Is the Nociceptive Blink Reflex Associated with Psychological Factors in Healthy Participants?

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Aims: To evaluate the possible association between the nociceptive blink reflex (nBR) and various pain-related psychological measures: the Anxiety Sensitivity Index-3 (ASI-3), the Fear of Pain Questionnaire III (FPQ-III), the Pain Vigilance and Awareness Questionnaire (PVAQ), the Somatosensory Amplification Scale (SSAS), the Pain Catastrophizing Scale (PCS), and the Situational Pain Catastrophizing Scale (S-PCS). Methods: The nBR was evaluated in 21 healthy participants. It was elicited by a nociceptive-specific electrode placed over the entry zone of the right supraorbital nerve, infraorbital nerve, and mental nerve, as well as the left infraorbital nerve. The outcomes were (1) nBR measurements: (a) individual electrical sensory threshold (I_{0}) and pain threshold (I_{p}) ; (b) root mean square (RMS), area under the curve (AUC), and onset latencies of R2 responses; (c) stimulus-evoked pain on a 0 to 10 numeric rating scale (NRS); and (2) the ASI-3, the FPQ-III, the PVAQ, the SSAS, the PCS, and the S-PCS. Pearson correlation coefficient was used to evaluate the association between the means of nBR measurements from all sites and the questionnaires The significance level was set up after a Bonferroni correction (adjusted $\alpha = .8\%$). **Results:** There was no correlation for any pair of variables at the adjusted significance level (P > .008). There was only a single significant correlation at the standard significance level (P < .05), where the pain intensity (NRS) at 50% of $I_{\rm p}$ presented a positive and small to moderate correlation with the PCS (r = 0.43, P = .04). **Conclusion:** It appears that the nBR and its associated psychophysical measures are not associated with psychological factors in healthy participants. J Oral Facial Pain Headache 2016;30:120–126. doi: 10.11607/ofph.1598

Keywords: nociceptive blink reflex, pain catastrophizing, pain-related anxiety, pain vigilance, somatosensory amplification

The development of the biopsychosocial medical model and the identification of motivational and cognitive aspects of pain can be regarded as important milestones in the understanding of pain mechanisms and pain experience in all its complexity.^{1,2} Many studies have highlighted the crucial role of psychological factors in pain perception.³⁻⁵ Psychological characteristics are of significant importance for the etiology,⁶ diagnosis,⁷ treatment,⁸ and prognosis⁹ of pain disorders and also for experimental pain outcomes.^{10,11} Hence, it is essential to consider psychological factors when dealing with pain in the clinical and research fields.

The nociceptive blink reflex (nBR) is designed to activate nociceptive afferents.¹² This electrophysiologic test has been used to elucidate aspects of pain mechanisms (eg, modulation of pain perception and alterations in pain processing) and is regarded as a valid method to assess trigeminal nociceptive function.^{13–15} The physiology and anatomy behind the reflex is as follows: the peripheral pathways consist of trigeminal cutaneous fibers (the afferent limb) and a group of motor fibers of the facial nerve (the efferent limb), and the central pathways consist of interneurons located in the main sensory nucleus and spinal trigeminal sensory nucleus as well as the facial nucleus. Considering this anatomophysiologic arrangement, the nBR may help in the diagnosis of lesions that could affect the afferent and/or efferent limb.¹⁶

Although there is no consensus about the complete validity of the nBR to activate only nociceptive fibers, mainly because of lack of neurophysiologic evidence supporting selective small-fiber activation, pain mechanisms of primary headaches and chronic orofacial pain have been addressed using the nBR paradigm.¹⁷⁻²⁰ Furthermore, important studies have been published concerning the technical aspects of the nBR, eg, stimulation parameters²¹ and the description and properties of the electromyographic (EMG) recordings.²² However, to the best of the authors' knowledge, there have been no studies about the possible association between the nBR and psychological factors.

Because of the painful nature of the nBR test, an association between the nBR and psychological variables might be expected, especially when considering that the nBR can be influenced by the startle response.²³ There is evidence that the startle response can be influenced by psychological factors, since high levels of anxiety sensitivity are associated with heightened startle reactivity.²⁴ Finally, there is also evidence of the influence of attention in the perceptual processing of BR responses.²⁵ Therefore, this presumed association between psychological variables and the nBR is a plausible hypothesis.

Based on the information in the literature, the aim of this study was to investigate the possible association between the nBR and various pain-related psychological measures: the Anxiety Sensitivity Index-3 (ASI-3),²⁶ the Fear of Pain Questionnaire III (FPQ-III),²⁷ the Pain Vigilance and Awareness Questionnaire (PVAQ),²⁸ the Somatosensory Amplification Scale (SSAS),²⁹ the Pain Catastrophizing Scale (PCS),³⁰ and the Situational Pain Catastrophizing Scale (S-PCS).³¹ Although the objective was to determine specific associations, the overall hypothesis was that the nBR is associated with psychological factors.

Materials and Methods

Participants

Healthy participants of both genders were recruited for this study by using the convenience sampling method. All participants were staff members at Aarhus University and from the local community. Inclusion criteria were age > 18 years and good health without any orofacial pain complaints or headache disorders. The exclusion criteria were serious dental or medical illness, self-reported psychiatric or personality disorders, and inability to communicate or read in English.

This study was performed in accordance with the Helsinki Declaration II and had the approval from the Central Denmark Region Ethics Committee. All participants gave their voluntary consent after a full explanation of the experiment procedures.

Variables

The outcomes of this study were the results of the nBR test and the following six scales and questionnaires: the ASI-3,²⁶ the FPQ-III,²⁷ the PVAQ,²⁸ the SSAS,²⁹ the PCS,³⁰ and the S-PCS.³¹

nBR Test

The nBR was performed in a guiet and acclimatized room (20°C). Two self-adhesive EMG electrodes (Neuroline 720, Ambu) were placed on both orbicularis oculi muscle regions to record the muscle activity and the ground electrode was attached to the wrist.^{17,18} The recorded signals were amplified and bandpass filtered between 20 and 1,000 Hz with a sampling rate of 2,000 Hz (Nicolet Viking, Natus Medical). A custom-built planar concentric electrode consisting of a central metal cathode and external anode ring with diameters of, respectively, 0.5 and 5 mm was used to elicit the reflex by stimulation of all three branches of the trigeminal nerve.¹² Each sweep comprised a train of three pulses with duration of 0.3 milliseconds each and an interpulse interval of 3 milliseconds. The pulse was applied to the skin directly above the entry zones of the right supraorbital nerve (V1R), infraorbital nerve (V2R), and mental nerve (V3R), and also the left infraorbital (V2L) nerve.¹⁸ The stimulation order among the branches was previously randomized by a computer-generated sequence.

The individual sensory threshold (I_o) and pain threshold (I_p) to the electrical stimulation were determined prior to the nBR recordings by using an up-down staircase method consisting of five series of ascending and descending stimuli (0.2 mA increment rate).²¹ The I_o was defined as the lowest stimulus intensity that evoked a sensation, whereas the I_p was the lowest intensity that evoked a sharp pinprick, pain-like sensation.^{17,18}

For each stimulation site (V1R, V2R, V3R, and V2L), the nBR recordings consisted of six stimulation blocks, which each consisted of six individual sweeps with an interstimulus interval of 15 to 17 seconds between each sweep to minimize habituation.¹⁶ The intensities of the blocks were 50%, 100%, 150%, 200%, 300%, and 400% of $I_{\rm p}$, and the order was also randomized by a computer-generated seguence. To avoid overlapping with the startle reaction and the related R3 responses, the first stimulus of each block was clearly announced to the participant. Furthermore, the participants were asked to score the stimulus-evoked pain intensity at the end of each block with the aid of a 0 to 10 numeric rating scale (NRS), with 0 indicating "no pain at all" and 10 indicating "worst pain imaginable."17,18

The analyzed outcomes for the nBR evoked from each site were: (1) the I_0 (mA); (2) the I_p (mA); the EMG recordings of the R2 responses at each stimulus intensity, quantified as (3) the root mean square (RMS) (μ V) and (4) area under the curve (AUC) (μ V × millisecond) of the rectified and averaged sweeps in the time window from 27 to 87 milliseconds;²² (5) the onset latencies (in milliseconds) of the R2 responses at 200% and 300% of I_p measured for the averaged sweeps; and (6) the stimulus-evoked pain intensity (NRS) at each stimulus intensity.

ASI-3

The ASI-3 is a self-report questionnaire consisting of 18 items that is used to measure anxiety sensitivity (ie, fear of anxiety-related sensations considering that they have adverse consequences).²⁶ The items are rated on a 5-point scale ranging from 0 ("agree very little") to 4 ("agree very much") and the final score is the sum of all individual items.²⁶ Its psychometric properties have shown acceptable values for factorial validity (comparative fit index = 0.97) and reliability (Cronbach alpha > 0.75).²⁶

FPQ-III

The FPQ-III is a self-report questionnaire consisting of 30 items that is used to measure fear related to specific stimulus situations (eg, fear related to severe pain such as breaking your leg).²⁷ The items are rated on a 5-point scale ranging from 1 ("not at all") to 5 ("extreme") and the final score is the sum of all individual items.²⁷ Its psychometric properties have shown acceptable values for factorial validity (robust-comparative fit index = 0.91) and reliability (Cronbach alpha = 0.93).³²

PVAQ

The PVAQ is a self-report questionnaire consisting of 16 items that is used to measure attention to pain.²⁸ The items are rated on a 6-point scale ranging from 0 ("never") to 5 ("always") and the final score is the sum of all individual items.²⁸ Its psychometric properties have shown acceptable values for retention (corrected item–total score correlations ranging from 0.36 to 0.76) and reliability (Cronbach alpha = 0.92).³³

SSAS

The SSAS is a self-report questionnaire consisting of 10 items that is used to measure sensitivity to unpleasant bodily experiences.²⁹ The items are rated on a 5-point scale ranging from 1 ("not at all true") to 5 ("extremely true") and the final score is the sum of all individual items.²⁹ Its psychometric properties have shown acceptable values for concurrent validity (linear regression coefficient ranging from 0.20 to 0.63) and reliability (Cronbach alpha = 0.71).²⁹

PCS

The PCS is a self-report questionnaire consisting of 13 items that is used to measure the impact of catastrophic thoughts on past painful experiences.³⁰ The items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("all the time") and the final score is the sum of all individual items.³⁰ Its psychometric properties have shown acceptable values for factorial validity (robust-comparative fit index = 0.98) and reliability (Cronbach alpha = 0.95).³⁴

S-PCS

The S-PCS is a self-report questionnaire consisting of 6 items adapted from the PCS questionnaire that is used to measure thoughts or feelings experienced during laboratory procedures (eg, the nBR test).³¹ The items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("all the time") and the final score is the sum of all individual items.³¹ Its psychometric properties have shown acceptable values for reliability (Cronbach alpha = 0.87).³¹

Design

One examiner evaluated the nBR in a single session lasting approximately 1.5 hours, and all questionnaires were applied immediately after the nBR measurements were taken.

Statistical Analyses

The nBR measurements (I_0 , $I_{\rm pr}$ RMS, AUC, latency, and NRS) taken from all four sites were expressed as means and standard deviations (SDs). The questionnaire outcomes were expressed as mean (SD), range (maximum and minimum), and 95% confidence interval (CI). All the quantitative variables were assessed for normal distribution by using the Kolmogorov-Smirnov test, and a log 10 transformation was performed when the test results were significant considering an alpha level of 5% (P < .05).

The Pearson product-moment correlation coefficient was used to evaluate the association between the nBR, measured as the means of all nBR measurements $(I_0, I_{P}, RMS, AUC, latency, and NRS)$ taken from all four sites (V1R, V2R, V3R, V2L) as an overall measure of the nBR elicited by electrical stimulation of the trigeminal nerve, regardless of the branch, and all the questionnaires (ASI-3, FPQ-III, PVAQ, SSAS, PCS, and S-PCS). The strength of correlation was evaluated based on the r coefficient, and the following score system was used to interpret the results: small (r = 0.3), moderate (r = 0.5), or strong (r = 0.7) correlation.³⁵ The sample size in this study was insufficient for use of regression models. Accordingly, in order to adjust for multiple comparisons, a prior planned Bonferroni correction lowered the significance level to 0.8% (P = .008) as the cutoff point to establish the statis-

Table 1 Psychological Characteristics of the Sample								
Questionnaire	Mean ± SD	95% CI of Mean Range		Population Mean \pm SD ^a				
ASI-3	12.0 ± 9.1	7.9–16.2	0-41	12.8 ± 10.6				
FPQ-III	81.9 ± 23.7	71.0-92.7	37–133	78.2 ± 18.1				
PVAQ	38.2 ± 14.7	31.5-45.0	9-67	33.54 ± 13.18				
SSAS	27.9 ± 6.1	25.0-30.7	16-37	26.1 ± 7.0				
PCS	16.7 ± 10.7	11.8–21.6	0-35	13.87 ± 10.11				
S-PCS	3.0 ± 2.6	1.8-4.2	0-10	$4.93 \pm 3.89^{\text{b}}$				

^aThese values are described in the following references: Taylor et al,²⁶ Osman et al,³² McWilliams and Asmundson,³³ Sullivan et al,³⁸ and Campbell et al.³⁹ ^bValues based on suprathreshold heat stimuli and cold pressor tests (See Campbell et al³⁹).

ASI-3 = Anxiety Sensitivity Index-3; FPQ-III = Fear of Pain Questionnaire III; PVAQ = Pain Vigilance and Awareness Questionnaire;

SSAS = Somatosensory Amplification Scale; PCS = Pain Catastrophizing Scale; S-PCS = Situational Pain Catastrophizing Scale.

tical significance considering the correlation between the means of nBR measurements and the questionnaires. Each nBR measurement was considered as a family of comparisons regardless of the stimulation intensity, and all the questionnaires were regarded as another family. Therefore, the familywise error rate was established considering six multiple comparisons and, according to the Bonferroni formula (.05/k, where k = number of comparisons), an alpha level of P = .008 was established. All tests were carried out using the software STATISTICA, v 12 (StatSoft Inc).

Results

This study included 21 healthy participants with a mean age \pm SD of 29.3 \pm 3.7 years; 62% (n = 13) were female and 38% (n = 8) were male. The mean (SD) of I_0 and I_p were 0.5 ± 0.1 and 0.7 ± 0.2 mA. The pain intensity (NRS) ranged from 0.0 \pm 0.1 at 50% of $I_{\rm p}$ to 5.2 ± 1.8 at 400% of $I_{\rm p}$. Likewise, the RMS and AUC varied from 4.0 \pm 2.4 μ V and 202.2 \pm 113 μ V.ms at 50% of $I_{\scriptscriptstyle \rm D}$ to 12.3 \pm 7.9 μV and 542.0 \pm 347.9 μ V.ms at 400% of $I_{\rm p}$. The latency was 41.8 ± 1.5 ms at 200% and 41.1 (1.1) at 300% of $I_{\rm P}$. The description of the questionnaire scores is presented in Table 1. None of the participants rated the score as maximum in any particular questionnaire, and the means of all the questionnaires, except the FPQ-III and the SSAS, were below 50% of the maximum score. Of the sample, 4.7% rated the minimum score for the ASI-3, 9.5% rated the minimum score for the PCS, and 14.2% rated the minimum score for the S-PCS.

There was no significant correlation for any pair of variables after the Bonferroni correction (P > .008). However, there was a significant correlation at the standard significance level (P < .05), where the pain intensity (measured on an NRS) at 50% of I_p presented a positive and small to moderate correlation with the PCS (r = 0.43, P = .04) (Table 2).

Discussion

The results of this study did not support the hypothesis that an association exists between psychological factors and the nBR. After the correction for multiple comparisons, no significant correlations were found between the psychological factors and the nBR measurements.

Considering that healthy participants comprised the sample, one could expect the psychological assessment outcomes to be within a range of "normal" values. In fact, the mean results in this sample for the ASI-3 indicated normative forms of anxiety sensitivity (score < 13).²⁴ Furthermore, the values of the FPQ-III and the PVAQ were also similar to clinical nonpain samples.32,33 SAS scores over 30 could reflect high somatization, and normal values range from 24 to 29,36,37 which agreed with the study mean score of 27.9 (Table 1). The PCS scores were also similar to nonpatient populations.³⁴ However, the mean values of the S-PCS scores were lower in comparison with the S-PCS scores of healthy participants under laboratory-induced pain tests (eg, heat pain tolerance).³¹ This could be explained by differences in the applied procedures. Since the S-PCS is closely related to the painful experience, lower values could be expected for less painful tests. Finally, it could be speculated that previous pain experiences might have affected the participants' responses, even though none of them reported to have painful conditions and all questionnaires have previously been successfully applied in the general population.^{26,29,31-34}

The lack of any significant associations between the nBR and the associated psychophysical measurements after the adjustment for multiple comparisons was an interesting finding. Considering the nociceptive nature of the test and the battery of stimulation intensities, significant associations could be expected, at least between the reported pain intensities from the nBR and some of the questionnaires. For instance, there is evidence that the PCS

Table 2 Pearson Product Moment Correlations for the Six Questionnaires and the Nociceptive Blink Reflex (nBR) Measurements

	Correlations (r / <i>P</i> value)						
nBR measurements	ASI-3	FPQ-III	PVAQ	SAS	PCS	S-PCS	
Thresholds (mA)							
I _o	0.33 / .13	0.18 / .42	0.16 / .48	0.41 / .06	0.20 / .38	0.19 / .39	
I_{P}	0.25 / .26	0.29 / .18	0.05 / .82	0.43/.05	0.16 / .47	0.24 / .29	
Pain Intensity (NRS) – % of I_P							
50	0.17 / .44	-0.20 / .37	0.10 / .64	0.16 / .46	0.43 / .04	0.27 / .22	
100	-0.00 / .99	0.10 / .65	0.20/.36	-0.06 / .77	0.20 / .37	0.29 / .19	
150	0.05 / .80	0.25 / .27	0.31 / .16	-0.01 / .95	0.24 / .28	0.31 / .17	
200	-0.05 / .82	0.28 / .20	0.16 / .46	-0.15 / .50	0.03 / .87	0.35 / .11	
300	-0.07 / .73	0.29 / .19	0.15 / .49	-0.13 / .55	0.04 / .83	0.35 / .10	
400	0.04 / .86	0.17 / .51	-0.09 / .73	-0.17 / .52	-0.06 / .80	0.36 / .15	
RMS (μ V) – % of I_P							
50	-0.18 / .42	0.34 / .13	0.03 / .88	0.04/.84	0.18 / .41	0.19 / .40	
100	0.21 / .33	0.26 / .23	-0.03 / .88	0.27 / .22	0.08 / .72	0.29 / .19	
150	0.28 / .21	0.27 / .21	-0.05 / .82	0.34 / .12	-0.04 / .85	0.30 / .08	
200	0.42 / .05	0.29 / .19	0.05 / .82	0.39/.07	0.04/.84	0.34 / .12	
300	0.41 / .06	0.17 / .43	-0.11 / .62	0.40 / .07	-0.08 / .72	0.41 / .06	
400	0.43/.09	0.26 / .38	-0.03 / .88	0.25 / .33	0.20 / .43	0.44 / .08	
AUC (μ V x ms) – % of I_P							
50	-0.18 / .41	0.35 / .11	0.05 / .82	0.03 / .87	0.20 / .36	0.19 / .39	
100	0.20 / .37	0.28 / .20	-0.00 / .98	0.27 / .22	0.11 / .62	0.30 / .17	
150	0.27 / .23	0.28 / .21	-0.03 / .89	0.32 / .15	-0.02 / .90	0.38 / .08	
200	0.42 / .05	0.31 / .16	0.09 / .67	0.41 / .06	0.07 / .75	0.34 / .12	
300	0.39 / .07	0.18 / .41	-0.09 / .66	0.41 / .06	-0.04 / .83	0.41 / .06	
400	0.41 / .12	0.25 / .34	-0.04 / .87	0.23 / .38	0.20/.44	0.43 / .08	
Latency (ms) – % of I_P							
200	-0.30 / .22	0.18 / .47	-0.18 / .46	-0.32 / .19	-0.32 / .18	-0.18 / .47	
300	-0.41 / .08	-0.03 / .88	-0.01 / .94	-0.24 / .33	0.07 / .75	-0.16 / .51	

 I_0 = individual sensory threshold; I_p = individual pain threshold; NRS = numeric rating scale; RMS = root mean square; AUC = area under the curve; ASI-3 = Anxiety Sensitivity Index-3; FPQ-III = Fear of Pain Questionnaire III; PVAQ = Pain Vigilance and Awareness Questionnaire;

SSAS = Somatosensory Amplification Scale; PCS = Pain Catastrophizing Scale; S-PCS = Situational Pain Catastrophizing Scale.

is significantly correlated with cold pressor-induced pain intensity³⁸ and the S-PCS is strongly associated with experimental pain outcomes and predicted pain thresholds in healthy participants.³⁹ In addition, healthy participants with high levels of anxiety sensitivity show a short detection latency for electrical stimuli.40 The normal-level profile for anxiety sensitivity presented by the current study's sample could account for the lack of an association between the I_0 and I_P and the ASI-3. The relationship between the perception of experimental pain and the FPQ-III, which also measures pain-related anxiety constructs, is influenced by gender differences, being associated with low pain tolerance levels to heat pain in healthy women.⁴¹ So, considering that pain-related anxiety could be affected by gender differences,41 the gender distribution pattern of the current study could partially account for the lack of an association. Furthermore, pain vigilance was related to sensitivity to heat pain in experimental models.⁴² It is plausible that the association between psychological factors measured by these questionnaires and experimental pain outcomes is test-dependent and could not be regarded as a general association with experimental pain experiences. Finally, there is no evidence of a relationship between the SAS and experimental pain conditions, although patients with a history of myofascial pain report high levels of somatosensory amplification.⁴³

There were no significant correlations after correcting for multiple comparisons, and even when employing the standard significance level of 5% there was only one significant association, which was

potentially caused by chance given the high number of computed correlations. Therefore, the nBR seems not to be strongly related with psychological factors and it may be less prone to bias regarding psychological confounders. These confounders are important to control for when considering other tests used in pain research, such as quantitative sensory testing.⁴⁴

This study had several limitations that must be highlighted. First, the sample size was considered insufficient for use of regression models, which is the best approach to analyzing multiple correlations related to a single dependent variable. Second, the high number of questionnaires could be considered unnecessary and confusing given the sample size. Nevertheless, the objective was to perform a potentially hypothesis-generating screening and the inclusion of the specified questionnaires was based on their potential to be associated with pain tests, as already described. Furthermore, the possible influence of other psychological aspects not properly assessed with the applied questionnaires, such as attentional bias, trait anxiety, and symptoms of depression, could not be ruled out and warrant future research. One technical aspect that deserves to be mentioned relates to the placement of the stimulation electrode. Even though the electrode attachment was defined according to previous studies using the same technique,^{12,17,18} other areas with a high concentration of nerve fibers (eg, lips) could provide a more effective pain stimulus. Future studies are warranted to address this topic. Finally, the results should be generalized with caution, considering that in a patient population with chronic pain disorders, the relationship between psychological factors and the nBR may be different.

Conclusions

The results indicate that the nBR and its associated psychophysical measures may not be significantly associated with psychological factors related to pain-related anxiety, pain vigilance, somatosensory amplification, or trait and situational pain catastrophizing. However, these conclusions remain to be confirmed and further investigations are required in pain populations with more pain-related psychological distress.

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