Tese de Mestrado Integrado em Medicina

Influence of Diffuse Noxious Inhibitory Control, Temporal Summation and Expectation on pain perception in healthy volunteers

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Artigo científico para obtenção do grau de Mestre em Medicina pela Universidade do Porto.

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Content

Artigo

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Abstract

Introduction: Understanding the subjective perception of pain is important to learn how pain is endogenously modulated (1).

Objectives: To study the influence and reliability of Temporal Summation (TS), Diffuse Noxious Inhibitory Control (DNIC) and Expectation on pain perception.

Methods: 28 volunteers received painful transcutaneous electrical stimuli of the suralis nerve. As a conditioning stimulus, the volunteers were asked to immerse their contralateral hand in water at 33ºC or 46,5ºC. 35 electrical stimuli were applied, followed by 20 stimuli simultaneously with the conditioning stimuli and afterwards 20 electrical stimuli without the conditioning stimuli. After each stimulus, volunteers rated the pain 0-100. 30 minutes later, these measurements were repeated. Volunteers were asked whether they expected that immersion in hot water would attenuate pain. After 4 weeks the trial was repeated to test the reliability of the results.

Results: Pain after the first stimulus was 50,02±14,9 and after the last of the 35 initial stimuli applied over 160sec pain was 51,2±13,7: Wilcoxon test did not show a difference in pain rating (Test: P=0.234; Retest: P=0.521), and thus no TS. DNIC was assessed as the difference between average pain rating during stimulation with and without the conditioning stimulus. Pain rating after immersion in hot water decreased in 25 out of 28 volunteers (average: 8,65±10,4; P<0.001 for n=28); immersion in water at 33ºC did not change pain rating significantly (0,57±7,64). Volunteers were grouped according to their expectation about whether the conditioning stimulus would attenuate pain. Chi square test showed no significant Expectation effect (Test: P=0.45; Retest: P=0.81).

Conclusions: There was a significant and reliable DNIC effect when a painful conditioning painful stimulus was added to the initial painful stimuli. Temporal Summation was not observed, probably due to the short duration of exposure to painful stimulation. No effect of expectation was found, perhaps because volunteers were not induced to expect relief.

Key Words: Pain, DNIC, Temporal Summation, Expectation, Reliability

Introduction

According to the definition of the International Association for the study of Pain, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Acute pain is an important mechanism of alarm and allows the subject to defend himself from a noxious stimulus. When pain becomes chronic, it no longer serves as a defense mechanism, lowering quality of life and contributing to high morbidity of the affected individuals (2). Therefore it is of the utmost importance to achieve a better understanding of the subjective perception of pain and how pain is endogenously modulated.

The comprehension of the diffuse noxious inhibitory control (DNIC) is an aim of the present study. DNIC is the phenomenon in which pain from one part of the body inhibits pain elsewhere (1). Impaired DNIC has been found in healthy women (3), fibromyalgia patients (4) and chronic tension-type headache patient (5). The intensity of TS and DNIC in healthy volunteers was evaluated in this study.

An important phenomenon regarding pain mechanisms is the effect of Temporal Summation (TS) defined as the increase in pain perception after repetitive stimulation at constant stimuli (1). Increased TS has been described in healthy women (6), fibromyalgia patients (7) and chronic tension-type headache patients (8).

Another aspect focused in this study is the effect of expectation on perceived pain. Expectation mediated analgesia has been described in previous studies (9), (10) and understanding this phenomenon may lead to a better management of chronic pain.

Finally the reliability of the above mentioned effects (TS, DNIC and expectation) is object of investigation. A previous study (1) showed acceptable test-retest reliability of TS and DNIC, nevertheless with high interindividual variation.

Objectives

The aim of the present work is to study the previously mentioned phenomena TS and DNIC on healthy volunteers and how the expectation affects the perception of pain.

The following hypotheses were tested:

- Pain perception increases with repeated stimuli of the same intensity.
- Pain perception of noxious stimuli in one part of the body decreases when other painful stimuli are elicited elsewhere in the body simultaneously. Perceived pain

does not decrease when other neutral stimuli are applied in another part of body.

- Expectation of an analgesic effect of conditioning stimuli lowers the pain perception of other painful stimuli elsewhere in the body; the opposite is also true.
- The effects of TS, DNIC and expectation remain constant in time and are thus reliable.

Methods

Subjects

Subjects considered for the study were healthy volunteers above the age of 18. The experimental sessions took place in a room at the Charité Universitätsmedizin – Campus Mitte between 08.00 and 12.00, from Monday to Sunday. 28 healthy volunteers participated in the study, 12 of which were females and 16 were males between the ages of 20 and 33.

Absolute exclusion criteria were chronic pain diseases (including tension headache and migraine), neurological conditions and intake of analgesic drugs, alcoholic beverages or recreational drugs less than 12 hours before the tests. The following quality criteria were regarded: no chewing gum before the tests, no moderate physical effort 2 hours before the trial, no caffeinated beverages 6 hours before the measurements, no alcohol consumption and no extreme physical effort 24 hours before the tests and no intake of analgesic drugs 48 hours before the experiments. If the volunteers did not match one or more of the quality criteria, the tests would be postponed.

The healthy volunteers were taught about the subjective numeric scale of pain (0-100), 0 meaning no pain and 100 corresponding to severe unbearable pain. Finally, each volunteer was asked about their expected change in pain perception when confronted with a simultaneous neutral stimulus (contralateral hand in water of 33ºC) or a simultaneous painful stimulus (contralateral hand in water of 46,5ºC). The possible answers were: no change, increase or decrease in pain perception.

Volunteers were allowed to quit the study anytime they wanted without further explanation or if they could not bear the stimuli. No side effects were expected; the electrical and thermal stimuli were forcefully painful for the purposes of the study, but were designed not to cause permanent damage of the affected extremities.

Charité Universitätsmedizin Ethic commission approved the study. Written consent by the volunteers was mandatory after being informed of the objectives and procedures of the study. A compensation of 50€ was awarded after the finishing of the tests. Oral propaganda was used to recruit volunteers. Confidentiality of the data and personal information of the volunteers was guaranteed.

Trial

In the present study, the painful stimuli were achieved through transcutaneous electrical stimulation of the sural nerve below the lateral malleolus in the left lower extremity. Two adhesive electrodes at a distance of 2 cm were used. The stimuli were applied with an interval of 8 seconds (7,5 stimuli/minute) and their intensity was set in a pre-test to obtain a pain intensity of 50 in a subjective numeric rating scale of 0-100.

As a conditioning stimulus, the volunteers were asked to immerse their contralateral (right) hand in water of 33ºC or of 46,5ºC.

Volunteers‘ perceived pain was measured twice in each session, some starting with lukewarm water as conditioning stimulus followed by hot water as conditioning stimulus in the second measurement. Other volunteers would start with hot water followed by lukewarm water as conditioning stimulus. Subjects were randomized before the tests, some being allocated to start with lukewarm water (33ºC) and some to start with hot water (46,5ºC).

35 electrical stimuli were applied, followed by 20 electrical stimuli simultaneously with the conditioning stimuli (lukewarm water or hot water). Finally 20 electrical stimuli were applied without the conditioning stimulus. After an interval of 30 minutes, these measurements were repeated. As stated earlier, the intensity of the electrical stimuli was set in a pre-test to obtain a pain intensity of 50 in a subjective numeric rating scale of 0-100.

After 4 weeks the trial was repeated to test the reliability of its results (Retest). Volunteers were allocated to start with the same conditioning stimulus as in the first test session.

Data Analysis

Temporal Summation was assessed as the difference between the pain rated in the last and first stimulus of the stimuli series before the entry of the conditioning stimulus. Of the group of 35 electrical stimuli applied before the entry of the conditioning stimulus, only the last 20 were used for this analysis, since the first 15 stimuli were used when needed to optimize the intensity of the electrical stimuli to achieve pain intensity values near 50 (0-100). These 20 stimuli lasted 160 seconds. For each

volunteer it was possible to perform 4 measurements of TS (2 in the Test and 2 in the Retest).

Difference between average pain rating during stimulation with and without the hot water conditioning stimulus was used to asses DNIC. Another relevant analysis performed was the difference between average pain rating during stimulation with water at 46,5ºC and water at 33ºC.

Finally volunteers were grouped according to their expectation about whether the conditioning stimulus would attenuate pain.

Statistical Analysis

Statistics used the non-parametric Wilcoxon test for paired data (TS, DNIC) and Chi square Test for grouped data (Expectation).

A linear regression was employed to compare perceived pain intensity of the hot water and intensity of the electrical stimuli needed to obtain a pain perception of 50 in a numeric rating scale of 0-100. For n=28, R was considered significant above 0,3809 for an uncertainty coefficient of 5%.

Microsoft office Excel 2007 and SPSS v. 18 were the software used to perform the above mentioned analysis.

Results

A total of 28 volunteers participated in the study, 12 were females and 16 were males between the ages of 20 and 33. All signed an informed consent.

The intensity of the electrical stimulus used to produce pain in the ankle rated as 50 in the numerical rating scale was 14,2±5,3 mA.

Pain caused later on the experiments by the immersion of one hand in hot water was 49,2±23,1 NRS units.

There was a negative correlation between the intensity of the stimulus applied to the ankle and pain caused by immersion in hot water (R^2=0,2397; P<0,002);(Fig. 1)

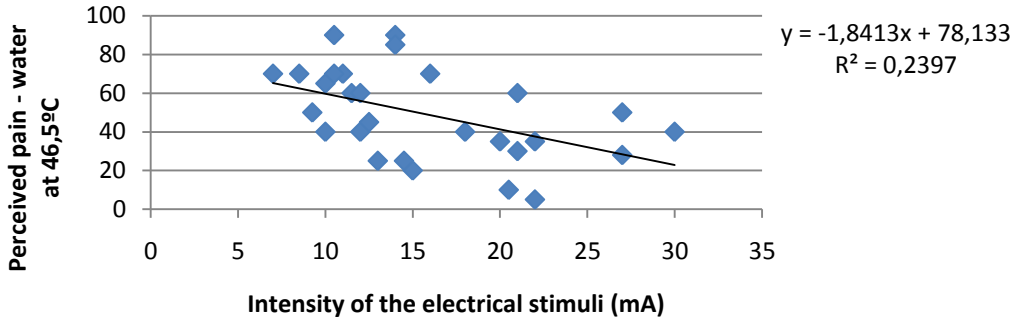

Fig 1: Correlation between the intensity of the electrical stimuli set in the pre-test and perceived pain caused by water at 46,5ºC in the Test. Linear regression of the data showed a significant decrease of the perceived pain intensity of the hot water with increasing intensities of the electrical stimuli needed to achieve a pain intensity of 50 in the NRS of 0-100 (R=0,5828).

In the Retest (intensitity of electrical stimuli: 17,1±6,5mA; perceived pain caused by hot water:55,9±19,2) no significant correlation between the intensity of the stimulus applied to the ankle and pain caused by immersion in hot water was observed and thus no reliability of this effect was evidenced (R^2=0,0122; P>0,5);(Fig. 2).

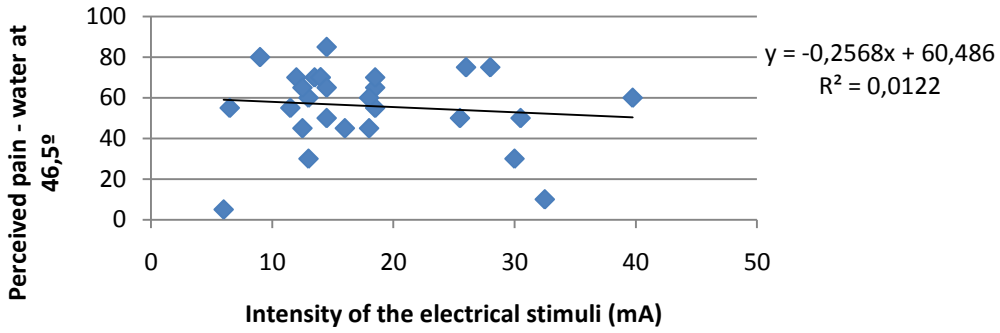

Fig 2: Correlation between the intensity of the electrical stimuli set in the pre-test and perceived pain caused by water at 46,5ºC in the Retest. Linear regression of the data showed no significant decrease of the perceived pain intensity of the hot water with increasing intensities of the electrical stimuli needed to achieve a pain intensity of 50 in the NRS of 0-100 (R=0,1105).

Diffuse Noxious Inhibitory Control

Following hand immersion in hot water 25 out of 28 volunteers showed a decrease in pain perception (average pain decrease from 50,8±14,1 to 42,2±13,8). Average pain decrease for all the volunteers was 8.65±10.40 ($p<0.001$ for $n=28$). In the Retest a reduction was observed in 22 volunteers; average: 7.67±9.23 ($P<0.001$ for $n=28$), (average pain decrease from 50,2±14,4 to 42,5±15,9). Fig. 3 and Fig. 4 illustrate this change in pain perception in the Test and Retest respectively.

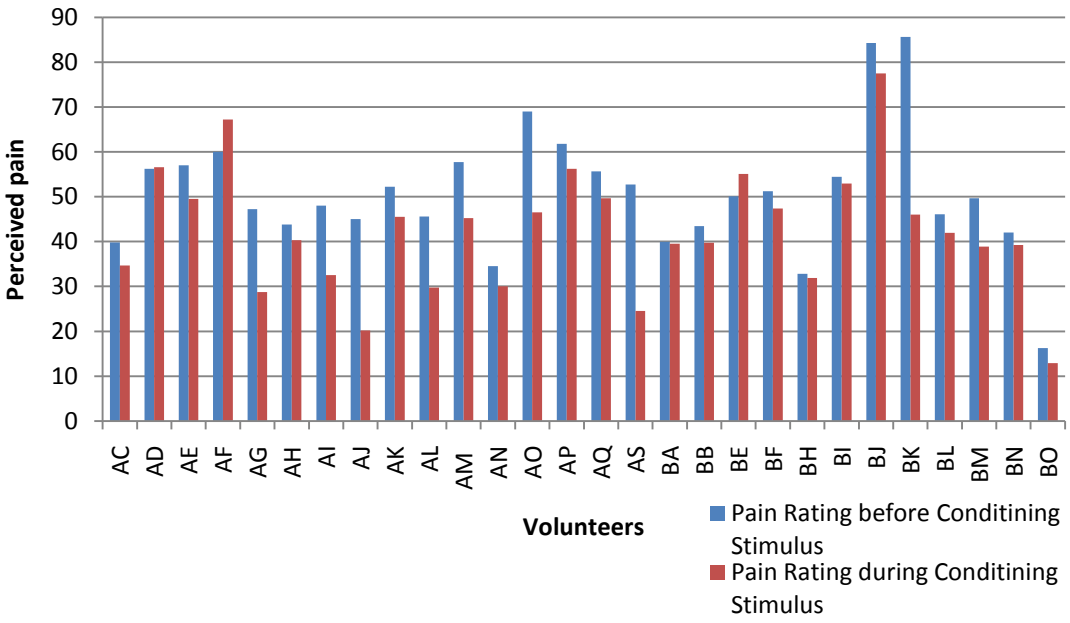

Fig 3: Volunteers' perceived pain before and during the hot water conditioning stimulus in the Test. Following hand immersion in hot water 25 out of 28 volunteers showed a decrease in pain perception. There was overall a significant decrease in perception ($P<0.001$ for $n=28$).

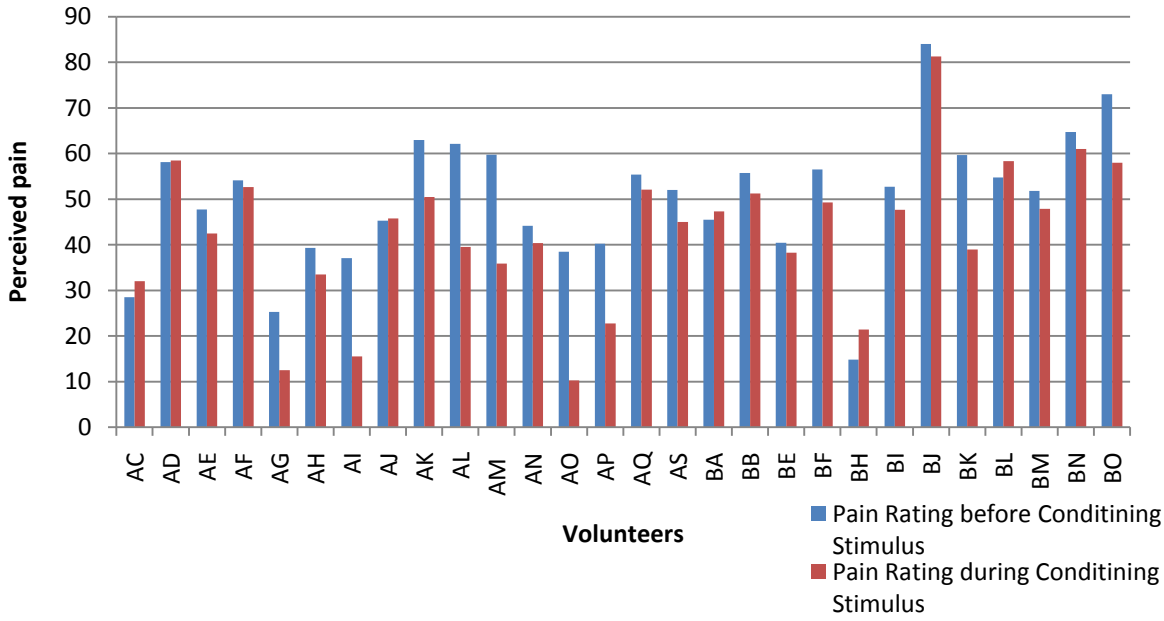

Fig 4: Volunteers' perceived pain before and during the hot water conditioning stimulus in the Retest. Following hand immersion in hot water 22 out of 28 volunteers showed a decrease in pain perception; Wilcoxon test showed a significant decrease in pain perception (P<0.001 for n=28).

When volunteers immersed their hand in lukewarm water, pain rating decreased in only 9 volunteers. When all volunteers were considered, there was a non significant increase in pain rating (average of 0,57±7,64; P=0,173 for n=28), as can be seen in Fig. 5. In the Retest (Fig. 6) similar results were seen. There was a reduction in pain perception in 18 subjects with an average of 3,3 ± 6,51 (P=0,051 for n=28).

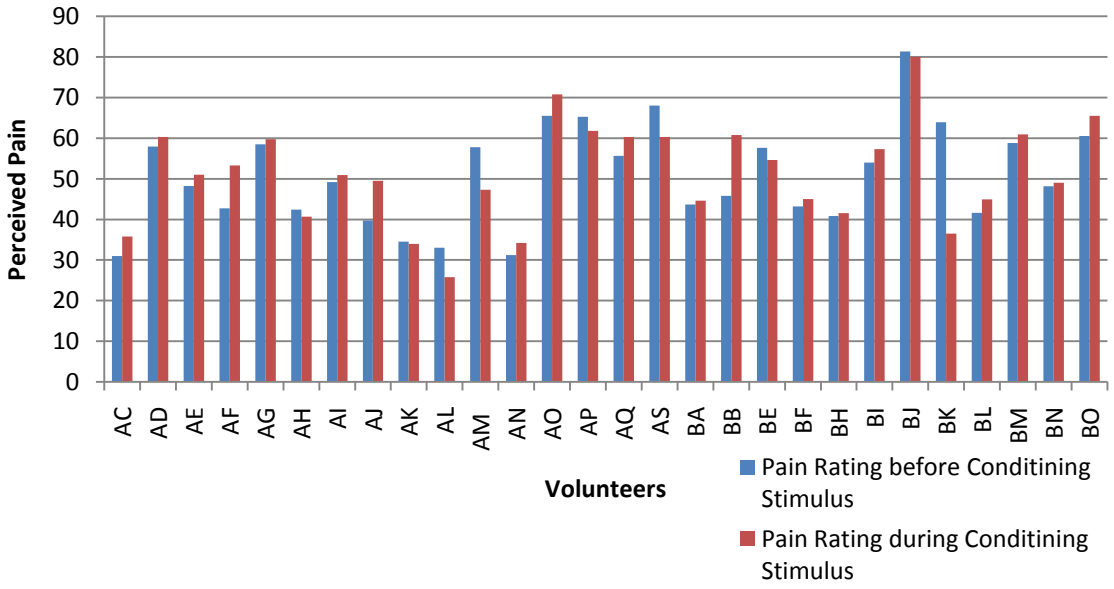

Fig 5: Volunteers' perceived pain before and during the lukewarm water conditioning stimulus in the Test, showing a non-significant reduction in pain perception. (P=0,173 for n=28).

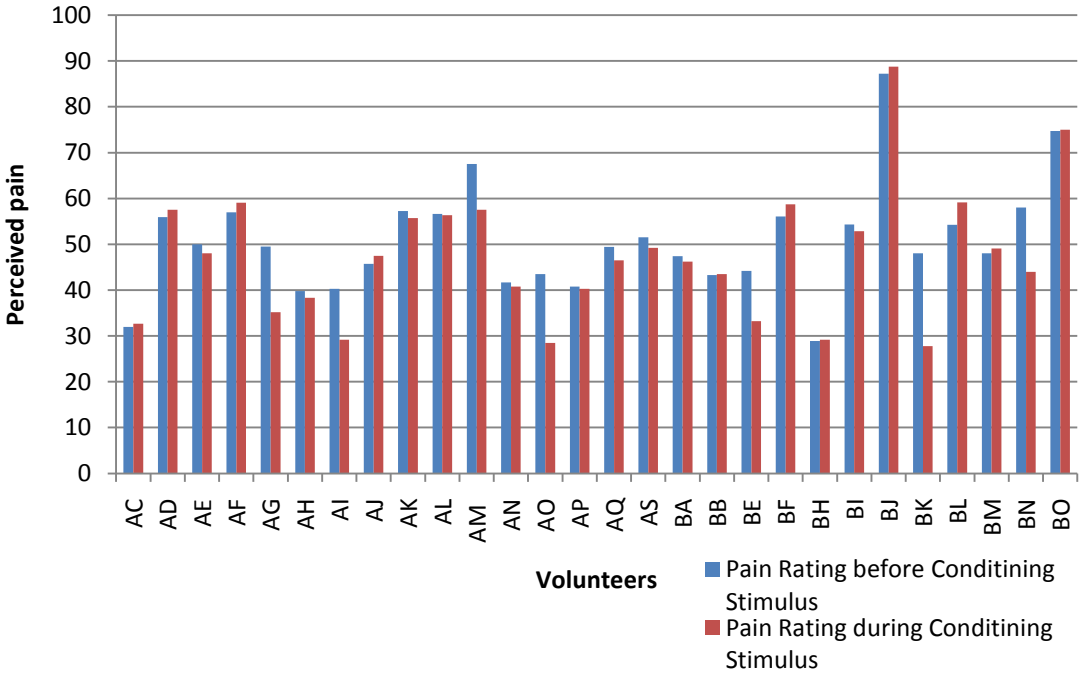

Fig 6: Volunteers' perceived pain before and during the lukewarm water conditioning stimulus in the Retest, showing a non-significant reduction in pain perception. (P=0,051 for n=28).

In the Test a significant decrease (Average: -9,22±8,94; p<0.001) of pain rating was also observed during the immersion of the hand in water at 46.5ºC (8.65±10.40) when compared with the immersion in water at 33ºC (0.57±7.64), which can be seen in Fig. 7. Fig. 8 shows the same phenomenon 4 weeks later in the Retest. A significant decrease (Average: -4,33±7,68; P=0,04) of -7,67±9,29 during the immersion of the hand in hot water was seen in comparison with the immersion in lukewarm water (-3,33±6,51).

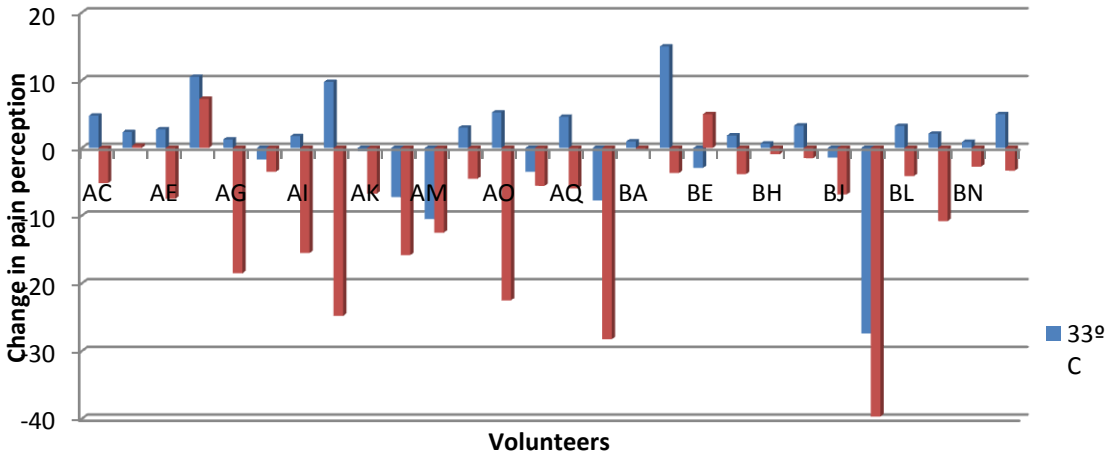

Fig 7. Pain perception in the Test decreased significantly following immersion of the hand in hot water, but not following immersion in lukewarm water (P<0.001)

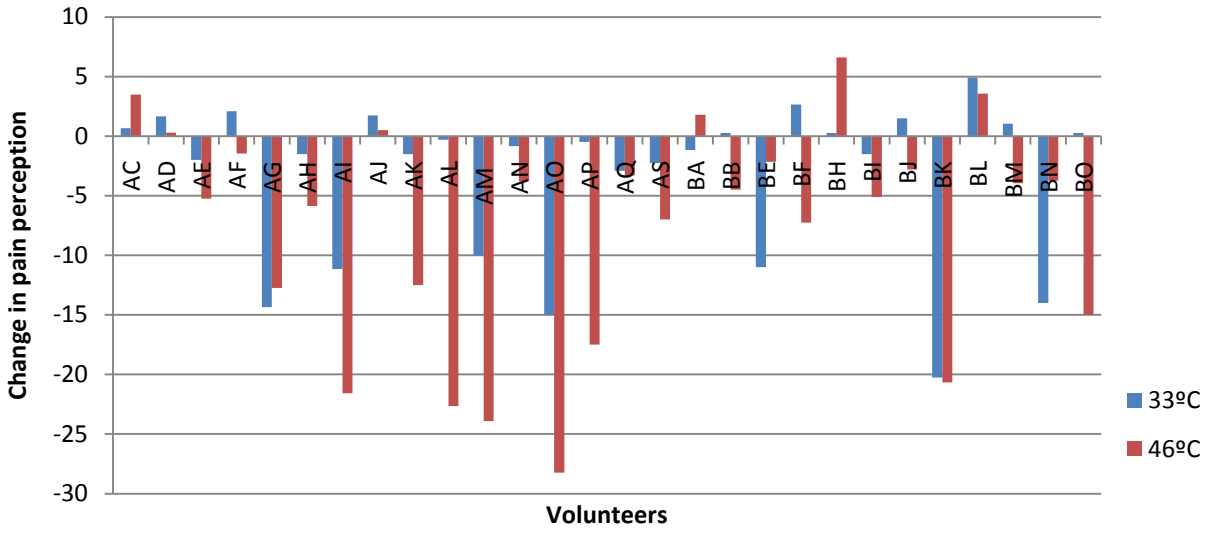

Fig 8: Pain perception in the Retest decreased significantly following immersion of the hand in hot water, but not following immersion in lukewarm water (P=0,04).

Average pain during immersion in hot water was 42,2±13,9; once the hand was removed from the hot water pain was 48,2±15,3. As noticed in Fig. 9 an increase in pain was seen in 24 of the volunteers; average increase for all the volunteers was 6,08±7,96 ($P<0.001$ for $n=28$). When pain during and after immersion in hot water was compared for the total 28 volunteers a significant increase was seen ($P<0.001$ for $n=28$).

This effect has also been detected in the Retest (Fig. 10) and is therefore reliable. Average pain during immersion of the hand in hot water was 42,5±15,9; after the removal of the conditioning stimulus pain increased to the average of 47,5±14,3. An increase in pain perception was observed in 24 subjects (average: 5,0±5,9; $P<0.001$ for $n=28$).

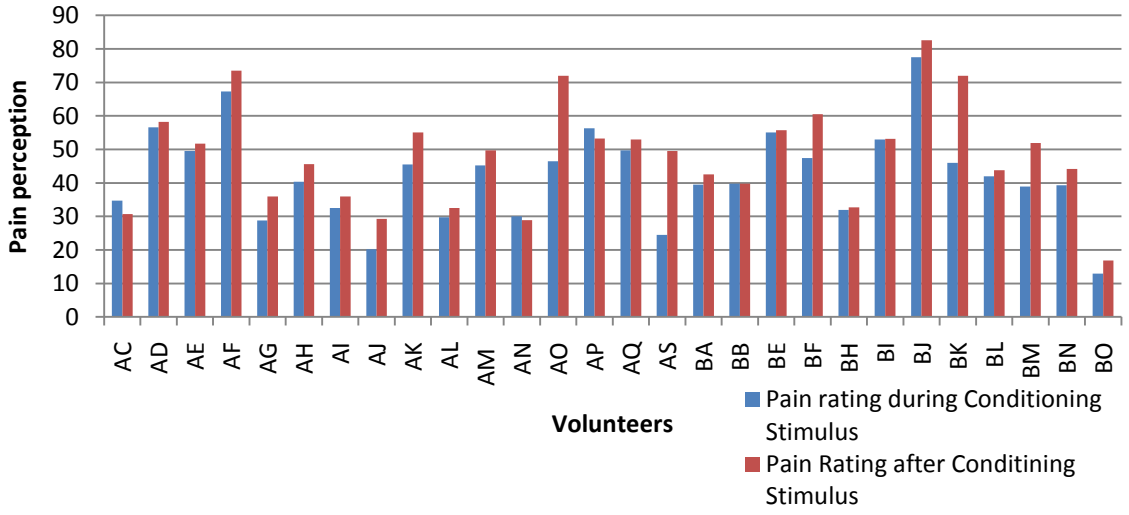

Fig 9: Volunteers' perceived pain during and after the hot water conditioning stimulus in the Test. Following removal of the hand from the hot water 24 out of 28 volunteers showed an increase pain perception. There was overall a significant increase in pain perception (P<0.001 for n=28).

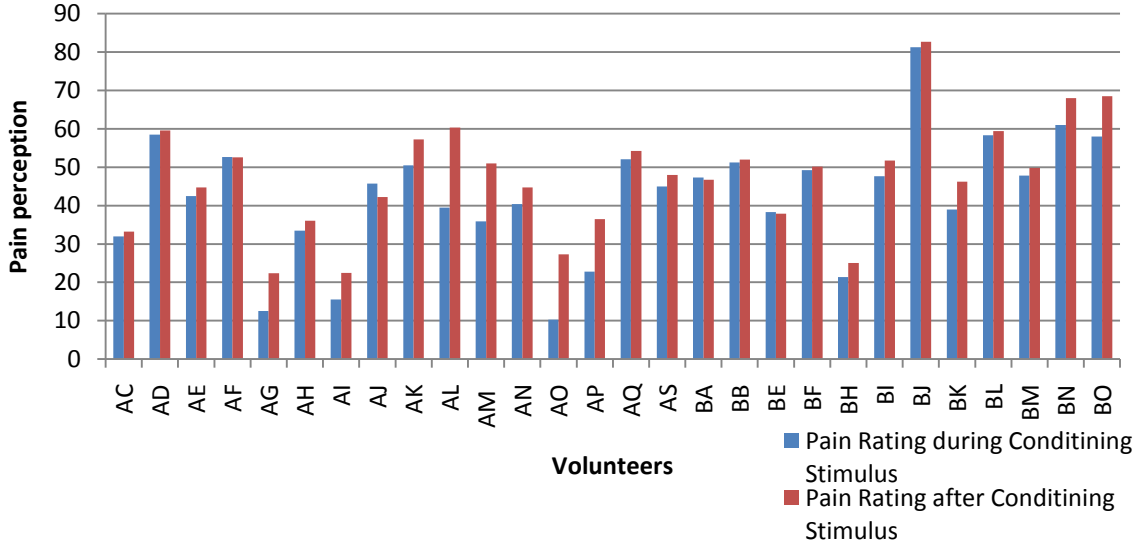

Fig 10: Volunteers' perceived pain during and after the hot water conditioning stimulus in the Retest. Following removal of the hand from the hot water 24 out of 28 volunteers showed an increase pain perception. There was overall a significant increase in pain perception (P<0.001 for n=28).

After removing the hand from the lukewarm water, volunteers did not experience a significant change in pain perception of the electrical stimuli (Test: P=0,377 for n=28; Retest: P=0,319 for n=28). In the Test (Fig. 11), an increase was detected in 15 volunteers (average: 1,66±6,60), whereas in the Retest (Fig. 12), 14 volunteers reported a raise in pain perception (average: 1,32±5,03).

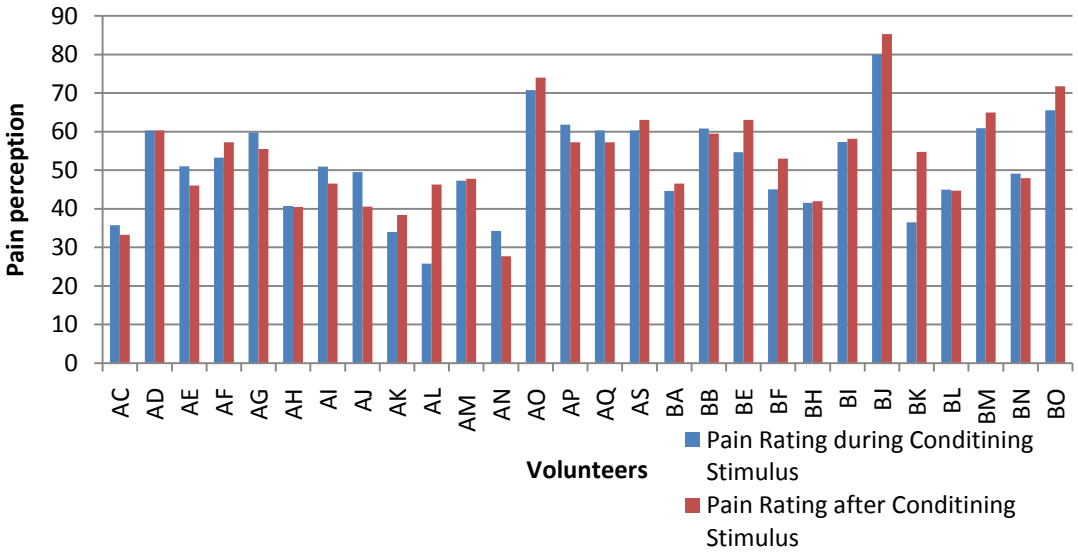

Fig 11: Volunteers' perceived pain during and after the lukewarm water conditioning stimulus in the Test, showing a non-significant increase in pain perception (P=0,377 for n=28).

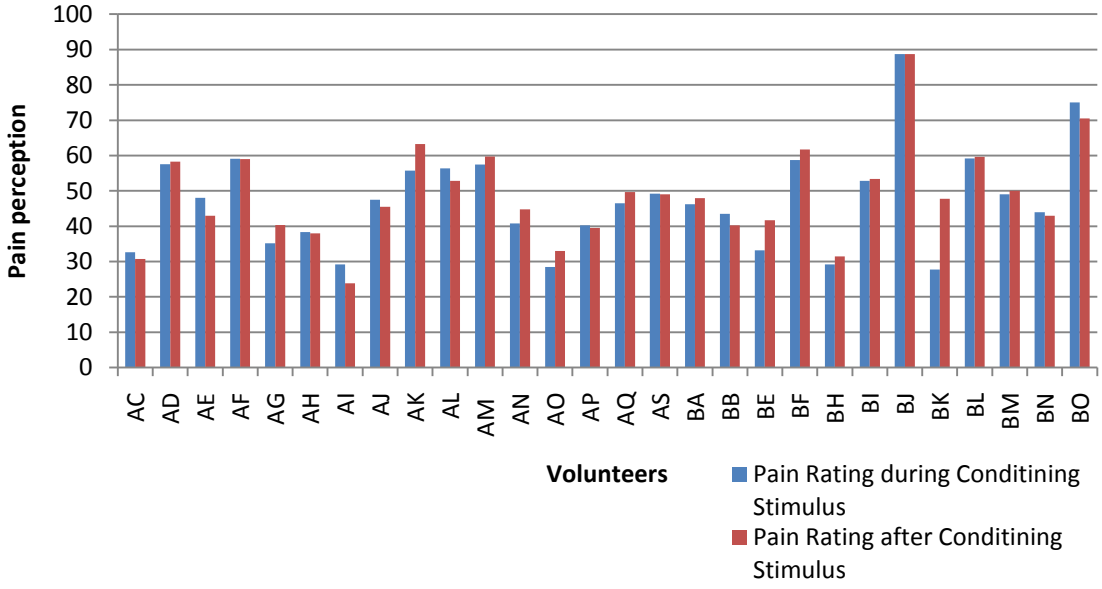

Fig 12: Volunteers' perceived pain during and after the lukewarm water conditioning stimulus in the Retest, showing a non-significant increase in pain perception (P=0,319 for n=28).

Finally in the Test (Fig. 13) a significant increase (Average= 4,66±7,97; P=0.086) in pain rating was demonstrated after the volunteers removed the hand from the hot water conditioning stimulus (6,08±7,96) when compared to the removal of the hand of water at 33ºC (1,66±6,60). This effect was reliable, since the increase was also significant (Average: 6,35±7,85; P=0.009) in the Retest (Fig. 14), in which an increase of 5,04±5,88 was observed when the volunteers took their hand off the hot water in comparison with the removal from lukewarm water (-1,31±5,09).

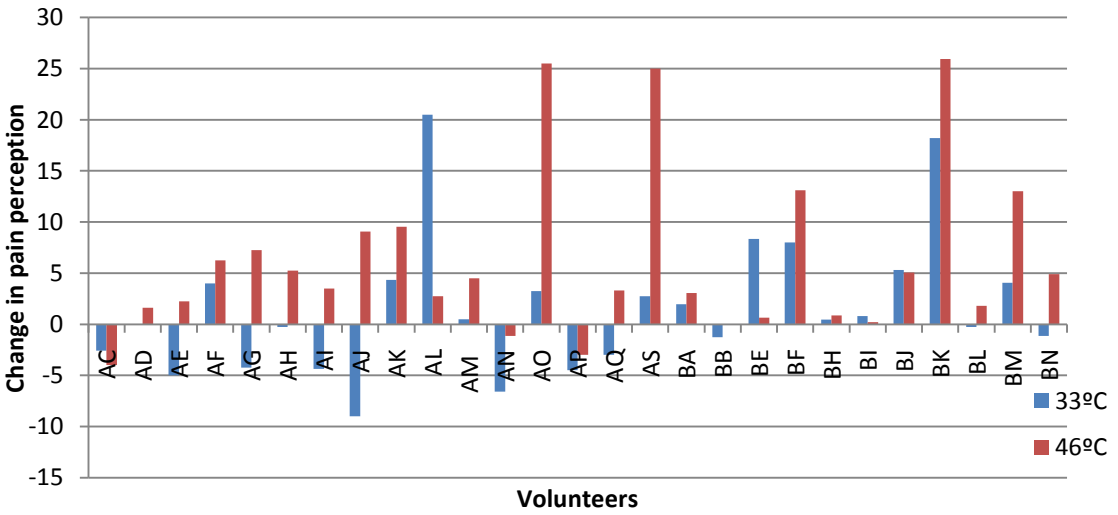

Fig. 13: Pain perception in the Test increased significantly following removal of the hand from the hot water, but not following removal of the hand from the lukewarm water (P=0,086).

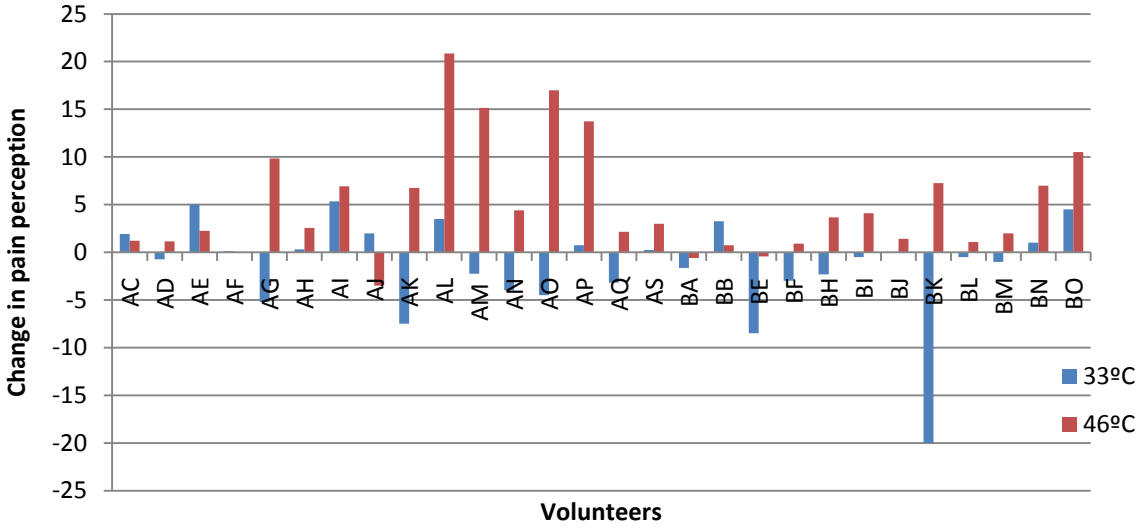

Fig. 14: Pain perception in the Retest increased significantly following removal of the hand from the hot water, but not following removal of the hand from the lukewarm water (P=0,009).

Temporal Summation

To analyze this effect only the stimuli before the conditioning stimulus (lukewarm water or hot water) were considered. Perceived pain trends following 20 consecutive stimuli (from stimulus 16 to 35) in 2 volunteers were shown in figure 15 and 16: While an increase in pain seemed present in volunteer BA (Fig. 15), such effect was clearly not present in volunteer AC (Fig. 16).

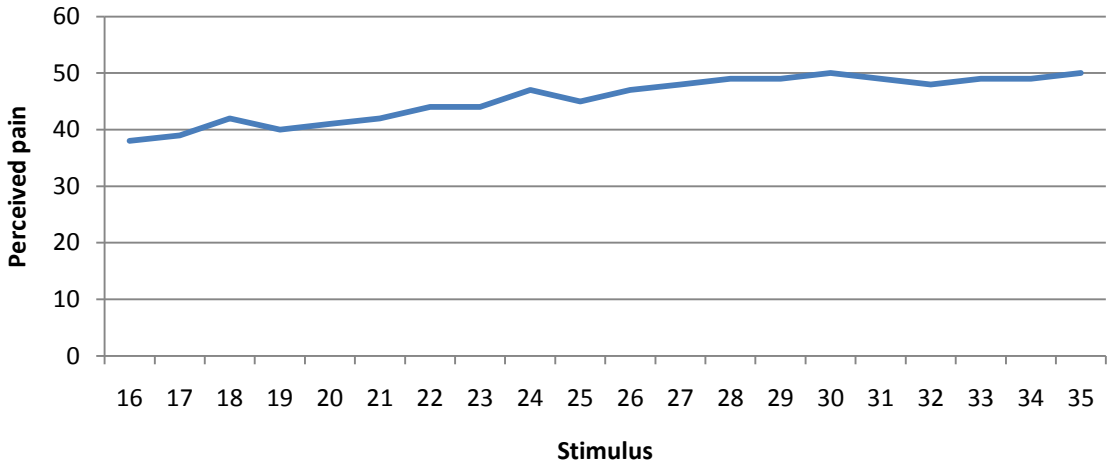

Fig. 15: Pain perception following 20 consecutive stimuli (160sec) of the same intensity in volunteer BA. An increase in pain perception is in this case evident.

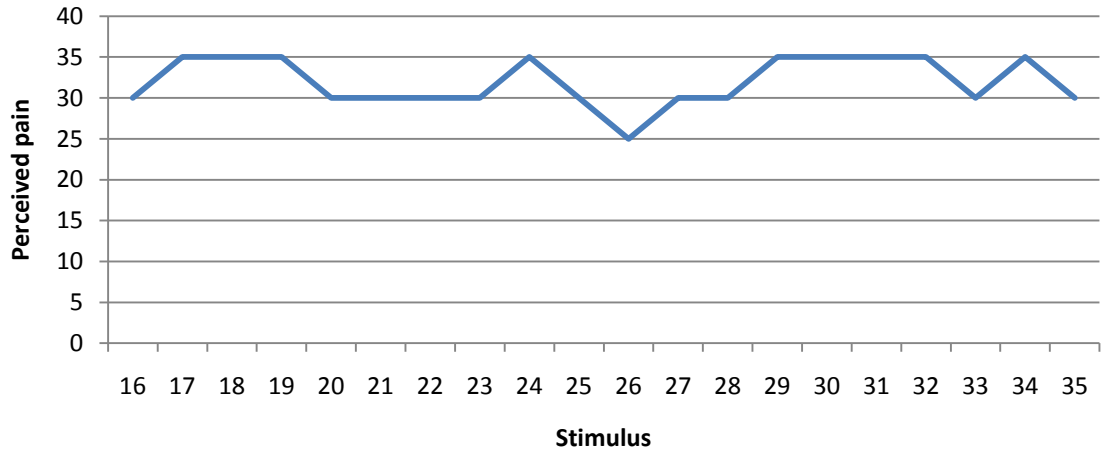

Fig. 16: Pain perception following 20 consecutive stimuli (160sec) of the same intensity in volunteer AC. No increase in pain perception is present here.

To assess TS for all volunteers, 4 perceived pain measurements were conducted for each volunteer (Test before the 33ºC water, Test before the 46,5ºC water, Retest before the 33ºC water, Retest before the 46,5ºC water).

Data for all the volunteers is shown in Table 1. The sum effect was assessed by comparing the perceived pain after stimulus 16 and after stimulus 35.

Both in the Test and Retest, no significant increase in pain rating from the first (Test: 50.02±14.94; Retest: 50.21±15.65) to the last stimulus (Test: 51.20±13.71; Retest: 50.34±14.65) has been observed. Wilcoxon Test calculated P=0.234 in the Test and P=0.521 in the Retest.

		Test		Retest	
Volunteer		**Stim 16**	**Stim 35**	**Stim 16**	**Stim 35**
AC	1	40	40	35	25
	2	30	25	30	30
AD	1	57	61	53	58
	2	58	58	52	60
AE	1	65	45	45	50
	2	50	50	40	40
AF	1	40	45	58	60
	2	50	65	62	60
AG	1	60	60	42	50
	2	40	45	15	40
AH	1	40	40	40	35
	2	45	45	35	40
AI	1	38	55	35	40
	2	45	48	43	34
AJ	1	30	45	35	50
	2	50	45	55	45
AK	1	35	37	50	65
	2	50	55	60	60
AL	1	50	50	82	40
	2	30	25	55	65
AM	1	75	65	75	65
	2	60	45	65	65
AN	1	27	34	48	52
	2	25	40	41	43
AO	1	80	70	50	30
	2	40	40	50	20
AP	1	75	60	35	35
	2	65	75	40	40
AQ	1	50	57	55	50
	2	55	55	53	59
AS	1	60	70	50	45
	2	50	50	55	50
BA	1	44	43	45	45
	2	38	44	38	50
BB	1	45	55	50	55
	2	45	50	30	40
BE	1	55	60	45	45
	2	48	52	35	38
BF	1	30	50	73	60
	2	45	50	60	50
BH	1	38	40	31	32
	2	33	33	15	15
BI	1	53	57	55	57
	2	54	57	55	51
BJ	1	80	80	83	88
	2	82	80	87	83
BK	1	88	85	55	65
	2	60	65	45	45
BL	1	55	52	47	58
	2	50	44	52	60
BM	1	55	60	44	50
	2	46	48	48	53
BN	1	45	35	70	70
	2	47	47	50	70
BO	1	25	15	75	65
	2	75	65	85	75
Mean		50,0	51,2	50,2	50,4
Wilcoxon		P=0,234		P=0,521	

Table 1: Data for the assessment of TS. Perceived pain evaluated by the volunteers following the application of stimulus number 16 and stimulus number 35 that is the last stimulus before being subjected to the conditioning stimulus. Summation was assessed in 4 times in each volunteer: in the first test before immersion of the hand in water at 33ºC or 46,5ºC and on the Retest under the same order.

Expectation

In the Test, 25 volunteers declared that they expected a reduction in pain perceived at the ankle following immersion of the hand in hot water, while 3 expected no reduction in pain perception. From the 25 volunteers who expected the pain reduction, 21 actually experienced this and 4 had no change or an increase in pain perception. From the 3 volunteers who anticipated no change in pain perception by the 46,5ºC water, all of them rated the pain during the conditioning stimulus as lower than before the immersion of the hand in hot water. Table II resumes these results. There was no correlation between the expectation and the change in pain perception (P=0,45; Chi square test).

Table II: Effect of Expectation on DNIC in the Test. Volunteers expectation regarding the effect of immersing the hand in hot water was correlated with the actual effect of hot water on perceived pain at the ankle. A Chi square test (P=0,45) showed no effect of the subjects expectation on the DNIC.

	Pain reduction present	Pain reduction not present
Pain reduction expected	21	4
Pain reduction not expected	3	0

In the Test, 25 volunteers declared that they expected an increase in pain perceived at the ankle following removal of the hand from the hot water, while 3 did not expect this effect. From the 25 volunteers who expected the pain increase, 22 actually experienced this and 3 did not. From the 3 volunteers who anticipated no change in pain perception by the 46,5ºC water, 2 of them experienced an increase in pain perception after removal of the hand from the hot water. Again, there was no correlation between the expectation and the change in pain perception (P=0,32; Chi square test). Table III resumes these results.

Table III: Effect of Expectation on DNIC in the Test. Volunteers' expectations regarding the effect of the removal of the hand from the hot water was correlated with the actual effect on the perceived pain at the ankle. A Chi square test (P=0,32) showed no effect of the subjects expectation on the DNIC.

	Pain increase present	Pain increase not present
Pain increase expected	22	3
Pain increase not expected	2	1

Equivalent data was object of analysis in the Retest. In the Retest, 15 volunteers said that they expected a reduction in pain perception at the ankle following immersion of the hand in hot water, whereas 13 expected no reduction in pain perception. From the 15 volunteers who expected the pain reduction, 11 actually experienced this and 4 did not. From the 13 volunteers who anticipated no change in pain perception by the 46,5ºC water, 9 of them actually experienced a reduction and 4 did not, as can be seen in Table IV. Chi square test showed no correlation between the expectation and the change in pain perception (P=0,81; Chi square test).

Table IV: Effect of Expectation on DNIC in the Retest. Volunteers' expectations regarding the effect of immersing the hand in hot water was correlated with the actual effect of hot water on perceived pain at the ankle. A Chi square test (P=0,81) showed no effect of the subjects expectation on the DNIC.

	Pain reduction present	**Pain reduction not present**
Pain reduction expected	11	4
Pain reduction not expected	9	4

In the Retest, 15 volunteers anticipated an increase in pain perceived at the ankle following removal of the hand from the hot water, while 13 expected no increase in pain perception. From the 15 volunteers who expected the pain increase, 13 actually experienced this and 2 had no change or a decrease in pain perception. From the 13 volunteers who anticipated no change in pain perception by the 46,5ºC water, 11 actually experienced an increase in pain perception. Again, there was no correlation between the expectation and the change in pain perception (P=0,88; Chi square test);(Table V).

Table V: Effect of Expectation on DNIC in the Retest. Volunteers' expectations regarding the effect of the removal of the hand from the hot water was correlated with the actual effect on the perceived pain at the ankle. A Chi square test (P=0,88) showed no effect of the subjects expectation on the DNIC.

	Pain increase present	Pain increase not present
Pain increase expected	13	2
Pain increase not expected	11	2

Discussion

DNIC

In our experiments it was clearly demonstrated that immersing one hand in hot water diminished the perceived pain caused by the electrical stimulation; by removing the hand from the hot water, pain perception on the sural nerve increased. These results confirm a DNIC effect. The second set of trials applied to all volunteers 4 weeks after the first experiment showed results that were similar to the results obtained in the first experiments. This Retest demonstrated that the DNIC effect observed was reliable.

Previous studies have elicited DNIC by various different mechanisms. Cold water (3), heat pain (4) and electrical stimuli (11) have been used as conditioning stimuli whereas electrical (12), thermal (4) and pressure pain (13) have been used as the primary painful stimulus.

Nociceptors are free nerve endings that are stimulated by electrical, thermal, mechanical and biological stimuli. Myelinated A-fibers transmit sharp and fast pain, while unmyelinated C-fibers are responsible for the constant burning pain. Pain impulses reach the dorsal horn of the spinal cord, travel to the substantia gelatinosa and arrive at the thalamus, from where the impulses travel to the limbic system and cerebral cortex to produce pain (14). It is thought that nociceptive neurons in spinal and trigeminal dorsal horns are inhibited by noxious stimulation remote from the neurons' excitatory receptive field, which explains the so called DNIC effect. It has been shown that DNIC was more effective on C-fibre than A-fibre mediated pain (15).

DNIC, defined as the inhibition of pain in one part of the body by a painful stimulus applied elsewhere in the body (1), is a phenomenon receiving recently wide attention because of its possible implication in the mechanisms involved in the pathophisiology of chronic pain syndromes. Fibromyalgia (3), for instance, is a condition, where it has been found that DNIC may be impaired. Further understanding of DNIC will allow a better comprehension of these diseases and hopefully contribute to a better treatment.

A reduction in pain rating in the ankle was not observed with the immersion of a hand in water at 33ºC, nor was the pain perception on the sural nerve higher after the removal of the lukewarm water. A similar result could be reproduced 4 weeks later, showing that this observation was reliable.

Pain perception on the sural nerve decreased significantly more during the immersion of the hand in hot water compared to immersion in lukewarm water, both in the Test and Retest. This finding was in agreement with the results mentioned above.

In addition, in the Test and Retest the increase in pain rating was higher after removal of the hot water conditioning stimulus in comparison to the lukewarm water.

A result from our study was that only a painful conditioning stimulus decreased pain perception elicited by another painful stimulus applied elsewhere in the body; a neutral conditioning stimulus did not elicit DNIC.

It is also important to refer that these trials were performed on healthy volunteers. In some chronic conditions, such as fibromyalgia (3) or chronic tension headache (5) DNIC has been shown to be impaired. The pathologic mechanisms are not yet understood and further research is necessary.

In 13% of the volunteers in the Test and in 18% of the volunteers in the Retest DNIC was not elicited. This may suggest that lack of DNIC may be present in a small percentage of individuals.

Interestingly, pain caused by hot water was rated 49,2±23,1 NRS units that is very similar to pain at the ankle. This suggests that the conditioning painful stimulus does not need to be more intense than the original stimulus to cause DNIC.

In this context, it is appropriate to mention TENS (Transcutaneous electrical nerve stimulation), in which electric current is applied to stimulate specific nerves and consequently reduce pain. Effectiveness of TENS has been shown in conditions such as osteoarthritis, musculoskeletan pain and postoperative pain. Beta and delta opioid receptors are activated both spinally and supraspinally, when TENS is applied. Depending on the frequency used, there is also reduced glutamate release and increased GABA and seretonin release in the spinal cord and activation of central muscarinic receptors that cause analgesia. Unlike DNIC, TENS does not produce analgesia by causing pain elsewhere in the body; it is a non painful stimulation of the nerve involved in the painful condition that causes analgesia (16). In the present study it was shown that a neutral conditioning stimulus in the hand did not cause decrease in pain perception in the ankle, therefore it seems that a conditioning stimulus has to be painful to cause analgesia elsewhere in the body.

Another non painful technique worth of mention is acupuncture, which treats pain (and other conditions) by insertion of needles in specific points of the body. The effectiveness of this treatment is still controversial. Its effect is thought to be due to stimulation of the peripheral nervous system and release of endorphins and other neuropeptides by the insertion of needles (17).

In the Test it was noticeable that the intensity of the electrical stimuli needed to achieve a pain intensity of 50 was negatively correlated to the perceived pain of water at 46,5ºC. This clearly shows that some subjects may be more sensitive to noxious stimuli than others. However this correlation was not significant in the Retest. These results must be interpreted with caution. In a future work, a higher number of volunteers would possibly improve the results and eventually show the test-retest reliability that was not proven in the present work.

Temporal Summation

Understanding how repetitive noxious stimulation affects pain perception is an important step in the comprehension of chronic pain conditions, since some of these conditions, for instance fibromyalgia (7) or chronic tension-type headache (8) show increased TS.

Cathart et al. elicited TS using pressure applied by an algometer as the painful stimulus and showed the test-retest reliability of this effect (1). Further, it was demonstrated that TS can be elicited both at superficial and deep tissue sites (1). TS has been demonstrated applying thermal, electrical and mechanical stimuli (1).

In TS, an increase in response magnitude of second-order nociceptive neurons and higher structures (18) to repetitive noxious stimulation (19) can be observed. C-polymodal afferent's activity decrease with repetitive noxious stimulation (20) while peripheral nociceptors show fatigue from repeated painful stimulation (21).

In our study, TS did not occur. This was possibly due to the short duration of stimulation (160s). Also, according to Nielsen et al., TS is more unlikely to occur with long intervals between stimuli (22). In our study, electrical stimuli were applied with an interval of 8 seconds, which is a long interval considering previous studies (22). In

future studies, extended duration of stimulation and shorter intervals between stimuli would be desirable.

Expectation

Expectation in the clinical setting is the phenomenon by which a patient develops a positive attitude that leads him to believe that the therapy will be effective (23).

Individual expectation, namely induced expectation, may explain efficacy of a placebo, that is the efficacy of therapeutics, in which drug treatment is accompanied by strong suggestion of its efficacy or psychological support.

It is of the utmost importance to study the effect of expectation on pain perception. It may contribute to a better understanding and management of pain, especially of conditions in which chronic pain mechanisms play a major role.

Dorsolateral, orbifrontal and medial pre-frontal cortex (24), (25), (26) as well as several midbrain nuclei (25), (27) are thought to be involved in descending inhibitory control, which when activated may result in a reduction of pain perception.

Goffaux et al. (28) studied the effect of expectation on pain perception by analyzing the effect of arm immersion in cold water on sural nerve pain, which was being electrically stimulated. They concluded that changes in pain due to the immersion of the arm were significantly correlated to the expected changes in pain perception.

In the present work, the expectation volunteers expressed regarding the effect of immersion of their hand in hot water had no influence on sural nerve perceived pain. Expectation was addressed in our study using an original approach that differed from what is usually done. Goffaux et al. divided the volunteers in two groups: in one volunteers were told that immersion in cold water would attenuate pain on the sural nerve; in the other group, volunteers were told the opposite (28); in our study, volunteers were asked to declare whether they expected immersion in hot water to reduce pain or not. No suggestion was made by the investigators regarding the expected effect. Our findings suggest that one's spontaneous expectations may not be as strong as externally induced expectation. This is an interesting result. While it can be interpreted as a negation of the occurrence of the well documented expectation effect, it should be in fact regarded as a demonstration of a possible mechanism

behind expectation. In our opinion, our results suggest that if a positive effect is not suggested the likelihood that it will occur is reduced.

It is important to point out that there was a problem with the design chosen to explore the expectation effect: By not suggesting if hot water would attenuate pain or not, there were only 3 subjects who did not expect a decrease in pain perception with the immersion in the first experiments This complicated the statistical analysis, since one of the groups had only 3 subjects. In the Retest, the distribution of the volunteers (probably by chance) concerning their expectation was more balanced, still expectation effect was not observed. So the results of the Retest reinforce our conclusion. A larger number of volunteers would be important in order to better study the effect of expectation on pain perception in future studies.

Placebo effect is the improvement of a medical condition by administration of an inert substance. Expectation may play a major role in this effect, since expecting an improvement may lead to a positive effect, whereas the opposite is also true (nocebo effect). It has been described in the literature, that once patients stopped viewing the placebo as a helpful substance, its effect decreased significantly (29). Endogenous opioids probably play an important role in this effect, since naloxone can block placebo analgesics. In the present study a similar expectancy effect was anticipated, but did not occur (29).

In Conclusion

In conclusion, the present study showed a significant and reliable DNIC effect when a painful conditioning stimulus was added to the original painful stimulus applied elsewhere in the body. It also showed that a non-painful conditioning stimulus did not decrease pain perception.

The fact that 13% of the volunteers (18% in the Retest) did not elicit a DNIC effect may suggest that lack of DNIC may be present in a small percentage of individuals and eventually account for a different behavior towards chronic pain syndromes.

Also the higher the intensity of electrical stimulation volunteers needed to achieve a pain intensity of 50, the less painful was pain perception caused by water at 46,5ºC, demonstrating a population variability in pain perception.

Unlike previous studies, no Temporal Summation was observed in our study. Our results suggest that for this phenomenon to occur a shorter interval between stimuli and a longer period of exposure to the noxious stimulus may be necessary to produce TS.

Finally our study suggests that self opinion on the expected effect of a therapy, even if a positive one, did not result in a more pronounced effect, suggesting that the phenomenon of expectation depends on external persuasive induction.

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Resumo

Introdução

Dor aguda é um importante mecanismo fisiológico de defesa, que permite ao indivíduo defender-se do estímulo nóxico. Quando a dor se torna crónica, deixa de funcionar como mecanismo de defesa e contribui para um aumento da morbilidade dos doentes afectados (2). É por isso relevante obter uma melhor compreensão dos mecanismos de percepção da dor e como a dor é modulada endogenamente.

O presente trabalho debruça-se sobre 3 fenómenos importantes relativos à Dor: Diffuse Noxious Inhibitory Complex (DNIC), Somação Temporal (TS) e Expectativa.

DNIC é o fenómeno pelo qual, dor numa parte do corpo inibe dor noutro local do corpo (1).

Outro mecanismo de dor importante é a TS, em que a aplicação de estímulos dolorosos de intensidade semelhante provoca um aumento da percepção da dor (1). Verificou-se DNIC comprometido e TS aumentado em mulheres saudáveis (3), (6), pacientes com fibromialgia (4), (7) e com cefaleias crónicas de tensão (5), (8).

Também o efeito da expectativa na percepção da dor foi objecto de análise neste trabalho. Estudos anteriores (9), (10) mostraram analgesia provocada pela expectativa e a compreensão deste fenómeno poderá ajudar num melhor tratamento da dor.

Finalmente a reprodutibilidade destes efeitos foi também estudada.

Objectivos

O presente trabalho tem como objectivo o estudo dos fenómenos previamente mencionados (DNIC, TS, Expectativa) em voluntários saudáveis bem como a sua reprodutibilidade.

As seguintes hipóteses foram testadas:

- A percepção da dor aumenta com a aplicação repetitiva de estímulos de igual intensidade.
- A percepção da dor provocada por um estímulo condicionante nóxico diminui a percepção de um outro estímulo doloroso noutra parte do corpo (efeito DNIC). Estímulos condicionantes neutros não provocam diminuição da percepção da dor.

- A expectativa de analgesia provocada por um estímulo condicionante doloroso diminui a percepção de dor do estímulo original.
- DNIC, TS e expectativa são efeitos reprodutíveis.

Métodos

Foi aplicado a 28 voluntários saudáveis (16 do sexo masculino, 12 do sexo feminino) estímulos dolorosos transcutâneos no nervo sural com um intervalo de 8 segundos e com uma intensidade previamente determinada num *pre-test* para se obter uma intensidade dolorosa de 50 numa escala numérica de 0-100. Como estímulo condicionante, os voluntários imergiram a mão contralateral em água morna (33ºC) ou dolorosamente quente (46,5ºC). Em cada sessão de testes, realizaram-se duas medições, sendo que os voluntários foram previamente randomizados para começar com a água quente seguido de água morna ou vice-versa.

Na primeira sessão de testes *(Test)*, aplicaram-se 35 estímulos eléctricos no tornozelo, seguidos de 20 estímulos eléctricos concomitantemente com o estímulo condicionante (água morna ou quente). Por fim, aplicaram-se 20 estímulos eléctricos sem o estímulo condicionante. Após cada estímulo eléctrico, os voluntários classificavam a intensidade da dor provocada pelo estímulo (0-100), sendo que a intensidade dos estímulos eléctricos se manteve constante.

Trinta minutos depois, o teste foi repetido aplicando-se se o outro estímulo condicionante conforme anteriormente referido. Estas medições foram repetidas 4 semanas mais tarde *(Retest)* com o intuito de testar a reprodutibilidade dos resultados, aplicando-se os estímulos condicionantes pela mesma ordem.

Antes da sessão de testes, foi perguntado aos voluntários se esperavam alguma alteração da percepção da dor com a imersão da mão em água a 46,5ºC.

Análise de Dados e Estatística

Para avaliar o efeito DNIC, recorreu-se à diferença entre a média da percepção de dor durante a estimulação eléctrica com e sem o estímulo condicionante de água a 46,5ºC. Também se estudou a diferença entre as médias de percepção da dor durante a estimulação com água quente e com água morna.

TS foi analisada calculando a diferença da percepção da dor entre o último e primeiro estímulo eléctrico antes de se aplicar o estímulo condicionante. Do grupo dos 35 estímulos eléctricos aplicados antes da entrada do estímulo condicionante, apenas se usaram os últimos 20 estímulos, visto que houve ajustes na intensidade do estímulo eléctrico nos primeiros 15 estímulos, de modo a se obter uma intensidade de dor mais próxima de 50. Estes 20 estímulos tiveram uma duração de 160 segundos. Foi possível fazer quatro análises de TS por voluntário (2 no *Test* e 2 no *Retest*)

Finalmente, para o estudo da expectativa, os voluntários foram agrupados consoante a sua expectativa relativamente ao efeito da água quente na percepção da dor no tornozelo.

Uitilizou-se o teste de Wilcoxon para dados emparelhados (DNIC, TS) e o teste de Qui quadrado para dados agrupados (expectativa).

Resultados

DNIC

Ao imergir a mão em água quente, 25 de 28 voluntários obtiveram uma diminuição significativa da percepção da dor no tornozelo (média 8,65±10,40; P<0,001). No *Retest* resultados semelhantes foram obtidos, tendo-se observado diminuição da percepção da dor em 22 voluntários (média 7,67±9,23; P<0,001); (ver Figura 3 e 4).

Quando os voluntários imergiram a mão em água a 33ºC, observou-se uma diminuição da percepção da dor em apenas 9 voluntários no *Test* (média: 0,57±7,64, P=0,173) e 18 no *Retest* (média: 3,3±6,51, P=0,051);(ver figuras 5 e 6).

Comparando a diminuição da percepção da dor provocada pelos estímulos eléctricos durante a imersão da mão em água quente com a diminuição da percepção da dor durante a imersão em água morna, verificou-se que a diminuição foi muito superior quando o estímulo condicionante foi a água a 46,5ºC tanto no *Test* (média: -9,22±8,94; P<0,001) como no *Retest* (média: -4,33±7,68; P<0,001), o que pode ser visto nas figuras 7 e 8.

Após retirar a mão da água quente, 24 voluntários vivenciaram um aumento significativo da percepção da dor no tornozelo (média 6,08±7,96; P<0,001). No *Retest,*

resultados idênticos foram obtidos, tendo-se observado diminuição da percepção da dor em 24 voluntários (média 5,0±5,9; P<0,001);(ver Figura 9 e 10).

Quando os voluntários retiraram a mão da água a 33ºC, observou-se um aumento da percepção da dor em apenas 15 voluntários no *Test* (média: 1,66±6,60, P=0,377) e 14 no *Retest* (média: 1,32±5,03, P=0,319);(ver figuras 11 e 12).

Comparando o aumento da percepção da dor provocada pelos estímulos eléctricos após a retirada da mão da água quente com o aumento da percepção da dor após a retirada da mão da água morna, verificou-se que o aumento foi muito superior quando o estímulo condicionante foi a água a 46,5ºC tanto no *Test* (média: 4,66±7,97; P=0,086) como no *Retest* (média: 6,35±7,85, P=0,009), o que pode ser visto nas figuras 13 e 14.

Somação Temporal

TS foi analisada calculando a diferença da percepção da dor entre o último e primeiro estímulo eléctrico antes de se aplicar o estímulo condicionante. O teste de Wilcoxon não demonstrou uma diferença significativa na intensidade da dor provocada pelo último (50,02±14,9) e o primeiro (51,2±13,7) estímulo eléctrico (*Test*: P=0.234; *Retest*: P=0.521). Os dados de todos os voluntários podem ser vistos na Tabela I).

Expectativa

Agrupou-se os voluntários consoante a sua expectativa relativamente à influência do estímulo condicionante na dor no tornozelo. Tanto no *Test* como no *Retest*, o teste do Qui quadrado não demonstrou influência da expectativa na percepção da dor, o que pode ser observado nas Tabelas II; III; IV, V).

Discussão

DNIC

No nosso estudo verificou-se que a imersão da mão em água dolorosamente quente diminuiu a percepção de dor causada pela estimulação eléctrica no tornozelo. Ao retirar-se a mão da água quente, a percepção da dor no tornozelo aumentou. Estes resultados confirmam um efeito DNIC. Quatro semanas depois, os resultados dos testes foram semelhantes, o que indica que o efeito DNIC é reprodutível.

Nociceptores são terminações nervosas, que são activadas por estímulos eléctricos, térmicos, mecânicos ou biológicos. Fibras nervosas tipo A conduzem rapidamente dor aguda, enquanto fibras tipo C são responsáveis pela dor em queimação e transmitem a dor mais lentamente. Os impulsos nervosos chegam ao corno posterior da medula espinal, são transportados até ao tálamo, de onde são distribuídos para o sistema límbico e córtex cerebral para produzir dor (14). Demonstrou-se também que neurónios nociceptivos nos cornos dorsais espinais e trigeminais são inibidos por estimulação nóxica longe da área receptora de excitação nervosa, o que explica o efeito DNIC. DNIC parece ser mais eficaz em fibras C do que A (15).

DNIC, definido como a inibição da dor numa parte do corpo por um estímulo doloroso noutra parte do corpo (1), é um fenómeno que tem atraído recentemente as atenções da comunidade científica, devido à sua possível implicação nos mecanismos envolvidos na patofisiologia da dor. Certas patologias, como por exemplo fibromialgia (3), apresentam alterações do efeito DNIC. Uma maior compreensão do efeito DNIC possibilitará porventura perceber melhor os mecanismos da dor e assim obter uma melhor terapêutica da dor.

No nosso trabalho não se observou uma redução da percepção da dor no tornozelo quando os voluntários imergiram a mão em água morna. Isto demonstrou que um estímulo condicionante neutro não alterou a percepção da dor do estímulo original e, como tal, não provocou DNIC.

É ainda importante referir que este estudo foi realizado em voluntários saudáveis. Em certas patologias, como por exemplo fibromialgia (3) ou cefaleias crónicas de tensão (5), verificou-se DNIC alterado.

Neste contexto é relevante referir a TENS (neuroestimulação eléctrica transcutânea), em que corrente eléctrica é aplicada em nervos específicos para os estimular e consequentemente reduzir a dor. TENS tem sido usada com sucesso em diversas situações clínicas, nomeadamente osteoartrite, dor musculoesquelética e dor pós-operatória. Documentou-se a activação de receptores opiódes beta e delta a nível espinal e supraespinal, bem como um aumento da libertação de GABA e serotonina e uma diminuição da libertação de glutamato a nível espinal. Ao contrário do que sucede no DNIC, a TENS não produz analgesia por causar dor noutra parte do corpo. Trata-se de uma estimulação não dolorosa do nervo envolvido no processo patológico, que provoca dor. No nosso trabalho, foi demonstrado que um estímulo neutro na mão não causou decréscimo da percepção da dor no tornozelo; um estímulo deverá ter que ser doloroso para provocar analgesia noutra parte do corpo.

Outra técnica digna de nota é a acupunctura, na qual são inseridas agulhas em certos pontos específicos do corpo. A eficácia da acupunctura ainda é controversa. Pensa-se que os seus efeitos se devem á estimulação do sistema nervoso periférico e à libertação de endorfinas e outros neuropéptidos (17).

Somação Temporal

Entender como a estimulação nóxica repetida altera a percepção dolorosa é um passo fundamental na compreensão dos mecanismos da dor.

Na TS, observou-se um aumento de resposta de neurónios nociceptivos de 2ª ordem e de estruturas superiores (18), quando submetidos a estimulação nóxica repetitiva (19). Além disso, verificou-se uma diminuição da actividade de fibras C aferentes polimodais com estimulação repetitiva (20), enquanto nociceptores periféricos mostraram fadiga na TS (21).

No nosso estudo, não se observou TS. Isto provavelmente dever-se-á ao longo intervalo entre estímulos (8s) e à curta duração da exposição a estímulos (160s). Em trabalhos futuros será importante optar por a uma exposição mais prolongada e por um intervalo mais curto entre estímulos.

Expectativa

Expectativa no contexto clínico é o fenómeno, no qual o doente desenvolve uma atitude positiva relativamente a uma terapêutica, que o leva a acreditar que será bem sucedida (23). Perceber este fenómeno permitirá uma compreensão mais abrangente dos mecanismos da dor e assim um melhor tratamento de certas condições patológicas, em especial aquelas em que a dor crónica assume um papel importante.

Cortex dorsolateral, orbifrontal e prefrontral (24), (25), (26) assim como núcleos mesencefálicos (25), (27) estão envolvidos no controlo inibitório descendente, o que, quando activados, pode resultar numa redução de percepção da dor.

Goffaux e colegas estudaram o efeito da expectativa na percepção da dor, analisando o efeito da imersão do braço em água fria na dor sentida no tornozelo, que estava a ser estimulado electricamente. Concluíram que as alterações na percepção da dor no tornozelo se correlacionavam com a expectativa dos voluntários relativamente ao efeito da água fria. Nesse estudo, os voluntários foram divididos em 2 grupos: no primeiro dizia-se aos voluntários que a água fria iria contribuir para uma diminuição da percepção da dor no tornozelo, enquanto no outro grupo se afirmava o contrário (28).

No nosso estudo, optou-se por um design diferente. Perguntava-se aos voluntários, qual a sua opinião relativamente ao efeito da água quente na dor no tornozelo, não se sugerindo qualquer efeito. Como afirmado previamente, no nosso estudo não se observou correlação entre a expectativa dos voluntários e o efeito da água quente na percepção da dor no tornozelo. Parece ser necessário induzir externamente uma expectativa nos voluntários, para que ela exerca efeito; a simples expectativa não induzida não parece ser suficiente para causar efeito.

Conclusões

O presente estudo mostrou um efeito significativo e reprodutível de DNIC, ao adicionar-se um estímulo condicionante doloroso a um estímulo doloroso inicial aplicado noutra parte do corpo. Também se demonstrou que um estímulo condicionante não doloroso não fez diminuir a percepção da dor do estímulo original.

Não se observou o efeito de Somação Temporal no nosso estudo. Os nossos resultados sugerem que para que este efeito ocorra, é necessária uma exposição mais prolongada ao estímulo nóxico, assim como intervalos entre estímulos mais curtos.

Finalmente, o presente trabalho indica que a expectativa que um individuo tem relativamente a uma terapia não resulta num efeito positivo relevante no êxito da terapia, sugerindo que a expectativa induzida externamente (por exemplo pelo terapeuta) tem um efeito mais pronunciado no sucesso da terapia.