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Enhanced cortisol secretion in acute transient global amnesia

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ABSTRACT

Introduction: Stress-related transient inhibition of memory formation in the hippocampus has been hypothesized as one of the underlying pathomechanisms of transient global amnesia (TGA). TGA episodes, during which patients cannot encode and recall new information (anterograde amnesia affecting episodic long-term memory), are frequently preceded by a psychologically or physically stressful event.

Methods: We measured salivary cortisol during acute TGA in 14 patients, as well as cortisol day-profiles and the effect of experimental exposure to stress (using the socially evaluated cold pressor test) on cortisol levels during the subacute phase. We assessed psychiatric comorbidity as well as depression, trait anxiety and chronic stress. These findings were compared with data of 20 healthy controls.

Findings: Nine patients reported a precipitating stressor and all 14 developed typical hippocampal lesions on follow-up MRI. During TGA, salivary cortisol levels were more than 3-fold higher compared to time-matched day levels. While there was no difference in mean cortisol levels of the diurnal rhythm, we found a significant interaction between groups during experimental stress exposure ($p = 0.049$) with the TGA group revealing a higher cortisol increase. The TGA group reported higher levels of depressive symptomatology (CES-D) and higher scores of chronic stress (TICS) compared with the control group and there was a significant correlation between cortisol increase during TGA and the results of self-rating according to the CES-D ($r = 0.615$; $p = 0.004$), as well as to the STAI ($r = 0.702$; $p = 0.001$).

Conclusion: Our findings of enhanced secretion of cortisol in acute TGA patients correlating with symptoms of depression and anxiety and a persisting hyperreactivity to experimental stress in the subacute phase support the hypothesis that stress might be significant for the pathogenesis of TGA.

1. Introduction

Transient global amnesia (TGA) is a clinical syndrome characterized by a sudden and severe disturbance in memory, which interferes with the learning of novel information and usually resolves within several hours. During the episode, patients cannot encode and recall new information (anterograde amnesia affecting episodic long-term memory), and therefore, repeatedly ask the same questions concerning their environment. In many, but not all patients a partial or “patchy” impairment of retrograde episodic long-term memory is also present; patients have difficulty encoding and recalling episodic information that was learned (hours, days, months or even years) before the onset of the amnestic attack, however this is clinically far less prominent (Jager et al., 2009). In 1990, Hodges and Warlow reported 114 cases with acute transient amnesia and established the clinical diagnostic criteria that are still in use today (Hodges and Warlow, 1990):

- Attacks must be witnessed and information available from a capable observer who was present for most of the attack.
- There must be a clear-cut anterograde amnesia during the attack.
- Clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment limited to amnesia (that is, no aphasia, apraxia, etc).
- There should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterwards.
- Epileptic features must be absent.
- Attacks must resolve within 24 h.
- Patients with recent head injury or active epilepsy (that is, remaining on medication or one seizure in the past two years) are excluded.

The cause of TGA has been a matter of long standing debate among researchers. Several groups have suggested that the pathophysiological mechanisms leading to the memory disturbance may be similar to those

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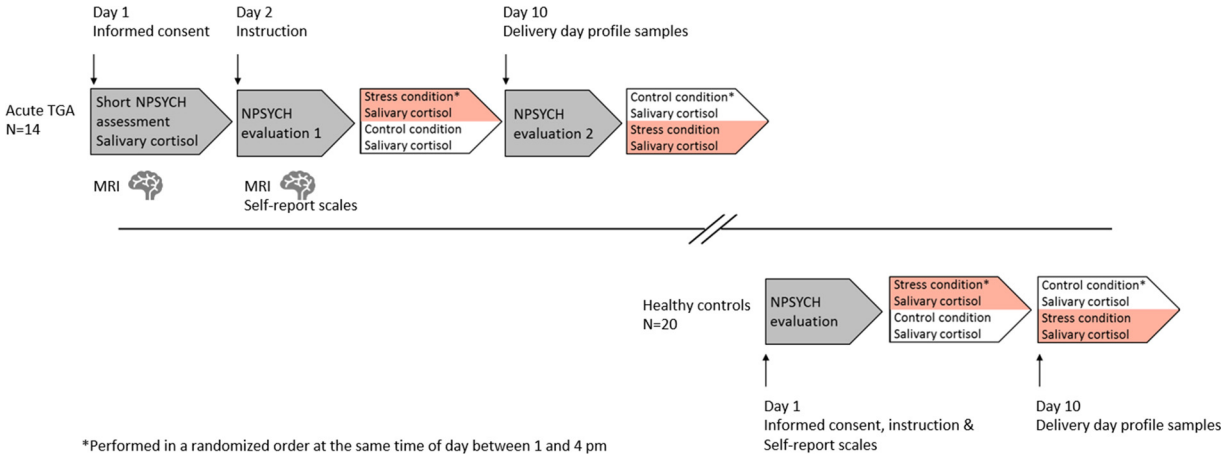

Fig. 1. Experimental study design.
We measured cortisol levels during acute TGA as assessed by neuropsychological examination in the ER. MRI was performed in the patient group on days 1 and 2. In all patients and healthy subjects, we measured response to experimental stress exposure versus a control procedure on days 2 and 10. In addition, we assessed HPA axis activity by measuring the cortisol day-profile and dexamethasone feedback inhibition.

of cerebral ischemia, epilepsy, or migraine (Frederiks, 1993). However, there is no definitive evidence supporting any of these mechanisms. In addition, there is no evidence for an increased rate or intensity of cerebrovascular risk factors, of microangiopathy, or of ischemic strokes in TGA patients (Enzinger et al., 2008; Zorzon et al., 1995). More recently, a disturbance of venous hemodynamics has been hypothesized, but again without any scientific proof for such an underlying mechanism (Baracchini et al., 2012). Due to the nature of the cognitive impairment during TGA, a transient dysfunction of the medial temporal lobes, especially of the hippocampus, has been repeatedly postulated (Bartsch and Deuschl, 2010). In up to 80% of patients, diffusion-weighted MRI (DWI) shows small, uni- or bilateral lesions in the lateral aspect of the hippocampal formation that become detectable approximately 24–48 hours after symptom onset (Bartsch et al., 2007; Gass et al., 1999; Sedlaczek et al., 2004). While this finding links the disorder to the CA-1 subfield of the hippocampus anatomically, the exact etiology of these small lesions remains uncertain. Nevertheless, due to the selective memory impairment, the transient nature and the specific hippocampal lesions TGA can be considered a reversible human lesion model of a dysfunction of the hippocampus.

The observation that in up to 90% of reported TGA cases, a precipitating event - usually described as physical, emotional, or behavioral stress - precedes the amnestic episode implies that stress triggers TGA (Quinette et al., 2006a; Szabo, 2014). Newer hypotheses postulate glutamate-mediated hyperexcitability with consecutive cytotoxic damage of the hippocampus, especially of the hippocampal CA1 neurons. These hypotheses focus on the possible role of stress and its effects on memory (Bartsch and Deuschl, 2010).

Previous findings suggest that in TGA patients ineffective coping strategies and an elevated anxiety level might increase susceptibility to psychological stress, which in turn may facilitate the pathophysiological cascade seen in TGA (Dohring et al., 2014). Concerning the hypothalamic-pituitary-adrenal (HPA) axis, stronger pharmacological cortisol suppression and higher cortisol levels in anticipation of experimental stress in participants with a previous TGA episode, both of which indicate hypersensitivity of the HPA axis, have been described (Griebe et al., 2015).

Under the assumption that TGA is caused by a transient stress-related inhibition of memory formation in the hippocampus via the HPA axis, we measured the cortisol secretion in subjects during the acute episode of TGA and the effect of experimental exposure to stress on cortisol levels in the postacute phase. We hypothesized that acute TGA patients have a higher stress reactivity demonstrated by higher cortisol levels during acute TGA in the ER as well as in response to experimental stress exposure in the subacute phase. In addition, we assessed HPA axis activity by measuring the cortisol day-profile and dexamethasone feedback inhibition.

2. Methods

2.1. Subjects

During a period of 12 months, 14 patients presenting to our emergency department with an acute episode of TGA were included in the study. A standardized neuropsychological assessment was performed during TGA in the ER to confirm ongoing anterograde episodic long-term memory disturbance. We documented possible stress-related triggers and psychiatric comorbidity. The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University. Written informed consent was obtained before inclusion and was repeated in acute TGA patients after symptom resolution. All patients received routine cranial MRI examinations at presentation and after 24 h including DWI parallel to the long axis of the hippocampus. These were analyzed for the occurrence of typical hippocampal hyperintense lesions. The control group consisted of the spouses of TGA patients from our database, who were free from neurological or psychiatric illness and were not taking corticosteroid medication. For study design see Fig. 1.

2.2. Cortisol expression in response to stress

Saliva samples were collected into Salivette tubes (Sarstedt, Nümbrecht, Germany) in each acute TGA patient in the ER. All patients and the control group were exposed to the socially evaluated cold pressor test (SECPT) or a control procedure with warm water on days 2 or 10 performed in a randomized order at the same time of day between 1 and 4 pm (Schwabe et al., 2008). They were instructed to immerse their right hand including the wrist in ice water (0–4 °C) for 3 min or until they could no longer tolerate it. They were informed that they would be videotaped for analysis of facial expression and they were supervised by an unfamiliar person during the procedure. All participants also underwent the control condition with warm water (35–37 °C) during which they were not filmed. Saliva samples collected into Salivette tubes (Sarstedt, Nümbrecht, Germany) were kept at -20 °C until analysis. Free cortisol levels in saliva were measured using a commercially available immunoassay (IBL, Hamburg, Germany). Salivary samples of 2 patients and 1 control subject during SECPT and salivary samples of 2 patients during the control procedure were not

sufficient for cortisol determination.

2.3. HPA axis activity

All participants collected cortisol samples for an awakening response and a daytime profile on one day and a low dose dexamethasone suppression test on a second day. Cortisol samples were collected by the patients and healthy subjects at home and delivered at follow-up examination on day 10. Details of data collection have been reported previously (Griebe et al., 2015). To estimate the cortisol response during TGA, we calculated the differential increase by subtracting the individual time-matched day profile value from the value measured during the TGA episode ($\Delta TGA_{cortisol}$) in each patient. Salivary sample of 1 patient during TGA was not sufficient for cortisol determination, and 1 healthy control did not finish daytime sample collection.

2.4. Self-report scales of depression, anxiety and stress

The participants completed self-report scales on the first day after TGA (day 2) in the patient group and on the first study day in the control group. The German version of The Center for Epidemiological Studies Depression Scale (CES-D) was used to measure depressive symptomatology (Hautzinger and Bailer, 1993). The Trier Inventory for Chronic Stress (TICS) was used to assess the level of chronic psychosocial stress arising from environmental and internal demands in several domains in a defined timeframe (Schulz and Schlotz, 1999). Anxiety was measured using the German version of the State-Trait Anxiety Inventory (STAI) consisting of 20 questions on a self-report basis (Laux et al., 1981).

2.5. Statistical analysis

Self-ratings were analyzed by independent samples t-tests or Mann-Whitney-U-tests as appropriate. Group differences in the circadian profiles of cortisol concentrations between both TGA groups and controls were calculated by one-way repeated measures ANOVA with 12 within-group levels. To compare cortisol levels for each sampling point we used independent samples t-tests. The areas under the curve with respect to the ground (AUCg) and increase (AUCi) were calculated for both circadian profiles of cortisol and compared between groups by independent samples t-tests (Pruessner et al., 2003). Group differences in cortisol responses to SECPT and the control procedure respectively were calculated by one-way repeated measures ANOVA with 3 within-group levels. Thereafter, data for each of the three sampling points were compared by independent samples t-tests and alterations in the time course were calculated by dependent samples t-tests. To compare duration of SECPT and self-ratings of reactive stress and pain between groups we performed independent samples t-tests.

3. Results

3.1. Patient characteristics

Table 1 summarizes the characteristics of the study population. The mean time span from symptom onset of acute TGA to study inclusion was 145.5 min (± 85.90). Three patients had a history of psychiatric illness (1 anxiety disorder, 1 burn-out, 1 depression). While initial MRI was normal, DWI detected typical hippocampal hyperintense lesions performed on day 2 in all 14 cases (for an example see Fig. 2). In the present study, follow-up imaging beyond the subacute phase has not been carried out.

3.2. Neuropsychological assessment and self-report scales

All 14 acute TGA patients were neuropsychologically tested in the emergency room: We documented an ongoing disturbance of episodic long-term memory in every patient. Five patients reported physical extortion, while 6 patients related on acute psychological stress immediately before symptom onset with sadness/grief being the most often reported emotion (n = 3). Additionally, 11 patients stated that they suffered from chronic emotional stress with sadness/grief being the most often named stressor (n = 4). The acute TGA group had higher levels of depressive symptomatology and higher scores of chronic stress compared to the control group as assessed by the CES-D (p = 0.016) and the TICS (p = 0.009), respectively. There was no significant difference between the two groups for scores of anxiety as measured by the STAI (p = 0.091).

Table 1
Characteristics of the study population.

	Acute TGA	Controls	P value acute vs. controls
Number	14	20	
Age, years; mean (SD)	69.14 (± 10.95)	66.50 (± 7.22)	0.402
Sex male; number	7	8	0.563
Formal education, years; median (range)	12 (8–18)	13 (8–17)	0.478
Psychiatric comorbidities[a], number	3	1	0.283
Precipitating stressor	9	NA	
Perceived pain (ER); median (range)	0 (0–55)	NA	
Perceived stress (ER); median (range)	44 (0–100)	NA	
Hippocampal DWI lesion	14	NA	

SD = standard deviation; ER = emergency room; DWI = diffusion-weighted MRI.
[a] includes previously diagnosed depression or anxiety disorder.

3.3. Cortisol during acute TGA

Mean cortisol levels during acute TGA episode were significantly higher than the corresponding time-matched value of the day profile collected during the postacute phase (26.2 mmol/l versus 7.6 mmol/l; p = 0.006). We found no statistical difference between cortisol values in patients with versus those without a clear-cut stressful trigger (p = 0.734) (for results of all cortisol analyses see Table 2).

3.4. Diurnal cortisol rhythm

We found no differences in mean cortisol levels during the awakening response or in the daytime cortisol profile between the acute TGA patients and the group of healthy controls. Likewise, there were no differences in mean cortisol levels during the awakening response or in the daytime cortisol profile between the two groups after administration of low-dose dexamethasone (see Fig. 3).

3.5. Socially evaluated cold pressor test

Two participants (2 controls) did not immerse their hand for the full 3 min in ice water. Both acute TGA patients as well as controls showed an increase of cortisol in response to acute stress elicited by the SECPT. The repeated measures ANOVA revealed a significant group X time interaction effect for experimental stress exposure (p = 0.049) with a more pronounced increase in TGA patients. For the control procedure, the repeated measures ANOVA showed a significant group effect (p = 0.019). Fig. 4 shows the change across the three time points during both procedures for subjects with acute TGA and the controls. The acute TGA group perceived the SECPT as less painful (< 0.001) but not as more stressful (p = 0.950). We found no statistical difference between stress reactivity when comparing those patients in whom the

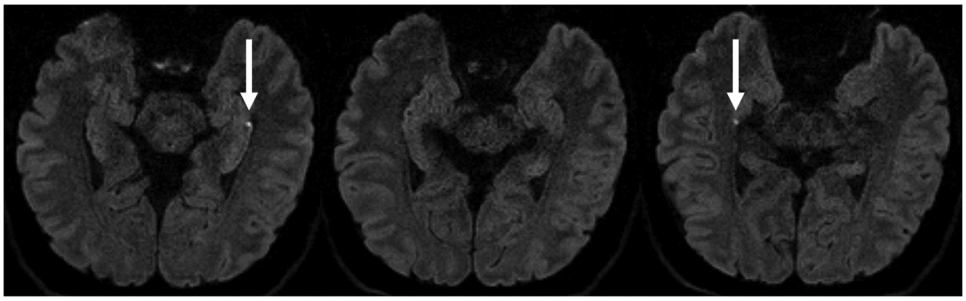

Fig. 2. Hippocampal MRI in TGA patients.
Representative, consecutive slices of diffusion-weighted MR (DWI) images 22 h after TGA demonstrates bilateral DWI lesions of the hippocampus. Slice positioning parallel to the long axis of the hippocampus.

SECPT was performed on day 2 with those in whom SECPT was performed on day 10 after TGA (p = AUCi p = 0.212; AUCg p = 0.492; cortisol increase p = 0.311).

3.6. Self-rating scales and cortisol during acute TGA

We found a significant correlation between $\Delta TGA_{cortisol}$ and the results of self-rating according to the CES-D (r = 0.615; p = 0.004), as well as to the STAI (r = 0.702; p = 0.001) in acute TGA patients.

4. Discussion

In this study, we aimed to investigate the possible role of stress as an acute trigger of TGA. We observed a hyperresponsivity of cortisol a) during the acute episode with a significantly increased cortisol secretion in comparison to a time-matched value of the day-profile and b) during the postacute phase with a higher increase of cortisol in response to experimental stress exposure in comparison to controls. We did not however, find a basal dysregulatory process of the HPA axis as demonstrated by a lack of difference of cortisol day profiles and values after dexamethasone challenge in comparison to the control group. The acute TGA group reported higher scores of depressive symptomatology and stress, while cortisol increase during TGA correlated positively with depressive symptomatology and anxiety.

4.1. TGA – a stress-induced disorder?

In their paper, published in 2000, Pantoni et al. were one of the first to elaborate the lack of convincing evidence supporting previously discussed pathomechanisms (i.e. ischemia, seizure discharge, and migraine) of TGA. They advocated the hypothesis that TGA may be related to psychological disturbances causing transient alteration in brain metabolism and, consequently, amnesia (Pantoni et al., 2000). They argued, that in their previously published series TGA often occurred in connection with emotional arousal or phobogenic events and that these may lead to hyperventilation and subsequent temporal vasoconstriction (Inzitari et al., 1997). The observation that TGA occurs in overworked and hyperactive individuals was made as early as in 1956 (Guyotat and Courjon, 1956). Supporting this hypothesis, imaging studies performed during TGA had shown a decrease of CBF in the mediotemporal regions (Oghino et al., 1989). After the confirmation of DWI lesions of the hippocampus emerging after an episode of TGA, the possible role of a

Table 2
Results of personality trait evaluation and cortisol levels.

	Acute TGA	Controls	P value acute vs. controls
Self-report scales	N = 14	N = 20	
CES-D, sum; mean (SEM)	17.83 (± 3.15)	8.5 (± 1.39)	**0.016**
STAI sum; mean (SEM)	40.92 (± 2.95)	31.0 (± 2.12)	0.091
TICS sum; mean (SEM)	59.20 (± 3.16)	59.2 (± 3.16)	**0.009**
Cortisol status	N = 14	N = 19	
Cortisol awakening response, AUCg; nmol/l*h; mean; (SEM)	102.38 (± 11.97)	109.64 (± 7.32)	0.610
Cortisol awakening response, AUCi; nmol/l*h; mean; (SEM)	−1.31 (± 8.42)	20.91 (± 7.58)	0.061
Cortisol daytime profile, AUCg; nmol/l*h; mean (SEM)	79.07 (± 7.55)	78.02 (± 6.44)	0.916
DST awakening response, AUCg; nmol/l*h; mean (SEM)	10.11 (± 4.32)	8.34 (± 2.68)	0.716
DST awakening response, AUCi; nmol/l*h; mean (SEM)	1.27 (± 2.01)	0.33 (± 0.91)	0.644
DST daytime profile, AUCg; nmol/l*h; mean (SEM)	25.64 (± 563)	20.06 (± 3.50)	0.384
Socially evaluated cold pressor test (SECPT)	N = 12	N = 19	
Salivary cortisol level before SECPT, nmol/l; mean (SEM)	8.33 (± 0.68)	7.12 (± 0.75)	0.280
Salivary cortisol level after SECPT, nmol/l; mean (SEM)	7.58 (± 0.70)	7.92 (± 0.86)	0.788
Salivary cortisol level after 15 minutes, nmol/l; mean (SEM)	18.68 (± 3.28)	12.25 (± 1.41)	0.091
Control procedure (warm water)	N = 12	N = 20	
Salivary cortisol level before procedure, nmol/l; mean (SEM)	11.71 (± 1.84)	8.14 (± 0.61)	0.088
Salivary cortisol level after procedure, nmol/l; mean (SEM)	10.89 (± 1.36)	8.23 (± 0.59)	**0.048**
Salivary cortisol level after 15 minutes, nmol/l; mean (SEM)	10.74 (± 1.31)	7.75 (± 0.64)	**0.029**
Cortisol during TGA	N = 13		**P value ER vs. day-profile**
Value in emergency room (SEM)	26.16 (± 5.72)	NA	
Value of day-profile (time-matched)	7.58 (± 1.37)	NA	**0.006**

CES-D, Center for Epidemiological Studies Depression Scale; SEM, standard error of the mean; STAI, state-trait anxiety inventory; TICS, trier inventory for chronic stress. AUCg, area under the curve with respect to ground; AUCi, area under the curve with respect to increase; DST, dexamethasone suppression test; SEM, standard error of the mean. Bold font indicates p < 0.05.

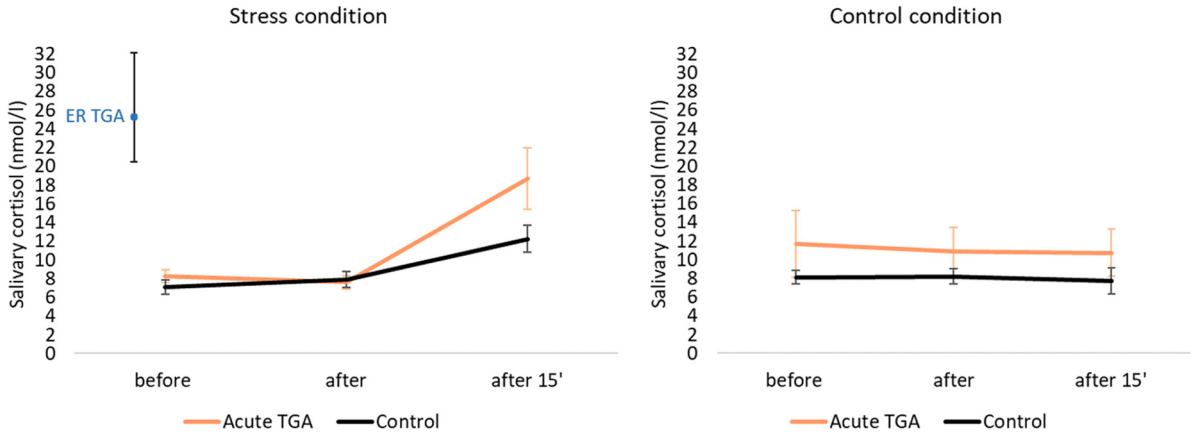

Fig. 3. Diurnal cortisol rhythm.
(A) Daytime profile of salivary cortisol levels. Twenty-four-hour cortisol profile in 14 acute TGA patients and 20 healthy controls.
(B) Salivary cortisol levels after dexamethasone challenge.
Twenty-four-hour cortisol profile in 14 acute TGA patients and 19 healthy controls following the administration of 0.5 mg dexamethasone at 11 p.m. on the day before.
Data are presented as the mean (in nmol/l) at predefined sample times (awakening, +15, +30, +45, + 60 min, thereafter daytime profile) across subjects.

stress-induced cascade of steroid-mediated glutamatergic cytotoxicity, affecting the structural integrity of CA-1 neurons in the hippocampus in the pathophysiology of TGA was refined (Bartsch and Deuschl, 2010). Stress has been shown to disturb the function of the hippocampus via glucocorticoid receptor activation with consequences on different processes including of synaptic plasticity, neuronal survival, hippocampal neurogenesis and hippocampal connectivity (de Kloet et al., 2005; McEwen and Milner, 2007; Sandi and Pinelo-Nava, 2007; Segal et al., 2010). High glucocorticoid levels have also been shown to induce a decrease in regional cerebral blood flow in the mesial temporal lobe, and to have a negative effect on cognition and memory (Lupien and Lepage, 2001). Recent evidence suggests that cortisol acts diff ;erentially via rapid and slow effects. While the rapid eff ;ects are believed to promote emotional behaviour via amygdala activation in reaction to acute stress, the delayed eff ;ects occurring after several hours are believed to restore homeostasis following episodes of stress and among others to promote consolidation, a function profoundly disturbed during TGA (Barsegyan et al., 2010; Henckens et al., 2012; Hermans et al., 2011; Joels et al., 2006).

The cortisol response in the stress hypothesis of TGA may well be elicited by the precipitating events occurring immediately before the TGA and reported in up to 90% (32–89.1%) of TGA cases. These have been mainly described as episodes of physical, emotional, or behavioral stress and include events such as attendance of a funeral, emotion-laden arguments, painful medical procedures, immersion in cold water and exhausting physical activity (Quinette et al., 2006a). However, measurements of cortisol during acute TGA have not been studied previously. Doehring et al. showed that TGA patients tend to cope with stress less efficiently and less constructively than controls and therefore postulated that disadvantageous coping strategies and an elevated anxiety level may increase the susceptibility to psychological stress which may facilitate the pathophysiological cascade in TGA (Dohring et al., 2014). According to recent research, depending on the timing of the stress exposure, stress can impair or improve memory processes in the hippocampus depending on whether stress is experienced within or outside the context of the learning episode (Joels et al., 2006; Schwabe et al., 2012). However, these theories do not readily explain, how a preceding stressful episode may inhibit memory in TGA as memory research links stress to an impaired retrieval and not an impaired encoding or storage of episodic memory as seems to be the case in TGA (Eustache et al., 1999; Quinette et al., 2006b) emphasizing the uniqueness of the disorder. The findings of recent resting-state fMRI examinations and previous studies using SPECT suggest that while the hippocampus might play a central role, TGA causes more widespread

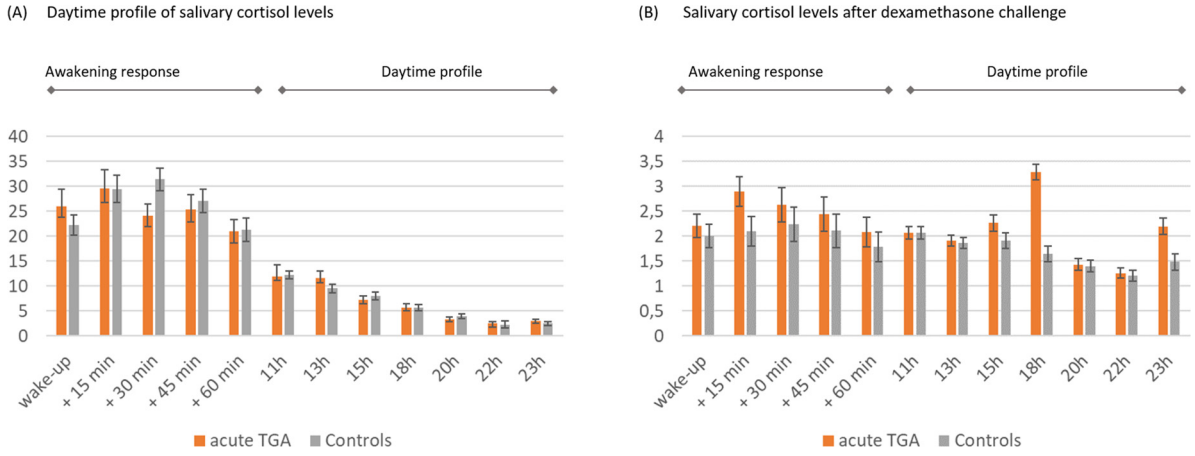

Fig. 4. Cortisol response to experimental stressor.
Salivary cortisol response (in nmol/l) to the socially evaluated cold pressor test (SECPT) in 12 patients with acute TGA and 19 healthy controls (left) and to the control procedure with warm water in 12 patients with acute TGA and 20 healthy controls (right). For demonstration purposes the figure includes the mean salivary cortisol measured during acute TGA. Data are presented as mean ± standard error of the mean.

alterations of cerebral connectivity and perfusion (Peer et al., 2014; Stillhard et al., 1990). In an experimental setting, psychosocial stress has been shown to lead to a deactivation of the limbic system, particularly the hippocampus (Dedovic et al., 2009). Interestingly, deactivation patterns of the hippocampus in response to acute social stress correlate with the magnitude of the cortisol stress response: (Dedovic et al., 2009). Therefore, we postulate that in TGA caused by pre-existing or external factors, a hyperresponsiveness of the HPA-axis leads to an exaggerated release of or a hypersensitivity to the stress-related release of cortisol. These factors may include age-related brain alterations, a genetic predisposition, personality traits, coping mechanisms, psychiatric comorbidity and life events or a combination of these (Heim et al., 2004; Kudielka et al., 2004; Wingenfeld and Wolf, 2014).

One of the main reasons for the stress hypothesis of TGA is the close temporal correlation of a highly emotional or physically exhausting event occurring before the attack. These precipitating events have been reported to occur either immediately (e.g. being the victim of an assault) or in the 24 h before the TGA episode (Griebe et al., 2014; Hodges and Ward, 1989; Miller et al., 1987; Quinette et al., 2006a). In a smaller number of cases, incidents preceding the episode by days, weeks or months have been described (Quinette et al., 2006a). However, also the TGA episode itself with the circumstances of being brought to the emergency room by ambulance is a stressful experience for the patients. These effects are difficult to differentiate from the initial stressful trigger that in our study was present in 9/14 patients. One patient for example had attended the funeral of a close friend when she developed symptoms of TGA and was transported to our hospital. We cannot rule out that cortisol increase in our cohort was in part also a consequence of the medical circumstances and environment. Studies with comparable ER patient cohorts are rare. One previous study investigated the relationship between the acute psychological and psychobiological trauma response and the subsequent development of posttraumatic stress disorder and depressive symptoms in 53 accident survivors attending an emergency department (Ehring et al., 2008). They report mean salivary cortisol levels of 12.18 mmol/l. In comparison in our cohort salivary cortisol levels were more than twice as high. However, when studying the effects of the environment, a recent study found that older adults had significantly higher cortisol levels and lower memory performance when compared to younger participants (Sindi et al., 2013).

4.2. Psychopathological factors of TGA

Certain aspects of personality have been suggested to be more common in TGA patients: In 1997, Inzitari et al. found phobic personality traits in 82% of 51 TGA patients and in some even presented with symptoms resembling a panic attack during TGA (Inzitari et al., 1997). Depressive symptoms and a personal or family history of psychiatric comorbidities have also been shown to be more common in TGA patients (Neri et al., 1995; Pantoni et al., 2005). In their series of 142 patients, Quinette et al. report a high frequency of a personality disorder, an anxious depressive profile or emotional instability suggesting that TGA patients might be particularly vulnerable to psychological stress (Quinette et al., 2006a). In a recent review Noel et al. discuss that in a subgroup of patients, the role of depressive and anxious symptoms may intervene at different moments in TGA namely during triggering, course and even recovery and coin the term the “emotional TGA subtype”. (Noel et al., 2015). We observed a hyperresponsivity of cortisol a) during the acute episode with a significantly increased cortisol secretion in comparison to a time-matched value of the day-profile and b) during the postacute phase with a higher increase of cortisol in response to experimental stress exposure in comparison to controls. We did not however, find a basal dysregulatory process of the HPA axis as demonstrated by a lack of difference of cortisol day profiles and values after dexamethasone challenge in comparison to the control group. The intact cortisol awakening response is in sharp contrast to the absent cortisol awakening response occurring in patients with global (non-transient) amnesia and in patients with hippocampal damage (Buchanan et al., 2004; Wolf et al., 2005). In a different study design, patients after an acute sexual assault and a prior history of assault showed diminished acute cortisol responsivity at the emergency room visit (Walsh et al., 2013). In a recent study, the Trier Social Stress Test was implemented to assess the HPA-axis reactivity in patients diagnosed with panic disorder. The authors report a hypo-responsiveness of the HPA-axis to stress (Petrowski et al., 2013). These data imply a specific pathomechanism in acute TGA that lacks a sufficient model postulated in other stress-related disorders as a comparison. Future studies might benefit from the sampling of hair cortisol concentrations that measure cortisol levels over extended periods of time and allow the investigation of real-life stressors and long-term cortisol exposure (Wester and van Rossum, 2015).

4.3. Experimental versus real-life stress

There is an extensive body of literature studying the influence of laboratory stress on memory processes under experimental conditions and salivary cortisol is commonly used as a measure of the endocrine stress response. According to Admon et al. a cortisol increase greater than 2.5 nmol/L after stress induction is typically taken as a threshold for “stress response” (Admon et al., 2017; Foley and Kirschbaum, 2010). The cortisol increase of our control group is well in line with previously reported when using the SECPT (Minkley et al., 2014). As an example of a more intense stress procedure condition, Taverniers et al. explored effects of high endogenously evoked cortisol concentrations on visuo-spatial declarative memory elicited by a prisoner of war exercise (Taverniers et al., 2010). They report cortisol values in a similar range to that found in our acute patient group, underlining the assumption that the cortisol response in TGA might be enhanced and lead to memory impairment. Further comparison of our results from TGA patients is more difficult, as the literature concerning either real-life acute stressors and stress response in disease is limited. Among the few disorders that have been shown to present with enhanced or exaggerated cortisol responses to psychosocial stress are major depression and obesity (Chopra et al., 2009; Epel et al., 2001). In the light of these findings, we postulate that the personality traits found in TGA patients may represent a prerequisite for an enhanced cortisol reaction to stress that, when combined with vulnerability, leads to TGA. Concerning the HPA axis, we previously found stronger pharmacological cortisol suppression and higher cortisol levels in anticipation of experimental stress in completely recovered patients with a history of TGA compared to a control group, indicating a hypersensitivity of the HPA axis (Griebe et al., 2015). This is a pattern consistently reported in patients with posttraumatic stress disorder but opposed to non-suppression in patients with major depressive disorder and might possibly represent the consequence of a TGA episode (Handwerger, 2009).

The main ambiguity of every pathophysiological hypothesis postulated for TGA is the finding that TGA in most patients occurs only once in a lifetime. The interpretation of this is very challenging and implies the existence of a temporally limited vulnerability factor that has yet to be identified. Another possibility is that TGA is more common in individual patients than hitherto appreciated. This might be due to the following reasons: 1) Patients may not report to a hospital (or the same hospital) in the event of a reccurent TGA after they have been informed about the benignity of the disorder. 2) As TGA affects predominantly older patients, age-related occurrence of other and more severe disorders may obscure recurrent, short TGA episodes. In this context interesting is emerging evidence that TGA may coincide with Takotsubo cardiomyopathy (also termed “stress cardiomyopathy”), a cardiological disorder with very similar stress-related pathophysiological implications (Bobinger et al., 2013; Finsterer and Stollberger, 2017; Pelliccia et al., 2017). This finding indicates that TGA may be only one consequence of an underlying disturbance that may manifest in different

systems.

5. Conclusion

In summary, we report a psychophysiological hyperresponsivity of cortisol secretion in TGA patients as a reaction to naturally stressful external stimuli during the acute episode that persisted in response to an experimental stress condition during the subacute phase. These results support the hypothesis that stress as well as symptoms of depression and anxiety might be significant for the pathogenesis of TGA.

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Declarations of interest

None

Contributions

Martin Griebe, MD: Major role in the acquisition of data; drafted the manuscript for intellectual content

Anne Ebert, PhD: Major role in the acquisition of data and statistical analysis, revised the manuscript for intellectual content

Frauke Nees, PhD: Designed and conceptualized study; analyzed and interpreted the data; revised the manuscript for intellectual content

Benjamin Gerber, MD: Major role in the acquisition of data, revised the manuscript for intellectual content

Katharina Katic: Data acquisition and analysis. revised the manuscript for intellectual content

Kristina Szabo, MD: Designed and conceptualized study; major role in the acquisition of data, drafted the manuscript for intellectual content

All authors have approved the final article.

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