Impaired trigeminal nociceptive processing in patients with episodic and chronic trigeminal neuralgia

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Background:

Trigeminal neuralgia (TN) usually leads to paroxysms of short lasting but very severe pain. Between the attacks the patient is generally asymptomatic, but a constant dull background pain may persist in some cases. The mechanisms associated with the development of this chronic pain are not well understood.

Objective:

To determine trigeminal nociceptive fiber impairment in patients comparing symptomatic and non-symptomatic with trigeminal neuralgia (TN) using the nociceptive blink reflex (nBR) and pain-related evoked potentials (PREP) and to identify possible central mechanisms of pain chronicity.

Methods:

We investigated 24 TN patients without, and 18 TN patients with concomitant chronic facial pain. PREP and nBR were investigated following nociception specific electrical stimulation on both sides of the face and in each division of the trigeminal nerve (V1, V2, and V3).

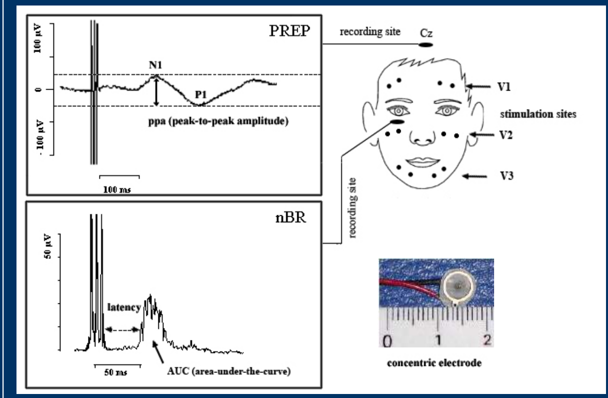

Figure 1: Example description of pain-related evoked potential (PREP) and nociceptive blink reflex (nBR) findings. Stimulation sites along the three branches of the trigeminal nerve (V1, V2, V3) on either side. Sites of simultaneous recording of PREP at Cz and nBR infraorbitally. Concentric electrode design and proportions.

NBR and PREP were recorded simultaneously. PREP were recorded with electrodes placed at Cz referenced to linked earlobes according to the international 10-20 system. NBR were recorded using bilateral surface electrodes placed infraorbitally referenced to the orbital rims. The following recording parameters were used: bandwidth 1 Hz to 1 kHz, sampling rate 2.5 kHz, sweep length 300 ms (1401plus, Signal, Cambridge Electronic Design, UK). The first sweep was rejected to avoid contamination by startle responses. The remaining 14 sweeps were averaged. Analyzed were N1 (negative peak) and P1 (positive peak) latencies, as well as NP peak-to-peak amplitudes. Areas under the curve (AUC) were calculated between 27 and 87 ms after rectifying and averaging of the 14 sweeps of the block. Mean values of the stimulation blocks for each subject and subsequent mean values for each group were calculated. PC-based offline analysis was performed with custom written software (Matlab 6.5, MathWorks, Natick, Massachusetts, USA).

Patient characteristics	*TN [total]*	*TN*	*TNcp*	*Group comparion*
Number of patients	42	24	18	
gender [women/ men]	18 / 24	10 / 14	6 /12	p = 0534
age [years]	63.6 ± 10.9	64.9 ± 10.1	61.7 ± 11.1	p = 0.182
duration of illness [years] (range)	8.4 ± 6.5 (range: 1-29)	8.5 ± 5.8 (range: 1-22)	8.2 ± 7.5 (range: 1-29)	p = 0.858
duration of chronic pain [years] (range)	-	-	5.6 ± 3.1 (range: 2-14)	
attack frequency [per day]	8.7 ± 10.3 (range: 1-50)	9.3 ± 12.0 (range: 1-50)	8.0 ± 7.8 (range: 1-30)	p = 0.693
pain location V1 / V2 / V3 [%]	41 / 79 / 50	42 / 75 / 46	39 / 83 / 56	p = 0.800 / 0.363 /0.384
pain intensity [VAS]	7.2 ± 2.3	6.8 ± 2.4	7.9 ± 2.1	p = 0.447
Hypoaesthesia [no of pat.]	4	0	4	
Medication [%]				
Carbamazepine	55	54	56	p = 0.879
Gabapentin	22	17	28	p = 0.067
Pregabalin	14	21	6	p = 0.036
None	10	8	11	p = 0.231

TN = trigeminal neuralgia; TNcp = trigeminal neuralgia with concomitant chronic facial pain
VAS = visual analogue scale; Group comparison TN vs. TNcp, level of significance was set to $p < 0.05$.

Results:

- In confirmation of previous electrophysiological, pathological and imaging study results we found peripheral damage to the trigeminal nerve near the root entry zone in the brainstem due to demyelination and axonal degeneration or due to isolated advanced axonal damage on the symptomatic side in all investigated patients with TN independent from presence or absence of chronic facial pain (Figure 2).

- In the subgroup of TN patients with concomitant chronic facial pain we additionally found facilitation of central trigeminal processing most likely at a supraspinal level which might be an underlying pathophysiological mechanism for the development of chronic facial pain (Figure 3).

		TN		*TN with concomitant chronic facial pain*	
PREP		**Latencies**	**Amplitudes**	**Latencies**	**Amplitudes**
symptomatic side	*V1*	137.1 ± 7.8*	22.5 ± 1.7*	131.6 ± 6.0*	29.7 ± 2.9*++
	V2	140.1 ± 8.6*	20.4 ± 1.5*	128.7 ± 7.1*	28.5 ± 2.5*++
	V3	138.8 ± 7.4*	22.3 ± 2.2*	136.9 ± 10.0*	25.0 ± 3.1*
non-symptomatic side	*V1*	109.7 ± 4.4	28.9 ± 2.1	113.7 ± 5.4	41.7 ± 4.8++
	V2	108.6 ± 6.4	29.5 ± 1.5	111.9 ± 7.1	46.6 ± 7.5++
	V3	113.7 ± 5.5	29.5 ± 1.9	115.5 ± 8.2	45.3 ± 3.4
nBR		**Latencies**	**AUC**	**Latencies**	**AUC**
symptomatic side	*V1*	51.8 ± 3.1*	422.1 ± 40.7	53.9 ± 3.3*	347.4 ± 26.8
	V2	52.2 ± 3.0*	442.3 ± 40.9*	56.4 ± 2.4*	334.7 ± 28.4*
	V3	54.6 ± 3.4	410.4 ± 40.7	56.4 ± 3.0	328.8 ± 23.1
non-symptomatic side	*V1*	48.5 ± 3.0	462.4 ± 40.9	44.2 ± 2.1	441.2 ± 26.1
	V2	48.2 ± 2.4	483.4 ± 41.2	45.8 ± 2.3	468.8 ± 36.8
	V3	52.3 ± 3.3	460.2 ± 39.5	45.9 ± 2.9	417.9 ± 23.6

Table 2: Pain-related evoked potentials (PREP) and nociceptive blink-reflex (nBR) latencies [ms] and amplitudes [µV] / area-under-the-curve (AUC) [µV x ms] ± standard error of the mean (SEM). * = statistically significant comparing symptomatic and non-symptomatic side; ++ = statistically significant comparing TN vs. TN with concomitant chronic facial pain. Level of significance was set to $p < 0.05$.

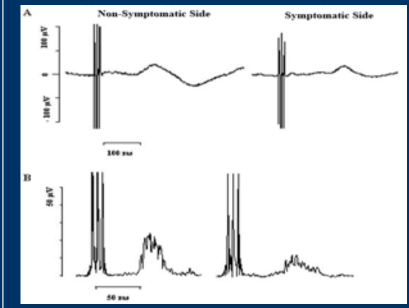

Figure 2: Typical recordings of pain-related evoked potentials (PREP) (A) and nociceptive blink reflex (nBR) in patients with TN (B). There is a pronounced decrease in amplitudes (µV) and delay in latencies (ms) on the symptomatic side (right) compared to the non-symptomatic side (left) in patients with TN, suggesting peripheral damage to the trigeminal nerve.

Pain-related evoked potentials

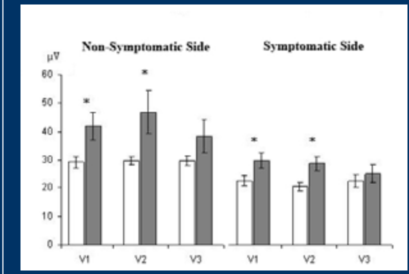

Figure 3: Pain-related evoked potential (PREP) amplitudes of the non-symptomatic side (A) and the symptomatic side (B) in TN (white) vs. TN with concomitant chronic facial pain (grey) including standard error of the mean (SEM). Statistical significance was set at $p<0.05$ (*). Central sensitization is reflected by increased PREP amplitudes on the affected side as well as non-affected side of TN patients with concomitant chronic facial pain compared to TN patients without chronic pain.

Nociceptive Blink Reflex

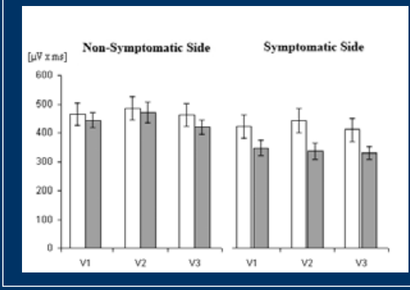

Figure 4: Nociceptive blink reflex area-under-the-curve (AUC) of the non-symptomatic side (A) and the symptomatic side (B) in TN (white) vs. TN with concomitant chronic facial pain (grey) including standard error of the mean (SEM). Statistical significance was set at $p<0.05$ (*). Lack of facilitation suggests a supraspinal mechanism in the central sensitisation of chronic facial pain.

Conclusion:

The data suggest an impairment of the trigeminal nociceptive system due to demyelination and/ or axonal dysfunction on the symptomatic side and locate this defect close to the root entry zone in the brainstem. Moreover, central facilitation of trigeminal nociceptive processing was observed in TN patients with concomitant chronic facial pain indicating over activation of central sensory transmission. This may represent a possible adaptive mechanism for the development of chronic pain in these patients.