Hypnotizability and pain modulation: a body-mind perspective

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Running head: pain, hypnotizability and heart rate

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The present study was aimed at assessing whether the interoceptive, cardiac activity and the cognitive-emotional traits sustained by the Behavioural Inhibition/Activation System (BISBAS) contribute to the hypnotisability-related pain modulation. Nociceptive stimulation obtained through cold pressor test (CPT) was administered to healthy participants with high (highs) and low (lows) hypnotizability in the presence and in the absence of suggestions for analgesia. Analysis of baroreflex sensitivity - the rate of change of the RR time interval (=1/heart rate) of the ECG - was performed immediately before the occurrence of pain threshold and between it and the termination of hand immersion.

RR decreased abruptly at the beginning of nociceptive stimulation in all participants; then, only *highs* exhibited positive RR rate of change indicating decreasing heart rate for the entire duration of hand immersion. In addition, in *highs* pain threshold negatively correlated with heart rate during the suggestions of analgesia. The activity of the Behavioural Inhibition /Activation System partially accounted for the observed hypnotizability related differences in the possible relevance of interoceptive activity in pain experience.

Keywords: hypnotizability; pain; heart rate; baroreflex; suggestions; analgesia

Introduction

The suggestions of analgesia are widely used to control acute and chronic pain. Hypnotisability is known to modulate their efficacy (Milling, Kirsch, Allen, & Reutenauer, 2005); in fact, after suggestions, individuals with high hypnotisability scores (*highs*) report lower pain intensity than participants with lower scores (*lows*) both under hypnosis and in the ordinary state of consciousness (Meyer and Lynn, 2011; Derbyshire, Whalley, & Oakley, 2009).

The subjective experience of ipoalgesia/analgesia induced by suggestions is seldom associated with congruent autonomic correlates. This was originally observed by Hilgard and Morgan (1975), has been repeatedly confirmed (Paoletti et al., 2010; Santarcangelo et al., 2008, 2013) and could be accounted for by the large variability of the "cardiac defense response" against nociceptive stimulation, which is known to be influenced by several cognitive/motivational factors (Fillingim, 2005; Payne, Kishor, Worthen, Gregory, & Aziz, 2009). However, separate controls may act on the subjective, somatic and autonomic responses to nociceptive stimulation (Pichè, Arsenault, & Rainville, 2010). This implies that congruent changes in these domains are not necessarily expected and that the absence of autonomic correlates of pain and pain modulation following suggestions of analgesia does not challenge the concreteness of the suggestion induced analgesia, which is associated with the modulation of cerebral activities (De Pascalis, Cacace, & Massicolle, 2008; Derbyshire,Whalley, & Oakle., 2009; Valentini, Betti, Hu, & Aglioti, 2013; Madeo, Castellani, Mocenni, & Santarcangelo, 2015) and somatic responses (Kiernan, Dane, Phillips, & Price, 1994; Danziger et al., 1998).

The specular question – whether the autonomic activity contributes to suggestions induced pain modulation - has not been addressed, even though it has been ascertained that the autonomic state is monitored at cerebral levels and integrated in the individual experience (Critchley, 2009; Macovac et al., 2015). In particular, imaging studies of the human insular cortex, involved in the representation of autonomic responses and of the changes in visceral state, have shown that the right anterior insula

supports integration of visceral arousal with conscious processing (Craig, 2002; Critchley, 2009; Makovic et al., 2015).

In a previous study we reported that, during suggestions of analgesia, the response to cold pressor test (a classical condition of sympathetic activation leading to increased blood pressure) is associated with the same increase in heart rate and blood pressure in *highs* and *lows*, despite the *highs*' higher pain threshold and tolerance and their lower pain intensity. In both groups, suggestions modulated only the ECG, which exhibited RR intervals (distances between consecutive R waves corresponding to 1/heart rate) longer than those observed in their absence (Santarcangelo et al., 2013). In that study, autonomic variables (RR, systolic blood pressure, skin conductance) were analyzed over the entire stimulation intervals (that is the total time of immersion in cold water). This did not allow to correlate pre-threshold RR changes with pain threshold values and to associate post-threshold RR changes with pain tolerance (time interval between threshold occurrence and immersion termination).

In a body-mind perspective, we may assume that if heart rate contributes to pain experience, then a negative correlation between pre-threshold heart rate and pain threshold as well as between post-threshold heart rate and pain tolerance should occur**.** Theoretically, beyond RR values and their variability (Critchley, 2009), also the RR rate of change, indicated by the slope of the RR series, could be monitored by cerebral structures. Indeed, it is a measure of the baroreflex sensitivity (La Rovere, Pinna, & Raczak, 2008) and it is known that baroreceptor stimulation modulates the activity of several cortical and brainstem regions (Macovac et al., 2015). Baroreflex sensitivity is inversely related to experimental pain sensitivity and to the severity of clinical pain (Dusche, Werner, & Reyes Del Paso, 2013).

With normal levels of arterial pressure, baroreceptors are constantly active and exert a continuous inhibition on sympathetic efferent activity. Their activation by increased blood pressure, as occurs during cold pressor test (Mourot, Bouhaddi, & Regnard, 2009; Tousignant-Laflamme, Bourgault,

Gelinas,& Marchand, 2010), leads to increased discharge of vagal cardio-inhibitory neurons and decreased discharge of sympathetic neurons controlling the heart and peripheral blood vessels (Kirchheim, 1976; Abboud and Thames, 1983).

The main aim of the present study was to assess whether heart rate and its rate of change in the time interval between hand immersion and the occurrence of pain threshold (pre-threshold) as well between pain threshold and the test termination (post-threshold) is different in *highs* -who accept the suggestions of analgesia- and *lows,* who do not respond to them.

We have shown that hypnotisability interacts with the activity of the Behavioral Inhibition/Activation System (BISBAS) (Gray, 1990). In fact, BIS/BAS activity, which is measured by scales (Carver and White, 1994), accounts for the cortical dynamics associated with pain modulation (Madeo, Castellani, Mocenni, & Santarcangelo, 2015) and for the low efficacy of the *highs*' pain imagery (Santarcangelo et al., 2013). BIS/BAS is a cognitive emotional system based in limbic and hypothalamic structures projecting to the prefrontal cortex, to the *locus coeruleus* and to the nuclei of the median *raphe*. BIS is sensitive to signals of punishment/non-reward and is involved in the negative feelings induced by these cues, whereas BAS is associated with high levels of dopamine and is sensitive to potential rewards and motivation to seek out positive experiences (for review see De Pascalis et al., 2010). High levels of BIS predict higher levels of negative affect (Hundt et al., 2013; Leen-Feldner, Zvolensky, Feldne, & Lejuez, 2004) and high risk for anxiety and depressive disorders (Muris et al., 2001), whereas high levels of BAS are associated with greater reduction of negative affect during positively perceived situations (Hundt et al., 2013) and higher overall positive affect (Meyer and Hofmann, 2005). In chronic pain patients BIS has shown significant non-linear associations with pain intensity and headache frequency whereas BAS has been found non-linearly associated with the frequency of severe headaches (Jensen, Tan, & Chua, 2015).

Thus, another aim of the study was to assess whether individual cognitive-emotional characteristics sustained by the activity of the Behavioral Inhibition/Activation System influence the possible heart–dependent pain modulation by interacting with hypnotizability.

In brief, in the present study we investigated i) the role of the baroreflex sensitivity in the subjective experience of pain and suggestion induced pain modulation, and ii) the possible influence of the cognitive-emotional traits measured by BISBAS scales on both heart rate and pain experience.

Methods

The study analyzes data collected in 29 out of 45 participants enrolled in an earlier study (Santarcangelo et al., 2013) conducted according to the Declaration of Helsinki. These subjects could be included in the present analysis because at the time of the earliest study they had completed the BISBAS questionnaire (Carver, 1994).They were healthy volunteers (age (mean+SD): 22$\pm$1.9 yrs) divided in 15 high (*highs*, score (mean$\pm$SD): 9.6$\pm$ 1.4; 8 females) and 14 low hypnotizable individuals (*lows*,score: 1.7$\pm$ 1.2;7 females) according to the Italian version of the Stanford Hypnotic Susceptibility Scale, form C (Weitzenhoffer and Hilgard, 1962).

Experimental procedure

The study protocol (Figure 1A) consisted of a basal condition (B1, 5 min) preceding a condition of cold pressor test (CPT), and of another basal condition (B2, 5 min) preceding a condition of cold pressor test associated with suggestions for analgesia (CPT+AN). The two sequences (B1-CPT, B2-CPT+AN) were randomly administered among subjects. The latest 2 min of Basal conditions were considered for analysis.

The cold pressor test was performed by immersion of the left hand in icy cold water (0°–1°) up to the wrist. The test was terminated as soon as the subjects reported unbearable pain (cpt duration, sec), and interrupted at min 4 in the subjects not reporting unbearable pain yet. Before immersion, participants

were instructed to declare when they began to feel pain (pain threshold, time from immersion, sec) by saying only ‘‘ora’’ (now), in order to avoid ECG artefacts. Pain tolerance (sec) corresponded to the difference between the cpt total duration (time of immersion, sec) and the occurrence of the pain threshold.

ECG was recorded through 3M Red Dot Ag/AgCl disposable electrodes placed according to the standard first ECG lead (DI) and amplified by a LACE-Elettronica System amplifier (Pisa, Italy). QRS complexes were automatically detected, artefacts/abnormal beats were discarded and the distances between consecutive R waves of the ECG (RR (msec), instantaneous heart rate= 1/RR) were computed. For details, see Santarcangelo et al., 2013.

In the present study, the ECG was analyzed in order to study the RR series of pre- and post-threshold cpt intervals and its rate of change, expressed as the slope of the RR series least square best fitting line during CPT and CPT+AN.

Statistical analysis.

All analyses were performed through the SPSS.15 statistical package. Hypnotizability and Gender were between subjects factors. BISBAS scores were analyzed through multivariate ANOVA; pain threshold and pain tolerance were analyzed through repeated measures ANOVAs (2 Hypnotizability (*highs, lows*) x 2 Gender (females, males) x 2 Conditions (CPT, CPT+AN) design).

The RR value and its rate of change (RR series slope) were analyzed through 2 Hypnotizability (*highs, lows*) x 2 Gender (females, males) x 2 Conditions (CPT, CPT+AN) x 3 Levels (basal, pre-threshold, post-threshold) design. The analysis of psychophysical and cardiac variables was also repeated with BIS or BAS as covariates. The Greenhouse-Geisser correction for non sphericity was applied when necessary. Contrast analysis between levels and unpaired t test between hypnotisability and gender groups were used for post-hoc analysis. After Bonferroni correction applied to subjective and cardiac variables separately, the significance level for subjective experience (pain threshold, pain tolerance)

and cardiac variables (RR value, RR series slope) was set at p<.025. Pearson correlation coefficients between psychophysical and cardiac variables were computed (significance level, p<.05).

Results

Subjective experience

There was no significant difference between *highs* and *lows* and between females and males in BIS (mean+SD; *highs*, 15.4±1.45; *lows*, 14.93±1.54) and total BAS scores (*highs*, 47.6±4.66; *lows*, 49.79± 5.81).

Decomposition of the significant Hypnotizability x Condition interaction (F(1,25)=8.781, p<.007) revealed that there was no significant difference between *highs* and *lows* in pain threshold during CPT, whereas pain threshold was significantly higher in *highs* than in *lows* (Condition, F(1,14)=8.850, p<.010) during CPT+AN (Figure 1B). These interaction did not survive after controlling ANOVA for BIS (p<.060) or BAS (p<.040).

There was a significant Hypnotizability effect for pain tolerance (F(1,27)=6.561, p<.016) which was reduced controlling for BIS and abolished controlling for BAS.

RR value and baroreflex sensitivity (RR rate of change)

RR mean values and SD are reported in Table 1. In all subjects RR (Figure 1C) was significantly lower in CPT than in CPT+AN (Condition effect, F(1,25)=15.983, p<.0001). Contrast analysis applied to the significant Level effect (F(1,25)=42.737, p<.0001) revealed that this consisted of higher RR values in basal than in pre- (F(1,25)=6.762, p<.0001) and post-threshold conditions (F(1,25)=20.843, p<.0001) independently from the presence of suggestions;

Controlling for BIS maintained the Condition effect significant ($p<.019$; level, $p<.019$), but abolished the Level effect ($p<.028$). Controlling for BAS abolished all effects (Condition, $p<.075$; Level, $p<.081$).

A significant Gender x Condition x Level interaction ($F(1,25)=4.361$, $p<.018$) was observed. It survived after controlling for BIS ($p<.021$), but not for BAS ($p<.035$). Its decomposition showed no significant effects/interactions in males likely due to their larger variability (Table 1) and significant Condition (CPT<CPT+AN, $F(1,14)=13.280$, $p<.003$) and Level effects in females ($F(2,28)=18.454$, $p<.001$). The latter was sustained by significant differences between basal and pre-threshold ($F(1,28)=32,172$, $p<.0001$) and between basal and post-threshold values ($F(1,28)=12.690$, $p<.003$), whereas pre-threshold and post-threshold RR did not differ significantly ($F(1,28)=4.363$, $p<.055$). In males, despite the absence of significant effects and interactions, significant differences were found between CPT and CPT+AN at all levels (basal, $F(1,27) =3.466$, $p<.006$; pre-threshold, $F(1,26)=3.080$, $p<.005$; post-threshold, $F(1,26)=2.292$, $p<.002$).

No significant Hypnotizability related effect was found. Since the effect size for the Hypnotizability effect ($\eta^2=.001$) and the Condition x Level x Hypnotizability interaction ($\eta^2=.037$) was quite low, theoretically we cannot exclude that hypnotizability effects/interactions may become significant in larger samples. However, Table 1 shows that RR values and their variability (SD) were quite similar in the two groups.

The absence of hypnotisability-related differences in the pre-threshold RR intervals in the presence of significant differences in pain threshold could be due to hypnotisability-dependent relationship between pre-threshold RR and BAS activity . In fact, the latter was negatively correlated with RR during CPT in *highs* ($R= -.530$, $p<.042$) and positively correlated with it during both CPT ($R=.559$, $p<.031$) and CPT+AN ($R=.533$, $p<.05$) in *lows* (Figure 2). In addition, in CPT+AN *lows* exhibited a positive correlation between BAStot and the post–threshold RR ($R=.555$, $p<.039$).

No significant correlation between psychophysical and autonomic variables was found in CPT. In contrast, in CPT+AN all subjects displayed a significant positive correlation between pain threshold and pre-threshold RR ($R=.440$, $p<.017$), which survived after controlling for BIS ($R=.440$, $p<.019$) and BAS ($R=.459$, $p<.014$**).** Splitting by hypnotizability, this correlation remained significant only in *highs* ($R=.615$, $p<.019$).

Baroreflex sensitivity (RR series slope) was modulated by hypnotisability (Condition x Hypnotizability, $F(1,27)=5.788$, $p<.024$) and gender (Condition x Gender ($F(1,27)=7.984$, $p<.013$). Decomposition of these interactions revealed significant differences between highs and lows ($F(1,27)=8.786$, p<,007) only in CPT, who exhibited positive and negative slopes, respectively (Figure 3A) and between females and males ($F(1,27)=7.131$, $p<.013$) who showed positive and negative slopes, respectively (Figure 3B). Both interactions survived controlling for BIS (Condition x Hypnotizability, $p<.012$; Condition x Gender, $p<.024$) whereas only the Condition x Gender interaction survived controlling for BAS ($p<.017$). Although not statistically significant, it may be noteworthy that during CPT+AN lows exhibit a tendency to change the direction of their RR modulation from negative slopes (indicating increasing heart rate) into positive slopes indicating decreasing heart rate (Figure 3A). The same can be observed in males (Figure 3B).

Discussion

Subjective reports are in line with those observed in the original, larger sample (Santarcangelo et al., 2013). Findings on RR (a) and RR rate of change (b) support our hypothesis that the cardiac activity may be involved in the subjective experience of pain. Psychophysical and cardiac variables as well as their relation are influenced by hypnotizability and, even more, by the Behavioral Inhibition/Activation System.

a) The positive correlation between pre-threshold RR and pain threshold observed during suggestions of analgesia indicates that in *highs* longer pre-threshold RR (that is lower heart rate) may be associated with higher pain thresholds, thus supporting a body-mind view of the subjective experience of pain modulation.

The possible role of interoception in the hypnotizability-related modulation of experience has been highlighted also by our earlier experiments showing that in a single experimental session specific suggestions of relaxations associated with imagery of fearful situations reduce the heart rate in hypnotized highs reporting unchanged fear (Sebastiani et al., 2007). This autonomic modulation preceding the changes in the subjective experience of fear may account for the efficacy of systematic desensitization, which might be viewed as an effect of bodily changes (Davison, 1968; Marks, 1987; Craske, 1999).

The Behavioral Inhibition/Activation System modulates the effects of the nociceptive stimulation on heart rate as a function of hypnotizability. In fact, the activity of the Behavioral Activation System and heart rate were negatively correlated in *highs* and positively correlated in *lows.* In the former, the association of higher heart rate with lower BAS scores may be the result a conflict between the high motivation to approach novel situations indicated by BAS scores and the high absorptive tendencies characterizing *highs* (Tellegen and Atkins, 1974) and possibly preventing them to distract their attention from pain.

b) Significant hypnotisability-related differences emerge in the analysis of baroreflex sensitivity (RR rate of change). In fact, soon after hand immersion *highs* and *lows* exhibited positive and negative RR slopes, respectively. This indicates two different autonomic strategies of response to nociceptive stimuli and is in line with findings obtained in studies of blink reflex (Santarcangelo et al., 2016) in which the "turbulence" induced in the RR series by short-lasting electrical nociceptive stimulation is larger but shorter in highs with respect to lows.

Although the difference between *highs'* and *lows'* baroreflex sensitivity was significant in CPT but not CPT+AN, the different directions of the RR rate of change may have been important in the *highs*' later occurrence of pain threshold during suggestions and in their higher pain tolerance in both the absence and the presence of suggestions of analgesia. In fact, low pre-operative level of baroreflex sensitivity is associated with higher post-operative pain intensity (Nielsen et al., 2015), and the gain of baroreceptor control is inversely related to the pain intensity in chronic pain patients (Zamuner et al., 2015). Together with the larger parasympathetic component of heart rate variability in resting conditions (Santarcangelo et al., 2012) and the endothelial nitric oxide larger availability during mental stress and nociceptive stimulation (Jambrik, Santarcangelo, Ghelarducci, Picano, & Sebastiani, 2004; Jambrik et al., 2005), greater baroreflex sensitivity, which is associated also with greater vessels' sensitivity to nitric oxide (Gmitrov, 2015), can represent a favourable prognostic factor for cardiovascular health in the highly hypnotizable individuals.

The absence of any correlation between RR slopes and psychophysical variables could depend on the different role of the Behavioural Activation System in *highs* and *lows*; in fact, controlling for BAS abolishes the effects of the interaction of hypnotisability and gender on the RR slope, and pain threshold is oppositely correlated with BAS scores in *highs* and *lows*.

Theoretically, the interaction of the Behavioural Inhibition/Activation System with hypnotisability in the modulation of psychophysical and cardiac variables may be quite important in pain treatment; in fact, the individual traits sustained by the BISBAS could become the targets of individualized psychotherapies aimed at enhancing the efficacy of suggestions.

In conclusion, despite the limitation due to the small effect size of a few comparisons, our findings support the idea that autonomic functions may influence pain experience as a function of hypnotizability. In addition, they prompt further investigation of the complex interaction of hypnotizability with the activity of the Behavioral Inhibition/Activation System.

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Figure legend

Figure 1. Study protocol, pain threshold and RR interval. A) experimental design; pain arrows indicate pain threshold (th, mean±SE) during hand immersion in the absence (CPT) and the presence (CPT+AN) of suggestions of analgesia. B) pain threshold. Line, significant difference between conditions (CPT, CPT+AN); *, significant difference between highs and lows. C) RR (mean±SE) in females and males. Significant differences between Conditions (CPT, AN) and Levels (b, pre th, post th) are reported in the Results section.

Figure 2. Correlation between BAS scores and mean RR values. Highs, left panels; lows, right panels; CPT, upper panels; CPT+AN, lower panels

Figure 3. Baroreflex sensitivity. RR series slopes (mean±SE) in highs and lows (upper panel) and in females (f) and males (m) (lower panel) during cold pressor test in the absence (CPT) and in the presence of suggestions of analgesia (CPT+AN). *, significant difference between Hypnotizability and Gender groups

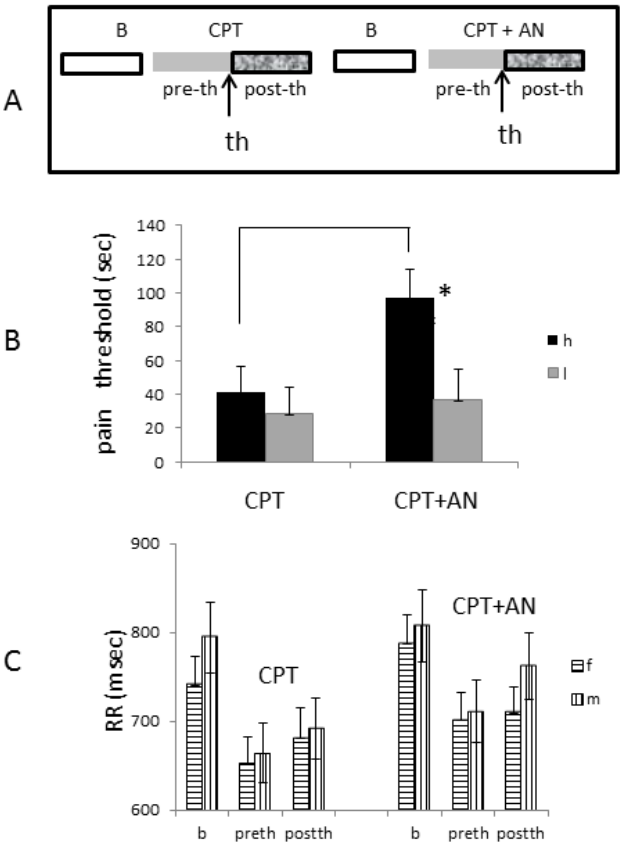
A
B
CPT
B
CPT + AN
pre-th
post-th
th
pre-th
post-th
th
B
pain threshold (sec)
140
120
100
80
60
40
20
0
*
h
l
CPT
CPT+AN
C
RR (msec)
900
800
700
600
CPT
CPT+AN
f
m
b
preth
postth
b
preth
postth

Fig 1

Fig. 2

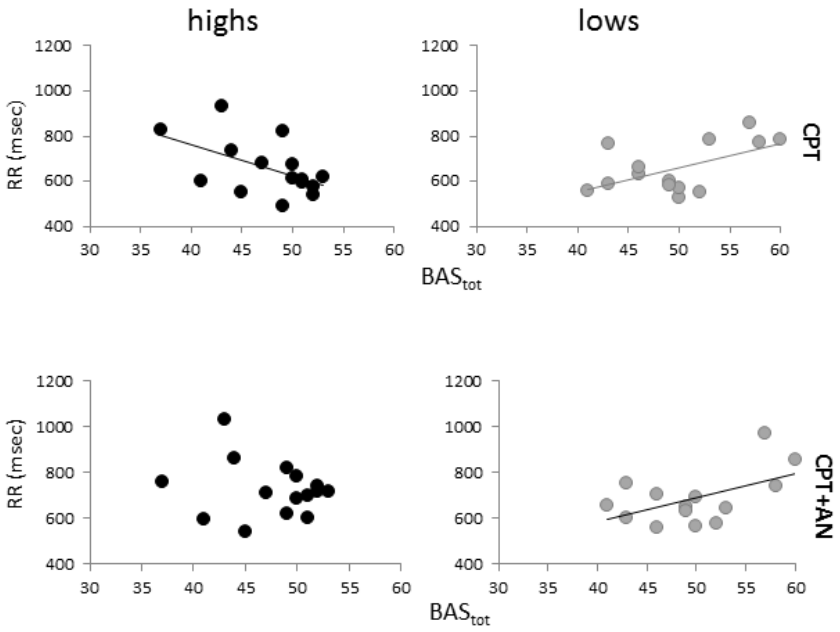
highs
lows
RR (msec)
BAS$_{tot}$
CPT
CPT+AN
1200
1000
800
600
400
30
35
40
45
50
55
60

Fig. 3

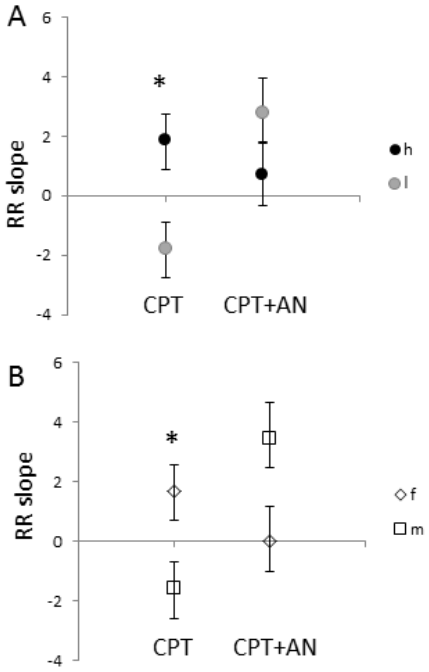

Table 1. Mean RR and RR slope in basal conditions, before and after pain threshold occurrence

			RR (msec)				RR rate of change (slope)			
			CPT		CPT+AN		CPT		CPT+AN	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
level	hypn	gender								
basal	**highs**	F	741,83	106,57	776,09	85,65	2,55	3,76	-1,60	2,21
		M	775,96	162,26	808,14	169,16	0,89	1,30	0,20	0,76
		Total	**757,75**	**131,42**	**791,05**	**127,30**	**1,77**	**2,92**	**-0,76**	**1,88**
	lows	F	743,07	41,73	802,86	101,18	-0,58	2,92	-0,35	0,92
		M	814,41	148,75	807,29	142,30	-7,28	10,91	14,58	28,73
		Total	**778,74**	**111,29**	**805,07**	**118,65**	**-3,93**	**8,42**	**7,12**	**21,01**
pre th	**highs**	F	659,51	89,70	708,21	102,26	2,77	6,68	1,48	2,05
		M	654,79	160,93	745,81	145,46	1,74	2,22	1,73	1,54
		Total	**657,31**	**123,00**	**725,76**	**121,13**	**2,29**	**4,97**	**1,59**	**1,77**
	lows	F	645,63	95,58	695,54	90,81	0,97	2,32	-0,84	2,87
		M	674,41	130,07	676,96	143,43	-7,17	11,95	2,27	5,06
		Total	**660,02**	**110,67**	**686,25**	**115,73**	**-3,10**	**9,28**	**0,72**	**4,27**
post th	**highs**	F	704,71	104,92	733,66	94,59	2,04	3,83	1,31	3,24
		M	684,67	167,94	792,16	150,90	1,27	3,52	0,93	1,65
		Total	**695,36**	**133,04**	**760,96**	**123,06**	**1,68**	**3,58**	**1,14**	**2,54**
	lows	F	655,80	115,83	684,00	84,53	2,42	5,63	-0,06	1,94
		M	699,50	133,10	732,53	117,12	0,98	2,07	1,09	2,43
		Total	**677,65**	**121,99**	**708,26**	**101,31**	**1,70**	**4,14**	**0,52**	**2,20**