Chapter 9
Pathogenesis of TGA

Abstract This chapter considers the pathogenesis of TGA, examining the evidence for and against the commonly considered possibilities, including cerebrovascular disease (arterial or venous), epilepsy and migraine. At time of writing, the pathogenesis of TGA remains enigmatic, and the possibility that this is a heterogeneous disorder cannot be excluded. Some possible applications of connectionist and computational neural network models to TGA pathogenesis and their mechanistic implications are considered.

Keywords TGA · Pathogenesis · Cerebrovascular disease · Epilepsy · Migraine · Genetics

9.1 What Is the Cause of TGA?

The pathogenesis of TGA remains unknown, although it has been much discussed in the six decades since the first clear descriptions of the condition [1–5]. It is not only a subject of interest to clinicians but also to patients and their relatives, who frequently pose the question at clinical consultation after the event.

Considering factors relevant to the epidemiology of TGA, the recognised predisposing (Chap. 7) and precipitating factors (Chap. 8) may give pointers to pathogenesis but without currently providing a compelling account of its origins.

Any pathogenetic theory faces a number of stern challenges to explain the empirically observed clinical and epidemiological features of TGA. It must take into account factors such as the very low frequency of recurrence (i.e. non-recurrence in the majority of cases), as well as the recognised predisposing and precipitating factors (at least the better established of these). Raymond Adams was of the view that "an explanation for episodic global amnesia must take into account the lack of morphologic change" (cited in [6], p.145).

It must also be borne in mind that the search for a unifying pathogenetic explanation for TGA, what might be described as the application of Ockham's (or Occam's) razor, may be a chimaera: as Caplan ([7], p.205) pointed out, TGA "might be caused

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by diverse processes sharing only a predilection for involvement of anatomical and physiological regions critical for memory registration and retrieval", hence different instances of TGA may simply be phenocopies of different disorders resulting from differing pathogenetic pathways. Roach argued for TGA as a symptom complex rather than a specific disease entity [8], and Quinette et al. thought TGA might refer to a single expression of several pathophysiological phenomena [9]. Certainly, some authors consider TGA to be a "heterogeneous disorder" ([10], p.188).

What strategies or investigations might be undertaken to elucidate TGA pathogenesis? The brevity and infrequency of episodes make investigations during the ictus difficult, but not impossible, as seen for a number of clinical investigations (as described in Chaps. 4 and 5). Traditionally, case–control studies and population-based studies have been used to try to address questions of disease aetiology, of which the latter are much preferred since they are free of many of the inherent biases of the former. Although numerous case–control studies of TGA have been reported (e.g. [11–18].), nationwide population-based cohort studies of TGA using large databases have only become available in recent times (e.g. [19–22].). Likewise, systematic reviews [23–27] and meta-analyses [26, 28, 29] of the evidence base in TGA are relatively recent.

A number of possibilities, sometimes referred to as theories or hypotheses, have repeatedly been advanced to try to explain TGA, including but not limited to: cerebrovascular disease (arterial or venous), epilepsy and migraine. These mirror to some extent the disorders with which TGA may be confused clinically and which enter the differential diagnosis (Chap. 3). Each of these possibilities is now considered, prior to an attempted formulation of the evidence.

9.2 Cerebrovascular Disease

9.2.1 Arterial

The abrupt onset of TGA may resemble that of a stroke or transient ischaemic attack (TIA). This has prompted considerations of transient arterial occlusion or cerebrovascular insufficiency as the causative factors for TGA from the time of the earliest descriptions, so much so that some authors were ready to classify TGA as a vascular phenomenon (e.g. [30–32].), a view which persisted in some quarters up until the 1990s [33]. Clinicians unfamiliar with TGA may still, not unreasonably, consider the possibility of stroke when they encounter patient with TGA [34]. Stroke mimicking TGA (i.e. "amnesic stroke") is uncommon but increasingly recognised with MR imaging studies (Sect. 3.1.2. and Table 3.4).

However, the evidence from prospective series of TGA cases is fairly conclusive that TGA does not share the same vascular risk factors as TIA (Sect. 7.11) and that there is no increased stroke risk at follow-up [19] although there is contradictory evidence [20] (Sect. 6.3.3). Such observations argue against a cerebrovascular

aetiology, at least of thromboembolic origin: "there is no evidence to support thrombo-embolic disease as the cause of TGA in the majority of cases" ([35], p.137–8). Paradoxical embolism of platelet aggregates into the posterior cerebral circulation via a patent foramen ovale (PFO) is another suggested mechanism [36], but the evidence for an increased frequency of PFO in TGA patients is not compelling (Sect. 3.1.6).

The absence of thromboembolic risk factors does not necessarily preclude an arterial origin for TGA: some form of vasculopathy might also be implicated. Based on the association with migraine, Caplan et al. thought that "vascular spasm" might explain TGA in some patients, even those without evident migraine [37], and Caplan characterised the possible vascular changes as "acute arterial dyscontrol" [7].

The confident rejection of a cerebrovascular aetiology based on case–control studies comparing TGA and TIA cases was given pause with the findings of diffusion-weighted magnetic resonance imaging (MR-DWI) (Sect. 5.1.2; Fig. 5.1) showing transient signal changes evolving within the hippocampus, particularly the CA1 region, which were thought by some authors to be consistent with an ischaemic aetiology (Sect. 5.1.2.6). However, the frequency with which these imaging findings are seen seems to increase for the 2–3 days immediately post-event, unlike the findings in acute stroke, followed by resolution of the changes. This pattern has prompted some authors to suggest that TGA is not related to cerebral arterial ischaemia (e.g. [38].). Follow-up imaging to show persistence of changes is surely required to prove stroke as the aetiology of TGA (Sect. 3.2).

If these transient ischaemic signal changes within the hippocampus are not a consequence of vascular occlusion, then perhaps they might reflect enhanced vasoreactivity (Caplan's "acute arterial dyscontrol"?), with focal vasoconstriction inducing changes in the areas of the hippocampus, specifically CA1, known to be particularly vulnerable to ischaemia [39]. These changes might be of neurovascular origin, perhaps related to autonomic activation (a probable consequence or accompaniment of many of the recognised precipitating factors for TGA; Chap. 8), resulting in enhanced vasoreactivity and vasomotor instability/dysregulation. However, Baracchini et al. found no evidence for intracranial arterial vasoconstriction in TGA [40], although this does not necessarily indicate what is happening at capillary level within the hippocampal watershed.

9.2.2 Venous

Prompted in part by the inadequacy of other explanations for TGA, Lewis proposed that venous ischaemia in diencephalic or medial temporal lobe structures might be the cause of TGA. Noting that a Valsalva manoeuvre may be a factor common to many of the precipitating causes of TGA (Sect. 8.9), the argument was put forward that this might block venous return through the superior vena cava secondary to raised intrathoracic pressure, with retrograde transmission of high venous pressure into the cerebral venous system with resultant focal venous ischaemia [41].

Lewis's hypothesis has been influential and received a substantial boost with the consistent finding of internal jugular vein valve incompetence in greater frequency in TGA patients compared to controls (e.g. see the meta-analysis of Modabbernia et al. [29]; Sect. 4.3.3.2). This anatomical abnormality might be supposed to predispose to venous reflux, for example in association with a Valsalva manoeuvre, with resultant venous hypertension. Some authors have expressed strong support for a venous aetiology (e.g. [42, 43].). However, studies which have examined intracranial venous circulation in TGA have found little or no difference compared to controls (e.g. [44, 45].). Hence, the relevance of internal jugular vein valve incompetence to the pathogenesis of TGA remains uncertain [46]. Furthermore, the MR-DWI findings in TGA are said not to resemble venous congestion or infarcts [47]. Controlled Valsalva manoeuvre in patients with previous TGA produced no recurrence of symptoms or typical MR-DWI findings [48] (Sect. 8.9). Hence, at time of writing, Lewis's hypothesis is not proven.

Solheim and Skeidsvoll further developed the venous hypertension hypothesis by suggesting that most cases of TGA may be due to small thrombi in the deep cerebral venous system [49]. Although clinical reports of TGA in association with cerebral venous thrombosis are extremely rare (Sect. 3.1.4), Solheim and Skeidsvoll tried to pre-empt this objection by suggesting that small venous thrombi which are difficult to visualise with modern imaging technology may be responsible.

9.3 Epilepsy

The abrupt onset of TGA prompted consideration of an epileptic aetiology from the earliest studies [3, 4]:

> In our opinion the episodes, by virtue of their brevity, transiency, reversibility, and associated suspension of memory recording, bear a close resemblance to the amnesic spells described in temporal lobe seizures. … If the episodes are temporal lobe seizures, all prodromal and ictal phenomena other than the impairment of memory and possibly slight incoherence of thought were stripped away ([4], p.46).

A form of seizure affecting the hippocampal–diencephalic system remained Fisher's favoured explanation for TGA [50], notwithstanding the long duration of TGA attacks compared to most epileptic seizures. A form of non-convulsive status has been mooted, and the lack of EEG signature (Sects. 4.2.1 and 4.2.2) ascribed to the electrical changes occurring deep within the hippocampus and hence undetectable by traditional EEG methods.

Another stumbling block for the epilepsy hypothesis related to the usual single event phenotype of TGA, whilst epilepsy is usually recurrent, indeed this was one of the factors which helped to differentiate transient epileptic amnesia (TEA; Sect. 3.2.1) from TGA. Although an epileptic origin for TGA seems highly unlikely in the majority of cases, nonetheless TGA and TEA may not be mutually exclusive;

the possibility remains that there may be a pathogenetic interaction between them (Sect. 3.2.2).

Disturbances of brain electrical activity in a non-seizure form might still be pertinent to TGA pathogenesis, in the form of spreading depolarisation (Sect. 9.7.5).

9.4 Migraine

Many early authors posited a TGA-migraine connection (e.g. [37, 51, 52].) and this has been borne out by the high frequency of migraine consistently observed in series of patients with TGA, around one-third, (Sect. 7.9). The most reductive view is that "TGA is probably a migraine aura in most cases" ([53], p.125–30, 168).

Perhaps the strongest objection to this possible explanation of TGA pathogenesis is that migraine is generally understood as a recurrent condition whereas TGA is not, being a single event in most cases. That said, migraine can certainly manifest as an episode of transient amnesia (Sect. 3.4.1) which might be mistaken for TGA and hence may be included in the differential diagnosis, and as a precipitating event for TGA (Sect. 8.6).

If TGA is not migraine, nevertheless there is probably a link between the two conditions, as shown by the frequency of migraine in patients who have suffered from TGA (Sect. 7.9) and in familial cases of TGA (Sect. 7.8).

Patient age might also be relevant here. Clearly, TGA is more common with increasing age, at least until the seventh decade (see Sect. 7.4; Fig. 7.2), suggesting that the ageing brain is more vulnerable, and/or the younger brain is protected against or less susceptible, to whatever process(es) underpin(s) TGA. Migraine may manifest as a different phenotype in younger people, acute confusional migraine, which has been noted to have some similarities with TGA (Sects. 3.4.1 and 7.4). The paucity of reports of TGA after 80+ years may suggest that the oldest old brains may also be protected against TGA (Sect. 7.4). Of possible note, de novo presentation of migraine with aura in the eighth decade is unusual [54]. Primary headache associated with sexual activity (also known as coital cephalalgia), which is another acute neurological disorder related to sexual activity [55], also seems to show an increased incidence with age. Another possibility might be that TGA and migraine could be different phenotypic reflections of common underlying pathophysiological mechanisms, possibly related to particular genotypes.

As for TGA, the mechanisms underpinning migraine aura and headache remain a subject of debate, but the possible relevance of the neurophysiological process of cortical spreading depression (CSD), first described by Aristides Leão in 1944 [56] has been suggested, initially by Milner in 1958 [57] and then independently by Lauritzen [58] and Pearce [59], both in 1985. The possibility that hippocampal CSD might be a causative mechanism in TGA was first postulated by Olesen and Jorgensen in 1986 [60]. CSD is now characterised as part of the process of spreading depolarisation which is considered further in Sect. 9.7.5.

9.5 Genetics

The role of genetic factors in TGA pathogenesis has been relatively infrequently discussed because of the limited number of familial cases reported (see Sect. 7.8 and Table 7.3). However, some authors have explicitly questioned whether TGA might be genetic (e.g. [61, 62].), although clearly not a Mendelian disorder.

Given the infrequency of TGA, Arena and Rabinstein suggested that familial clusters may not be coincidental, and may possibly reflect a common genetic predisposition to migraine and TGA [63]. However, migraine was specifically mentioned in only a minority (16/53) of the familial cases reported in the literature (Sect. 7.8 and Table 7.3). This might simply represent incomplete reporting, although many of the studies were explicit about the absence of a migraine history (e.g. Case Study 7.1). In this context, Dupuis et al. reported (in abstract) a higher recurrence rate and history of migraine in those TGA patients with a positive family history of TGA (10 families) in a cohort of 219 patients seen over an extended period of time (1999–2016) [64]. The possible linkage of family history of TGA, migraine and recurrence merits further examination in large patient cohorts [65].

Another possibility might be that TGA and migraine could be different phenotypic reflections of common underlying pathophysiological mechanisms related to a particular genotype, or possibly to age: if childhood migraine may sometimes present as acute confusional migraine, it might be credible to argue that adult migraine (sometimes adult-onset migraine) might present as TGA (Sect. 9.4). The possible associations of TGA with psychological profile and psychiatric disorders on the anxiety–depression axis (Sect. 7.10) might also reflect shared pathophysiology, underpinned by polygenic mechanisms.

What genetic factors might be implicated? To date, genetic studies of TGA are few. Agosti et al. looked at the V66M polymorphism in the gene encoding brain-derived neurotrophic factor (BDNF) which had previously been demonstrated to affect human memory and hippocampal function in the development and maintenance of adult neurones. In a cohort of 98 TGA patients, there was no difference in the distribution of this BDNF genotype compared to controls [66]. This targeted approach to specific polymorphisms, although hypothesis-driven, is akin to searching for a needle in a haystack. Unbiased genome-wide association studies might potentially shed further light on any genetic factors which could be implicated in TGA pathogenesis.

Many paroxysmal neurological disorders have been found to be due to dysfunction of membrane ion channels [67], so the possibility that TGA might be a form of channelopathy seems a reasonable consideration. To date, I am not aware of any empirical evidence in favour of this possible explanation. Moreover, it is difficult to see why this explanation, as for stroke, epilepsy and migraine [67], would fit for a disorder usually characterised by single rather than recurrent events. Nevertheless, subtle changes in ion channel kinetics might contribute to TGA pathogenesis [68] (Sect. 9.7.5).

9.6 Psychiatry

The possibility that TGA might be a psychogenic disorder, explicable by "functional mechanisms", is mentioned here only to dismiss it. As previously described (Sect. 1.2), cases of possible TGA which predate the papers of Fisher and Adams [3, 4] might have been "immersed in the literature on psychogenic amnesia" ([35], p.4). Possible examples may be found in the publications of Kanzer (1939) [69] and Kennedy and Neville (1957) [70]. From the 1960s onwards, there was a decrease in reports of "hysterical amnesia".

Psychogenic amnesia is now conceptualised as a disorder distinct from TGA, although it enters the differential diagnosis (see Sect. 3.3). However, in view of the recognition of emotional factors as a frequent precipitating event for TGA (Sect. 8.1), it is not difficult to see why TGA might once have been considered a psychogenic disorder if onset was associated with evident psychological stresses [71]. Neurology is replete with disorders once thought to be psychiatric in origin (e.g. Tourette disorder, dystonia) now considered "organic".

9.7 Formulation: Towards a Neural Network Hypothesis

In the first edition of this book, some speculations as to the aetiopathogenesis of TGA were suggested but no hypothesis was attempted ([72], p.125–7). Although nothing in that general account now appears particularly objectionable or in need of refutation or withdrawal, the opportunity for further reflections has permitted the development of ideas and a tentative hypothesis of TGA pathogenesis based on neural network models. But before presenting these models, some consideration of existing models of TGA is in order.

9.7.1 Existing Models of TGA: Experimental and Theoretical

Whilst many models of memory and amnesia have been proposed, those specifically addressing TGA are few.

Considering experimental animal models, many have been developed in the investigation of the mechanisms underpinning amnesia, including transient amnesia (e.g. [73]). Although animal studies purporting to model aspects of TGA, specifically concurrent anterograde and retrograde amnesia, have been published [74, 75], to my knowledge these animal models have not been used to inform the understanding of TGA.

Experimental induction of TGA episodes in humans, which might permit in vivo studies, has been reported, but to my knowledge there are only two published

examples, both unintentional. Moreover, the first of these reports can probably be discounted.

Castellani et al. [76] described a volunteer ("Subject 13") for an experiment examining the effects of repeated cold water (20 °C) immersion who, on a third exposure, developed "altered affect … whimpering, anxious delirium-like state" for 20 min, of which he subsequently had no recollection. Despite the authors' statement that TGA is "typically 20 min in duration" ([76], p.154), this episode was in fact rather brief for such an attack, TGA rarely lasting less than 1 hour (Sect. 2.1.4). It was also atypical in the subject's age (23 years) and in the reported features, hence does not appear (retrospectively) to conform to suggested diagnostic criteria for TGA [77].

The second report described a 66-year-old patient with segmental dystonia which was treated with deep brain stimulation (DBS) of the globus pallidus interna. Baezner et al. reported that testing of one of the DBS electrodes, two years after implantation, at >6 V stimulation resulted in the patient questioning where she was and what was happening, with evidence of retrograde amnesia for the past few years, lasting for about 60 minutes. The stimulated electrode was found on subsequent MR brain imaging to have been misplaced in the right hippocampus [78]. The authors reported that all TGA criteria [77] were fulfilled and suggested that the stimulation procedure caused either "inhibition of local neuronal activity or fibre activation by high current density via direct electrical stimulation of hippocampal structures" ([78], p.336). Although too much weight should not be placed on single case studies, as they constitute the lowest (anecdotal) level of clinical evidence, the empirical observations reported by Baezner et al. might be pertinent to any proposed model of TGA pathogenesis. DBS may be characterised as creating "a virtual lesion by inducing electrophysiological silence in a neural circuit" and has even been suggested as a possible mechanism to erase memories ([79], p.120, 122).

Even if TGA could be reliably induced experimentally, there would be significant ethical questions to consider [79], the generally excellent prognosis of TGA notwithstanding (moreover, the prognosis of TGA, particularly if recurrent, may not be entirely benign; see Chap. 6).

Theoretical models of amnesia, as for experimental animal models, have been developed, but few specifically address TGA.

Meeter and Murre [80] developed the TraceLink model, inspired in part by David Marr's computational theory of archicortical function [81], to explain various forms of amnesia, in which the hippocampal complex was characterised as part of a link system involved in regulating its own plasticity through a modulating system. Simulation of TGA was achieved through suppressing any activity in the link layer, which showed both anterograde amnesia and temporally graded retrograde amnesia ([80], p.572–3 and Fig. 7). Gradual increase in link layer activity simulated the gradual lifting of TGA, with only amnesia for the pattern learned during the attack remaining thereafter, with resolution of all other amnesia. Based on their TraceLink model simulation of TGA, Meeter and Murre advanced an empirical claim that it should be possible to detect pathologically low activity level within the link system (i.e. medial temporal lobe structures) [80].

In the subsequent Memory Chain Model developed by Murre et al. [82], there was no explicit mention of TGA, although the retrograde amnesia in two TGA cases reported by Kritchevsky and Squire [83] (Sect. 4.1.1.3) was modelled ([82], p.13, and Table 3 rows o and p; and p.16, Fig. 13 plots o1,o2, p1, p2). In the discussion, it was reported that the expected lifetime of a single memory trace in the medial temporal lobe in TGA was 0.2–4 years, compared to 3–30 days from animal data ([82], p.16). No modelling or discussion of TGA anterograde amnesia was presented in this paper.

9.7.2 State-Transition Models

Because there is a finite probability of its recurrence (Sect. 6.2), TGA may be conceptualised using a simple state-transition type of Markov process which allows for repeated uncertain events. Two mutually exclusive clinical states are represented in the state-transition diagram (Fig. 9.1), TGA ("acute") and not-TGA (i.e. normal, or, because of the risk of repeated events, "dormant"). These might also be labelled, respectively, as hippocampal dysfunction and normal function. Patients are most likely to remain in the not-TGA (dormant) state over successive time periods. Since TGA events are not frequent, a cycle of 1 year has been used in the illustrated model, permitting use of empirically measured annual recurrence rates (Sect. 6.2.1) to denote the transition probabilities. As the patient is envisaged as being in one of two states and mortality is not involved, this is a non-absorbing model.

An implication of this modelling is that TGA is a stochastic process, evolving over time with associated uncertainty. Whether or not the behaviour of the process in any cycle is independent of the prior or future history of that cycle

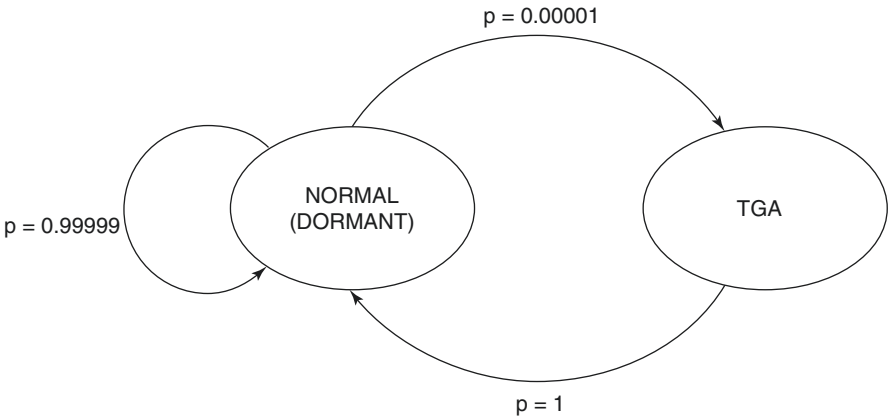

Fig. 9.1 State-transition diagram, or two-state Markov process. Numbers adjacent to arrows indicate probabilities of making that transition. The sum of the probabilities leading out of any state must be one

("memorylessness"), that being the restriction which defines a Markov process (Fig. 9.1 might also be described as illustrating a two-state Markov process), is uncertain for TGA (see discussion of recurrent TGA in Sect. 6.2.2). Clearly for other paroxysmal neurological events such as epilepsy or migraine, this "lack of memory" for the process does not hold. However, it remains possible that in TGA there is "memorylessness" for amnesia!

A rapid change in a network's connectivity, from local to global or vice versa, characterises phase transition. Such networks may be described using percolation theory as developed by Broadbent and Hammersley [84] and are subject to Kolmogorov's zero-one law such that an infinite network will have or not have (= probability one or zero) an infinite cluster. Hence, there is a percolation threshold, no matter what the shape of the network. Such networks are at risk of a sudden loss of connectivity. Based on these considerations, TGA might be envisaged as a consequence of a rapid phase transition in a neuronal network from normal to abnormal connectivity, specifically loss of connectivity, the threshold being variable between individuals (dependent upon their existing predisposing factors and susceptibility to precipitating factors). Unlike theoretical infinite networks, which have sharp phase transitions, such a real-world finite (and messy) network as the hippocampal formation would be anticipated to have more rounded transitions. At the cellular level, one might envisage that if hippocampal neurones become refractory for any reason, they might effectively drop out of the network which might eventually reach a threshold at which there is a sudden loss of connectivity.

Evidently, such state- or phase-transition models pay little, if any, attention to the underlying neurobiology of TGA (although Markov chains have been used to simulate neocortical function [85]). Along with the previously mentioned theoretical models (Sect. 9.7.1), they may be characterised as "top down" approaches, based on an attempt to model clinically observed phenomena. The general inadequacy of connectionist models in terms of biological plausibility suggests a need for further models of TGA based on large-scale dynamic circuit level analysis. Accordingly, two neural network models, which are not mutually exclusive, are postulated (Sects. 9.7.3 and 9.7.4). These are based on hippocampal formation neuroanatomy and neuronal functioning, and hence might be characterised as "bottom up" approaches to modelling TGA.

9.7.3 Feedback Loop Model

The hippocampus has an established role in memory function. Accordingly, it would seem plausible to suggest that TGA is predicated on the neuroanatomy of the hippocampal formation. Describing this neuroanatomy in 1911, Santiago Ramón y Cajal (1852–1934) outlined a functional circuit [86] which governs the direction of impulse flow through the hippocampal formation. This was also recognised in the later notion of a "trisynaptic circuit" [87] which, although now recognised to be an oversimplification, emphasised unidirectionality. Hippocampal anatomy is now

characterised as a series of multiple, embedded loops (Fig. 9.2) which are briefly described here.

The hippocampal formation may be described as comprising a number of regions: the entorhinal cortex (EC), dentate gyrus (DG), subfields of the hippocampus proper denoted CA1 and CA3 (nomenclature derived from the work of Lorente de Nó, [88], one of Cajal's pupils) and the subiculum. CA3 is the major input to CA1 via the collaterals first described by, and now named for, Schaffer [89]. CA1 projects to the subiculum (Sub), and both CA1 and Sub project to EC, with CA1 axons returning to the same EC region from which they receive their input. A projection from the deep to the superficial layers of the EC completes the closed loop [90]. The outputs of the hippocampal formation are via the Sub and EC, respectively mainly subcortical (via the fimbria–fornix pathway) and cortical projections.

Hence, a long loop runs from EC via the perforant path (PP) to DG and then to the subfields of the hippocampus proper, with output via Sub and/or EC. As EC receives inputs from many areas of associative neocortex (parietal, prefrontal, temporal) via the parahippocampal gyrus and perirhinal cortex, this pathway funnels highly processed multimodal sensory information into the hippocampal formation. DG granule cells project mossy fibre axons to the CA3 field pyramidal cells. DG is recognised to have a gating function [91], filtering afferent inputs to the hippocampus proper (CA3), thus enacting a sparse coding scheme which permits overlapping

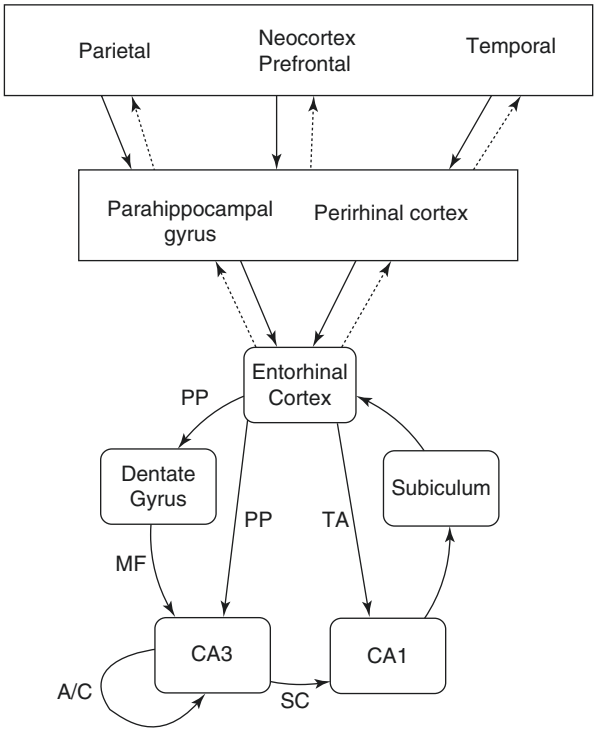

Fig. 9.2 Simple schematic block diagram representation of the major pathways of signal flow from cortex to hippocampal formation and back to cortex, showing embedded hippocampal loops. *PP,* perforant path; *MF,* mossy fibres; *TA,* temporoammonic pathway; *A/C,* associative/commissural loop; *SC,* Schaffer collaterals

or very similar inputs to the hippocampus to be separated from one another, the process of pattern separation, and hence many different memories to be encoded and stored.

In addition to the long loop, an intermediate loop runs from EC directly to CA3 via PP, hence to CA1, Sub and/or EC; whilst a short loop runs directly from EC to CA1 via the temporoammonic projection (TA) running in the alvear pathway, hence to Sub and/or EC. There are no immediate reciprocal connections to preceding regions (i.e. no projection of DG to EC, of CA3 to DG or of CA1 to CA3).

CA3 receives not only the aforementioned mossy fibre inputs from DG and a direct PP projection from EC but also has recurrent collateral connections extending throughout CA3, sometimes known as the associative/commissural (A/C) loop. These latter connections far outnumber PP and DG mossy fibre inputs to CA3 (in the rat, 12,000, vs 3600 and 46, respectively, per CA3 cell). CA3 may thus be a final convergence point for inputs from DG mossy fibres, EC and CA3 recurrent collaterals.

In addition to the excitatory connections, there are also inhibitory connections within the hippocampal formation (not shown in Fig. 9.2), both feedforward (DG to CA3 interneurons to CA3 pyramidal cells) and feedback (CA3 pyramidal cells to CA3 interneurons).

The operation of these hippocampal CA3 circuits is considered to be central to memory encoding and recall [92]. The recurrent, autoassociative connections of CA3 (further considered in Sect. 9.7.4) may underpin the retrieval of memories when inputs to the hippocampus are incomplete or degraded, the process of pattern completion. Such an autoassociative network is not found in CA1.

The characterisation of multiple loops embedded within the neuroanatomy of the hippocampal formation prompts consideration of the possible role of feedback mechanisms in hippocampal function and dysfunction. The concept of feedback, implying circularity of action, has a long history and many recognised applications in diverse disciplines, including mechanical and electrical engineering, chemistry, economics, meteorology, as well as biology and human physiology. Feedback loops are a feature of complex adaptive systems, and feedback is a central concept in the disciplines of control theory and cybernetics, pioneered in the 1940s and 1950s by mathematicians such as Norbert Wiener and John von Neumann. These interests extended to other disciplines including biology, and it may be noted that Lorente de Nó, who described the fine anatomy of the hippocampus [88], attended the early cybernetics meetings (also known as the Macy Foundation meetings) with von Neumann ([93], p.188; [94]). Morris Bender, one of the first clinicians to describe TGA, also attended as a guest on one occasion ([94], p.286), but I am not aware of any evidence to suggest he may have envisaged the “isolated episode of confusion with amnesia” [1, 2] in terms of feedback loops.

A distinction may be drawn between negative, or self-correcting, feedback, which tends to increase the stability and accuracy of operation of a system; and positive, or self-reinforcing, compounding or exacerbating, feedback in which amplification rather than stabilisation occurs but which risks exponential growth and instability.

Generally, negative feedback is a characteristic of purposeful or goal-directed actions or behaviours wherein error-signal controlled regulation typically involves integration causing asymptotic or oscillatory behaviour. In contrast, positive feedback systems tend to show exponential behaviour and hence achieve signal amplification, but the process is liable to collapse if unchecked and may risk being detrimental to the system. Generally, some form of negative feedback kicks in sooner or later to curtail unchecked positive feedback.

Negative and positive feedback may be characterised in terms of reduced or increased loop gain (= output/input) respectively. A feedback loop may be represented by a simple schematic block diagram (Fig. 9.3) where A and β represent arbitrary causal links or relations which denote the flow of causality (A = open-loop gain; β = feedback factor). The overall or closed-loop gain, G_c, may be expressed as:

$$G_c = A / (1 + \beta A)$$

where βA = loop gain. Hence, if β = 0 (i.e. no feedback), then product βA = 0, and so G_c = A (i.e. open-loop gain). If βA > 0, then as (1 + βA) > A, there is negative feedback from input to output. If βA < 0, then as (1 + βA) < A, a positive feedback from input to output occurs. As βA approaches −1, the gain may be very large, an asymptotic increase typical of a reciprocal function. If βA = −1, then (1 + βA) = 0, so G_c = A/0, infinite gain. In this circumstance, a "runaway" situation will develop. For any function $f(x) = 1/x$, $x = 0$ corresponds to a discontinuity or singularity where the function "explodes" to +/− ∞ and so is not defined.

Might these feedback concepts be applicable to hippocampal function? Hebb characterised short-term memory as a reverberation of the closed loop of hippocampal cell assemblies [95], and negative feedback was an integral component of Marr's computational theory of archicortical function [81] (although the understanding of hippocampal neuroanatomy was somewhat different at the time Marr was writing).

If, based on its particular neuroanatomy, the hippocampal formation is characterised at the neural network level as a system of multiple, embedded loops, a feedback

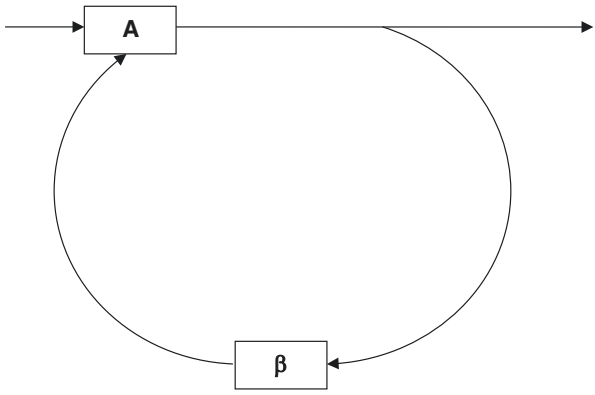

Fig. 9.3 Simple schematic block diagram representation of a feedback loop. A = open-loop gain; β = feedback factor. Closed-loop gain $G_c = A/(1 + \beta A)$

loop model of TGA pathophysiology may be envisaged. The proposed chain of causation is as follows.

Changes in the internal and external environment, the recognised precipitating factors of TGA (e.g. emotional, physical stressors; Chap. 8), lead to changes in interoceptive and exteroceptive signalling which converge on EC from association cortices. These increased inputs, perhaps acting on a predisposed system (as evidenced by, for example, an underlying migraine tendency, or genetic predisposition from a family history of TGA; Chap. 7), result in increased activation through the rest of the hippocampal formation. This might occur in various ways, involving the long, intermediate and/or short hippocampal formation loops. Specifically, opening of the dentate gate (i.e. less filtering) with repeated stimulation [91]; increased transmission through the TA pathway from EC to CA1; and/or enhanced autoassociation in CA3 recurrent collaterals (see Fig. 9.2). Positive feedback in any or all of the embedded loops would lead to amplified, neural firing, exacerbated if there were concurrent impairment or failure of inhibitory mechanisms (negative feedback from inhibitory interneurons) to stabilise inputs to the hippocampal closed-loop circuits. If gain within any or all of the loops becomes infinite, runaway neural firing results in a singularity or discontinuity: there is failure of synaptic transmission around the circuit, or elements thereof, with consequent failure of hippocampal mnestic functions, manifest clinically as the anterograde and retrograde amnesia typical of an episode of TGA. The duration of the TGA episode is then determined by the time required for the refractory system to re-establish normal synaptic transmission through the feedback circuit (see Sect. 9.7.5 for a consideration of pathogenic mechanisms).

Of course, this feedback loop model of TGA has limitations. Whilst simple systems may be described as exemplars of either negative or positive feedback, this categorisation may not be so easily established in the presence of multiple loops. Complex systems, wherein the loops are not independent (i.e. non-linear), may have complex behaviours and may best be treated as a whole.

9.7.4 CA3 Autoassociative Attractor Model

Inspired by the work of Brindley (1969) [96] and of Marr (1971) [81], and by the first analysis for operation of a synaptic network of Barlow and Levick (1965) [97], Bennett et al. suggested that the CA3 pyramidal neuronal connections formed an autoassociative network [98]. The random connections of CA3 neurones through recurrent collaterals were envisaged as the neuroanatomical substrate for the retrieval of memories under specific conditions. (Note that, in light of the application of linguistic philosophical considerations, discussed by Bennett and Hacker [99] and ultimately dating to Wittgenstein, Bennett subsequently reinterpreted his model ([100], p.106–7,112,114)). Following this, CA3 has been characterised as a single, global autoassociative attractor network [101].

Attractor networks, based on the cortical anatomy of recurrent collateral excitatory synaptic connections between pyramidal neurones, may constitute a fundamental principle of cerebral cortical function. This architecture has been used to develop computational models of attentional, perceptual, mnestic and decision-making functions and has also prompted predictions about impaired function in certain clinical disorders of the brain [101–104].

In a simple attractor network (Fig. 9.4), external inputs to neurones, e_i, produce output (postsynaptic) firing, r_i. Through recurrent collateral synapses, w_{ij}, e_i is associated with itself through presynaptic firing, r_j. Associative learning results in a change in synaptic weight, δw_{ij}, dependent on pre- and postsynaptic firing:

$$\delta w_{ij} = k.r_i.r_j$$

where k is a constant. The network behaves probabilistically, influenced by the strength of inputs, settling in a stable fixed attractor state or, in terms of an energy landscape, basin of attraction: either a spontaneous low firing rate state, or one or more persistent high firing rate states, respectively shallower or deeper basins of attraction.

Positive feedback is inherent to the operation of attractor networks, implemented through the recurrent collateral connections. The risk of exponential growth and instability, with runaway neural firing, is prevented in the attractor network by the non-linear activation function of neurones, such that they function in a binary (i.e. firing or non-firing) rather than a continuously graded (linear) mode. The threshold is set in part by negative feedback from inhibitory interneurons.

In the particular case of the CA3 autoassociative attractor network, positive feedback via recurrent collateral connections between CA3 pyramidal neurones can sustain persistent neuronal firing, thus implementing different memories. Because of

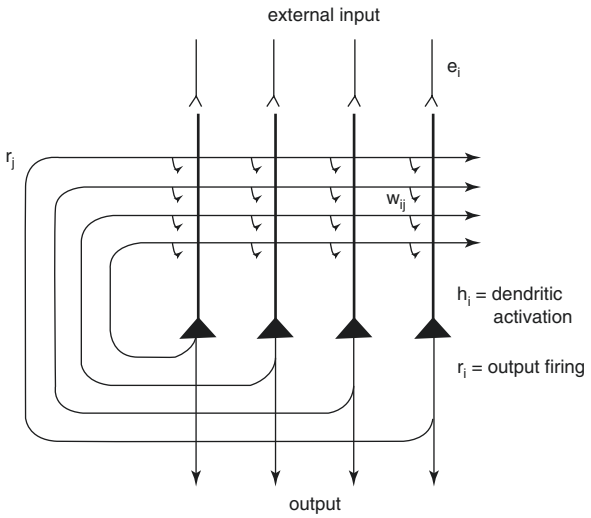

Fig. 9.4 Autoassociative attractor network

the widespread nature of the CA3 recurrent collateral connections, there is a fair chance that any one set of active neurones may be associated with any other set, these arbitrary associations forming a potential mechanism for implementing the different aspects of an episodic memory. CA3 attractor dynamics determine whether a new memory is stored, as a consequence of pattern separation with formation of a new basin of attraction, or an existing memory is retrieved, as a consequence of pattern completion and reactivation of an existing basin of attraction. Recoding in CA1 of information from CA3 is proposed to set up associatively learned back projections to the neocortex, itself modelled as multiple local attractor networks, based on the local recurrent collateral connections of neocortical pyramidal cells, to allow subsequent retrieval of information.

Applications of attractor theory to explain certain neurological and psychiatric diseases, such as obsessive-compulsive disorder, schizophrenia and depression, have been presented ([103], p.305–35). In addition, age-related impairments of episodic memory have been characterised as a reduction in the depth, and hence stability, of the basins of attraction of hippocampal attractor memory-related networks ([103], p.335–43; [104]). These conceptualisations might be extended to the case of TGA.

If, based on its neuroanatomy, hippocampal CA3 is characterised at the neural network level as a single global autoassociative attractor network, a model of TGA pathophysiology may be suggested [105]. The proposed chain of causation is as follows.

Positive feedback through the recurrent collateral CA3 connections becomes excessive as a consequence of changes in interoceptive and exteroceptive signalling converging on EC from association cortices, related to the recognised precipitating and predisposing factors for TGA (emotional stress, physical effort, etc.). There is enhanced activation of CA3 pyramidal cells via PP and DG inputs from EC to CA3 (Fig. 9.5). The binary mode functioning of CA3 neurones (firing or not firing) consequent upon their non-linear activation function renders them susceptible to not firing due to changes in threshold, related to concurrent impaired negative feedback from CA3 inhibitory interneurons. A runaway situation with infinite gain in the short CA3 feedback loop develops, resulting in a singularity or discontinuity, with failure of synaptic transmission (these steps overlap with those outlined in the feedback loop model in Sect. 9.7.3).

In terms of the attractor schematic (Fig. 9.4), postsynaptic firing, r_i, tends to zero, and hence the change in synaptic weight, δw_{ij}, also tends to zero. With no change in synaptic weights, no encoding of new memories or reactivation of existing memories within the hippocampus can occur. With loss of the output (CA3) neuronal firing (r_i), the network cannot compensate. There is loss of fault tolerance, one of the recognised properties of attractor networks, with catastrophic collapse of function, rather than the graceful degradation (proneness to error) anticipated with increased noise in a neural network, as may occur in age-related episodic memory impairment or Alzheimer's disease. In terms of the energy landscape, the system is unstable and flips to a shallower basin of attraction.

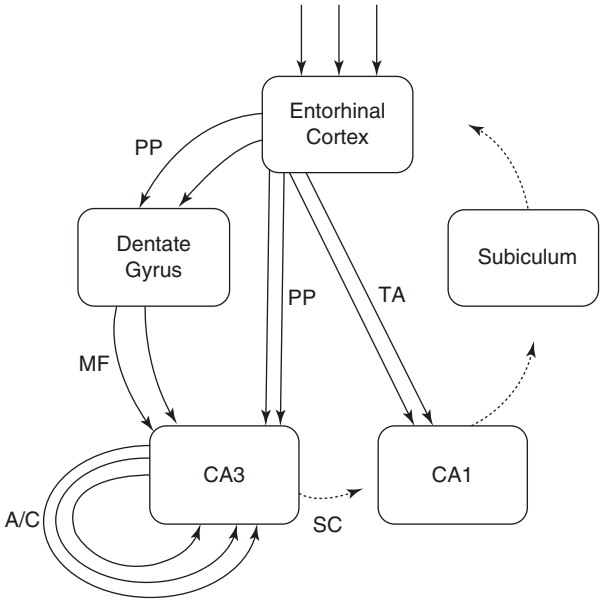

Fig. 9.5 Detail from Fig. 9.2 showing proposed hypothesis of TGA pathogenesis: excessive positive feedback in A/C loop following increased neocortical input to entorhinal cortex causes functional ablation of CA3 and failure of onward synaptic transmission to CA1 and neocortex. *PP,* perforant path; *MF,* mossy fibres; *TA,* temporoammonic pathway; *A/C,* associative/commissural loop; *SC,* Schaffer collaterals

Inactivation of the hippocampal CA3 attractor network accounts for inability to encode new associations (anterograde amnesia) and to retrieve some existing memories (retrograde amnesia). In addition to impaired recognition memory (pattern completion), evidence for impairment of pattern separation during acute TGA has been presented [106].

The consequent failure of feedforward excitation of CA1 from CA3, and hence of back projections to the neocortex from CA1 (Fig. 9.5), may also contribute to the failure to retrieve previously learned information, hence contributing to the retrograde amnesia (and possibly explaining its variable duration).

The intrinsic indeterminacy of attractor networks may also have some mechanistic corollaries of clinical relevance to TGA. Because of the stochastic operation of autoassociative attractor networks (as in the state-transition model; Sect. 9.7.2), it might be predicted that some TGA episodes may occur without obvious precipitants or triggers, but as a consequence of an inherently noisy system (possibly related to predisposing factors) flipping to a spontaneous low firing rate state as the most stable basin of attraction in the energy landscape.

Interindividual variation in the stability of the global CA3 attractor network may render some individuals at greater risk of episodes of TGA and their recurrence.,

This vulnerability might be structural or physiological, perhaps related to developmentally defined alterations in brain networks [68] or subtle variations in ion

channel kinetics. Genetically determined factors may also be relevant, such as migraine tendency and/or family history of TGA, putting these individuals at greater risk of TGA.

9.7.5 Spreading Depolarisation

The feedback loop and CA3 autoassociative attractor models (Sects. 9.7.3 and 9.7.4) of TGA may be predicated on hippocampal anatomy and function, but what mechanism(s) might underpin these neural network models?

As previously mentioned in the context of migraine (Sect. 9.4), Olesen and Jorgensen suggested more than 30 years ago that the cortical spreading depression (CSD) first described by Leão [56] was "theoretically … a very likely pathogenetic mechanism of TGA", and more specifically that "A highly emotional experience excites the hippocampus. Neuronal activity liberates glutamate, which triggers a spreading depression resulting in reversible functional ablation of the hippocampus" ([60], p.220). The initial observations of hippocampal changes on MR-DWI in TGA (Sect. 5.1.2; Fig. 5.1) were interpreted as evidence in favour of a CSD mechanism in TGA (e.g. [107, 108]). The mechanism of spreading depression remains a potential candidate explanation for TGA [109]. A revision of this suggestion may align with the postulated neural network models of TGA pathogenesis.

Spreading depression is now characterised as part of a continuum with spreading depolarisation (SD). SD is a wave of electrophysiological hyperactivity followed by a wave of inhibition which propagates across the cerebral cortex at around 1–10 mm/min. SD may be triggered by different processes, including severe ischaemia, hypoxia, hypoglycaemia and epileptic events. SD is thought to disrupt neuronal electrical activity through changes in extracellular ion concentrations, particularly increased $[K^+]$, toxic release of glutamate, dispersion of electrochemical gradients (failure of Na^+/K^+-ATPase pumps), mitochondrial dysfunction and cytotoxic oedema, leading to prolonged neuronal membrane depolarisation and refractoriness to neuronal impulse and synaptic transmission (for more detail on SD, see reviews [110–112]).

Extracellular glutamate accumulation may exacerbate neuronal depolarisation via glutamate receptors, a further positive feedback loop. NMDA receptors, with their high conductance and slow kinetics compared to AMPA receptors, may be particularly significant. In simulations of attractor dynamics, relatively small changes in NMDA receptor conductance can result in reduced firing rate, synaptic strength, basin depth and signal-to-noise ratio [101]. With the gradual restoration of ionic electrochemical gradients through the action of energy-dependent ion pumps, which also promote glutamate uptake, neuronal membranes repolarise and synaptic transmission resumes. This restoration may correlate with recovery from the clinical episode of TGA and resumption of episodic memory function.

SD is recognised to be a heterogeneous entity, the exact nature of which is affected by the triggering event and by genetic background. It has been implicated

in various disease processes, including stroke, traumatic brain injury, epileptic seizures and sudden unexplained death in epilepsy, as well as migraine aura, but recent reviews of SD do not mention, other than in passing, the previously postulated role in TGA. Many of the proposed mechanisms of SD are shared with epileptic seizures and ischaemia [113], but their occurrence in a hippocampal formation with essentially normal synaptic structure and perfusion may result in no significant long-term structural change. The vascular response to SD is variable, including both vasoconstriction and vasodilation. This might account for some of the variability in the changes in brain diffusivity seen on MR-DWI in TGA.

If SD is a "universal principle" of lesion development ([112], p.1572), it may be that TGA is a symptom complex which occurs as a consequence of SD. Current understandings of the pathogenesis of TGA (epilepsy, stroke, migraine) may not necessarily be mutually exclusive, indeed might be reconciled by the mechanisms of SD. For example, the TGA-migraine link may indicate a shared susceptibility to SD.

If the TGA rubric encompasses different entities, with TGA being a symptom complex [8] rather than a single specific disease entity, this might explain contradictory findings of epidemiological studies on factors such as the presence or absence of particular vascular risk factors. SD has also been proposed as an explanatory mechanism for seizures following migraine (migralepsy) and for migraine stroke or migrainous infarction [114].

9.7.6 Hypothesis: Proposal, Evidence, Predictions and Shortcomings

Could the proposed models of TGA, in particular the CA3 autoassociative attractor neural network catastrophic degradation model (Sect. 9.7.4), and the mechanism of spreading depolarisation (Sect. 9.7.5) be developed into a hypothesis of TGA pathogenesis which has an evidential basis and can make testable, falsifiable, predictions?

The hypothesis for the CA3 autoassociative attractor model may be stated as follows [105]. Proposal: An episode of TGA results when excessive positive feedback through the short recurrent collateral loops in the hippocampal CA3 region causes a temporary functional ablation of an autoassociative attractor neural network, flipping it to a spontaneous low firing rate state as the most stable basin of attraction in the energy landscape. Mechanistically, this is caused by a wave of spreading depolarisation which results in a cascade of biochemical and biophysical changes which produce prolonged neuronal membrane depolarisation and refractoriness to neuronal impulse and synaptic transmission, manifest clinically as the episode of anterograde and (variable) retrograde amnesia.

Some existing evidence may be deemed consistent with this hypothesis. Reports of functional neuroimaging studies, almost invariably undertaken post-TGA, have

generally shown hypoperfusion (SPECT) and hypometabolism (PET) in and beyond medial temporal lobe structures (Sect. 5.2.1 and 5.2.2), but these imaging modalities are known to have low spatial resolution. Resting-state functional MR imaging has shown reduction in functional connectivity within the episodic memory network bilaterally during TGA, including but not limited to the hippocampus, and more evident in the hyperacute phase and fully reversible with time (Sect. 5.2.6). Unintentional induction of TGA when testing deep brain stimulation electrodes, found on subsequent MR brain imaging to have been misplaced in the right hippocampus, was interpreted as caused by either inhibition of local neuronal activity or fibre activation by high current density via direct electrical stimulation of hippocampal structures [78] (Sect. 9.7.1).

Evidence which may falsify, rather than verify, a hypothesis is acknowledged to be the most stringent test, as any hypothesis that cannot be rejected is outside the realm of the empirical. Studying TGA in vivo is difficult since experience indicates that opportunities are few and of relatively brief duration (e.g. [115].). Hence, any falsifiable clinical predictions of the hypothesis would be difficult to test logistically. The most parsimonious test would be to look for changes consistent with SD in the hippocampal CA3 region during a TGA episode, since its absence would falsify the hypothesis. However, clinical monitoring of SD is currently limited to the use of subdural electrode strips placed by highly invasive neurosurgical intervention [116]. This ultimate test of the hypothesis must await the development of other, less invasive, technologies which can reliably detect SD in vivo.

The rostrocaudal extent of the hippocampal formation is about 5 cm in length, and hence SD, propagating at 1–10 mm/min, would be anticipated to progress through it in about 5–50 min, too short a time to be observed by any investigative modality unless by extreme chance a patient developed TGA whilst in close proximity to suitable equipment. Were that to be the case, then powerful structural imaging, for example with 7 Tesla MR, might be predicted to detect the acute changes of cytotoxic oedema which typically accompany SD within the hippocampus (follow-up 7 T MR imaging studies of TGA showed no visible sequelae [117]). Other investigational options might include magnetoencephalography (MEG) to image hippocampal activity [118] or high-resolution MR spectroscopy [119]. AC/DC-EEG to measure propagated negative DC potentials, which are thought to be markers of SD, might also be used [120].

In addition to clinical investigations during an episode of TGA, testable predictions at the epidemiological level may be made in light of the hypothesis. For example, SD is recognised to reduce seizure threshold [111]. If this were the case following TGA, patients might be predicted to have increased vulnerability to the emergence of epileptic seizures. There is some tentative evidence in favour of this (see Sect. 6.3.4 for summary). Instances of TEA following TGA (Sect. 3.2.2) in association with medial temporal lobe structural abnormalities on standard MR imaging sequences might also be taken as support for the prediction of the hypothesis.

The proposed hypothesis is, of course, not without shortcomings. Two particular limitations may be highlighted: firstly the observed age-related incidence of TGA

(Sect. 7.4) and secondly the MR-DWI findings (Sect. 5.1.2). The increasing incidence of TGA with age might be explicable in terms of aging-related vulnerability of the hippocampal attractor network to noise-related instability, as for aging-related decline in episodic memory ([103], p.335–43; [104]), but the apparent decline in TGA incidence in the latest decades of life would not be predicted by this mechanism. This might possibly be an artefact of case underascertainment and/or underreporting of TGA in the very elderly. If genuine, it might be related to declining susceptibility of the brain to SD with age [121]. A lower experimental threshold for SD induction in females [111] might be consistent with the female preponderance seen in most TGA cohorts [26] (Sect. 7.5).

The MR-DWI neuroimaging findings suggesting the evolution of neuronal metabolic stress in CA1 elude definitive explanation, although might be a consequence of enhanced transmission through the direct TA pathway from EC to CA1. The variable vascular response to SD may also be relevant. The time course with which these imaging changes evolve suggests they may be downstream and non-specific events [122], a transient diaschisis related to the relative vulnerability of the CA1 hippocampal sector to hypoxic and ischaemic insults which has long been recognised [123, 124] and may perhaps be a consequence of mitochondrial dysfunction [125]. Notwithstanding the neuroimaging findings, the suggested model does not envisage TGA to be simply a consequence of a lesion or lesions restricted to CA1 (see also Sect. 5.1.2.6).

9.8 The Future?

How might the understanding of TGA be taken forward in the coming years? One might anticipate developments both at the individual and epidemiological levels.

At the individual level, investigation of patients in the acute phase of TGA using neuroradiological and neurophysiological methods of increasing sophistication might shed further light on pathogenesis (Sect. 9.7.6). This poses significant logistical challenges, including transporting patients to hospital as soon as possible after onset of TGA and provision of suitable facilities for assessment and investigation in emergency care or acute neurology settings. Addressing some of these challenges might be facilitated by awareness raising measures delivered to both clinicians and the general populace. However, since the most significant elements of TGA pathogenesis (e.g. spreading depolarisation) may predate clinical mnestic and behavioural symptomatology, even this may not be sufficient for meaningful investigation of pathogenesis, since by the time of assessment only downstream events might be accessible to study. Remote monitoring of patients susceptible to recurrent TGA, if these could be identified (Sect. 6.2.2), might address this, if suitable technology could be developed (the neuronal equivalent of a cardiac loop recorder?) and patients could be persuaded to accept its use.

To better understand possible predisposing factors such as age, gender, ethnicity, and history of migraine and psychiatric/psychological disorders, as well as

precipitating factors, further large epidemiological studies of TGA are required. Ideally, such studies should be population-based to avoid bias. Ideally, there should be a minimum dataset collected for each patient, inquiring about pertinent clinical issues. Further consideration may need to be given to revising the Hodges and Warlow (1990) diagnostic criteria for TGA [77] to include MR-DWI (as has been previously suggested, e.g. [126]., p.109; see Sect. 2.2.2) to ensure relatively homogeneous patient cohorts and to exclude TGA mimics. Unbiased genome-wide association studies based on patients recruited to such studies, as well as metabolomic studies, might potentially shed further light on factors involved in TGA pathogenesis.

It may eventually be possible to move beyond purely descriptive neuroscience. As understanding of brain functional mechanisms develops, it may become possible to undertake computer-modelling of normal and pathological hippocampal neuronal network functions, perhaps using simulations of models such as those suggested here (Sects. 9.7.2, 9.7.3, and 9.7.4). By factoring in changes such as spreading depolarisation, it may be possible to see if TGA-like changes can be reproduced.

9.9 Closing Summary

Although much has been learned about TGA in the six decades since its first clear description, much still remains to be learned. The enigma of TGA pathogenesis will undoubtedly continue to intrigue clinicians and neuroscientists, and prompt further studies of this fascinating symptom complex/condition, not only because of its clinical significance but also because of the light it may shed on the cognitive architecture and mechanisms of human memory.

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