



Universiteit  
Leiden  
The Netherlands

## Trigger factors and mechanisms in migraine

Schoonman, G.G.

### Citation

Schoonman, G. G. (2008, September 11). *Trigger factors and mechanisms in migraine*. Retrieved from <https://hdl.handle.net/1887/13094>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/13094>

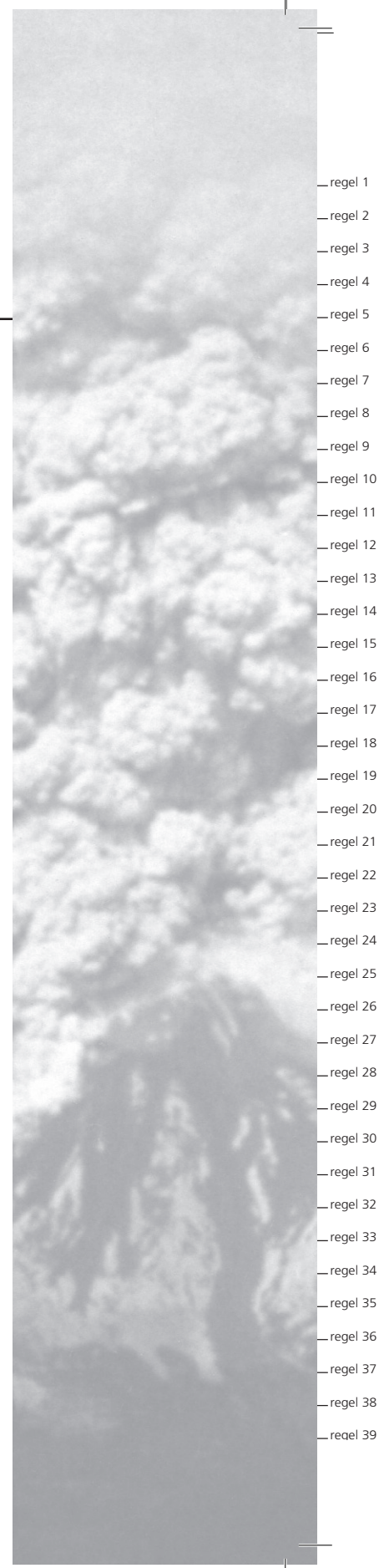
**Note:** To cite this publication please use the final published version (if applicable).

## CHAPTER 2

---

# IS STRESS A TRIGGER FACTOR FOR MIGRAINE?

*Psychoneuroendocrinology 2007;32:532-8*



— regel 1  
— regel 2  
— regel 3  
— regel 4  
— regel 5  
— regel 6  
— regel 7  
— regel 8  
— regel 9  
— regel 10  
— regel 11  
— regel 12  
— regel 13  
— regel 14  
— regel 15  
— regel 16  
— regel 17  
— regel 18  
— regel 19  
— regel 20  
— regel 21  
— regel 22  
— regel 23  
— regel 24  
— regel 25  
— regel 26  
— regel 27  
— regel 28  
— regel 29  
— regel 30  
— regel 31  
— regel 32  
— regel 33  
— regel 34  
— regel 35  
— regel 36  
— regel 37  
— regel 38  
— regel 39

## ABSTRACT

### *Background*

Although mental stress is commonly considered to be an important trigger factor for migraine, experimental evidence for this belief is lacking.

Objective: To study the temporal relationship between changes in stress related parameters (both subjective and objective) and the onset of a migraine attack.

### *Methods*

This was a prospective, ambulatory study in 17 migraine patients. We assessed changes in perceived stress and objective biological measures for stress (saliva cortisol, heart rate average [HRA], and heart rate variability [low frequency power and high frequency power]) over four days prior to the onset of spontaneous migraine attacks. Analyses were repeated for subgroups of patients according to whether or not they felt their migraine to be triggered by stress.

### *Results*

There were no significant temporal changes over time for the whole group in perceived stress ( $p=0.50$ ), morning cortisol ( $p=0.73$ ), evening cortisol ( $p=0.55$ ), HRA ( $p=0.83$ ), low frequency power ( $p=0.99$ ) and high frequency power ( $p=0.97$ ) prior to or during an attack. Post-hoc analysis of the subgroup of nine stress-sensitive patients who felt that  $>2/3$  of their migraine attacks were triggered by psychosocial stress, revealed an increase for perceived stress ( $p=0.04$ ) but no changes in objective stress response measures. At baseline this group also showed higher scores on the Penn State Worry Questionnaire ( $p=0.003$ ) and the Cohen Perceived Stress Scale ( $p=0.001$ ) compared to non stress-sensitive patients.

### *Conclusions*

Although stress-sensitive patients, in contrast to non stress-sensitive patients, may perceive more stress in the days before an impending migraine attack, we failed to detect any objective evidence for a biological stress response before or during migraine attacks.

## INTRODUCTION

Migraine is a multifactorial brain disorder characterised by recurrent, disabling attacks of headache, associated autonomic features and, in one third of patients, neurological aura symptoms<sup>75</sup>. Although the pathogenesis of the migraine features is reasonably well understood, it is not clear how migraine attacks are actually triggered. Mental stressors are psychological events that in potential threaten homeostasis of a living organism<sup>143</sup> and they are commonly perceived as important trigger factors by both patients and physicians<sup>88</sup>, although direct evidence for this claim is lacking. In retrospective questionnaire studies, up to 62% of migraine patients reported that psychosocial stress was an important trigger-factor for their attacks<sup>25,29,89</sup>, but patients have a tendency to overestimate stress on retrospective measures<sup>90</sup>. In cross-sectional studies, migraine patients were found to have elevated plasma levels of cortisol, an indicator for stress, both outside a migraine attack compared to healthy volunteers<sup>91</sup> and during attacks compared to the inter-ictal phase<sup>92</sup>. Stress-provocation studies, involving mental and physical stressors, have suggested sympathetic and parasympathetic changes in migraine patients outside attacks compared to healthy volunteers<sup>93-96</sup>. However, experimental prospective studies examining whether stress-related biological changes are actually temporally related to the onset of migraine attacks, are conspicuously lacking. We therefore performed a prospective, longitudinal ambulatory study, assessing perceived stress and objective stress-related biological changes in the four days prior to an impending migraine attack. We included both patients who claimed that stress would trigger the majority of their attacks (stress-sensitive) and patients who denied such a relationship (non stress-sensitive).

## METHODS

### *Subjects*

A total of 69 migraine patients were recruited from our headache outpatient clinic and 27 patients were included in the study. Inclusion criteria were (1) diagnosis of migraine with or without aura according to the criteria of the IHS (code 1.1. and 1.2.1;<sup>3</sup> and at least one migraine attack per month in the previous six months. Exclusion criteria were (1) pure menstrual migraine, (2) more than 15 days of headache per month, (3) use of beta-blockers and (4) inability to differentiate between migraine and other types of primary headache syndromes. We asked the patients whether they felt that their attacks were triggered by stress and if so, in what proportion. Patients who claimed that

— regel 1  
— regel 2  
— regel 3  
— regel 4  
— regel 5  
— regel 6  
— regel 7  
— regel 8  
— regel 9  
— regel 10  
— regel 11  
— regel 12  
— regel 13  
— regel 14  
— regel 15  
— regel 16  
— regel 17  
— regel 18  
— regel 19  
— regel 20  
— regel 21  
— regel 22  
— regel 23  
— regel 24  
— regel 25  
— regel 26  
— regel 27  
— regel 28  
— regel 29  
— regel 30  
— regel 31  
— regel 32  
— regel 33  
— regel 34  
— regel 35  
— regel 36  
— regel 37  
— regel 38  
— regel 39

regel 1 \_\_\_\_\_ >2/3 of their attacks were triggered by stress were considered “stress sensitive” and  
regel 2 \_\_\_\_\_ those who reported that <2/3 of their attacks was triggered by stress were considered  
regel 3 \_\_\_\_\_ “stress non-sensitive”. The study was approved by the local medical ethical committee  
regel 4 \_\_\_\_\_ and the subjects gave informed consent prior to the start of the study. The study was  
regel 5 \_\_\_\_\_ conducted in the period January to August 2004.

### ***Procedure***

regel 6 \_\_\_\_\_ Patients filled out two stress questionnaires at the start of the observation period.  
regel 7 \_\_\_\_\_ The first was the Cohen Perceived Stress Scale (Cohen PSS)<sup>144</sup> which is a measure for  
regel 8 \_\_\_\_\_ perceived stress in the past month. It is a 14 item questionnaire and the score ranges  
regel 9 \_\_\_\_\_ from 0 (no stress) to 56 (maximum stress). The second questionnaire was the Penn State  
regel 10 \_\_\_\_\_ Worry Questionnaire (PSWQ)<sup>145</sup>, a 16 item questionnaire to assess the trait of worrying  
regel 11 \_\_\_\_\_ (ranging from 16 (minimal worries) to 80 (maximum)). Both questionnaires are used to  
regel 12 \_\_\_\_\_ characterize the study population.  
regel 13 \_\_\_\_\_  
regel 14 \_\_\_\_\_

regel 15 \_\_\_\_\_ The observation period started at least three days after an attack and lasted up to the  
regel 16 \_\_\_\_\_ first day of the next attack. Migraine symptoms and stress events were scored daily  
regel 17 \_\_\_\_\_ around 22.00 hours using an electronic diary (described below). Saliva samples were  
regel 18 \_\_\_\_\_ taken 3 times per day (30 and 45 minutes after waking up and around 22.00 hours,  
regel 19 \_\_\_\_\_ before filling out the stress and migraine questionnaire); Heart rate was measured daily  
regel 20 \_\_\_\_\_ between 18.00 and 22.00 hours using an ambulatory monitoring system. The timings  
regel 21 \_\_\_\_\_ were chosen in such a way that the recordings would be influenced as little as possible  
regel 22 \_\_\_\_\_ by physical activity during the day.  
regel 23 \_\_\_\_\_  
regel 24 \_\_\_\_\_

### ***Perceived daily stress and migraine symptoms***

regel 25 \_\_\_\_\_ ‘Personal digital assistants’ devices (Palm Tungsten E) were used as electronic diaries.  
regel 26 \_\_\_\_\_ Data were entered daily around 22.00 hours using a database application (Pendragon  
regel 27 \_\_\_\_\_ Forms 3.2, Pendragon Software Corporation, Libertyville, USA)<sup>146</sup>. Perceived daily stress  
regel 28 \_\_\_\_\_ was measured with the validated Daily Stress Inventory (DSI). In short, this is a 58 item  
regel 29 \_\_\_\_\_ inventory of events experienced in the last 24 hours<sup>147</sup>. The amount of stress felt in  
regel 30 \_\_\_\_\_ response to each event is rated on a Likert-type scale (0 = event did not happen, 1 =  
regel 31 \_\_\_\_\_ event occurred but was not stressful to 7 = event caused panic). The perceived daily  
regel 32 \_\_\_\_\_ stress is the sum total of all ratings (DSI-sum). Migraine symptoms were assessed using  
regel 33 \_\_\_\_\_ the criteria of the IHS. The diaries were easy to use and retrospective data entry or  
regel 34 \_\_\_\_\_ alterations were disallowed by the PDA program. An alarm sounded daily at 22.00  
regel 35 \_\_\_\_\_ hours to remind patients to fill out the questionnaires.  
regel 36 \_\_\_\_\_  
regel 37 \_\_\_\_\_  
regel 38 \_\_\_\_\_  
regel 39 \_\_\_\_\_

***Salivary cortisol***

Saliva samples for cortisol assessment were obtained with 'Salivette' saliva collection tubes (Sarstedt, Germany). Each day patients collected three saliva samples. 30 minutes and 45 minutes after waking up and around 22.00 hours. Patients were instructed not to eat, exercise, smoke or brush their teeth 30 minutes prior to sampling. Patients stored the samples at 7 °C until the end of the observation period. At the end of the observation period patients were asked to report sampling problems. After centrifugation, samples were stored at -80 °C until analysis. Cortisol concentrations were determined using Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The functional sensitivity of this assay is 2 nmol/L<sup>148</sup>.

***Heart rate and heart rate variability***

Heart rate was measured using the Vrije Universiteit Ambulatory Monitoring System (VU-AMS, version 4.6, Vrije Universiteit Amsterdam)<sup>149</sup> between 18.00 and 22.00 hours during periods of 10 minutes every half hour. R-R wave intervals were recorded on line from a 3-lead ECG. Fast Fourier transformation was used to calculate spectral power of the RR interval<sup>150</sup>; a trend was removed from the data to reduce the influence of very low frequencies. A cubic spline function corrected for missing values in the time series to result in regularly sampled time series. The data were multiplied by a Tukey window and transformed from the time domain to the frequency domain with the discrete Fourier transform. The spectra were smoothed by a triangular window (width ~0.01 cycles per RR interval). After integration of the area under the curve, the low frequency (0.05-0.15 Hz) power (LF), reflecting a mix of sympathetic and parasympathetic activity, and the high frequency (0.15-0.30Hz) power (HF), largely reflecting parasympathetic activity were calculated.

***Statistical analysis***

Temporal changes and differences between the two stress sensitive subgroups in perceived stress, cortisol (morning and evening), HRA, LF and HF power were analysed using a linear mixed model, with observation day and subgroup as fixed factors. A maximum of four pre-migraine days were included in the analysis since the premonitory phase may start up to 48 hours prior to the onset of the headache phase<sup>4,134</sup>. Cohen PSS and PWSQ differences between stress sensitive subgroups were tested using an unpaired t-test. The Bonferroni correction was applied for multiple testing and P<0.025 was considered significant.

— regel 1  
 — regel 2  
 — regel 3  
 — regel 4  
 — regel 5  
 — regel 6  
 — regel 7  
 — regel 8  
 — regel 9  
 — regel 10  
 — regel 11  
 — regel 12  
 — regel 13  
 — regel 14  
 — regel 15  
 — regel 16  
 — regel 17  
 — regel 18  
 — regel 19  
 — regel 20  
 — regel 21  
 — regel 22  
 — regel 23  
 — regel 24  
 — regel 25  
 — regel 26  
 — regel 27  
 — regel 28  
 — regel 29  
 — regel 30  
 — regel 31  
 — regel 32  
 — regel 33  
 — regel 34  
 — regel 35  
 — regel 36  
 — regel 37  
 — regel 38  
 — regel 39

## RESULTS

### *Study population and observation periods*

Of the 27 patients included in the study, 17 patients had a migraine attack during the observation period (Table 1). In 10 patients we did not measure an attack: six patients dropped out because the ambulatory cardiovascular measurements interfered too much with daily activities and four patients did not have a migraine attack within the observation period. The duration of the pre-ictal observation period in the 17 patients who had a migraine attack was four days in 12 patients, three days in two patients, two days in two and only 1 day in one patient. Some patients developed an attack within a few days after starting the observation period which is the reason for the variability in observation duration. In 12 patients the migraine attack began in the morning and in 5 patients in the afternoon.

**Table 1** Demographic information of study participants.

|                                    | All patients<br>(n=27) | Patients<br><i>without</i> an<br>attack (n=10) | Patients <i>with</i><br>an attack<br>(n=17) | Stress<br>sensitive<br>patients<br>(n=9) | Stress<br>insensitive<br>patients<br>(n=8) |
|------------------------------------|------------------------|--|---|--|--|
| Mean age (SD)                      | 40.8 (9.9)             | 39.1 (10.1)                                    | 41.8 (9.9)                                  | 41.3 (8.5)                               | 42.3 (11.9)                                |
| Ratio of men to<br>women           | 7 : 20                 | 3 : 7  | 4 : 13                                      | 1 : 8                                    | 3 : 8                                      |
| Ratio MO to MA                     | 20 : 7                 | 7 : 3  | 13 : 4                                      | 8 : 1                                    | 5 : 3                                      |
| Attack frequency per<br>month (SD) | 4.4 (2.7)              | 3.9 (2.1)                                      | 4.7 (3.0)                                   | 3.7 (2.1)                                | 5.8 (3.6)                                  |
| PWSQ                               |                        |  |   | 58.3 ± 12.5                              | 39.0 ± 9.8*                                |
| Cohen PSS                          |                        |  |   | 29.4 ± 7.9                               | 16.4 ± 4.2**                               |

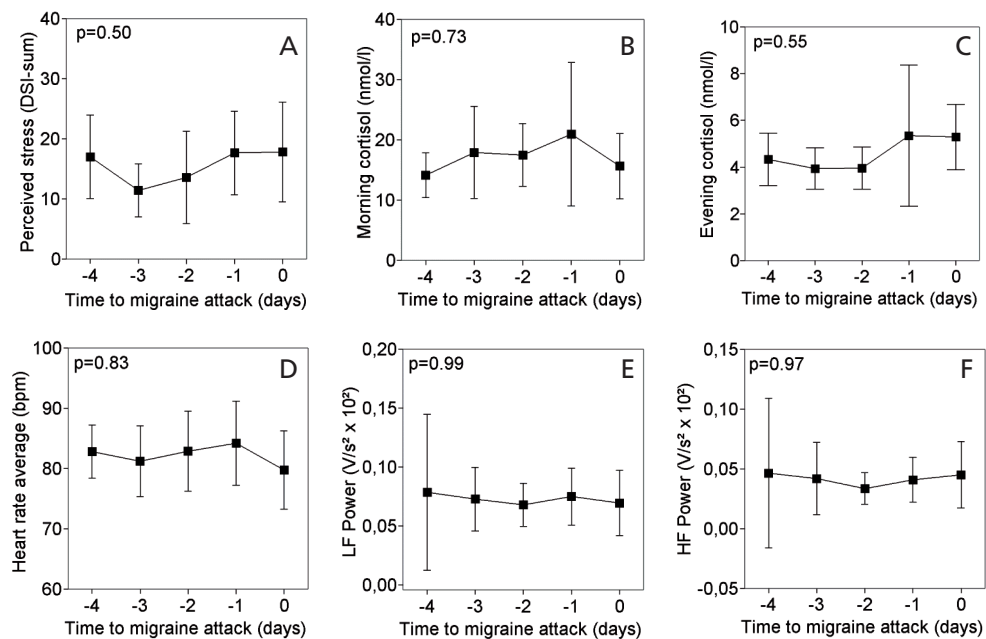
MO denotes migraine without aura, MA migraine with aura, PWSQ Penn State Worry Questionnaire and Cohen PSS Cohen Perceived Stress Scale. (\*p=0.003 and \*\* p=0.001).

### *Baseline characteristics*

The demographics of the total study population and the various subgroups are given in table 1. There were nine stress sensitive and eight stress non-sensitive patients. The baseline mean PSWQ and Cohen PSS scores were higher in the stress sensitive patients.

### Temporal changes in stress related variables

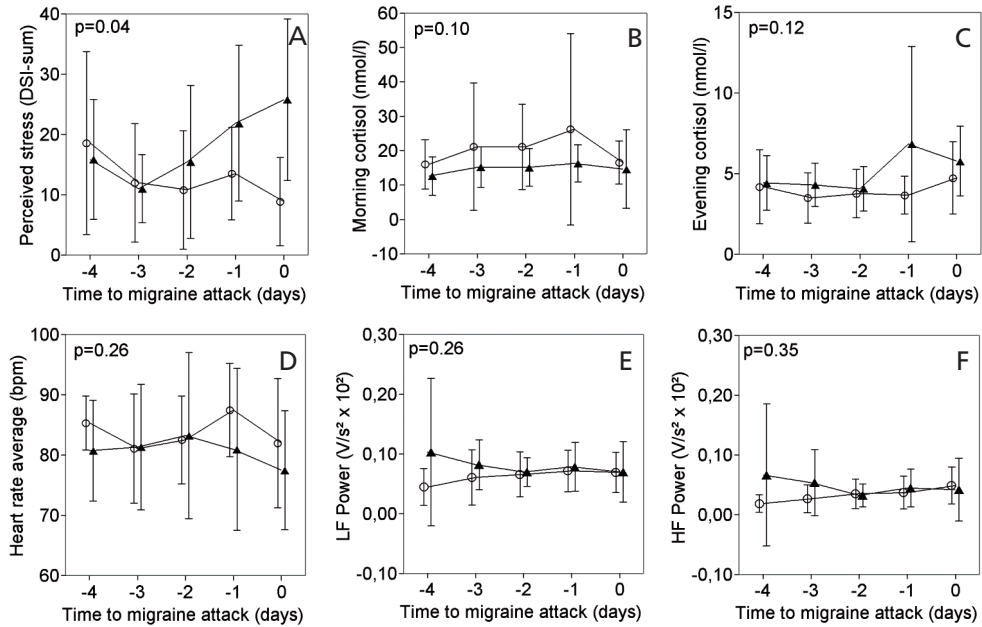
The temporal profiles of the mean scores for perceived stress, morning cortisol, evening cortisol, heart rate, LF and HF power are shown in Figures 1a-e for the whole study population and in Figures 2a-e for the subgroup of nine stress-sensitive patients compared to eight non stress-sensitive patients. In the total study population, the mean score for perceived stress was  $17.8 \pm 16.2$  on the migraine day, the mean morning cortisol  $15.6 \pm 9.7$  nmol/l, the mean evening cortisol  $5.3 \pm 2.7$  nmol/l and the mean heart rate  $79.7 \pm 12.1$  bpm. Differences between observation days were not significant. The comparison between the stress sensitive with non-sensitive patients revealed in the nine stress sensitive patients an increase in perceived stress in the days prior to an attack (Figure 2a), but no other differences between the two groups.



**Figure 1A** Perceived stress during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 1B** Morning cortisol during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 1c** Evening cortisol during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 1D** Heart rate average during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 1E** LF power during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 1F** HF power during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals.

regel 1  
 regel 2  
 regel 3  
 regel 4  
 regel 5  
 regel 6  
 regel 7  
 regel 8  
 regel 9  
 regel 10  
 regel 11  
 regel 12  
 regel 13  
 regel 14  
 regel 15  
 regel 16  
 regel 17  
 regel 18  
 regel 19  
 regel 20  
 regel 21  
 regel 22  
 regel 23  
 regel 24  
 regel 25  
 regel 26  
 regel 27  
 regel 28  
 regel 29  
 regel 30  
 regel 31  
 regel 32  
 regel 33  
 regel 34  
 regel 35  
 regel 36  
 regel 37  
 regel 38  
 regel 39





**Figure 2A** Perceived stress for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 2B** Morning cortisol for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 2C** Evening cortisol for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 2D** Heart rate average for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 2E** Mean LF power for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 2F** Mean HF power for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals.

## DISCUSSION

In this prospective longitudinal study we failed to find any objective evidence for a temporal relationship between perceived stress, biological indicators for a stress-response, and the onset of migraine attacks. Although stress-sensitive patients indeed reported an increase in perceived stress in the days before an attack, this was not accompanied by objective signs indicating a biological stress response. The present results extend earlier negative findings on the putative relationship between stress and migraine. Autonomic function tests during migraine attacks failed to show changes in heart rate variability, blood pressure reaction<sup>151</sup> or transcranial Doppler response in the middle cerebral artery<sup>44</sup>. In contrast, in the inter-ictal phase changes in both sympathetic and parasympatric autonomic function have been described<sup>95,96,152</sup>. The increase in perceived stress in stress-sensitive patients is in accordance with previous prospective studies in which, however, no biological stress markers were included<sup>42,43</sup>.

Stressors can be described as physical and psychological events that in potential threaten homeostasis of a living organism<sup>143</sup>. Both acute stressors and stressful daily events have shown to increase cortisol<sup>153,154</sup> and heart rate<sup>155</sup>. Although a profound effect of daily stressful events on migraine seems unlikely, we cannot fully exclude an association between mental stress and migraine. We could only measure 17 migraine patients because of the rather demanding design of the study (daily observations for, in some instances, several weeks because of the unpredictable timing of attacks). Due to the prospective nature of our study the pre-ictal interval varied between study subjects. Twelve out of 17 migraine patient were studied for the full length of 4 days, five patients for a shorter period of time because these five patients experienced their attack within a few days after starting the observation period. Because we did not observe differences for our parameters between day -4 and day -2 we believe that this shorter observation period will not influence our findings. Furthermore, the temporal resolution of our measurements was relatively low. Cortisol was measured only in the morning and evening, and heart rate only in the evening to reduce the effect of physical activity. Theoretically, a reduction in physical activity during evening hours because of the prodromal phase of a migraine attack<sup>156</sup> may have masked an association between changes in heart rate and migraine. Also theoretically, due to the low resolution of measurements this could have resulted in missing changes occurring immediately before the onset of an attack. We feel however that, based on the time course of premonitory symptoms, changes are to be expected to occur 12 to 24 hours prior to the onset of attacks<sup>134</sup>.

— regel 1  
— regel 2  
— regel 3  
— regel 4  
— regel 5  
— regel 6  
— regel 7  
— regel 8  
— regel 9  
— regel 10  
— regel 11  
— regel 12  
— regel 13  
— regel 14  
— regel 15  
— regel 16  
— regel 17  
— regel 18  
— regel 19  
— regel 20  
— regel 21  
— regel 22  
— regel 23  
— regel 24  
— regel 25  
— regel 26  
— regel 27  
— regel 28  
— regel 29  
— regel 30  
— regel 31  
— regel 32  
— regel 33  
— regel 34  
— regel 35  
— regel 36  
— regel 37  
— regel 38  
— regel 39

regel 1 \_\_\_\_\_  
regel 2 \_\_\_\_\_  
regel 3 \_\_\_\_\_  
regel 4 \_\_\_\_\_  
regel 5 \_\_\_\_\_  
regel 6 \_\_\_\_\_  
regel 7 \_\_\_\_\_

For our study we excluded pure menstrual migraine. Free salivary cortisol is decreased during the follicular phase of the menstruation period and in oral contraceptive users<sup>157</sup>. We did not correct for the temporal relation between menstrual cycle or oral contraceptive use and the occurrence of the migraine attack in the 13 women who were included in this study. Therefore, oral estrogens or the menstrual cycle might have influenced cortisol measurements.

regel 8 \_\_\_\_\_  
regel 9 \_\_\_\_\_  
regel 10 \_\_\_\_\_  
regel 11 \_\_\_\_\_  
regel 12 \_\_\_\_\_  
regel 13 \_\_\_\_\_  
regel 14 \_\_\_\_\_  
regel 15 \_\_\_\_\_  
regel 16 \_\_\_\_\_  
regel 17 \_\_\_\_\_

Future studies could include continuous measurements including the full 24 hours prior to the onset of attacks, although this will be logistically quite challenging. Although salivary morning cortisol is related to workstress<sup>158</sup>, short lasting daily stressors are probably better assessed using high frequent daily measurements<sup>153</sup>. The cortisol response after acute stressors has shown to normalize after 1 to 2 hours<sup>159</sup>. Future longitudinal stress studies in migraine could also include epinephrine and norepinephrine as indicators for sympathetic-adrenal-medullary system related changes after mental and physical stressors<sup>160</sup>. Both catecholamines can be measured in urine enabling environmental measurements<sup>161</sup>.

regel 18 \_\_\_\_\_  
regel 19 \_\_\_\_\_  
regel 20 \_\_\_\_\_  
regel 21 \_\_\_\_\_  
regel 22 \_\_\_\_\_  
regel 23 \_\_\_\_\_  
regel 24 \_\_\_\_\_  
regel 25 \_\_\_\_\_  
regel 26 \_\_\_\_\_  
regel 27 \_\_\_\_\_  
regel 28 \_\_\_\_\_  
regel 29 \_\_\_\_\_  
regel 30 \_\_\_\_\_  
regel 31 \_\_\_\_\_  
regel 32 \_\_\_\_\_  
regel 33 \_\_\_\_\_  
regel 34 \_\_\_\_\_  
regel 35 \_\_\_\_\_  
regel 36 \_\_\_\_\_  
regel 37 \_\_\_\_\_  
regel 38 \_\_\_\_\_  
regel 39 \_\_\_\_\_

In conclusion, we were unable to show objective evidence for a biological stress response before and during migraine attacks. This could reflect a true negative finding or be the result of the discussed study limitations. The reported association between perceived stress and migraine in a sub-population of stress sensitive patients might suggest that these attacks were triggered by mental stress. It could be that in these patients migraine attacks are triggered by mental stress or that events are perceived as stressful due to functional brain changes occurring in the very early phase of a migraine attack.