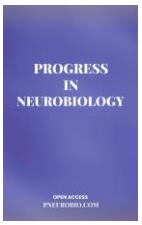

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Research Article

Association of Interoceptive Sensibility and Pain Psychophysics in Healthy Subjects and Chronic Pain Patients

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ABSTRACT

Objective: Interoception is the sense of the physiological condition of the body; it results from the integration of somatic information, including pain, with visceral information. The aim of the study was to assess whether interoceptive sensibility and awareness modulate the perception of experimental pain in healthy participants and recurrent/chronic pain patients. **Methods:** To assess whether interoceptive sensibility and awareness modulate the effects of experimental noxious stimuli, pain-free subjects (N=52) and patients with recurrent (N= 47) and chronic pain (N= 42) underwent the following psychophysical tests: von Frey filaments (punctate mechanical threshold), pressure pain threshold, heat and cold pain threshold and tolerance, and diffuse noxious inhibitory control (DNIC). They also completed the Body Perception Questionnaire Short Form (BPQ-SF), which discriminates between sub- and supradiaphragmatic interoception, and the Multidimensional Assessment of Interoceptive Awareness I (MAIA I), which measures multiple dimensions of interoceptive sensibility/awareness. **Results:** After controlling for age and psychopharmacological treatment, a significant difference in heat pain tolerance among groups ($F=3.16$; $p=.047$; $\eta 2=.06$) was found cancelled however by all BPQ dimensions and noticing of MAIA I. **Conclusion:** Different mechanism of experimental pain perception can be suggested in subjects with and without pain, based on the role of interoceptive sensibility.

Highlights

i. Old age affects on the perception of experimental noxious stimuli influencing the different perception of pain among subjects without and with pain.
ii. Body awareness and autonomic reactivity affects on the increased tolerance of heat pain stimulus in pain patients.
iii. The influence of body awareness and autonomic reactivity in the different tolerance to the heat pain stimulus does not change if the subject has recurrent or chronic pain.
iv. Noticing of MAIA I affects on the different tolerance to the heat pain stimulus when the individual begins to present pain, even if not persistent.
v. The relationship between interoceptive sensibility and pain perception change if we are handling subjects with and without pain.

1. Introduction

Recent advances in the anatomy and physiology of interoception have contributed to the knowledge of pain mechanisms. The Sherrington old definition of interoception as sensory representation of the interior of the body (viscera or internal milieu) has recently been enriched by the inclusion of somatosensory signals that come from the whole body [1] and by psychological components such as feelings defined as the mental representation of the body state [2]. Craig's research have also changed some pain-related concepts retained for several years, as pain is a fundamental part of interoception and not exteroception as suggested by Sherrington [3].

According to Cuenen *et al.* [4] we can define the interoception as the experience of the state of the body resulting from the integration of visceral and somatic information, including pain. Somatic and visceral afferents reaching lamina I of the spinal cord, carry information from

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many tissues and are conveyed to same brain structures, which explains why visceral sensations are frequently associated with somatic sensations [1]. Peripheral information is classified into homeostatic and non-homeostatic (i.e., maladaptive or dysfunctional), depending on its functional significance. Both homeostatic and non-homeostatic signals, as well as the associated somesthetic information, are integrated by brain structures that include the amygdala and the hippocampus, and converge on the mid-insula, which is regarded as the key structure for interoception integration [5].

Some authors suggest to disentangle the visceral information provided by the supradiaphragmatic ventral vagal complex (VVC), which contains myelinated components of the vagus, described as the phylogenetically and affectively most recent system, and the subdiaphragmatic dorsal vagal complex (DVC), phylogenetically older than the previous one, contributing to stress-associated "shut down" behavior [6, 7]. The conscious perception of interoception results from information converging from the mid-insula, anterior cingulate cortex, orbitofrontal cortex and dorsolateral prefrontal cortex into the right anterior insula [4]. The latter plays an important role in the encoding negative emotions, and in the elaboration of the aversive component of clinical pain [8].

According to Garfinkel *et al.*, [9], interoception can be subdivided into three different constructs: i) interoceptive accuracy, such as the ability to detect one's own heartbeats; ii) interoceptive sensibility, self-reported beliefs concerning one's own interoception, measured by questionnaires; and iii) interoceptive awareness, "the awareness of any type of information originated anywhere and everywhere within the body involving higher mental processes such as emotions, conscious awareness, and behavior" [10]. Awareness, however, is hardly disentangled from sensibility [11].

Pain and interoception share common pathways. One originates in lamina I and reaches area 3 in the primary sensory cortex through the ventral posterolateral thalamus, while the other one reaches the primary sensory cortex and the cingulate and insular cortices through the ventromedial posterior thalamus [1]. The relevance of this last subcomponent in the coding of the unpleasantness of pain has long been described by the studies of Donald Price *et al.*, [12] and resumed in subsequent research, highlighting the fundamental role in the mechanisms of pain modulation. The most recent studies on the coding of this component by the anterior region of the insula show that it is a component involved in pain [8], influencing the nociceptive plasticity that underlies chronic pain.

Some research report that subjects with chronic pain have no modifications of interoceptive accuracy, sensibility or awareness [13, 14], and there is evidence that pain threshold and tolerance are not correlated with interoceptive accuracy [15], which, however, is considered distinct from interoceptive sensibility [16]. It was the aim of this retrospective study to evaluate whether interoceptive sensibility/awareness can assist to understand the differences in the perception of experimental pain in healthy subjects, recurrent and chronic pain patients. Clinically, we classify pain according to its onset and persistence. Recurrent pain is characterized by transient, repeated episodes of pain (less than three times a month) not interfering with the everyday life, and persistence of diffuse noxious inhibitory control (DNIC) [17]. Chronic pain, on the other hand, lasts more than three months, interferes with daily activities, and therefore requires treatment [18].

2. Method

2.1 Sample

Analyses were performed on data collected earlier in participants studied for different purposes [14]. Pain patients were recruited among those attending a pharmacological and/or psychotherapeutic treatment program for chronic pain at the Center for Psychosomatic Medicine (GIFT Institute of Integrated Medicine, Pisa) in 2019-2020. Control subjects were trainees at the Aplysia APS non-profit association, part of the GIFT Institute of Integrative Medicine, Pisa, who volunteered for the study. Chronic pain assessment was performed according to the International Classification of Diseases, 11th Revision (ICD 11) [18], fibomyalgia, in line with a previous study [14], was diagnosed according to ACR 2016 criteria, and the diagnoses of tension-type headache and migraine were made according to the Kienbacher *et al.* [19] classification.

Subjects were classified according to the following pain criteria:
i) Pain free group (n=52): subjects without pain during the past two years.
ii) Recurrent pain group (n=47): patients with periods of pain transient which resolved with the intake of non-opioid analgesics and did not interfere with daily life activities.
iii) Chronic pain group (n=42): patients with musculoskeletal pain (n=28), patients with chronic primary headache or orofacial pain (n= 12), patients with chronic neuropathic pain (n=2) and one patient with chronic primary visceral pain. Musculoskeletal group includes also subjects who reported a diagnosis of fibromyalgia (according with the 2016 criteria) made from previous rheumatological consultation but which we could not ascertain because the scale of widespread pain and global severity index cut-off criteria have not administered.

2.2. Procedure

2.2.1. Pain Psychophysics

2.2.1.1. Von Frey Filaments Test

A series of von Frey monofilaments of different diameters [20] was applied perpendicularly to the volar skin area of the left forearm in ascending order, and the data generated were used to determine the punctate touch threshold (VonF). Each filament exerts a different force stimulus, expressed in grams or milli-Newton (range from 1.65 to 6.65, corresponding respectively to 0.008 and 300 g). As reported in the literature, von Frey filaments have also been used to investigate the normal sensibility to touch [21]. Using the ascending order, successive stimuli are applied for 2 seconds at 5-second intervals per filament to assess the sensory detection threshold. The patient is not able to see the filament being applied and is simply asked to report when a stimulus is felt. If the answer is negative, filaments of increasing diameter are applied. The mean positive perception of consecutive three lowest diameter von Frey filament stimuli is the sensory touch threshold.

2.2.1.2. Pressure Pain Threshold

An algometer (Wagner Instruments Greenwich CT FPK 40) was used to assess the pressure pain threshold (Pthr). In accordance with the Lautenbacher *et al.* [22] procedure, the experimenter applied a progressively increasing pressure (approximately 1 kg pressure/sec) to the base of the ring finger on the subject's non-dominant hand via a rubber tip (size: 1 cm^2), and stopped as soon as the pressure sensation became unpleasant/annoying. The procedure was repeated three times and the pressure values averaged.

2.2.1.3. Cold Pain Reactivity

The cold pain threshold (CPTh) and tolerance (CPTol) were assessed by immersing each subject's hand in water at 0-1 °C. The hand temperature was previously standardized by 2 min immersion in water at a temperature of 37 °C. The CPTh is the time (in seconds) elapsed between the immersion of the subject's hand and the earliest perception of pain. The cold pain suprathreshold (CPNRS6) is the time needed to perceive pain intensity = 6 (VAS = 0-10). The CPtol is the interval between hand immersion and the time at which the pain can no longer be tolerated [23]. Hand immersion is interrupted in the event of pain tolerance for longer than 2 minutes.

2.2.1.4. Heat Pain Reactivity

The heat pain threshold (HTh) and heat pain tolerance (Htol) were assessed by immersing the subject's dominant hand into a tub (Gen. Purpose Water Bath, Digital, 10 L, Polyscience, USA) containing water at 46.5°C. The HTh is the time (in seconds) elapsed between the hand immersion and the earliest perception of pain. The heat pain supra-threshold (HNRS6) is the time needed to perceive pain intensity = 6 (VAS = 0-10). The HTol (tolerance) is the time elapsed between hand immersion and hand emersion (due to heat intolerability). Immersions longer than two minutes were interrupted [24].

2.2.1.5. Diffuse Noxious Inhibitory Controls Paradigm (DNIC)

DNIC refers to an endogenous mechanism of pain modulation often described as "pain inhibiting pain". It occurs when the response to a painful stimulus is inhibited by a noxious stimulus which began earlier (at least 30 sec) and is administered to a site distant from the test stimulus. Baseline pressure pain threshold (pain score 1-10) was assessed by an algometer applied at the base of the ring finger of the non-dominant hand. The conditioning stimulus was generated by immersion of the other hand into a container with H_2O at 46.5°. The pressure pain threshold was re-evaluated when the heat pain reached 6 (heat pain scale: 0-10). The greater the difference between the two reported pain intensities, the greater the endogenous pain modulation [22].

2.2.2. Interoception

2.2.2.1. Body Perception Questionnaire (BPQ-SF)

The Body Perception Questionnaire-Short Form (BPQ-SF) is a 46-item self-report questionnaire measuring two domains of interoceptive sensibility: a) sensibility to interoceptive signals, and b) the experience of autonomic nervous system reactivity (ANS) [25, 26]. The latter has two subscales: i) the supradiaphragmatic reactivity subscale, which measures the response of autonomically-innervated structures above the diaphragm, and ii) the subdiaphragmatic reactivity subscale, a measure of gastrointestinal functions below the diaphragm, i.e., the unmyelinated vagus nerve, the sympathetic nervous system, and the enteric nervous system. Based on Porges' theory [7], a derived dimension is the ratio of supra/subdiaphragmatic reactivity subscale to explore the prevalence of one over the other. The item responses score the frequency of sensations, assessed on a 5-point likert-type scale (from "Never" to "Always"). We used a version derived from the forward- and back-translation procedure [27] of the english BPQ-SF of Porges [25].

2.2.2.2. Multidimensional Assessment of Interoceptive Awareness (MAIA I)

The MAIA I questionnaire is a self-report measure comprising 32 items on a 6-point likert scale. There are eight sub-scales: Noticing (awareness of pleasant, unpleasant and neutral bodily sensations), not-distracting (tendency not to ignore or to be distracted by pain sensations), not-worrying (ability to self-distract from unpleasant sensations), attention regulation (ability to support and direct attention to body sensations), emotional awareness (awareness of the connection between bodily sensations and emotional states), self-regulation (ability to regulate emotional suffering by paying attention to bodily sensations), body listening (active listening to the body for insight), and trusting (experience of one's body as safe and reliable). We used the validated italian version [28], whose Cronbach's alpha values are reported to range between 0.53 and 0.80-less than the original english version-and internal consistency reliability from .66 to .82; unstandardized alphas were over .70 for five of the eight scales [11]. In our study, the Cronbach's alpha was .675.

2.3 Statistical Analysis

The statistical package for social science (SPSS 26, IBM Corp. Released, 2022) was used for analyses. Kolmogorov-Smirnov test was applied to assess the normality of the studied distributions. Then, pain psychophysical variables were compared between groups (healthy, recurrent and chronic pain) through separate univariate ANOVAs. ANCOVA was applied controlling for age, pharmacological treatment and the dimensions of interoceptive sensibility. To measure the effect size, we used η2 (eta squared) according to [29] guidelines, i.e.: small effect: 0.01; medium: 0.059; and large: 0.138. A partial correlation was used to correlated the noticing variable of MAIA I to HTol. Statistical significance was set at $p<0.05$.

3. Results

As reported in an earlier paper, the chronic pain group was significantly older than the other groups, and used more psychotropic drugs. Moreover, as previously reported [14], higher body awareness scores were found in the chronic pain group than in the other groups, the autonomic reactivity self reported dimensions (BPQ-SF) were higher in the chronic pain group compared to other groups and to the sub-diaphragmatic reactivity. MAIA I scores did not differ among the three groups, except for the MAIA I not-distracting dimension, which was

higher in pain-free participants than in the recurrent pain group, and for the self regulation and trusting dimension, which were significantly lower in the chronic pain group [14].

3.1. Group Differences in Psychophysical Variables

As (Table 1) shows, the heat threshold (HTh), heat numerical rating Scale 6 (HNRS6) latency (suprathreshold stimulus) and heat pain tolerance (HTol) were higher in chronic pain patients with respect to both recurrent pain patients and pain-free participants. The difference of the first two psychophysical variables have a large effect size, unlike heat tolerance which is instead medium-low. Conversely, chronic pain subjects showed lower VonF threshold, with large effect size, compared the other two groups. There was a significant difference between pain free participants and recurrent pain patients in the HTol after Bonferroni correction (p=.036) (Table 1). Significant differences in HTh (p=.001), HNRS6 latency (suprathreshold stimulus) (p=.002) were found between chronic pain patients and pain-free participants. Significant differences in HTh were also found between recurrent and chronic pain patients (p=.036).

TABLE 1: Differences among groups in the psychophysics variables of experimental pain.

	Pain Free (A)			**Recurrent Pain (B)**			**Chronic Pain (C)**						**Bonferroni**		
	N.(%)	xM	sD	N.(%)	xM	sD	N.(%)	xM	sD	F	p	η2	A/B	A/C	B/C
	52			47			42								
Cold Threshold (sec)		10.54	7.82		11.67	7.80		14.07	14.14	1.15	ns	.02			
Cold NRS6 (sec)		27.24	19.80		26.34	15.41		27.89	17.65	.06	ns	.00			
Cold Tolerance (sec)		53.38	31.27		62.69	38.88		62.84	40.67	.88	ns	.01			
Heat Threshold (sec)		5.65	6.66		10.62	10.05		20.13	27.07	7.42	**.001**	.12	ns	**.001**	**.036**
Heat Intensity NRSH6 (sec)		18.46	14.63		27.09	16.39		35.34	27.63	6.43	**.002**	.10	ns	**.002**	ns
Heat Tolerance (sec)		52.28	36.81		73.23	40.33		62.11	35.77	3.27	**.042**	.05	**.036**	ns	ns
Pressure Threshold (sec)		5.57	2.11		5.56	2.33		5.27	1.99	.18	ns	.00			
DNIC score		1.21	1.39		1.42	1.59		1.56	1.12	.30	ns	.00			
Von Frey (mN)		3.32	.71		2.99	.89		2.39	.93	7.03	**.001**	.14	ns	**.000**	**.000**

F: Univariate ANOVAs with Bonferroni corrections;. η2: eta square effect size Anova; ns: not significant; sec: seconds; mN: milli-newton.

3.2 Role of Interoceptive Sensibility in the Groups Differences in Pain Psychophysics

Controlling for age and psychopharmacological treatment, maintained only the difference in HTol (F=3.16; p=.047; η2=.064). The HTol became nonsignificant after controlling for body awareness (F=2.2, p=.11), supradiaphragmatic (F=2.2, p=.11), sub-diaphragmatic reactivity (F=2.2, p=.11). Controlling for age and psychopharmacological treatment no significant difference in HTol was found between the recurrent versus chronic pain group, instead a difference was found between healthy and recurrent pain (F=5.341, p=.023, η2=.065). Comparing these two groups BPQ-SF dimensions influenced this difference through their deletion. In fact, when we add body awareness (F=3.35, p=.071, η2=.043), supradiaphragmatic (F=3.52, p=.064, η2=.065) and subdiaphragmatic reactivity (F=3.71, p=.058, η2=.048) to the covariates of age and psychopharmacological treatment, the difference in HTol between healthy and pain recurrent groups is cancelled.

Controlling for age and psychopharmacological treatment no differences in the MAIA I dimensions have been found among groups except noticing (awareness of pleasant, unpleasant and neutral bodily sensations) (Table 2). Different perception of Htol between groups was canceled comparing healthy subjects with recurrent pain patients when included noticing in the covariance (F=13.48, p=.066, η2=.043). Investigating the relationship between Htol and noticing using the partial correlation (correcting for age and psychopharmacological treatment) no significant positive correlation we found (r=.17). No statistically increased scoring of Noticing we found in subjects with pain (recurrent and chronic) compared healthy subjects (F=1.39, p=.25, η2=.02).

TABLE 2: Influences of interoceptive sensibility dimensions on the difference of the perception of experimental noxious stimuli among pain free, recurrent and chronic pain groups.

	CPTh			**CPNRS6**			**CPTol**			**HTh**			**HPNRS6**			**HTol**			**PThr**			**DNIC**			**VonFrey**		
Covariates	F	p	η2	F	p	η2	F	p	η2	F	p	η2	F	p	η2	F	p	η2	F	p	η2	F	p	η2	F	p	η2
Age plus Psychopharmacology	.59	.55	.01	.24	.78	.00	1.6	.20	.03	2.3	.10	.05	2.4	.09	.05	**3.1**	**.04**	**.06**	.15	.85	.00	.42	.65	.01	.76	.46	.02
BPQ																											
Body Awareness	.68	.50	.01	.11	.88	.00	1.2	.28	.02	1.7	.17	.04	1.2	.29	.03	**2.2**	**.11**	**.05**	.69	.50	.01	.66	.51	.02	.03	.96	.00
Supradiaphragmatic React.	.52	.59	.01	.11	.88	.00	1.2	.28	.02	2.0	.13	.04	1.5	.21	.03	**2.2**	**.11**	**.05**	.81	.44	.01	.65	.52	.02	.11	.89	.00
subdiaphragmatic React.	.77	.48	.01	.11	.89	.00	1.2	.28	.02	1.4	.23	.03	1.2	.30	.03	**2.2**	**.11**	**.05**	.94	.39	.02	.27	.76	.00	.10	.90	.00
MAIA																											
Noticing	.99	.37	.02	.40	.66	.00	2.1	.12	.04	1.8	.15	.04	1.8	.16	.04	**2.8**	**.06**	**.06**	.21	.80	.00	.31	.72	.01	.63	.53	.01
Not-Distracting	.43	.64	.00	.25	.77	.00	1.6	.19	.03	1.7	.17	.03	1.9	.15	.04	3.0	.05	.06	.10	.90	.00	.53	.59	.01	1.5	.23	.03
Not-Worrying	.59	.55	.01	.25	.77	.00	1.5	.21	.03	2.3	.09	.05	2.4	.09	.05	3.2	.04	.06	.15	.85	.00	.43	.64	.01	.61	.54	.01
Attention Regulation	.67	.51	.01	.55	.57	.01	2.0	.13	.04	2.3	.10	.05	2.5	.08	.05	3.6	.03	.07	.56	.56	.01	.49	.61	.01	.75	.47	.02
Emotional Awareness	.71	.49	.01	.27	.76	.00	1.7	.18	.03	2.0	.13	.04	2.1	.12	.04	3.0	.05	.06	.17	.84	.00	.36	.69	.01	.70	.50	.02
Self-Regulation	.56	.57	.01	.24	.78	.00	1.7	.18	.03	2.3	.10	.05	2.3	.09	.05	3.1	.05	.06	.14	.86	.00	.42	.65	.01	.75	.47	.02
Body Listening	.72	.48	.01	.24	.78	.00	1.6	.20	.03	2.0	.13	.04	1.9	.15	.04	3.0	.05	.06	.14	.87	.00	.54	.58	.01	.58	.56	.01
Trusting	.40	.66	.00	.30	.73	.00	1.6	.19	.03	2.2	.11	.04	2.1	.12	.04	3.1	.04	.06	.16	.85	.00	.28	.75	.00	.65	.52	.01

F: Univariate ANCOVA; η2: eta square effect size ANOVA.

4.Discussion

The aim of this study was to assess whether interoceptive sensibility differentially modulates the response to experimental pain in patients with recurrent or chronic pain, as compared to pain-free individuals. For this purpose, both BPQ-SF and MAIA I questionnaires were administered. This can be considered one of the strengths of the study, as they indicate different aspects of interoception, allowing both a distinction between the different roles of sub- and supradiaphragmatic components of interoception (BPQ-SF) and providing an estimate of the influence of interoceptive sensibility/awareness (indicated by MAIA I dimensions and BPQ-SF body awareness) in different types of pain patients.

The literature on the relationship between nociception and interoception in humans is often extrapolated from animal studies, and few investigations are conducted through experimentally induced painful stimulation often bringing to conflicting results [30].

4.1. Effects of Interoceptive Sensibility on the Different Responsiveness to Noxious Heat Stimuli Among Groups

The main finding of the study is that chronic pain patients exhibit only differences in the reaction to heat pain with respect to the other groups. Moreover, these differences are modulated by a few dimensions of interoceptive sensibility, in addition to well-known factors such as age and drugs consumption.

Quantitative sensory testing is usually performed by extremely localized skin phasic mechanical and thermal stimuli, whereas in the present study the reactivity to noxious thermal stimuli was assessed by hand immersion in cold and hot water, the latter test being investigated only in healthy subjects [31]. The higher HTh applied to the whole hand in chronic pain patients has never been reported following the heating of a small skin area. However, it must be underling the older age of our chronic pain patients [14]. In the past, the effect of age on pain perception has been greatly debated; nonetheless, there is now some agreement [32] that only HTh, tested on a restricted skin area by a thermode, is increased in chronic pain patients. We suggest that the peripheral dysfunction may affect the hairy skin, particularly the quickly adapting type II A fibers, which are vulnerable to repetitive heat stimuli [33]. In our experiments, the stimulation of a wide peripheral area with reduced Aδ fiber innervation could result in a reduced central summation, contributing to the increased HTh.

4.2 Interoceptive Sensibility Modulates the Group Differences, as Shown by the Loss in Difference of Tolerance to a Heat Painful Stimulus

Our previous finding highlighted the observations regarding the positive correlation between with maladaptive interoception attention style such as somatosensory amplification and somatization and somatic symptoms [14, 34]. With these results we highlight that, except heat tolerance, the significant differences in the HTh and HPNRS6 between groups, were abolished after controlling for age and treatments. On the other hand, after controlling for age and psychopharmachological treatments, the difference in tolerance to a heat painful stimulus remains, however canceled if we insert the dimensions of the BPQ in the covariates. This loss of difference is found between groups without pain and recurrent pain, while it is not evident between subjects with pain.

This is true also for Noticing dimensions of MAIA I that seem correlated positively with an increased of heat tolerance of experimental pain and affects on the different pain perception already from the presence of recurring pain allowing greater tolerance. Our results therefore show that interoceptive sensibility affects the perception of an experimentally induced painful stimulus (e.g. warm stimulus) when the individual begins to present pain, even if not persistent.

5. Conclusion

Interoceptive sensibility influences the experience of pain in healthy participants and pain patients. It may also buffer the role of age. Thus, findings indicate a different association between interoceptive sensibility and pain perception in health and disease states [35].

Limitation

An increased of number of subjects and the investigation of further individual and situational variables not investigated here [36] can increase the reliability of our result. Nonetheless, a retrospective survey provides important information about the condition of patients as they come to the observation of the clinician.

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