. 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;18:46–9.
84. Asada T, Matsuda H, Morooka T, Nakano S, Kimura M, Uno M. Quantitative single photon emission tomography analysis for the diagnosis of transient global amnesia: adaptation of statistical parametric mapping. Psychiatry Clin Neurosci. 2000;54:691–4.
85. Kim BS, Cho SS, Choi JY, Kim YH. Transient global amnesia: a study with Tc-99m ECD SPECT shortly after symptom onset and recovery. Diagn Interv Radiol. 2016;22:476–80.
86. Park YH, Jang JW, Yang Y, Kim JE, Kim S. Reflections of two parallel pathways between the hippocampus and neocortex in transient global amnesia: a cross-sectional study using DWI and SPECT. PLoS One. 2013;8:e67447.
87. Oghino Y, Yokoi F, Nishio T, Sunohara N, Satayoshi E. Positron emission tomography in two cases of transient global amnesia [in Japanese]. Rinsho Shinkeigaku. 1989;29:599–605.
88. 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.
89. Baron JC, Petit-Taboué 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.
90. 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.
91. 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.

92. Gonzalez-Martinez V, Comte F, de Verbizier D, Carlander B. Transient global amnesia: concordant hippocampal abnormalities on positron emission tomography and magnetic resonance imaging. Arch Neurol. 2010;67:510–1.
93. Jia J, Wang L, Yin L, Tang H. Contrast study on cognitive function with MRI and positron emission tomography imaging in transient global amnesia. Chin Med J. 2002;115:1321–3.
94. Meyer IA, Wintermark M, Démonet JF, Michel P. CTP in transient global amnesia: a single-center experience of 30 patients. AJNR Am J Neuroradiol. 2015;36:1830–3.
95. Zorzon M, Longo R, Mase G, Biasutti E, Vitrani B, Cazzato G. Proton magnetic resonance spectroscopy during transient global amnesia. J Neurol Sci. 1998;156:78–82.
96. Förster A, Al-Zghloul M, Kerl HU, Böhme J, Mürle B, Groden C. Value of dynamic susceptibility contrast perfusion MRI in the acute phase of transient global amnesia. PLoS One. 2015;10(3):e0122537.
97. Shimizu K, Hara S, Hori M, et al. Transient global amnesia: a diffusion and perfusion MRI study. J Neuroimaging. 2020;30:828–32.
98. Kim J, Lee DA, Kim HC, Lee H, Park KM. Brain networks in patients with isolated or recurrent transient global amnesia. Acta Neurol Scand. 2021;144:465–72.
99. LaBar KS, Gitelman DR, Parrish TB, Mesulam M-M. Functional changes in temporal lobe activity during transient global amnesia. Neurology. 2002;58:638–41.
100. 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.
101. Peer M, Nitzan M, Goldberg I, et al. Reversible functional connectivity disturbances during transient global amnesia. Ann Neurol. 2014;75:634–43.
102. Zidda F, Griebe M, Ebert A, et al. Resting-state connectivity alterations during transient global amnesia. Neuroimage Clin. 2019;23:101869.