Chapter

Neurocognitive Perspective of Transient Global Amnesia

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Abstract

Transient global amnesia (TGA) is a neuropsychological syndrome that involves a sudden and temporary episode of memory loss that includes inability to create new memories. It has been shown that this disorder is related with a transitory deficit of the hippocampus function. In this chapter, the preserved and impaired memory pattern of TGA patients will be discussed considering the classical memory systems model. The analysis of this perspective leads to some contradictory or unresolved issues. In order to try to resolve these inconsistencies and considering that TGA is associated with hippocampal perturbation, new research about the hippocampus is analyzed. This new perspective focused on the hippocampal function provides a deeper understanding of the memory loss pattern associated with TGA, and it points out new questions that are not studied yet in the TGA population.

Keywords: transient global amnesia, anterograde amnesia, retrograde amnesia, hippocampus, memory systems, spatial representation, temporal representation, relational memory

1. Introduction

Transient global amnesia (TGA) is a neuropsychological syndrome, which shows a severe, sudden, and transitory loss of the ability to create new memories and, to some degree, to recover past events [1, 2]. The main goal of this chapter is to provide a neurocognitive perspective of the deficits and preserved abilities of this type of amnesia. Cognitive neuroscience is the scientific field that studies the neural bases of the cognitive processes as memory and learning [3]. As it has been shown that TGA is related with a transitory deficit of the hippocampus function, in this chapter the cognitive consequences of this deficit will be discussed. These consequences are going to be framed in a classical memory systems perspective, which considers that the hippocampus is engaged in declarative and explicit memory but not in non-declarative and implicit memory. This perspective leads to some inconsistencies and unresolved issues that will be confronted having a more precise and updated description of the function of the hippocampus.

The chapter starts with a review of basic characteristics of TGA including diagnostic criteria, etiology, and differential diagnosis. Then, the preserved and impaired memory pattern of TGA patients will be discussed considering the classical memory systems model. This includes both, the analysis of the ability of the TGA patients to recall knowledge acquired before the TGA (retrograde amnesia) and to learn new knowledge during the amnesic episode (anterograde amnesia). And finally, based on new insights from the hippocampal function research, some inconsistencies derived from the memory systems perspective will be analyzed.

2. Transient global amnesia

2.1 Diagnostic criteria

In order to have a clear diagnosis of the TGA, the following diagnostic criteria [4, 5] must be fulfilled: (a) there must be clear anterograde amnesia (inability to create new memories) during the attack that it is witnessed by an observer. (b) Consciousness loss and personal identity loss must be absent, and the cognitive impairment must be limited to the amnesia. (c) The patient's neurological examination is otherwise normal. No signs of pathology should appear in the electroencephalogram (EEG) of the TGA patient, with no epileptic-form activity or postictal abnormalities [6]. (d) Epileptic features must be absent. (e) Patients with recent history of head trauma or seizures must be excluded from this diagnosis. (f) The amnesic episode must be resolved within 24 hours. (g) Mild vegetative symptoms (headache, nausea, or dizziness) might be present during the acute phase [7].

2.2 Epidemiology

Concerning TGA epidemiology, the annual TGA incidence varies between 3 and 10 per 100,000 in different studies [5, 8–11]. In population older than 50 years old, the TGA rate increases until 23–32/100,000 [9, 10], and it is very rare before 40 [5]. The second TGA episode recurrence rate varies between 6 and 15% [9, 12]; thus it is not very frequent to have another episode.

2.3 Characteristics of a TGA episode

During TGA, patients show severe anterograde amnesia, which makes them unable to create new memories and to have the sense of present. This makes them disoriented in space and specifically in time, but they do not produce confabulations (false memories which are taken by the patient as true to fill the gaps in memory) [13]. In a study with 17 TGA patients, there were no significant differences in spatial orientation with the control group, while the temporal orientation was severely affected during the amnesic episode, and it was recovered after a week [14]. This difference between spatial and temporal disorientation may be reflecting their ability to use contextual information and previous semantic knowledge to make inferences about where they are. But those inferences were not helpful enough to make them orientate in time. During amnesic episode, patients maintain their attention, and they are able to perform complex tasks as gardening or driving [15, 16]. Patients usually are aware of their disease state, but they are unable to identify the nature of their memory deficits and they overestimate their memory ability [14, 17].

Witnesses of TGA episode usually report a sudden expressive or behavioral change in the patient [18]. A characteristic feature of TGA is the repetitive comments or questions that are repeated using the same words and making the same comments to the answers that they receive [13]. The episode lasts some hours and then the memory is recovered gradually. But the memory of the period of the amnesic episode is never recovered.

2.4 TGA settings

The settings where the TGA episode usually occurs include immersion in water, temperature change, painful experiences (e.g., renal pain [19]), physical activity, emotional stress (e.g., increased work load [5, 20]), sexual intercourse [21], driving and traveling, medical procedures, Valsalva-associated maneuvers, and

other activities as walks, house works, meetings, etc. [12, 17, 22–27]. In most of the settings, the patient is doing a routine or automatized activity and usually is alone or not in an active communication with others. Thus, it seems that patients are in a default functioning state. Additionally, certain personality traits have been related with the TGA as psychological or emotional instability [12] and higher occurrence of personal or family history of psychiatric disorders [28]. TGA has been associated with the intake of different substances such as sildenafil, vasodilator drug for erectile dysfunction [29, 30], or ergotic drugs to treat migraine. But in both cases, it could be a coincidence of events, drug intake and amnesia, and not a causal relationship between them [31]. It is important to consider that the percentage of TGA without a triggering factor or special setting is high, between 44% [24] and 52% [12] with more than 800 patients in each review.

2.5 Etiology

MRI data suggest that during the TGA there is a temporary perturbation of the hippocampal function, mainly in the CA1 field of the hippocampus [6, 22]. Various factors such as migraine and vascular abnormalities have been suggested to be involved in the TGA etiology, but the causal mechanisms underlying these hippocampal perturbations remain unclear.

Several studies have reported a higher incidence of migraine in patients with TGA than healthy, age-marched controls [4, 12, 23, 32–34]. But patients do not usually have migraine episodes before TGA or migrainous features during TGA episode. TGA usually occurs after 50 years old, while migraine appears through the life-span [35] and migraine is a recurrent disease, and TGA usually has only one episode [28]. Thus, migraine could be a risk factor for TGA, and its correlation could reflect a sharing mechanism [36] but probably is not a direct cause of a typical TGA.

Some studies have related TGA with ischemic deficits, but even there are cases of transient amnesia with ischemic etiology (transient ischemic amnesia (TIA)) [1, 8], they do not share many characteristic with TGA. For example, TIA is associated with stroke risk factors that are not common in TGA patients [5, 7, 12, 32, 34, 37], and TGA patients usually do not develop cerebrovascular diseases [9, 15, 33].

Another transient amnesia is transient epileptic amnesia [38], which is caused by focal seizure activity, and it can be differentiated from TGA by the briefness and high frequency of the amnesic episodes [6].

Some data suggests that the impairment of the hippocampal function during TGA may be related to the metabolic stress of the hippocampal neurons [22]. This stress-related change may trigger a hypometabolic event associated with the *cortical spreading depression*, which is described as a short-lasting depolarization wave followed by neuronal depression and regionally decreased blood flow [22, 39]. In support to this idea, decreased oxygen and cerebral blood flow in the temporal region has been reported in TGA patients [40–43]. Furthermore, CA1 region of the hippocampus shows a selective vulnerability to metabolic stress caused by different situations as neurotoxicity [44].

In the same direction, Kessler et al. [45] proposed that TGA might be related with the biochemical imbalance associated with psychological stress and anxiety through the increase of stress hormones' level. There is an overlap between the brain areas affected during TGA, as hippocampus, and regions with high density of glucocorticoid receptors, which are stress hormones [45]. In fact, a special sensitivity of the TGA patients to psychological stress [12] and high prevalence of emotional stress in these patients have been suggested [32]. Additionally, several studies have pointed out that emotional, physical, and behavioral stress situations lead to the onset of TGA in many cases [22]. And studies on the animal hippocampus

have shown that emotional and behavioral stresses impair long-term potentiation and enhance long-term depression in CA1 neurons, disturbing the hippocampus-dependent memory [46].

In conclusion, the causal mechanisms underlying hippocampal perturbations of TGA remain unclear, but it seems probable that TGA is related with metabolic stress of hippocampal neurons.

3. Memory systems and TGA

Traditionally, a memory system perspective has been used to describe which processes are affected and preserved during amnesia. From this perspective, memory is considered as a not unitary entity, with relatively independent but interacting systems that process different types of information, which have different cognitive rules and that are implemented in specific cerebral networks [47]. In order to define this systems, animal and human, behavioral, clinical, neuropsychological, and neuroimaging studies have been used [48–50]. The combination of these findings has helped to classify the different memory systems.

In order to describe the complexity of memory, initially binary models were suggested. Cohen and Squire [51] proposed that long-term memory could be subdivided between declarative memory, which is representational, can be verbalized, and is severely impaired during amnesia, and procedural memory, which is expressed through action, is independent from conscious awareness, and is preserved during amnesia. On the other hand, Graf et al. [52] suggested that long-term memory is divided into implicit memory that is acquired and used unconsciously and explicit memory that is conscious and intentional.

Later, a more complex model was proposed, which is considered a classical classification model of memory systems [47, 53]. This model includes the following memory systems: episodic memory, working memory, semantic memory, priming, and procedural memory. This proposal assumes that there is a continuum between explicit/implicit and declarative/procedural dimensions through different memory systems. In the following sections, each system will be defined, and the impairments and preservation pattern associated with the TGA will be described.

3.1 Procedural memory

Procedural memory is the system that allows no-conscious acquisition, maintenance, and the use of motor and cognitive skills. It is characterized by gradual or progressive acquisition, which typically results in increased speed or accuracy with repetition. It includes heterogeneous set of subsystems: motor and cognitive abilities, habits, conditioning, and nonassociative learning. It is implicit and non-declarative, it is not hippocampal dependent, and it is spared in amnesia [53].

3.1.1 Skills acquired before the TGA

During the TGA episode, patients are able to perform complex but automatized activities learnt before the attack. For example, they are able to play the organ [54], conduct a talk [17], cook [24], drive a car [55], or conduct a concert [56]. These and similar activities, which are usually quite complex, when becoming routine procedures no longer need the involvement of the hippocampus. Thus, during the TGA procedural memories acquired before the TGA tend to be preserved [56].

3.1.2 Acquisition of new procedural skills during the TGA

In addition, the ability to learn new procedural skills remains preserved as well during TGA episode. For example, Eustache et al. [40] showed that TGA patients are able to acquire mirror-reading skill at the same learning speed as the control group.

Another example of implicit learning phenomenon is the mere exposure effect, which is defined as preference enhancement to previously exposed stimuli [57]. Mere exposure effect is preserved in TGA patients during the amnesic episode, showing enhanced preference for previously exposed faces, in spite of the severe anterograde memory loss [27].

Classical conditioning is another subtype of procedural memory that is based on associative learning. In classical conditioning, repeated pairings of a neutral conditioned stimulus (CS), such as a tone, and an unconditioned stimulus (US) such as an air-puff to the eye result in the CS alone, eliciting conditioned response (CR) such as an eyeblink [58]. Traditionally, it is considered that fear and eyeblink conditioning are unaffected in patients with hippocampal damage [59, 60]. So far, there are no studies with TGA patients assessing these types of classical conditioning, but more complex conditioning paradigms, as trace conditioning and fear conditioning, seem to be affected in TGA population. This contradictory result will be described in Section 3.

3.2 Perceptual representation system

The perceptual representation system [47] facilitates word and object identification identification based on form and structure information , but not considering meaning or associative properties. It is pre-semantic, implicit, not hippocampal dependent, and Usually it is spared in amnesia. Priming is a phenomenon dependent of this system. It implies a behavioral change that is reflected in speed or accuracy change with stimulus processed following prior exposure [61]. For example, the word "plane" will produce faster response when it is preceded by the word "rain," because both words are auditorily similar, comparing when it is preceded by the word "frog."

There is some empirical evidence that suggests that PRS remains preserved during TGA episodes. Kapur et al. [62] showed that perceptual priming was spared during TGA through a fragmented figure completion task with visually degraded drawings. And even 1 week after the amnestic episode, the patient continued to show priming effect with the figures studied during the TGA episode compared with new figures. This result has been confirmed using different learning materials as fragmented numbers [13] and verbal material with a word completion task [40].

3.3 Semantic memory

Semantic memory refers to the acquisition, retention, and use of general knowledge (facts, concepts, vocabulary, and knowledge about the world and the individuals). It is declarative, independent of contextual information, and it is usually not affected in amnesia [63].

3.3.1 Retrieval of semantic knowledge acquired before the TGA

During the TGA, language is intact. According to Caplan [17], patients show spontaneous speech and normal vocabulary, and they do not present aphasic errors.

They maintain the ability to repeat oral language, to read, and to write. They can describe not present objects, geographical details, and familiar places using their semantic knowledge. Patients with TGA are able to recognize and name objects and colors [64] and to point at drawings in response to words [65]. In addition, nonverbal semantic knowledge, assessed with a task that requires matching conceptually related figures, is also preserved [65].

Regarding verbal fluency tasks, in which participants have to produce as many words as possible from a category in a given time, there are contradictory results. While in some studies [40, 45, 66–68], TGA patients presented lower production of category examples than the control group, both with words within a semantic category (category fluency) and with words starting with a given letter (letter fluency); in other investigations [64, 65, 69, 70] no significant differences were found between TGA patients and the control group, although the former produced more perseverations.

Regarding knowledge about the world, memory for past public events and famous people is impaired during TGA [62], especially for events and people from recent decades [64]. TGA patients are able to differentiate between real events from fictional events, probably based on their implicit knowledge. But their ability to localize these events in time, primarily those from the closest decades to the amnesic episode, is impaired [71, 72]. Recognition of famous people faces seems to be preserved in some cases [64, 71], but there is some contradictory data [72], especially regarding faces linked to recent experiences.

3.3.2 Acquisition of new semantic knowledge during the TGA

It is not clear if TGA patients are able to learn new semantic memory during amnesic episode. It is important to address this question. Interestingly, there is evidence of preserved semantic priming during TGA [73, 74]. TGA patients showed semantic priming during TGA episode, and this effect persisted for 1 day [73]. But there is no data about the ability of TGA patients to acquire semantic facts. Previous research has shown that the left hippocampus is involved in successful incidental acquisition of new facts about the world [75].

Furthermore, there is evidence of patients with medial temporal lobe lesions that are impaired to learn new semantic knowledge [76]. Thus, it would be interesting to study this issue with TGA patients. Based on permanent amnesia impairment pattern, new semantic knowledge acquisition is expected to be affected during TGA.

3.4 Working memory

Short-term memory implies the conscious retention for information over a few seconds, often through active rehearsal. When the information held in short-term memory is manipulated or another task is performed, this is often referred to as working memory [77].

Based on previous research, TGA patients have preserved capacity to maintain activated a limited amount of information for a brief period of time. This has been addressed using digit span task [13, 71, 78–80], immediate memory for rhythms [81, 82], memory for spatial positions measured with the Corsi block-tapping task [45, 70, 71, 78, 80], and immediate recall for letters and objects [81]. Regarding working memory during TGA, there are no conclusive results, probably due to the diversity of required processes and the variability of complexity level through different tasks. **Table 1** summarizes the data.

Task	During TGA	References
Stroop task (inhibition to avoid reading and focus on the ink color)	Preserved	[64, 65, 68, 70]
Card sorting task (flexibility to change matching criteria)	Impaired. Only one classification criteria of the six possible	[13]
Trail making test (connect fastest possible numbers placed randomly in a paper sheet)	Preserved	[65, 68]
Backward memory span (recall stimuli in reverse order of the presentation)	Preserved	[70, 71]
	Impaired	[78, 80, 83]
Updating task (listen to auditory-presented letters, and decide if each letter that is added matches one of the previous three letters)	Preserved	[70]
Brown-Peterson's experimental paradigm (retain three consonant letters while performing a distractor task)	Deficit with 3- and 6- second delay intervals	[70]
Raven's progressive matrices (nonverbal abstract reasoning: to find a missing element to complete a pattern)	Preserved	[65]

Table 1.
Summary of studies assessing working memory in TGA patients with different tasks.

3.5 Episodic memory

Episodic memory encodes, stores, and recovers memories about past events in a spatio-temporal context. This memory allows to reexperience the past episodes as in a mental "time travel." The episodic system is declarative, explicit, hippocampus dependent, and severely damaged in amnesia [63].

3.5.1 Acquisition of new episodic information during the TGA

One of the most characteristic features of TGA is the deficit to form lasting memories of new episodic information. This impairment affects the acquisition of any kind of information: visual (figures and words), tactile, olfactory, or auditory (environmental sounds and speech) [84].

Different laboratory tests have been used to measure episodic memory. Free recall, the ability to reproduce previously presented material, is severely impaired, using visually presented words [40, 66, 67, 70, 78], auditory-presented words [27, 64, 85], semantically unrelated word pairs [72, 86], prose passages [40, 62, 72, 81, 86], or complex geometric figures [40, 64, 78, 85, 86].

Regarding cue-recall, the ability to retrieve information with a recovery cue that guides searching processes, there are no conclusive data. Some patients obtain preserved cue-recall scores, and other patients show significantly lower performance than the control group [27, 69, 70, 81]. And it seems that is not related with the type of cueing methods but with the patient, since contradictory outputs have been found using the same method. In a study with a bigger sample, there was a significant difference between TGA patients and the control group in cue-recall, being impaired for the patients [27].

Regarding recognition, the ability to recognize previously presented stimuli, is impaired in patients with TGA, both with words and drawings [41, 66, 69, 80, 85]. Recognition is usually subdivided into two component processes: recollection and familiarity, frequently measured with the "remember/know" (R/K) paradigm.

Recollection implies the retrieval of contextual details of the previous event, and familiarity is based on the feeling that the event was previously experienced but without details or context [87]. Recollection has been traditionally linked with episodic memory and hippocampal function, while familiarity is related with semantic memory and it is independent from the hippocampus [88]. Impaired R/K response pattern has been shown in TGA patients [70, 89], with usually lower recollection scores in TGA patients than in controls, while no significant difference in familiarity scores between TGA and controls [80].

3.6 Autobiographical memory

Autobiographical memory is a uniquely human system that integrates memories of past experiences into a life narrative [90], and it allows to mentally travel in time [63]. There are two components of autobiographical memory: episodic and semantic autobiographical memory. Episodic autobiographical memory refers to the memories of our personal past, and it is usually assessed with interviews that cover events from childhood until hours before the amnesic episode. Semantic autobiographical memory refers to the recollection of personal facts and general self-knowledge independent of a specific time and space [91]. This division between episodic and semantic components of autobiographical memory is based on dissociations found with amnesic patients as KC [92], which shows an episodic autobiographical memory disturbed while the semantic component is preserved.

3.6.1 Acquisition of new autobiographical information during TGA

TGA patients are not able to create autobiographical memories during the TGA episode showing a severely anterograde amnesia for this self-related information. When recovering from the TGA episode, patients show a memory gap of those hours that is never recovered.

3.6.2 Retrieval of autobiographical memories acquired before the TGA

Neuropsychological studies of TGA patients have shown that they have problems to remember their past, even though this deficit is milder than anterograde deficit. During TGA, episodic autobiographical memories from different periods of life are affected, showing deficit of details, absence of spatial and temporal context, and even sometimes confusion between memories [67, 69, 72, 89]. This retrograde amnesia usually is temporally graded [22], and it follows Ribot's Law [93], which implies deeper impairment of the closest memories compared with remote memories.

In contrast, semantic autobiographical memory is preserved. TGA patients usually recall personal information such as age, place of birth, past addresses, phone number, names of teachers, and educational and professional history [17, 94].

3.7 Conclusion about memory systems and TGA

This section has shown the memory deficit pattern of TGA based on the classical memory systems perspective, which considers that the hippocampus is engaged in declarative and explicit memory but not in non-declarative and implicit memory. This perspective leads to some inconsistencies. For example, it seems that some types of classical conditioning as trace conditioning and fear conditioning are affected in TGA patients, but based on the memory systems perspective, they should be preserved. Furthermore, working memory should be preserved as well

in TGA patients, but some complex working memory tasks seem to be affected. It is also important to point out that there is not much understanding of the TGA patients' ability to acquire very complex stimuli as people's faces or complex semantic knowledge during the TGA. In the following section, in order to try to resolve these inconsistencies, new research about the hippocampus is analyzed.

4. New insights from the hippocampal function research

Since the famous case of the HM patient, the hippocampus has been considered a key structure for memory. HMs' medial temporal lobe (including hippocampi) was removed in order to try to control intractable seizures [95]. This produced him a profound amnesia specially to acquire new memories. Since that time, extensive research has been conducted in order to understand the hippocampus involvement in learning and memory and in other cognitive domains.

As it was mentioned before, there is a temporary perturbation of the hippocampal function during the TGA. Therefore, this section reviews the theories about the hippocampal function and its consequences to interpret the amnesic pattern of TGA patients. These theories are organized based on the nature of the memory processes involved and the type of information that is processed.

4.1 Memory processes

There are three main processes involved in human memory: encoding, which allows converting perceived information into a more permanent form; consolidation, which stabilizes a memory trace after its initial acquisition; and retrieval, which involves re-accessing events or information from the past [96]. There is a general agreement that episodic memories depend on the hippocampus during the encoding of new memories [95]. But the involvement of the hippocampus on retrieving remote memories is controversial.

The Standard Model of Consolidation considers that episodic and semantic memories become less dependent on the hippocampus until they are completely independent [97]. On the contrary, multi-trace theory defends that the hippocampus is crucial for acquisition of both, episodic and semantic memories. But the recollection of episodic memories remains dependent on the hippocampus in order to retrieve contextual and detailed memories, whereas semantic memories become independent from the hippocampus [98].

There is a historic debate whether the hippocampus is required to retrieve remote autobiographical memories [99]. Considering this type of memories, two patterns emerge from the literature about patients with medial temporal lobe damage: complete autobiographical memory loss across all time points, recent and remote [100, 101], and memory loss with a temporal gradient, with recent memories lost but remote memories preserved [102]. These patterns could be reflecting at least two different explanations: that autobiographical memories become less detailed and more semanticized over time and thus less dependent of the hippocampus, which could explain the apparent preservation of remote autobiographical memories in some patients [98], or that the brain damage extension is different between patients and those with widespread damage are the ones showing remote autobiographical memories impaired [103].

In fMRI studies, it has been shown that the hippocampus is associated with retrieving autobiographical memories, which are detailed and vivid, anytime that they are recalled, regardless of age of the memory [75, 104]. And studies using multivoxel pattern analysis (MVPA) has shown that more recent memories engage

the anterior hippocampus but the posterior hippocampus is especially essential for remote memories [105] . This shows that there is a temporal gradient representation within the hippocampus itself. Thus, the neuropsychological loss pattern of each patient may depend on the location and extent of the damage within the hippocampus.

In TGA patients, the autobiographic memory loss has two different patterns: a continuous pattern, when memories from a limited period are affected, and an irregular pattern, when memory loss is selective without a clear time interval [78, 86, 105]. This could be related with the temporal gradient shown within the hippocampus itself [105]. But in most cases, TGA patients follow Ribot's Law [93], so that recent memories are more likely to be lost than more remote memories. This is coherent with the pattern shown in patient with permanent hippocampal damage (e.g., [102]).

4.2 Type of processed information

4.2.1 Navigation and spatial representation

Spatial information is a type of information that has been proposed to be processed by the hippocampus. Animal studies have shown that place cells in the hippocampus encode location while moving in the environment, and these cells fire when a specific place field is entered, irrespective of where the animal is looking [106]. Thus, the hippocampus provides an internal space representation or cognitive map of the environment that is allocentric (world-centered) and not egocentric (self-centered) [107]. As it seems that the hippocampus is a relevant structure for both, episodic memory and spatial representation, it has been proposed that the spatial representations of the hippocampus could support spatial context to the episodic memories [108].

fMRI studies with humans support the idea that the hippocampus is engaged when mentally or virtually navigating an environment [109]. Furthermore, studies with permanent amnesic patients show that hippocampal damage impairs the spatial learning of new environments [101], but it is not essential to navigate in familiar places. In the same direction, TGA patients are able to return to familiar places or to drive in well-learnt routes [55]. This is coherent with the diminished hippocampal activation when navigating in familiar environment [110].

However, a further question important to address is if TGA patients are able to learn to navigate in a new environment while they are under the amnesic episode. Considering the hippocampus involvement in both, acquisition of new explicit knowledge and representation of space, an impaired performance is expected.

4.2.2 Temporal representation

Another type of knowledge that is related with the hippocampus is temporal information. There are some cell ensembles in the hippocampus, especially in the CA1 area, which fire when an animal is at a particular moment in a temporally structured experience. Firing patterns of these hippocampal neurons change gradually over time representing the flow of time in an experience [111]. Literature about patients with permanent temporal lobe amnesia shows that they are able to arrange information into a sequential narrative and they seem to understand the concept of time [112]. As we mentioned before, temporal orientation is severely affected during TGA [14], and they show an absence of temporal details when trying to remember their episodic autobiographical memories [67, 69, 72, 89]. But it would be interesting to study in more detail the concept of

time in TGA patients, including the representation of the duration of an event, the coding of temporal order of the elements in an episode, and the subjective sense of time [113].

4.2.3 Relational representation

The relational memory theory assumes that the hippocampus' main function is to represent associations between different elements in order to bind together multiple inputs into a single representation [114, 115]. In this sense, hippocampus may represent bindings between items (e.g., who and what) and context (e.g., where and when) [116, 117]. Furthermore, the hippocampus allows to recall these flexible relational representations and to use that information for inference in novel situations [118].

Regarding relational memory in TGA patients, two different types of contextual details have been studied: the recall of spatial information about the learning session (e.g., if words are presented on the top or bottom of the screen) and temporal information of specific items (e.g., if words belong to a first or second word list). TGA patients were very impaired remembering spatiotemporal details associated with individual items or events [67, 89].

Another insight from studies in patients with permanent hippocampal damage about relational memory is that these patients are able to recognize associations between items of the same domain (e.g., word-word), but they have problems to recognize associations between items of different kind (e.g., word-face) [119, 120]. Thus, when the task requires increased relational complexity, it is more dependent on the hippocampus and specially affected in patients with hippocampal damage. Thus, TGA patients may be impaired in across-domain association recognition as well, but this issue should be studied.

A further example of hippocampal involvement in complex processing is scene reconstruction. It has been proposed that the main function of the hippocampus is scene reconstruction [121], which may be considered as a special case of relational memory theory. Scene processing requires combining individual features across domains in a complex and coherent representation of the world. Scene components need to be integrated from modality-specific representation into a spatially coherent representation [108]. It has been shown that scene recognition is impaired in patients with medial temporal lobe damage [118, 119], and even though it has not been properly studied, it may be impaired in TGA patients as well.

There are additional examples about the hippocampal contribution when relational complexity increases, both in conditioning and in working memory. As it has been mentioned before, there is no hippocampus involvement in classical conditioning, but trace conditioning, which occurs when there is a time interval between offset of the conditioned stimulus and delivery of the unconditioned stimulus, requires hippocampal functioning [122]. Thus, the processing of a temporal contiguity delay in associative learning adds more complexity and requires the hippocampus. It would be interesting to study this type of conditioning with TGA patients. Contextual fear conditioning is another example of classical conditioning paradigm that requires complex associations and hippocampus involvement. This conditioning involves placing the animal in a novel environment, providing an aversive stimulus. When the animal is returned to the same environment, generally will recover the association between environment and the aversive stimulus and it will activate fear response (freezing response). TGA patients showed contextual fear conditioning impairment compared with the control group [123], which reflects the relationship between hippocampal functioning and relational complexity of the associations.

As it has been mentioned before, working memory has traditionally been considered as immune from hippocampal damage. But, it has been shown that when working memory task requires more complex stimuli or relational binding, then it shows to be affected when hippocampus is disturbed [108, 124]. This may partially explain the contradictory results of working memory in TGA that are considered in Section 2.

In order to account hippocampal sensitivity to complexity and precision, it has been proposed pattern separation as the underlying computational mechanism [99]. This pattern separation enables to differentiate with precision between items with overlapping features or relations [125]. It would be desirable to study this mechanism in TGA patients in order to understand deeply the deficit associated with this syndrome.

Thus, predictions from memory system model would expect that, for example, conditioning and working memory are immune to hippocampal damage and preserved during TGA. But a deeper analysis of the function of the hippocampus shows the hippocampal involvement, and its impairment in amnesia is related with the level of relational complexity of the processed information and with the computations needed in this processing.

4.2.4 Future and imagination

Traditionally, the hippocampus has been considered essential to retrieve memories from the past, but recent research suggests that it may also be related to envision and predict the future events and to imagine fictitious episodes [126]. It has been shown that the hippocampus and connected areas recombine elements of existing episodic memories to create new scenarios, and this allows creating a representation of the future and imagining new events [127]. Regarding the ability to imagine future events in patients with permanent hippocampal amnesia, usually they show problems answering questions about the future [128], and they show less richness and less integration of contextual details than the control group in imagining fictitious events or scenes [129, 130].

Research with TGA patients has shown that even though they can imagine past and future events, they provide fewer and less detailed events than the control group [131]. In another study, TGA patients showed prospective memory deficit, which involves remembering to perform an intended action at some point in the future [132], and this deficit was correlated with their retrograde impairment [68]. This probably reflects shared processes between remembering the past and projecting into the future.

In relation to future planning, mind-wandering is a form of spontaneous self-generated thinking independent from the current perceptual surrounding [133]. It has been shown that people with selective bilateral hippocampal damage are able to engage in mind-wandering as controls. However, their form and content of mind-wandering are different, showing less flexible and scene-based content and more abstract and semanticized representation [134]. An open question to be addressed is mind-wandering and creative thinking in TGA patients.

5. Conclusion

The main goal of this chapter was to present a neurocognitive perspective of the deficits and preserved abilities of TGA. In order to carry out this goal, basic characteristics of TGA were analyzed, including diagnostic criteria, etiology, and differential diagnosis. Then, the deficit pattern of TGA was presented based on the

classical memory systems model. This perspective assumes that declarative and explicit memory systems, as episodic and semantic memory, are severely affected during TGA. On the contrary, procedural and implicit memory systems, as procedural memory and perceptual representation system, and also working memory are preserved, while they are not dependent on hippocampal processing. The analysis of this perspective leads to some contradictory or unresolved issues.

Afterward, in order to try to understand these inconsistencies and considering that TGA is associated with transitory perturbation of the hippocampal function, new research about the hippocampus and its cognitive mechanisms are analyzed. It seems that declarative/procedural and implicit/explicit dimensions are not decisive to be affected by hippocampus damage. Nevertheless, processes as associative or relational binding and pattern separation, which operate regardless of declarative level and conscious awareness, are especially sensitive to hippocampal impairment. Moreover, the complexity level of those processes seems to be a modulating factor that affects the impairment degree both in permanent hippocampal amnesias and in TGA.

This new perspective focused on the hippocampal function has proportioned a better understanding of inconsistent results, and it has pointed out new questions that are not studied yet with TGA population.

Acknowledgements

I am grateful to Yeray Mera for his help to prepare the References section of this chapter.

Conflict of interest

The author declares no conflict of interest.

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