1. Date of test:
2. Technique (Choose all that apply):  nBR  PREP
3. Nociceptive Stimulation:
   1. Electrical
      1. Manufacturer:
      2. Model:
   2. Laser
      1. Manufacturer:
      2. Model:
   3. Chemical
      1. Method:
      2. Substance:
4. Recording system:
   1. Manufacturer:
   2. Model:
5. Stimulation frequency (include units):
6. Stimulus:  Single pulse  Double pulse  Triple pulse
7. Interpulse intervals:
8. Stimulation intensity (include units):
9. Duration of stimuli:
10. Recording parameters:  bandwidth (low-high)  sweep length (in ms)  sampling rate (in kHz)
11. Total number of averaged responses:
12. Number of sequential blocks of averaged responses & number of responses in each block:
13. Stimulation side (e.g. pain side):  Left  Right  Both
14. Stimulation target:  V1  V2  V3
15. Stimulation timing:  ictal  inter-ictal  peri-ictal
    1. If ictal, pain intensity at time of recordings:
    2. If ictal, duration of time since onset of headache (include units):
    3. If inter-ictal or peri-ictal, duration of time since end of last headache (include units):
    4. If inter-ictal or peri-ictal, duration of time until start of next headache (include units):

## General Instructions

Electrical trigeminal stimulation can performed in each division of the trigeminal nerve with two electrodes placed 10 mm above the supraorbital nerve (ophthalmic nerve V1), 10 mm below the infraorbital nerve (maxillar nerve V2) and lateral to the mental nerve (mandibular nerve V3), each with a two centimeter distance between electrodes. Stimulation is done on each side in pseudo randomized order. The participant’s/subject’s pain threshold is detected by two ascending and descending 0.2 mA stimulation sequences. Finally, blocks of 15 triple-pulses (monopolar square wave, intensity: 1.5 fold of the individual pain threshold, duration: 0.5 ms, pulse interval: 5 ms, interstimulus interval: 12-18 seconds, pseudo randomized) are applied. The electrical stimulus can be replaced by a Laser heat stimulus with comparable results. Chemical stimulation of the nasal mucosa with ammonia gas has been used up to now only in event-related fMRI studies.

Nociceptive BR and PREP are recorded simultaneously following trigeminal stimulation. PREP are recorded with electrodes placed at Cz referenced to linked earlobes (A1-A2) according to the international 10-20 system. Nociceptive BR are recorded using bilateral surface electrodes placedinfraorbitally. The following recording parameters are can be used: bandwidth 1 Hzto 1 kHz, sampling rate 2.5 kHz, sweep length 300 ms (1401plus,Signal, Cambridge Electronic Design, UK).

Signal analysis are performed by an investigator blinded to the study design and patient diagnosis. The first sweep are rejected to avoid contamination by startle responses. The remaining 14 sweeps are averaged. The following can be analyzed: N (negative peak) and P (positive peak) latencies, as well as NP (peak-to-peak) amplitudes of PREP as well as onset latencies and the area under the curve (AUC) of the nBR.

Blink reflex curves are rectified. Onset latencies are analyzed for each sweep separately and a mean value for the block is calculated. Areas under the curve are calculated between 27 and 87 ms after rectifying and averaging of the 14 sweeps of the block. Individual pain thresholds and subjective pain perception scores on a verbal rating scale (VRS) (0–10) are also analyzed.

Headache or migraine specific elements/measures that are not captured on this form but are important to the imaging analysis should be collected on other study-specific source documentation (e.g. Headache Diary, Concomitant Medications, recordings during headache or headache-free, time since last and to next headache).

Important note: All elements on this CRF are considered Supplemental and should only be collected if the research team considers them appropriate for their study.

## Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module.

* Date of test – Record the date/time according to the ISO 8601, the International Standard for the representation of dates and times ([Please click here for the International Organization for Standardization website](http://www.iso.org/iso/home.html)). The date/time should be recorded to the level of granularity known (e.g., year, year and month, complete date plus hours and minutes, etc.).
* Technique – Choose all that apply.
* Electrical or Laser Nociceptive Stimulation (manufacturer and model) – Indicate equipment manufacturer and model.
* Recording system (manufacturer and model) – Indicate equipment manufacturer and model.
* Stimulation frequency – Suggest random frequency 15-20 seconds.
* Stimulus – Triple pulse is suggested for electrical stimulation, single pulse for Laser.
* Interpulse Interval – No additional instructions.
* Stimulation intensity – Electrical: 1.5 x individual pain threshold; Laser: at pain threshold.
* Duration of stimuli – No additional instructions.
* Total number of pulses – 15-20 pulses suggested.
* Number of averaged responses – Indicate whether block averaging is used, number per block and interval between blocks.
* Stimulation side – Indication mandatory if recordings during an attack/lateralized pain.
* Stimulation target – No additional instructions.
* Stimulation timing – Report the timing of the study in relation the headache. The precise time windows for peri-ictal and inter-ictal vary with headache type. For episodic migraine, an interval of at least 72h from the last and before the next attack is generally accepted for “inter-ictal”.

References

* Ayzenberg I, Obermann M, Nyhuis P, Gastpar M, Limmroth V, Diener HC, Kaube H, Katsarava Z.Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures. Cephalalgia. 2006 Sep;26(9):1106-14
* Magis D, Ambrosini A, Bendtsen L, Ertas M, Kaube H, Schoenen J; EUROHEAD Project..Evaluation and proposal for optimalization of neurophysiological tests in migraine: part 1--electrophysiological tests. Cephalalgia. 2007 Dec;27(12):1323-38. Review.