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Sleep Modifications in Acute Transient Global Amnesia

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SCIENTIFIC INVESTIGATIONS

Study Objective: Transient global amnesia (TGA) is a temporary memory loss characterized by an abrupt onset of anterograde and retrograde amnesia, totally reversible. Since sleep plays a major role in memory consolidation, and in the storage of memory-related traces into the brain cortex, the aims of the present study were: (1) to evaluate changes in sleep macrostructure in TGA; (2) to assess modifications in sleep microstructure in TGA, with particular reference to the arousal EEG and to cyclic alternating pattern (CAP); (3) to compare sleep parameters in TGA patients with a control group of patients with acute ischemic events ("minor stroke" or transient ischemic attack [TIA]) clinically and neuroradiologically "similar" to the TGA.

Methods: TGA group: 17 patients, (8 men and 9 women, 60.2 ± 12.5 years). Stroke or TIA (SoT) group: 17 patients hospitalized in the Stroke Unit for recent onset of minor stroke or TIA with hemispheric localization; healthy controls (HC) group: 17 healthy volunteers, matched for age and sex. Patients and controls underwent full-night polysomnography.

Results: In the multivariate analysis (conditions TGA, SoT, and HC) a significant effect of the condition was observed for sleep efficiency index, number of awakenings longer 1 min, REM latency, CAP time, and CAP rate. TGA and SoT differed only for CAP time and CAP rate, which were lower in the TGA group.

Conclusions: Microstructural modification associated with TGA could be consequent to: (1) hippocampal dysfunction and memory impairment; (2) impairment of arousal-related structures (in particular, cholinergic pathways); (3) emotional distress.

Keywords: Transient global amnesia, memory, sleep, cyclic alternating pattern

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Transient global amnesia (TGA) is a temporary memory loss characterized by an abrupt onset of anterograde and retrograde amnesia; it is totally reversible. TGA typically lasts several hours, usually from 1 to 24, leaving only an amnesic gap for the acute episode and, often, for the hours before the episode.[1]

In 1956 Courjon and Guyotat described the TGA for the first time, and defined it as "Amnesic Stroke."[2] Subsequently, in 1964, Fisher and Adams[3] further characterized the syndrome, and introduced the term *transient global amnesia*. In 1990, Hodges and Warlow[4] attempted to define diagnostic criteria by analyzing the characteristics of the amnesic disorder. The most characteristic feature of the TGA is the sudden onset of an acute inability to retain new information (anterograde amnesia), associated with a significant reduction in the ability to recall past events (retrograde amnesia).[5] During the acute phase of TGA, which can last for a few minutes or hours, retrograde amnesia may involve events that occurred in the previous weeks or months. Some persons affected by TGA appear confused and disoriented in time and space, and repeatedly ask the same things.

Several hypotheses have been proposed to explain the etiology of the syndrome, such as ischemia, migraine, seizures, venous congestion, and psychological disorders,[6] particularly intense emotional stress.[7,8] In clinical practice the recent introduction of sequences of magnetic resonance in diffusion (diffusion weighted imaging [DWI]), has allowed demonstration that about 50% of patients suffering from TGA show a small area of restricted diffusion in the lateral formation of the hippocampus.[9] The hypothesis that TGA can be consequent to a small venous infarct of the hippocampus is debated.[5,10-13] Identification of TGA requires the exclusion of other causes of amnesia: head trauma or concussion, epileptic seizures, ischemia, drug intoxication, and psychogenic causes.[1] However, whatever the etiology, neuroimaging has provided evidence that TGA is due to a transient dysfunction of the mesial temporal lobe, particularly the hippocampus.[14-17]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep plays a major role in memory consolidation, so the aims of this study were: (1) to evaluate changes in sleep macrostructure in TGA; (2) to assess modifications in sleep microstructure in TGA, with particular reference to the arousal EEG and to cyclic alternating pattern (CAP); (3) to compare sleep parameters in TGA patients with a control group of patients with acute ischemic events ("minor stroke" or transient ischemic attack [TIA]) clinically and neuroradiologically "similar" to the TGA.

Study Impact: This study shows that microstructural modification associated with TGA could be consequent to: (1) hippocampal dysfunction and memory impairment; (2) impairment of arousal-related structures (in particular, cholinergic pathways); (3) emotional distress.

Table 1—Diagnostic criteria for transient global amnesia (Hodges and Warlow)[4] and clinical and instrument evaluation performed for patient selection

Diagnostic criteria for transient global amnesia (Hodges and Warlow)	Evaluations of TGA patients enrolled in the study
(1) The attack was witnessed and reported	Interview of partner, relatives, or other witnesses
(2) There was obvious anterograde amnesia during the attack	Three-word recall task
(3) There was an absence of clouding of consciousness	Mini-Mental State Examination
(4) There were no focal neurological signs or deficits during or after the attack	Neurological examination
(5) There were no features of epilepsy	Anamnesis, EEG in acute phase of TGA
(6) The attack resolved within 24 h	Clinical observation after admission
(7) The patient did not have any recent head injury or active epilepsy	Anamnesis, CT scan, EEG

Sleep and Memory

A recent hypothesis that has found increasingly frequent experimental evidence, is that sleep is useful in consolidation of learning and memory.[18] This reinforcement is due to an interaction between the neocortex and the hippocampus. In rats, hippocampal neurons are activated in a sequential spatial order (defined for this "space cells").[19] This means that when the rat goes one way, the place-cells are activated in a sequence that corresponds to the stimuli that the rat receives along the path itself; the same sequence of activity is also observed in the neurons of the visual cortex.[20] In normal sleep the hippocampal "place-cells" present a disorganized and chaotic pattern of activation. Conversely, during sleep following a visual experience (as, indeed, crossing a path), in the hippocampus of the rat it has been observed an ordinate activation of the "place-cells," with an activation sequence that corresponds to the sequence with which these cells have been stimulated and activated during wakefulness. This strengthens the synaptic connection between cells that have received "previous" stimuli and those who received the "next" stimuli; in addition, this sequential activation chain is transmitted to the visual cortex. In this way, during sleep the hippocampus plays its primary role, which is to "keep" temporary memory traces and transfer them in the cerebral cortex, where they are stored as permanent memory traces.

Several studies[18,20-22] have provided electrophysiological evidence of the involvement of the hippocampus and neocortex in memory processes during sleep, reflecting their active participation in the memory consolidation processes as proposed in theoretical models. Recently it has been suggested that distinct sleep mechanisms subserve different aspects of episodic memory and are jointly involved in sleep dependent memory consolidation.[23]

The aims of the present study were the following: (1) to evaluate the presence of changes in sleep macrostructure in the TGA acute phase, that is, in the night immediately following the onset of the amnesic episode; (2) to assess the presence of modifications in sleep microstructure in the TGA acute phase, with particular reference to the arousal EEG and to cyclic alternating pattern (CAP); and (3) to compare sleep parameters in TGA patients with a control group consisting of patients with acute ischemic events clinically and neuroradiologically similar to the TGA, such as "minor strokes" or transient ischemic attacks (TIAs).

METHODS

We enrolled 17 consecutive patients who had presented with an episode of TGA within 24 hours previous to our observation. Patients were recruited in the Department of Emergency and admitted to a Stroke Unit, where the study has been conducted. The diagnosis of TGA was made according to the criteria by Hodges and Warlow (1990)[4]; each criterion was clinically evaluated and, when possible, an instrumental confirmation was performed (**Table 1**). The Mini-Mental State Examination (MMSE) was performed. Hippocampal signal abnormalities in DWI MRI, performed 1 to 5 days after the onset of TGA, were considered an inclusion criterion. Although the diagnosis of TGA does not need the demonstration of abnormal hippocampal signal (which can be detected in about half of the patients), we applied this criterion in order to enroll only patients with neuroimaging-based evidence of involvement of the hippocampus.[24] The group consisted of 17 patients, 8 men and 9 women; average age was 60.2 ± 12.5 years. Patients taking drugs that affect the central nervous system (CNS) were excluded from the study. Sleep recordings were all been performed in the Stroke Unit during the night immediately following the acute episode of TGA, regardless of whether the episode had resolved or not. Therefore, polysomnographic recordings were performed without any adaptation of the environment of the examination. The main demographic and clinical data of the study population are summarized in **Table 2**. The study was approved by the local ethics committee, and all patients and control subjects gave their written informed consent to participate.

Control Groups

Sleep results in TGA patients (group TGA) were compared with findings in 2 separate control groups. The first control group was composed of healthy volunteers, matched for age and gender (group HC). The TGA population was also compared with a control group composed of patients hospitalized in the Stroke Unit for recent onset (within 24 h) of mild or transient neurological deficits (minor strokes[25] or TIA[26]) with hemispheric localization (group SoT); patients with symptoms or signs of focal or diffuse thalamic or brainstem dysfunction were excluded. The reasons for this choice are the following: (1) the polysomnographic recordings were performed in patients suffering from TGA admitted to the Stroke Unit, and therefore in a setting with the characteristics of intensive care, without the

Table 2—Demographic and clinical features in the population of TGA patients

Patient	Gender	Age	Duration of amnesia (hours)	Comorbidities	Trigger
1	M	31	n.d.	Hypertension	emotional distress
2	F	54	4-6		emotional distress
3	F	55	0.3		physical activity (sport)
4	F	67	7		emotional distress
5	M	72	3	Hypertension	emotional distress
6	M	70	3	Diabetes	emotional distress
7	F	71	7		physical activity (sport)
8	F	66	4	Hypertension	emotional distress
9	M	67	3		emotional distress
10	M	50	6.5	Diabetes	hypertensive crisis
11	F	69	2	Hypertension	emotional distress
12	F	71	2	Hypertension	emotional distress
13	M	54	8		hypertensive crisis
14	M	37	n.d.	Hypertension	emotional distress
15	F	72	2		emotional distress
16	F	52	0.5	Hypertension	physical activity (sport)
17	M	66	n.d.	Hypertension	emotional distress

Totals for patient gender are 8 males, 9 females. Mean (standard deviation) for patient age is 60.2 (12.5). n.d., not defined.

possibility of recording environment control offered by a sleep laboratory. Consequently, the control group had to be constituted by bedridden patients in the same unit; (2) as specified in the methods section, patients affected by TGA received polysomnographic (PSG) registration in the hours immediately after the admission, therefore without any previous adaptation to the environment. As a result, the control group had presented an acute and recent neurological disorder; (3) the cerebrovascular events defined as a TIA or minor stroke present clinical and neuroradiological features (for size of the region of brain tissue involved) entirely similar to those of the TGA; (4) patients with symptoms or signs of thalamic or brainstem dysfunction were excluded because such lesions location may be associated with dysfunction of the brain areas that control the sleep/wake cycle and the transition between the different stages of sleep (particularly the interplay of NREM/REM) and the arousal reaction.

The control group consisted of 17 subjects, 8 men and 9 women, (average age 64.2 ± 10.6 years), affected by minor stroke or TIA starting 24 hours before the study.

PSG Recordings

Nocturnal PSG recordings were performed using a dynamic Micromed Morpheus polygraph; the following parameters were recorded: EEG (surface electrodes positioned in F3, F4, C3, C4, O1, O2), EOG (2 electrodes placed 1 cm at the side and 1 cm above or below the external canthus of each eye), mastoid reference (A1 or A2), EMG (2 surface electrodes placed in submental region, in correspondence of the mylohyoid muscle), ECG (modified D1 derivation). For staging nocturnal sleep, we examined the portion of polysomnographic recording on the night between 23:00 (lights off) and 07:00 of the next morning (lights on), similar to recording time in standard polysomnographic recordings made in the laboratory. Together with PSG recording, patients underwent continuous cardiorespiratory monitoring recording the following parameters: ECG (4 branches), oxygen saturation (SpO_2) of hemoglobin obtained from pulse oximetry, noninvasive blood pressure measurement for nighttime periods, measurement of nasal and oral respiration (by means of a pressure transducer cannula), thoracic and abdominal movements recorded by using inductive plethysmography, and snoring sound (by means of a vibration sensor). This monitoring allowed assessment of the presence of pathological respiratory events during sleep. The scoring of sleep and respiratory events was performed according to standardized criteria.[27]

Sleep Microstructure

Sleep microstructure was evaluated by means of the detection of the fast-frequency EEG arousals and the analysis of cyclic alternating pattern (CAP). Arousal were visually detected and quantified in accordance to the rules of the ASDA[28]; separate arousal indexes (number of arousal / time) were calculated for the sleep period time, NREM sleep, and REM sleep. To evaluate the dynamics of arousal, we quantified arousal fluctuations during sleep by means of CAP. CAP scoring was performed visually, according to the criteria established by Terzano et al.[29] We quantified, within NREM sleep stages, the number of CAP sequences, of phases A (divided into the 3 subtypes—A1, A2, and A3), the mean duration of phases A and B, and the percentage of NREM sleep occupied by CAP. This ratio (CAP duration / NREM sleep), referred to as CAP rate, is the expression of the percentage of NREM sleep spent in a state of arousal instability.

Power Spectral Analyses

Sleep EEG recordings were further analyzed by means of quantitative EEG spectral analysis. Each 30-sec epoch was visually screened for artifacts (EMG, temporary disconnect spikes, sweating, body movements); epochs with artifacts were removed from further analysis. Also epochs in which a respiratory event occurred (apneas or hypopneas, central, mixed, or obstructive) were excluded from the analysis. The remaining data were ex-

Table 3—Results of the statistical comparison among groups

	Multivariate		TGA vs SoT		TGA vs HC	
	F-ratio	p-value	U-test	p-value	U-test	p-value
Sleep latency	1.470	0.240	163.0	0.524	107.0	0.196
Time in bed	1.959	0.152	171.5	0.352	200.0	0.056
Total sleep time	1.607	0.211	173.0	0.326	191.0	0.109
Sleep period time	1.243	0.298	176.0	0.278	199.0	0.060
Sleep efficiency index	6.011	**0.005**	157.0	0.667	63.0	**0.005**
Awakenings > 1 min	9.816	**< 0.001**	145.5	0.972	245.5	**< 0.001**
Wake after sleep onset	2.908	0.064	130.5	0.630	192.5	0.098
REM (%)	1.515	0.230	146.0	0.959	102.0	0.143
N1 (%)	0.239	0.788	162.0	0.547	176.0	0.278
N2 (%)	0.742	0.482	178.5	0.242	157.0	0.667
N3 (%)	0.481	0.621	130.0	0.617	149.0	0.877
N4 (%)	0.020	0.980	158.0	0.642	158.0	0.642
WAKE (%)	1.595	0.214	132.0	0.667	168.0	0.418
REM latency	13.081	**< 0.001**	158.5	0.630	289.0	**< 0.001**
CAP time	12.148	**< 0.001**	215.0	**0.015**	90.0	0.060
CAP rate	12.018	**< 0.001**	208.0	**0.029**	56.0	**0.002**
AHI	7.898	0.019	134.5	0.730	73.5	0.014
ODI	5.373	0.068	121.0	0.418	77.5	0.021

TGA, transient global amnesia; SoT, stroke or TIA; HC, healthy controls; CAP, cyclic alternating pattern; AHI, apnea-hypopnea index; ODI, oxygen desaturation index. Significant results are shown in bold.

tracted from the scored sleep data file by dedicated software (Rembrandt SleepView, Medcare) and stored in a separate binary data file. Spectral analysis was performed on 2-sec windows with a frequency resolution of 0.5 Hz using a discrete Fourier transform algorithm (Hanning window). Five power spectra bands were computed per 30-sec epochs for each EEG electrode for the entire recording period. The EEG bands analyzed were the following: delta (0-4 Hz), theta (4.5-7.5 Hz), alpha (8-13 Hz), beta (13.5-30 Hz), and sigma (spindle activity, 13-16 Hz). To compensate for variability among subjects and across the night in EEG power, the spectra were normalized: absolute power values in each frequency band (expressed in mV^2/Hz) were divided by the total power and multiplied × 100 (thus relative spectral values were expressed as percentage of the total spectral power). Spectra were finally converted to data file for statistical analysis.

Statistical Analysis

The comparison between the 3 groups was performed using a multivariate analysis of variance (MANOVA), in which the independent variable was the condition (groups TGA, HC, and SoT) and dependent variables were the macro- and microstructural sleep parameters listed in **Table 3**. Successively, the TGA group was compared with the SoT and the HC groups separately, by means of a nonparametric test (Mann-Whitney U-test). The threshold for statistical significance was $p < 0.05$. All statistics were performed using the SYSTAT 12 software, version 12.02.00 for Windows (SYSTAT Software Inc. 2007).

RESULTS

Useful recordings were obtained in all subjects of the TGA group and the control groups (HC and SoT). In the multivariate analysis, when we compared the 3 groups (TGA, SoT, and HC), a significant effect of condition was observed for sleep efficiency index ($F = 6.011$, $p = 0.005$); number of awakenings > 1 min ($F = 9.816$, $p < 0.001$), REM latency ($F = 13.081$, $p < 0.001$), CAP time ($F = 140.374$, $p < 0.001$), CAP rate ($F = 81.050$, $p < 0.001$), apnea-hypopnea index (AHI), and oxygen desaturation index (ODI). As a second step, we compared separately the TGA group with the SoT and with the HC. TGA and SoT differed only for microstructural CAP parameter: CAP time (U-test = 215.0, $p = 0.015$) and CAP rate (U-test = 208.0, $p = 0.029$). In the last comparison, between TGA and HC, significant differences were observed in for sleep efficiency index (U-test = 63.0, $p = 0.005$); number of awakenings > 1 min (U-test = 245.5, $p < 0.001$), REM latency (U-test = 289.0, $p < 0.001$), and CAP rate (U-test = 56.0, $p = 0.002$). As concerns sleep-related breathing pattern, both TGA patients and SoT group had higher AHI and ODI than normal subjects. Controls, by inclusion criteria, had AHI < 5 events/h: mean AHI = 2.4 ± 1.7 events/h; ODI = 3.5 ± 2.0 events/h). Respiratory indexes, however, were not significantly different between the TGA and SoT groups: AHI: TGA = 5.3 ± 3.5 events/h; SoT = 4.8 ± 3.4 events/h; U-test = 7.898, $p = 0.019$; ODI: TGA = 5.9 ± 3.2 events/h; SoT = 5.2 ± 3.4 events/h; U-test = 5.373, $p = 0.068$). Detailed results of the comparison of sleep parameters among the 3 groups are shown in **Table 2**.

As concerns the power spectral analyses, no significant differences were observed between the TGA and the SoT groups for any of the frequency bands analyzed.

DISCUSSION

The most relevant finding in the present study is the reduction of NREM sleep instability, expressed by CAP time and

CAP rate, in patients with TGA. This reduction is evident when compared with subjects with minor stroke or TIA, but much more evident when TGA patients were compared with healthy controls. In fact, in our study, HC had a mean value of CAP rate of 51%, very close to values reported in literature for healthy elderly people[30]; this value was reduced to 36% in the TGA group.

CAP is the expression of NREM sleep instability.[31] The generators of cortical electrical activity during sleep shift from the production of low-amplitude high-frequency electroencephalographic (EEG) activity (LAHF mode, typical expression of the massive activation of the cortical cells), to the production of high-amplitude low-frequency EEG activity (HALF mode, indicating a widespread synchronization of the cortical cells).[32-34] Within the concept of microarousal (MA) we include, besides the classical low-voltage fast-rhythm electroencephalographic (EEG) arousals, high-amplitude EEG bursts (delta-like or K-complexes), which can be described as a special kind of arousal process, mobilizing parallel anti-arousal swings. In physiologic sleep, slow and fast microarousals are not random but appear structurally distributed and represent state-specific arousal responses. High-frequency and low-frequency MA are differently distributed in the sleep cycles: slow-frequency MA occurs more frequently in the first cycles, particularly in the descending part of the cycles; whereas high-frequency MA prevail during the last third of sleep and in the descending branch of the cycles. Moreover, different MAs are associated with a different magnitude of vegetative activation, ranging hierarchically from the weaker slow EEG types (coupled with mild autonomic activation) to the stronger rapid EEG types (coupled with vigorous autonomic activation).[34]

Traditionally, arousals are a marker of sleep disruption, but they also represent elements that take part in the regulation of the sleep process.[34] Arousals during sleep are related to the processing of information. Periodic arousal fluctuations during NREM sleep are associated with the memory function.[35] Ferini-Strambi et al.[35] observed an increased number of periodic arousal fluctuations during NREM sleep (measured as CAP) in an individual with exceptional memory. This finding supports to the link between NREM sleep and declarative memory. Memory-related deficit in TGA seems to be specifically related to declarative memory.[36] Consolidation of declarative memory in healthy subjects is supported by slow wave sleep (SWS).[37] Declarative memory benefits mainly from sleep periods dominated by SWS, whereas there is no consistent benefit of this memory from periods rich in REM sleep.[38] Taken together these data may suggest that, in acute TGA, the impairment of declarative memory during daytime is associated with a reduction of EEG fluctuations during NREM sleep at night. On the other hand, recent data from animal models and human research indicate that NREM sleep stability is necessary for memory consolidation and that pre-sleep learning (particularly declarative memory tests) increases NREM sleep continuity and stability in elderly subjects.[39,40]

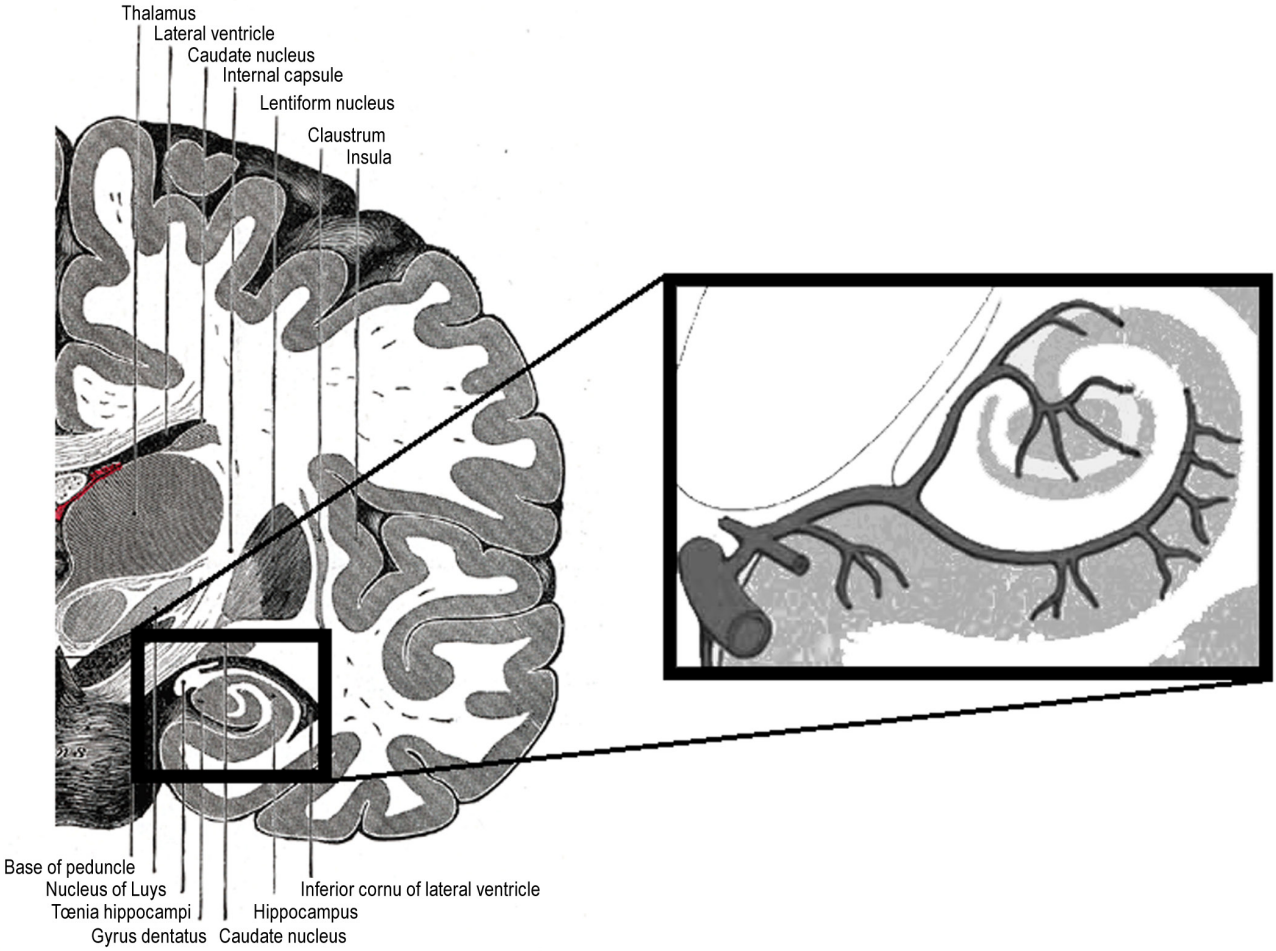
If there is a loss of declarative memory during wake preceding sleep, it may be that the memory-related contents which need to be processed during NREM sleep is decreased, and consequently the fluctuation of NREM sleep is reduced in parallel fashion. Therefore, in TGA patients, CAP is reduced, and the amount of residual fluctuation (around 35%) is the portion of CAP (structural CAP[41,42]) that is intrinsically necessary to maintain the physiological sleep architecture. In dyslexia, it has been hypothesized that, in order to overcome reading difficulties, dyslexic subjects overactivate thalamocortical and hippocampal circuitry to transfer information between cortical posterior and anterior areas; this overactivation is associated with increased CAP time and CAP rate.[43] Analogously, it seems conceivable that in TGA the hippocampal dysfunction produces hypoactivation of the hippocampal circuitry and a less efficient transfer of information between hippocampus and cortex; this hypoactivation could be expressed, in the surface EEG, by a reduced amount of CAP.

The hippocampus is a crucial structure for memory. It represents the site of storage of episodic memory[44] before it is transformed into long-term memory in the neocortex.[45] The hippocampus is a particularly vulnerable region of the brain. In particular, the CA1 region of the hippocampus, which seems to be selectively involved in TGA,[46] is one of the areas most vulnerable to ischemia.[47] This occurs because the hippocampal artery supplies an internal anastomosis forming a link between an upper and a lower artery: this creates a watershed area, called "hypoxia-susceptible sector of Sommer" (**Figure 1**). The hippocampus is also particularly vulnerable to excitotoxic mechanisms.[48,49] Therefore, stressful events, including emotional experiences, may overexcite the hippocampus and induce glutamate release, which triggers the spreading depression and the functional ablation of the hippocampus.[50,51] This excitotoxicity-induced damage can produce both EEG abnormalities[48,49] and hyperintense DWI signal.[52] All the previously described functional features account for the plastic, adaptive modifications which occur in the hippocampus after a traumatic stress. In fact, the hippocampus plays a crucial role, together the medial prefrontal cortex and the amygdala, in the brain response to stress: this is why alterations in hippocampal function and structure (volume reduction) have been observed in patients with posttraumatic stress disorder (PTSD).[53] Finally, a transient hippocampal impairment may occasionally have a protective role,[54] probably because amnesia minimizes the possibility of establishing a cognitive representation of the traumatic event.

An alternative explanation is based on the hypothesis of a cholinergic dysfunction. The cholinergic circuits play a primary role also in memory functions and learning, particularly at the level of the hippocampus and entorhinal cortex.[55,56] The decline of arousal, particulary of the fast-EEG arousal, which recognize a cholinergic genesis,[34,57] could be further confirmation of this hypothesis if supported by statistical confirmation in a larger populations.

Several data seem to suggest that TGA, at least in a majority of cases, may be triggered by intense emotions.[6-8] Seen in this view, the reduced CAP rate and CAP time could reflect a condition of emotional distress, which persist in the night following the TGA. At present, no data are available in the literature concerning modification of CAP in conditions characterized by acute or chronic emotional distress. Emotions can trigger more or less transient amnesic episodes, as may happen in dissociative disorders.[58] It could be speculated, therefore, that TGA is a sort of "minimal" dissociative memory-related disorder, triggered by emotional or physical distress, associated with a re-

Figure 1—Schematic representation of hippocampal vascularization



Left (black box): hippocampus in coronal view. Right (black box): detailed representation of the hippocampus with the hippocampal artery. Note: This original figure (modified here) is from a lithographic plate originally produced in *Gray's Anatomy* in 1918 and therefore has lapsed into the public domain. It is not part of the copyright that protects the remainder of this paper.

duced flow of information between hippocampus and cortex, during wake and sleep.

Further studies are necessary to evaluate the possible role of "emotional arousal" during sleep and its relation to memory processing.

Study Limitations

The present study has several limitations, most of which are a consequence of the choice to enroll acute patients in an emergency room setting. The main limitations are the lack of adaptation before PSG recording, the absence of formal memory evaluation during the acute phase of TGA, and the lack of a follow-up study. In particular, the absence of a follow-up polysomnographic recording makes the design of the study cross-sectional and does not allow collection of data concerning the sleep pattern of patients after recovery from TGA. We tried to overcome these limits by selecting an appropriate control group, and by performing an accurate clinical evaluation of the patients' memory function during the acute TGA. Finally, no definite conclusion can be established concerning the modifications of sleep and arousal following TGA: we presented some explanatory hypotheses, which require eventual confirmation from further research.

REFERENCES

1. Kirshner HS. Transient global amnesia: a brief review and update. *Curr Neurol Neurosci Rep* 2011;11:578-82.
2. Courjon J, Guyotat J. [Amnesic strokes]. *J Med Lyon* 1956;37:697-701.
3. Fisher CM, Adams RD. Transient global amnesia. *Acta Neurol Scand Suppl* 1964;40:SUPPL 9:1-83.
4. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *J Neurol Neurosurg Psychiatry* 1990;53:834-43.
5. Sander K, Sander D. New insights into transient global amnesia: recent imaging and clinical findings. *Lancet Neurol* 2005;4:437-44.
6. Quinette P, Guillery-Girard B, Dayan J, et al. What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases. *Brain* 2006;129:1640-58.
7. Della Marca G, Broccolini A, Vollono C, et al. The stolen memory: a case of transient global amnesia. *Biol Psychiatry* 2009;67:e31-2.
8. Marinella MA. Transient global amnesia and a father's worst nightmare. *N Engl J Med* 2004;350:843-4.
9. Cianfoni A, Tartaglione T, Gaudino S, et al. Hippocampal magnetic resonance imaging abnormalities in transient global amnesia. *Arch Neurol* 2005;62:1468-9.

10. Akkawi NM, Agosti C, Borroni B, Padovani A. Detection of intracranial venous reflux in patients of transient global amnesia. *Neurology* 2007;68:163; author reply 163.
11. Akkawi NM, Agosti C, Rozzini L, Anzola GP, Padovani A. Transient global amnesia and venous flow patterns. *Lancet* 2001;357:639.
12. Ameriso SF, Romano M. Transient global amnesia, cerebral veins, and the need to find the 'smoking gun'. *Stroke* 2012;43:2275-6.
13. Baracchini C, Tonello S, Farina F, et al. Jugular veins in transient global amnesia: innocent bystanders. *Stroke* 2012;43:2289-92.
14. Yang Y, Kim S, Kim JH. Ischemic evidence of transient global amnesia: location of the lesion in the hippocampus. *J Clin Neurol* 2008;4:59-66.
15. Jager T, Szabo K, Griebe M, Bazner H, Moller J, Hennerici MG. Selective disruption of hippocampus-mediated recognition memory processes after episodes of transient global amnesia. *Neuropsychologia* 2009;47:70-6.
16. Nakada T, Kwee IL, Fujii Y, Knight RT. High-field, T2 reversed MRI of the hippocampus in transient global amnesia. *Neurology* 2005;64:1170-4.
17. Sedlaczek O, Hirsch JG, Grips E, et al. Detection of delayed focal MR changes in the lateral hippocampus in transient global amnesia. *Neurology* 2004;62:2165-70.
18. Marshall L, Born J. The contribution of sleep to hippocampus-dependent memory consolidation. *Trends Cogn Sci* 2007;11:442-50.
19. Eichenbaum H, Dudchenko P, Wood E, Shapiro M, Tanila H. The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron* 1999;23:209-26.
20. Ji D, Wilson MA. Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat Neurosci* 2007;10:100-7.
21. Moroni F, Nobili L, Curcio G, et al. Sleep in the human hippocampus: a stereo-EEG study. *PloS One* 2007;2:e867.
22. Sterpenich V, Albouy G, Boly M, et al. Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLoS Biol* 2007;5:e282.
23. Griessenberger H, Heib DP, Kunz AB, Hoedlmoser K, Schabus M. Assessment of a wireless headband for automatic sleep scoring. *Sleep Breath* 2013;17:747-52.
24. Bartsch T, Butler C. Transient amnesic syndromes. *Nat Rev Neurol* 2013;9:86-97.
25. Crespi V, Braga M, Beretta S, Carolei A, Bignamini A, Sacco S. A practical definition of minor stroke. *Neurol Sci* 2013;34:1083-6.
26. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009;40:2276-93.
27. American Academy of Sleep Medicine. *International classification of sleep disorders - diagnostic and coding manual. second edition*. Westchester, IL: American Academy of Sleep Medicine, 2005.
28. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173-84.
29. Terzano MG, Parrino L, Smerieri A, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. *Sleep Med* 2002;3:187-99.
30. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. *Electroencephalogr Clin Neurophysiol* 1998;107:439-50.
31. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. *Sleep Med Rev* 2012;16:27-45.
32. Steriade M, Gloor P, Llinas RR, Lopes de Silva FH, Mesulam MM. Report of IFCN Committee on Basic Mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalogr Clin Neurophysiol* 1990;76:481-508.
33. Steriade M, Llinas RR. The functional states of the thalamus and the associated neuronal interplay. *Physiol Rev* 1988;68:649-742.
34. Halasz P, Terzano M, Parrino L, Bodizs R. The nature of arousal in sleep. *J Sleep Res* 2004;13:1-23.
35. Ferini-Strambi L, Ortelli P, Castronovo V, Cappa S. Increased periodic arousal fluctuations during non-REM sleep are associated to superior memory. *Brain Res Bull* 2004;63:439-42.
36. Muhlert N, Milton F, Butler CR, Kapur N, Zeman AZ. Accelerated forgetting of real-life events in transient epileptic amnesia. *Neuropsychologia* 2010;48:3235-44.
37. Goerke M, Cohrs S, Rodenbeck A, Grittner U, Sommer W, Kunz D. Declarative memory consolidation during the first night in a sleep lab: The role of REM sleep and cortisol. *Psychoneuroendocrinology* 2013;38:1102-11.
38. Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. *Learning Mem* 2004;11:679-85.
39. Conte F, Carobbi G, Errico BM, Ficca G. The effects of pre-sleep learning on sleep continuity, stability, and organization in elderly individuals. *Front Neurol* 2012;3:109.
40. Conte F, Ficca G. Caveats on psychological models of sleep and memory: A compass in an overgrown scenario. *Sleep Med Rev* 2013;17:105-21.
41. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). *Sleep Med Rev* 2000;4:101-23.
42. Terzano MG, Parrino L, Boselli M, Spaggiari MC, Di Giovanni G, Smerieri A. Sensitivity of cyclic alternating pattern to prolonged pharmacotherapy: a 5-week study evaluating zolpidem in insomniac patients. *Clin Neuropharmacol* 1997;20:447-54.
43. Bruni O, Ferri R, Novelli L, et al. Slow EEG amplitude oscillations during NREM sleep and reading disabilities in children with dyslexia. *Dev Neuropsychol* 2009;34:539-51.
44. Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev* 1992;99:195-231.
45. Hasselmo ME, McClelland JL. Neural models of memory. *Curr Opin Neurobiol* 1999;9:184-8.
46. Bartsch T, Alfke K, Stingele R, et al. Selective affection of hippocampal CA-1 neurons in patients with transient global amnesia without long-term sequelae. *Brain* 2006;129:2874-84.
47. Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. *Neuroscience* 1991;40:599-636.
48. Eid T, Ghosh A, Wang Y, et al. Recurrent seizures and brain pathology after inhibition of glutamine synthetase in the hippocampus in rats. *Brain* 2008;131:2061-70.
49. Eid T, Thomas MJ, Spencer DD, et al. Loss of glutamine synthetase in the human epileptogenic hippocampus: possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy. *Lancet* 2004;363:28-37.
50. Gorji A, Scheller D, Straub H, et al. Spreading depression in human neocortical slices. *Brain Res* 2001;906:74-83.
51. Olesen J, Jorgensen MB. Leao's spreading depression in the hippocampus explains transient global amnesia. A hypothesis. *Acta Neurol Scand* 1986;73:219-20.
52. Laurent D, Eis M, Sauer D, Theilkaes W, Allegrini PR. Reduction of excitotoxicity-induced brain damage by the competitive NMDA antagonist CGP 40116: a longitudinal study using diffusion-weighted imaging. *Neurosci Lett* 1996;213:209-12.
53. Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog Brain Res* 2008;167:171-86.
54. Joseph S, Masterson J. Posttraumatic stress disorder and traumatic brain injury: are they mutually exclusive? *J Trauma Stress* 1999;12:437-53.
55. Hasselmo ME. The role of acetylcholine in learning and memory. *Curr Opin Neurobiol* 2006;16:710-5.
56. Hasselmo ME, Giocomo LM. Cholinergic modulation of cortical function. *J Mol Neurosci* 2006;30:133-5.
57. Jones BE. Arousal systems. *Front Biosci* 2003;8:s438-51.
58. Reinhold N, Markowitsch HJ. Retrograde episodic memory and emotion: a perspective from patients with dissociative amnesia. *Neuropsychologia* 2009;47:2197-206.

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