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**DISRUPTION IN NORMAL CORRELATIONAL PATTERNS OF METABOLIC
NETWORKS IN THE LIMBIC CIRCUIT DURING TRANSIENT GLOBAL
AMNESIA**

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ABSTRACT

Transient global amnesia (TGA) is characterized by the sudden apparition of a severe episodic amnesia, mainly anterograde, associated with emotional changes. Even though the symptoms are stereotyped, cerebral mechanism underlying TGA remain unexplained and previous studies using positron emission tomography (PET) do not show any clear results or consensus on cerebral regions impacted during TGA. This study included a group of 10 TGA patients who underwent ^{18}F -fluorodeoxyglucose positron emission tomography during the acute or the recovery phase of the episode and 10 paired healthy controls. Episodic memory was evaluated with the Encoding-Storage-Retrieval (ESR) paradigm and a story recall test of the Wechsler's Memory Scale and anxiety was assessed with the Spielberger scale (STAI). We used statistical parametric mapping to identify modifications of whole-brain metabolism. Regarding hypometabolism, there was no brain region systematically affected in all TGA patients and the comparison between TGA patients and controls did not show any significant differences. To better understand the specific implication of the limbic circuit in the pathophysiology of TGA, we then conducted a correlational analysis that included regions of this network. Our findings showed that in healthy controls, regions of the limbic circuit seem to operate in a synchronized way with all regions being highly correlated to each other. On the opposite, in TGA patients, we observed a clear disruption of this normal correlational patterns between regions with the medial temporal lobe (the hippocampus, parahippocampal gyrus and amygdala) included in one cluster and the orbitofrontal cortex, anterior and posterior cingulate gyrus and thalamus gathered in the other one. Given the individual variability in the time course of TGA, the direct comparison between a group of patients and controls does not seem to favor the identification of subtle and transient alterations in regional metabolism. The involvement of an extended network, such as the limbic circuit, seem more likely to explain the symptoms of patients. Indeed, the synchronization of regions within the limbic circuit

seems to be altered during TGA, which could explain the amnesia and anxiety observed in TGA patients. The present study thus deepens our understanding of the mechanisms underlying not only amnesia but also the emotional component of TGA by considering it as a disruption in the normal correlational patterns within the limbic circuit.

Introduction

Even though transient global amnesia (TGA) has been clearly defined by Hodges and Warlow in 1990¹, its pathophysiology remains enigmatic. This stereotyped neurological syndrome is characterized by the sudden onset of a transient and massive anterograde amnesia. It is associated, during the acute phase, with a more variable retrograde amnesia, iterative questions and temporal disorientation², and is accompanied by mood changes including increased anxiety². The following recovery phase is characterized by the disappearance of temporal disorientation and iterative questions but with the persistence of deficient memory scores. According to Hodges and Warlow criteria, patients gradually recover within 24 hours and the attack does not result in any long-term neuropsychological sequels³. One of the striking characteristics of TGA is the absence of volume deficits in anatomical magnetic resonance imaging (MRI) examinations⁴.

TGA is usually classified as a hippocampal amnesia since the severe episodic memory deficits observed in TGA patients are supposed to be related to hippocampus alterations. Indeed, hyperintensities on diffusion-weighted imaging (DWI) MRI are often detected in the hippocampus and more specifically in the CA1 field of the hippocampal cornu ammonis in TGA patients⁴⁻⁶. Interestingly, the lesions are mainly observed 12 to 48 hours after the TGA onset. These abnormalities have been interpreted as a consequence of functional pathological brain events having occurred during the acute phase of TGA⁵.—The vulnerability of the temporal lobe was also highlighted in two single-case studies using fMRI, with a reduction in the BOLD signal being observed while TGA patients were encoding new information during the acute phase^{7,8}.

The use of positron emission tomography (PET) allows the study of brain functions at a molecular level. It is thus more sensitive to subtle and/or transient changes occurring with a pathological event and could be relevant to use in TGA. The PET scan requires the injection

of a radiotracer, such as the [¹⁸F]-2-fluoro-2-deoxy-D-glucose (FDG-PET), and allows, in that case, a measure of the cerebral metabolic rate of glucose. The measure of glucose consumption, necessary for neuron operations, likely reflects localized synaptic activity^{9,10}. However, PET studies conducted in TGA patients are very scarce with only six single-case studies (Table 1) and only two using an FDG-PET examination. It is indeed extremely difficult to recruit a group of TGA patients, especially during the acute and recovery phases. Besides, the use of PET scan requires access to specific facilities and expertise, which makes the study of brain metabolism in TGA patients even more challenging. All previous PET investigations used a region of interest (ROI) method and showed heterogeneous results with altered metabolism (hyper- or hypo-metabolism) in various regions^{11,12} including the hippocampus¹³⁻¹⁵, thalamus¹¹ or amygdala¹⁴.

Even though hippocampal dysfunction may contribute to TGA, there exists no consensus in the literature regarding the pathophysiological mechanisms that govern this pathology. In addition, the sole implication of the hippocampus cannot explain the emotional aspect of this syndrome. In effect, in parallel to amnesia, TGA patients in the acute phase also present emotional changes with increased anxiety and more depressed mood^{2,16}. Those changes, noticed in papers on TGA^{17,18}, can be associated to the higher increase of the cortisol level observed in patients during TGA compared to time-matched day level¹⁹ or to a control group, prior and after a stressful experimentation²⁰. These findings suggest that TGA patients might be hypersensitive to stress and have difficulties to cope with it²¹. However, the origin of those emotional symptoms and their relationships with amnesia are not clearly understood. They could either reflect a psychological reaction to the sudden onset of amnesia, or a symptom at the same level as amnesia due to brain dysfunction of regions involved in both memory and emotion²².

No region thus seems to be solely responsible for the symptoms seen in TGA. In fact, there is growing evidence towards TGA being rather due to a brain network dysfunction²³⁻²⁷, explaining the absence of- or heterogeneity in- results when investigating the implication of regions independently of each other rather than them working together as a network. The observation of both emotional and amnesic symptoms points to the implication of the limbic system, a set of brain regions known to support both emotions and memory²⁸. In this perspective, a dysfunction in synaptic activity within the limbic circuit could explain the combination of severe memory disorders and emotional changes observed in TGA patients. Studies on the limbic system have highlighted the potential existence of two sub-networks, one being involved in emotion (including the amygdala, orbitofrontal cortex and the anterior cingulate cortex) and the other in episodic memory (including the hippocampus, parahippocampal gyrus, thalamus and posterior cingulate cortex)^{29,30}. Also in accordance with the literature regarding the regions involved in amnesia^{31,32}, it seems thus more pertinent to study brain alterations in TGA patients within these regions as a network rather than each as their own entity.

The goal of the present study was to provide a better understanding of the pathophysiological mechanisms contributing to amnesia and anxiety in TGA. We aimed at explaining the absence of structural alterations and the heterogeneity of the previous PET results by testing the hypothesis that TGA is a transient network disorder²⁵ affecting the limbic circuit and leading to both memory deficits and anxiety. The objective was thus to examine brain metabolism using FDG-PET in a group of TGA patients in acute or recovery phases. We first used a voxel-based method to conduct an individual analysis of the variability among the group of TGA patients and to describe the pattern of glucose metabolism in the whole brain for the entire group. Then, since the inherent heterogeneity in the clinical state of TGA patients seems to make group comparisons difficult to interpret on their own, we also used an ROI

method and a correlational approach to specifically investigate brain metabolism in the regions of the limbic system^{29,30}. More generally, this study aims at providing novel insights on the understanding of human memory and its interactions with emotion using rare data collected in TGA patients.

Materials and methods

Participants

Ten TGA patients admitted to the emergency department of Caen University Hospital (France) were recruited, over five years, by expert neurologists (Table 2) according to the Hodges and Warlow criteria¹. Neurological examination (except regarding memory impairment) was normal. Individual TGA contexts are detailed in the Supplementary data 1. Ten healthy control subjects matched for age and education were recruited. All participants gave their written informed consent to participate to this study, approved by the local ethic committee.

Experimental design

At the emergency department, after the diagnosis of TGA, patients followed a specific research protocol (individual timelines are reported in Figure 1). First, psychological and neuropsychological evaluations were performed in the emergency department as early as possible after the diagnosis. Second, patients underwent an FDG-PET scan at Caen University Hospital (CHU) in the department of Nuclear Medicine and Medical biophysics. Depending on the arrival time of the patient at the hospital, the delay to obtain an FDG dose and the availability of the scanner, the PET scan was conducted between 3h25 and 27h after the onset of the TGA. Finally, an anatomical MRI examination was conducted days or weeks (3 to 107 days) after the TGA episode at the neuroimaging center (Cyceron, Caen) depending on the

slot availability. Healthy controls followed the same protocol, at the same place (CHU and Cycleron) and in the same conditions as patients.

Psychological and neuropsychological examination

Anxiety. State and trait anxiety was assessed by the parts A and B of the State-Trait Anxiety Inventory (STAI)³³. For this scale, the higher the score (out of 80), the more anxious the patient.

Memory. Episodic memory was evaluated with the Encoding – Storage – Retrieval (ESR) task³⁴. In this test, the participant has to learn a list of 16 words. During the learning (encoding) phase, the first two words are presented to the participant who is asked to produce a sentence with each word to promote deep encoding. After the encoding of these first two words, an immediate cued recall task is conducted to ensure that the items have been correctly encoded. The procedure is then repeated with the next two words until the end of the list. At the end of this learning process, a free recall task is conducted. Then, a recognition task (with the correct word being presented among three distractors) is carried out.

Since the PET scan was not systematically conducted exactly at the same time as the psychological and neuropsychological assessment, a story recall test (story A of the logical memory subset of the Wechsler's Memory Scale³⁵) was used just before or after the PET examination to estimate amnesia. The WMS test, based on spontaneous encoding, is a more sensitive test than the ESR task and therefore pertinent to use at the PET scan time.

Neuroimaging examination

Data acquisition

MRI. Each participant underwent a volumetric high-resolution T1-weighted MRI. All MRI data were acquired at the neuroimaging center (Cyceron, Caen), on a 3 Tesla Philips Achieva scanner (*Eindhoven*, Netherlands) (FSE; sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices; slice thickness = 1 mm; field of view = 256 x 256 mm²; matrix = 256 x 256).

FDG-PET. Data were collected at Caen University Hospital on the Siemens Biograph HD+ PET device (*Siemens Healthcare*, Germany) with isotropic resolution of 2.1 mm³ (FOV = 158 mm). 370 MBq of ¹⁸F-fluorodeoxyglucose (FDG) were injected intravenously 30 minutes before data acquisition in list mode³⁶. The images were reconstructed with ordered-subset expectation maximization – point spread function (OSEM-PSF) iterative reconstruction (3 iterations, 21 subsets, a voxel size of 1 x 1 x 2 mm³).

Data pre-processing

MRI data. The voxel-based morphometry (VBM) toolbox of SPM12 software (Statistical Parametric Mapping, Wellcome Trust Center for Neuroimaging, London, UK) was used to segment T1-weighted MRI data into grey matter, white matter and cerebrospinal fluid. The images were then spatially normalized into the MNI (Montreal Neurological Institute) standardized space (voxel size = 1 mm³; matrix = 156 x 189 x 157). Individual distortion parameters were saved to be applied on the PET images.

PET data. For each subject, PET scans were individually realigned on their respective MRI images and normalized into the MNI space by reapplying the previous distortion parameters. The final voxel size was 79x95x79 with an isotropic resolution of 2 mm³. No correction for

partial volume effects was performed retrospectively as partial volume correction had already been applied per se via reconstruction of PET data with resolution modeling³⁷.

For the quantitative normalization, the cerebellum was used as a reference region in order to control for the inter-individual variations in PET measurements and avoid an artificial increase of metabolism values in altered regions³⁸. The cerebellum has already been used in a previous study³⁸ of our laboratory.

Finally, all images were smoothed with a full-width at half-maximum (FWHM) Gaussian kernel of 8 mm³.

Statistical analyses

Psychological and neuropsychological profile. R 4.0.3 (R Core Team, 2020) and RStudio 1.4.1106 (RStudio Team, 2019) softwares were used for psychological and neuropsychological data analysis. Standard descriptive statistics were used, as well as non-parametric Mann Whitney *U* tests to compare patients and controls (*stats* 4.0.3 package).

Individual Z-scores were also calculated based on the performance of the control subjects and were considered as impaired for a Z-score inferior at -1.85 or superior at $+1.85$ depending on the variables (adjusted threshold for a small sample size, degree of freedom equal to 8 for $N=10$).

Whole-brain voxel-based between-group comparisons. Voxel-based analyses were performed using two-sample t-tests in SPM12 to compare glucose metabolism between patients and controls. Both contrasts (controls>patients and controls<patients) were carried out to examine hypometabolism and hypermetabolism respectively. A threshold of $p < 0.001$ (uncorrected for multiple comparisons) and a cluster size of 25 voxels (corresponding to 200 mm³) have been applied.

Z-Score frequency maps. The variability of the individual patterns of brain abnormalities in patients was analyzed through z-score maps. Voxel-wise z-score maps were calculated for each patient using mean and standard deviation from the control group. Each z-score map was then thresholded at +1.85 in order to obtain a binary map of all voxels deemed hypermetabolic and at -1.85 for a binary map of hypometabolic voxels. The hypermetabolic and hypometabolic binary maps were then summed to obtain a hypermetabolic frequency map and a hypometabolic frequency map respectively. Both maps contained voxels ranging between 0 and 10 and would indicate the number of TGA patients having significant hypermetabolic or hypometabolic voxels within the cohort. For example, if a voxel in the hypometabolic frequency map contained a value equal to 4, it implied that 4 TGA patients had significant hypometabolism in that voxel. The number of hypo or hypermetabolic voxels necessary to get a cluster with a significant size was thresholded at a minimum of 25 voxels.

Correlation between brain metabolism and temporal aspect. To measure the relationships between regional brain metabolism and the earliness of the PET scan examination in TGA patients, voxel-based correlations were performed in SPM12 between glucose up-take and a ratio that considers both the time at which the PET scan was performed and the estimated total duration of the acute phase of TGA (Ratio = PET scan delay in hours / Estimated acute phase duration in hours).

Correlations matrix. To better understand the specific implication of the limbic circuit in the pathophysiology of TGA, we conducted a correlational analysis that included the hippocampus, parahippocampal gyrus, thalamus, posterior and anterior cingulate cortex, amygdala and orbitofrontal cortex (OFC)^{29,30}. The AAL atlas (Automated Anatomical

Labelling)⁴⁰ was used to extract metabolic values from the specified regions. For patients and controls, regional metabolism measures were individually computed into a correlation matrix using R software (*corrplot* 0.84 package; Wei & Simko, 2017). In each group, a method of hierarchical clustering was applied on the correlation coefficients to classify the different regions into two clusters based on the magnitude and direction of their correlations.

Results

Psychological and neuropsychological profile. Anxiety and memory raw scores of the patients are reported in Table 3.

When considered as a group, patients were significantly more anxious than controls ($U = 4.5$, $p = 0.001$) on the STAI state but not on the trait scale. Z-scores analysis revealed that compared with controls, seven patients presented state anxiety and one had trait anxiety.

Regarding episodic memory performance, patients had lower results than controls on the cued recall ($U = 85$, $p = 0.002$), free recall ($U = 93$, $p < 0.001$) and recognition ($U = 80$, $p = 0.006$) tasks of the ESR. At the time of the PET analysis, patients still had episodic memory deficits on the WMS story recall ($U = 76$, $p = 0.002$) when considered as a group, with seven of them presenting altered individual z-scores (Table 3). All patients had at least one memory score (either ESR or WMS) significantly impaired, with very low z-scores.

As expected, we found in TGA patients a significant nonparametric correlation between the earliness of the neuropsychological assessment and the immediate cued recall ($\rho = 0.76$; $p = 0.009$), the free recall ($\rho = 0.67$; $p = 0.03$) and the recognition raw scores ($\rho = 0.72$; $p = 0.01$).

Whole-brain voxel-based between-group comparisons. The comparison between TGA patients and controls did not show any significant differences at $p < 0.001$ (uncorrected for multiple comparisons).

Z-score frequency maps. Regarding hypometabolism, there was no brain region systematically affected in all TGA patients (see individual *Z-Score maps* in Figure 1 and *Z-Score frequency maps* in Figure 2). Hypometabolic similar clusters of a significant size (minimum of 30 voxels) were found in only three patients in the right middle frontal gyrus. The pattern of brain hypermetabolism was even less consistent with each cluster of a significant size found only in one patient at a time.

Correlation between brain metabolism and temporal aspect. In TGA patients, there was no significant correlation between glucose metabolism uptake and the calculated ratio at $p < 0.001$ (uncorrected for multiple comparisons).

Correlations matrix.

The correlation matrices (Figure 3A and 3B) are depicted as a grid of ellipses. Positive correlations are depicted in blue and negative ones in red. The shade and width of the ellipses illustrate the strength of the correlation for each pair of regions studied. As the correlation coefficient, $r_{BP} \rightarrow 1$, the ellipse becomes narrower and takes a darker shade of blue. For example, as further illustrated in Figure 4, from Fig 3A, the left and right thalamus correlate highly and positively with each other ($r_{BP} = 0.97$) and the ellipse is narrow and dark blue. Similarly, when $r_{BP} \rightarrow -1$, again the ellipse becomes narrower as the scatter condenses but takes a darker shade of red (for example, from Fig 3B, where $r_{BP} = -0.16$ between left hippocampus and right anterior cingulate gyrus). As $r_{BP} \rightarrow 0$, the scatter plot becomes more sparse and assumes a lighter shade until it ultimately shows as a white square, hence indicating no significant correlation (for example, from Fig 3B, $r_{BP} = 0.046$ between left thalamus and left hippocampus).). Examples of r_{BP} are shown in Figure 4. All statistical analyses have been corrected for multiple comparisons using Bonferroni (all associated p-

values were multiplied by 14 and results were considered to be statistically significant when $p < 0.05$).

The hierarchical clustering method enabled the identification of two clusters of highly intercorrelated brain metabolic regions.

In controls (Figure 3A), even though the analysis showed two clusters, all regions included in the matrix highly and positively correlated with each other. For example, metabolism of the left thalamus (cluster 1) significantly and positively correlated with metabolism in the left OFC (cluster 2, $r_{BP} = 0.86$; $p < 0.001$).

In the patient group, the pattern was different (Figure 3B) with a clear dissociation between the two highlighted clusters. Regions of the medial temporal lobe (the hippocampus, parahippocampal gyrus and amygdala) were included in the same cluster (cluster 1). The OFC, anterior and posterior cingulate gyrus and thalamus were gathered in the other cluster (cluster 2). Remarkably, those two clusters were weakly correlated to each other, sometimes negatively, with the absence of significant correlation between regions of cluster 1 with most of the regions of cluster 2. For example, metabolism in the left hippocampus (cluster 1) did not correlate to metabolism in the left posterior cingulate gyrus (cluster 2, $r_{BP} = -0.09$, $p = 0.666$).

Discussion

The brevity of TGA makes it very difficult to study its pathophysiological mechanisms at an early stage, which explains the scarcity of neuroimaging studies conducted in these patients and the fact that they are limited either to case studies or to group studies where patients have been studied after the acute phase. In that context, our study provides novel data that has been scrupulously acquired over the past 10 years, all under the same conditions and having the same clinical, neuropsychological and neuroimaging examinations. Using this rare dataset of FDG-PET data collected in a group of ten TGA patients (three in acute and seven in recovery

phase), the present study aimed at investigating the contribution of glucose metabolism measure to the study of pathophysiological mechanisms underlying amnesia and anxiety in TGA.

Contrary to previous case studies having used an ROI approach and having reported regional hyper or hypometabolism^{11-15,41}, the present voxel by voxel investigation of glucose metabolism in the whole brain did not reveal any significant differences between TGA patients and healthy controls. This result could first be explained by the heterogeneity of the TGA sample. Indeed, even though TGA symptoms are usually stereotypically described, patients differ regarding the total length of the acute phase, the rapidity of the recovery phase, the arrival time at the emergency department, or the delay between the PET scan and the TGA onset. The analysis of variability within the TGA group confirms the absence of consistency regarding the pattern of metabolic abnormalities with no region being systematically significantly affected in all patients (Figure 2). We investigated the potential role of some factors such as the earliness of the PET scan. For example, we examined the relationships between regional glucose metabolism of TGA patients and a ratio considering the delay between the supposed onset of amnesia and the PET scan. The absence of significant correlations does not provide any further explanation of the between-subject variability. Visual examination of TGA individual PET results (Z-Scores maps, Figure 1) confirms that the patients who underwent the PET scan during the acute phase did not exhibit more severe metabolic abnormalities than those examined at the end of their episode. Examining a transient amnesia, which by definition does not lead to severe long-term deficits, requires the capture of very short-lived phenomena. Diffusion-weighted imaging (DWI) studies highlight the difficulty of detecting brain changes in the acute phase. Focal hippocampal lesions found in TGA patients in the cornu ammonis (CA) developed between 24 and 48 h following the onset of TGA. However, in a recent meta-analysis on DWI data, results showed that a

substantial number of patients with TGA, there were no visible DWI lesions of hippocampus even though they were amnesic⁴². These data suggest that TGA is associated with functional deficits of the brain that are more threshold-dependent⁴ than to the time (acute or post-acute) of the amnesic phase. A recent study using resting-state functional MRI in TGA showed altered functional connectivity, which can be observed when patients are compared to a control group, but cannot be detected when patients are compared according to the time (acute or post-acute) of the TGA phase⁴³. Given the individual variability in the time course of TGA, the direct comparison between a group of patients and controls does not seem to favor the identification of subtle and transient alterations in regional metabolism.

The absence of a clear pattern of metabolic alterations may also potentially be explained by the specific nature of the pathophysiological mechanisms involved in TGA. Diffusion-weighted imaging (DWI) studies suggest that functional and reversible alterations of the hippocampus may play a key role even though it may not be directly detected by a lower or higher glucose uptake in that region. A transient dysfunction of cortical spreading depression triggered by excessive glutamate release within an extended hippocampal network has also been hypothesized⁴⁴. Indeed, CA1 neurons are known to be vulnerable to metabolic and oxidative stress that may be caused by an overload of cellular glutamate⁴⁵. This would lead to a neural dysfunction with a particular mode of propagation within the hippocampus and more largely through the limbic circuit, potentially resulting in TGA. The above arguments therefore potentially favor the theory of metabolic dysfunction at a network level instead of being centered over a particular region. Indeed, a growing number of studies^{31,46} indicates not only the involvement of the hippocampus in episodic memory but also that of an extended network, suggesting that memory impairments could be considered as resulting from reduced network connectivity (for review see Jeong et al.⁴⁷) or altered coordinated action within that network⁴⁸. The involvement of an extended network in the pathophysiology of TGA would

also explain the other symptoms observed, such as mood changes and notably anxiety which is frequently observed in association with amnesia during the acute phase. Moreover, on a methodological point of view, using correlations instead of direct comparisons can help us to better understand networks mechanisms. Indeed, metabolism correlations between regions will stay supported regardless of the temporality of the TGA phase in which the patient is. In accordance with this assumption, our findings indicate differences in the functional connectivity between brain regions within the limbic circuit^{29,30} in controls vs. TGA patients. In healthy controls, regions of the limbic circuit seem to operate in a synchronized way with all regions being highly correlated to each other. On the opposite, in TGA patients, we observed a clear disruption of the correlational patterns between the two clusters, with the hippocampus, parahippocampal gyrus and amygdala being classified in one cluster that poorly correlated with the other brain regions of the limbic circuit. In terms of brain networks, such a disruption in the correlational patterns between the amygdala and the rest of the limbic regions could explain the frequency of anxiety in TGA patients. Interestingly, anxiety frequently observed during the TGA episode, decreased, conjointly with the level of salivary cortisol¹⁹, in parallel with episodic memory recovery². These observations support the idea that memory and emotional changes may be related. Such an alteration in synchronization within and between regions of the limbic system shows its dysfunction at a network-level and could explain the association of memory disorders and anxiety observed in these patients during the acute phase.

In agreement with our hypothesis, previous studies also reported changes in brain networks in TGA even though they did not focus on the limbic system. In 12 TGA patients seen in the acute phase, Peer et al.²⁶ reported a reversible reduction in functional connectivity in data-driven and literature-based episodic memory networks. This altered functional connectivity was more pronounced during the acute phase compared to the recovery phase and was not

present any more after recovery. Using single photon emission computed tomography, hypoperfusion was found in the left precuneus and inferior temporal and superior parietal areas in a group of 22 TGA patients⁴⁹. The authors concluded that these results may be related to a disruption of the posterior medial network⁵⁰, also described as involved in episodic memory⁵¹. Another study²⁵, using FDG-PET in TGA patients, 24 to 72 hours after onset, also reported decreased metabolism in the posterior medial network, suggesting that this network alteration may explain the symptoms appearing earlier, during the acute phase. Park et al.²³ investigated brain networks using diffusion tensor imaging and found altered structural connectivity and reorganization of network hubs in TGA patients, especially in the regions of the default-mode network.

Taken together, these studies and ours support the idea of a network disruption playing a key role in the pathophysiology of TGA. The present study deepens our understanding of the mechanisms underlying not only amnesia but also the emotional component of TGA by considering it as a disruption in the correlational patterns within the limbic circuit.

Technical and methodological considerations:

The sample size and the heterogeneity of the TGA group are the main limitations of the present study. However, TGA is a sudden and transient syndrome that makes difficult the recruitment of patients, especially in a PET study. As far as we know, our study is the first to investigate metabolic networks within the limbic system in a group of ten patients examined during their TGA episode.

Conclusions

To conclude, our findings indicate that the synchronization of regions within the limbic circuit is altered during the acute phase of TGA. A transient disruption of the correlational patterns

between those regions is consistent with the reversible nature of amnesia and the frequently associated anxiety observed in TGA patients. Our study thus offers a new approach to investigate the pathophysiological mechanisms underlying TGA and suggests that memory disorders and anxiety may be two expressions of the same transient network dysfunction.

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Figure legends

Figure 1. Individual timelines of examinations in TGA patients.

The individual timelines show, for each patient, the duration of the acute TGA phase and the timing of the psychological/neuropsychological evaluations and PET examination.

Patients are presented in “acute phase” or “recovery phase” based on the timing of the PET scan in regard to the onset of the episode. They are classified according to a ratio taking account the timing of the PET scan compared to the duration of the acute phase. A ratio <1 indicates that the PET scan was conducted during the acute phase.

Figure 2. Variability in the individual patterns of hypometabolism (A) and hypermetabolism (B) in TGA patients.

The color bar reflects the frequency (from 0 = absent in all patients to 10 = present in all TGA patients) of significant hypo- or hypermetabolism in each voxel of the patients' brains.

The scale reaches 9 for hypometabolism and 5 for hypermetabolism.

No voxels are found to be altered in all patients.

Figure 3. Correlations matrix of the regional metabolism in controls (A) and TGA patients (B).

Positive correlations are shown in blue and negative correlations in red. The narrower the ellipse, the closer the R_{BP} value is to 1 or -1. The darker the ellipse, the stronger the correlation between the pair of metabolic measurements. The two main clusters are marked in black. L = left, R = right. ACC = Anterior Cingulate Cortex; Hipp = Hippocampus; OFC med = Medial Orbitofrontal Cortex; ParaHipp = Parahippocampal gyrus; PCC = Posterior Cingulate Cortex

Figure 4: Interpretation of ellipses in correlational matrices of Figure 3

Three examples are shown. First, in controls, the high and positive correlation between the left and right thalami ($r_{BP} = 0.97$), depicted in blue here, is represented by a narrow and dark blue ellipse in Fig 3A. In the second example, the correlation observed in patients between the left hippocampus and right anterior cingulate gyrus, depicted in red here, is negative and weak ($r_{BP} = -0.16$). It is represented in Fig 3B by an ellipse that takes the shape of a circle and a light shade of red. In the third example, the correlation depicted in black here and observed in patients between the left thalamus and left hippocampus is close to zero ($r_{BP} = 0.046$) and represented in Fig 3B as a white square.

Axes denote Standardized Uptake Value ratios (SUVr).

Supplementary data

Supplementary data 1. Detailed TGA onset individual context.

PA01

Patient 01 was a 72 year-old right-handed woman, retired psychologist. The medical record reports that she was usually an anxious person. The patient came to the hospital for a 6 months follow-up control of a stomach surgery that did not show any problems. This medical visit did not come with any specific emotional reaction. The TGA episode started at one p.m. when PA01 left the appointment and her husband noticed iterative questions. PA01 arrived at the emergency department at 1:32 p.m. with her husband and the neuropsychological examination began around 2:40 p.m. The clinical interview showed a massive anterograde amnesia, a retrograde amnesia that covered at least the past three days (she did not remember a snow problem) and iterative questions about place and the current situation (“Where am I?”, “Who brought me here?”, “Where is my husband?”, “What is the matter with me?”). The acute episode was accompanied with a sensation of cold feet. The patient was no aware of her memory problem. PA01 started to recover around 8 p.m. The PET scan was carried out at 4:30 p.m., when the patient was still in the acute phase.

PA02

Patient 02 was a 59 year-old right-handed woman, who worked as a work inspector. She had no previous medical history except for a phlebitis 15 years earlier. She was getting ready as every day and just finished to drink a coffee when the episode started at 8:30 a.m. without any particular precipitating event. Her relatives noticed that she started asking the same questions repeatedly. The neuropsychological examination started at 11 a.m. It showed a retrograde

amnesia over a few days ago, but the patient remembered her job change 3 weeks ago (she had been previously working as a health and safety inspector for twenty years). She was not aware of her amnesia, and she admitted she had difficulties only after failing at the WMS test. The TGA episode was accompanied with iterative questions about the date and place and it lasted until 4:30 p.m. The PET scan was carried out at 1:30 p.m., when the patient was still in the acute phase.

PA03

Patient 03 was a 65 year-old right-handed woman, who worked as a nurse/child-minder. She had a history of arterial hypertension and migraine and had an episode of depression 20 years ago. According to her medical record she was generally anxious. The day of the TGA, the patient had an argument with her ex-husband on the phone earlier in the morning (10 a.m.). They divorced had 3 months ago and the call was very stressful and intense. The patient was getting ready and finished to dress up when the episode started, at 10:30 a.m. She just saw her neighbor who noticed nothing unusual and she called her daughter. On the phone, she declared that something was wrong without specifying a memory problem and started to ask iterative questions. Her daughter took her to the hospital for 11:51 a.m. where the neuropsychological examination started at 2:10 p.m. The episode was accompanied with iterative questions about place and worries (“How did I get here?”, “Does someone take care of the children?”). PA03 realized having a memory problem only after failing at the story recall test. The episode ended at 3:30 p.m and the PET scan was done at 4:15 p.m.

PA04

Patient 04 was a 69 year-old right-handed retired woman, with anxiety according to her medical record. The acute phase started at 9 a.m. after taking a shower. She called her

daughter, speaking of a general unease and her daughter immediately noticed a memory problem and iterative questions (“I don’t know if I’m waking up of a dream”, “I’m going out of the bathroom”). The patient arrived at the hospital at 11:54 a.m. and the neuropsychological examination started at 1:30 p.m. An important retrograde amnesia was noticed, the patient could not remember the last Christmas, 8 months ago. PA04 asked iterative questions about place and her current situation (“Where am I?”, “Did I take these clothes?”). The patient spontaneously talked about her memory problems. The recovery started around 6 p.m. and the PET scan was done at 8 a.m. the next morning. Interviewed after the TGA about the context of the amnesia’s onset, the patient reported a dispute between her daughter and grandchildren one week ago.

PA05

Patient 05 was a 61 year-old right-handed woman, retired nurse. She had a history of thyroid disease and she was naturally anxious according to her medical record. The TGA episode started at noon when she was at the swimming pool. At the end of the session, when she was going to take a shower, she cannot remember where she put her clothes. At 12:40 p.m., she arrived at her house and her husband noticed she didn’t recognized the house or her daughter’s boyfriend. The patient arrived at the hospital at 1:46 p.m. and the neuropsychological examination started at 2:50 p.m. The patient reported a headache during the attack. She could evoke a memory problem but only if she was specifically asked about it. The episode lasted until 7 p.m. The patient underwent the PET scan at 4:30 p.m. After recovery, she reported that she had been worried for a month about the health of her mother, who had entered the hospital the day before TGA. Two months later, when she was skiing, PA05 had another TGA episode that lasted 4 hour (from noon to 4 p.m.).

PA06

Patient 06 was a 60 year-old right-handed woman, who had been retired for 5 months. She had a head trauma after a motorcycle accident, a loss of consciousness 12 years before after a strangulation and a medically treated anxiety disorder for a month, 25 years ago. On the day of the episode, PA06 made coffee at 9 a.m. and she took a shower at 9:30 a.m. At 9:45 a.m., she told her daughter “I’m feeling weird”. The daughter noticed iterative questions (“What day is it?”, “What are we doing this weekend?”). At 10:57 a.m., they arrived at the hospital and the neuropsychological examination started at 12:23 p.m. The patient had no memory of her daughter’s birthday 4 days ago. During the examination, the patient complained of headache, and showed high emotionalism and with episodic crying. She asked repetitively about the date and worries (“What day is it?”, “What time is it?”, “What are we doing this weekend?”). The episode lasted until 1 p.m. She underwent the PET around 4:40 p.m. After having recovered, the patient reported that in the past three days, her son was at the hospital because of having got drunk at a party.

PA07

Patient 07 was a 69 year-old right-handed retired woman. She had a history of arterial hypertension and had migraines until the age of 53. On the 31st of December, she went to a New Year’s Eve dinner where everything went fine. At 5:30 a.m. she answered a phone call from her brother. In the morning when she woke up, around 10 a.m., her husband noticed something wrong. The patient could not remember the past day. PA06 arrived at the hospital at 12:04 p.m. and the neuropsychological examination started at 2:30 p.m. The patient asked iterative questions and repetitively said “I have a black hole”. She was aware of her memory problems. The episode lasted until 1 p.m. The patient kept no memory of the New Year’s Eve

dinner even after having recovered from her amnesia. The PET scan was done at 1 p.m. the following day.

PA08

Patient 08 was a 54 year-old right-handed woman with no previous medical history. The patient woke up at 6 a.m., had breakfast, took a shower and left to work at 7:10 a.m. She arrived at work at 7:30 but did not feel well. At 8:15 she realized she could not remember her colleagues' name. She continued her day at work but, in the hallways, she felt like a suffocative feeling, that she qualified as a "claustrophobia crisis". She phoned her husband at 9:30 a.m. to tell him she could not remember her colleagues' name. Her colleagues took her in an office and she had a loss of contact for two minutes. Firefighters arrived at 10:30 and drove her to the hospital. The panic attack could have been a precipitant factor of the TGA episode. The neuropsychological testing started at 12 p.m. She could not remember her present address where she had moved 3 weeks ago. After having recovered, the patient remembered the firefighters and spoke in the ambulance but she had a lacunar amnesia from the time of her arrival at the emergency department until the neuropsychological tests. There were no iterative questions but she worried about forgetting the names and her new address. PA08 seemed perplexed, lost in thoughts, with problems of concentration and difficulties to focus. The episode lasted until 2 p.m. The PET scan was done at 2:15 p.m.

PA09

Patient 09 was a 67 year-old left-handed retired man. He had a cranial trauma 17 years before and had been treated since for dizziness. His wife left the house at 9:45 a.m. A friend called him right after and found that PA07 was not feeling well. At 10 a.m., another friend came to visit him. The patient recognized him but started to ask iterative questions ("What day is it?",

ten times, “Why are you here?”). No precipitating event was noticed except for dizziness the day before. The patient arrived at the hospital at 12:13 p.m. and the neuropsychological examination started at 1:15 p.m. The retrograde amnesia extended over one week. PA09 asked iterative questions about the date and his current situation. The episode lasted until 6 p.m. The patient underwent the PET scan at 9 a.m. the next morning.

PA10

Patient 10 was a 62 year-old right-handed man who had been retired for 2 years. He had a history of anxiety disorder at the age of 30 and a depression episode 25 years before the TGA. He had been diagnosed with cancer four years before the TGA episode. He had spent some time in an intensive care unit, received morphine and was put in a coma during three weeks. Since that time he had trouble dating events. PA10 woke up at 7 a.m., had breakfast and went back to bed. The TGA episode started approximately at 10 a.m. At that time, his daughter called her mother to report that PA10 was unable to tell the date of the day. The patient arrived at the hospital at 10:45 a.m. and the neuropsychological examination started at 3 p.m. The patient remembered nothing of the week before. During the episode, the patient had nausea and a highly emotional state with cries. He asked repetitively about the date. The PET scan was done at 9 a.m. the next morning. After having recovered, the patient reported that he had conflicts with his daughter two weeks ago and that, the day of the episode, he was waiting for his daughter’s school exams.







