Observational Studies

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A retrospective observational study comparing somatosensory amplification in fibromyalgia, chronic pain, psychiatric disorders and healthy subjects

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Abstract

Objectives: Somatosensory amplification (SA) has been described as an important feature of somatoform disorders, and an "amplifying somatic style" has been reported as a negative connotation of body perception. As widespread pain (WSP) in fibromyalgia (FM) is due to a central sensitization (CS) rather than organic alterations, there has been discussion as to whether FM is equivalent to or distinct from somatization disorder (SD). Assuming SD and FM are two distinct entities, an increase in somatic amplification should be expected only in subjects who have SD, regardless of the type of pain they experience. Purpose of the study was to explore the magnitude of SA in FM, and whether this depends on the association with SD.

Methods: FM (n=159) other forms of chronic pain (OCP, n=582), psychiatric (Psy, n=53) and healthy (H, n=55) subjects were investigated using the Somatosensory Amplification Scale (SSAS), Illness Behavior Questionnaire, (IBQ), Italian Pain Questionnaire (IPQ), and Cold Pressor Test (CPT) in a retrospective observational study.

Results: FM subjects displayed higher SSAS scores than the other groups. High SSAS score was associated with FM (OR=8.39; 95%CI: 5.43–12.46) but not OCP. Although FM has the highest prevalence of SD (x^2=14.07; p=.007), high SSAS scores were associated with SD in OCP but not in FM.

Conclusions: Unlike in OCP, in FM high SSAS scores were independent of the presence of SD. From a biopsychosocial perspective, SSAS may be a factor associated with the onset of FM.

Keywords: chronic pain; fibromyalgia; sensitization; somatization; somatosensory amplification.

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Introduction

Background

Somatosensory amplification (SA) is defined as the tendency to experience somatic sensation as intense, noxious and disturbing [1]. SA includes three components: 1) body hypervigilance, 2) focusing on rare and weak body sensations, and 3) a cognitive-emotional reaction to the sensation. Somatosensory amplification has been described as an important feature of hypochondriasis, and an "amplifying somatic style" has been defined as a negative connotation of body perception [2]. Somatosensory amplification has also been associated with alexithymia [3, 4] and plays a critical role in the pathophysiology of somatization [1], that is the manifestation of psychological suffering through somatic symptoms with persistent clinically significant complaints about somatic symptoms.

Early on, this sensorial and cognitive-emotional dysfunction was conceptualized as "augmenting" [5] or "sensitization" [6], and was theorized by Barsky to be a stable trait likely sustained by a dysfunction in visceral and somatic afferent and sensory modulatory processing [7]. A central role in the circuit model of SA seems to be played by the mid-insula, considered an integrative zone where

affective and motivational information from the anterior cingulate cortex (ACC), amygdala and orbitofrontal cortex (OFC) influence the sensory processing driven by the posterior insula [7, 8]. A dysfunction in the connectivity of these areas has also been suggested for alexithymia [8–11], another dimension of somatization.

Two main dimensions of somatization, that is abnormal illness behavior and alexithymia, have been associated with fibromyalgia (FM) [12, 13]. In addition, greater amplification due to central sensitization has been shown in fibromyalgic subjects [14–16], and central sensitization has been associated with widespread pain, which is the main symptom of FM. Furthermore, high levels of illness behavior and somatic symptoms are predictors of chronic widespread pain (CWP) [17–20].

Several studies have investigated the neurobiological process of the somatosensory nervous system called central sensitization (CS) in FM; CS is an augmentation, amplification or facilitation of subthreshold synaptic inputs to nociceptive neurons due to an increased membrane excitability and synaptic efficacy in response to activity, inflammation and neural injury [21]. The clinical effect of CS is widespread pain, allodynia (pain in response to normally non-painful stimuli) and hyperalgesia (increased pain in response to normally painful stimuli) [22]. The association of FM with a dysfunctional central sensitization syndrome [23] prompted some researchers to describe the FM with a new terminology as a "nociplastic feature", which refers to the altered nociception in FM, as corroborated by psychophysics investigations [24]

Adverse events, especially occurring at an early age, have also been implicated in the pathogenesis of FM [25–27]. In fact, in our previous research we found associations between the number of stressful life events and increased SA, as well as increased somatic dissociation, and impairments in both emotional awareness and autobiographical memory [28]. Hence, early stressful life events, memory dysfunction and an increased level of somatosensory amplification could explain the hippocampal involvement showed in the SA circuit model derived from neurobiological investigations [7]. In fact, the association with memory of trauma (forgotten or increased) could make SA the embodied perceptual dimension that identifies the experience of trauma, as suggested by some authors, who define it "somatic threat amplification" [25, 2].

Somatosensory amplification, like somatization disorder (SD), has been investigated in the psychosomatic population [29], as well as in the subjects with health anxiety or generalized anxiety disorder [30]. Some psychiatric disorders are associated with an increase in somatosensory amplification [30–32]. However, somatosensory amplification has scarcely been investigated in chronic pain, in particular FM. Furthermore, there is little literature comparing the respective roles played by somatosensory amplification in psychiatric and chronic pain subjects.

The DSM-5 has led to a reclassification of the so-called "somatization disorders" (as per the DSM IV), which have been replaced by "somatic symptoms disorder" (SSD) [29]. While FM was previously considered a medically unexplained pain syndrome, and often considered equivalent to somatization disorder [21, 33, 34], now FM can be diagnosed in comorbidity with SSD, as both are considered separate entities [35]. Although SA has been widely investigated in SD, there is little literature demonstrating its association with the new SSD; indeed, when we began this study, the DSM-5 had not yet been introduced, which is why we relied upon the DSM IV classification of SD, assessing the effects of health anxiety using the illness behavior questionnaire (IBQ). If somatization disorder and FM are indeed two distinct entities, we should expect to see an increase in somatic amplification only in the pain patients exhibiting a somatization disorder, irrespective of the nature of pain.

Objectives

The main objective of this study was to compare somatosensory amplification scale (SSAS) scores, as a measure of SA, in subjects with FM and those experiencing other forms of chronic pain, as well as in healthy subjects and individuals with psychiatric disorders but no history of chronic pain. The second objective was to explore whether greater SA is associated with FM exclusively in the presence of somatization disorder, or independent of it.

Methods

Participants

This study is based on data collected from 2005 to 2017 at the Psychosomatic Center at the Pisa GIFT Institute of Integrative Medicine (PIMPC), Italy, in collaboration with Aplysia Onlus. The research was conducted in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects. Participants were identified by an alphanumeric code to guarantee their anonymity, and all signed informed consent. Being a retrospective study, no Ethics Committee approval was necessary [36]. The study adheres to the STROBE statement guidelines for observational research.

For the purposes of this study, participants were allocated one of four groups on the basis of their recorded diagnosis, namely

fibromyalgia (case group), or other chronic pain, psychiatric or healthy (control groups), as described below. Subjects exhibiting both a psychiatric disorder and a history of chronic pain over the previous year were excluded, as were those taking antidepressants or antiepileptics if they had started treatment less than 3 months previously, or if their dosage had been changed within that time. Similarly, patients were excluded if they were taking daily treatment for pain (analgesic, opioids, cannabis).

1. *Fibromyalgia* (FM): Although the most recent classifications have improved the assessment of FM [37, 38], in the 2005, when this study started, we had to use the current classification of ACR of 1990 (American College of Rheumatology, 1990) and keep the same criteria also in the enrolment of patients in later times[19]. However, already in the 2005, in our clinical practice we noticed the limited nature of this diagnostic system, and therefore integrated some indications suggested by Yunus in 2002 [39], and later refined [40, 41], specifically: a) ≥11 tender points for females and ≥4 for males (two tender points on each side of the body and two above and below the umbilical sagittal section); b) widespread pain (pain in both sides of the body, both above and below the waist), at a minimum of 4 sites in men and 7 sites in women; c) poor sleep quality; d) fatigue; e) stiffness; f) mood and/or anxiety problems (affirmative responses to the questions: "do you feel depressed?", "do you feel anxious?"); g) association with at least two of the following conditions: restless leg syndrome, irritable bowel syndrome, headache or migraine, temporomandibular joint dysfunction; h) thyroid problems; and i) negative blood parameters for inflammation and the absence of electrophoretic changes. Unexpectedly, the above assessment implementation of the FM that we used, with the exception of Symptom Severity Scale, covers almost of all of the 4 criteria of FM 2016 assessment revision.
2. The diagnosis of fibromyalgia was formulated only if all the above criteria had been present for almost all of the time during the preceding three months. Our assessment took into account all core symptoms and the diagnostic criteria described above
3. *Other chronic pain* (OCP) refers to the other forms of chronic pain with the exclusion of FM [42]. Although in clinical practice we are current using [43] the new ICD 11 assessment for chronic pain [44], these criteria were not yet out in 2005. Therefore, we enrolled patients for this study using the 1994 criteria of the International Association for the Study of Pain (IASP) chronic pain classification [45]. Pain syndromes are described in Table A of the Supplemental Material. All patients had been referred to the above center due to resistance to the usual treatments [19] provided by the primary and secondary tiers of the Italian National Healthcare System (NHS).
4. *Psychiatric* (Psy): With the introduction of the DSM-5 (Diagnostic and Clinical Manual of Mental disorders five edition), the classification of mental disorders has undergone an important change compared to previous editions [35]. From a categorical assessment, the diagnostic system moved into a dimensional and spectrum perspective. However, in 2005, when our study started, the researchers began to discuss the fragility of the at the current time classification system, in particular with regard to somatoform disorders [46], but it was still not possible to apply the new classification system. Therefore, like the diagnosis of fibromyalgia and other forms of pain, we had to use the previous classification system of the DSM IV-TR for psychiatric disorders, using the categorical assessment [47]. The diagnosis of psychiatric disorders was made using the Mini International Neuropsychiatric Interview (MINI), according to the DSM-IV TR, as described below [48]. When we the presence of more than one psychiatric disorder was detected, we selected as the main diagnosis that of earlier onset and longer duration.
5. *Healthy* (H): These were enrolled from among the graduate trainees at the psychophysics laboratory at the above center. As part of their training, center trainees conduct a self-assessment and peer assessment using the various diagnostic tools described below; those who signed informed consent to the anonymous use and publishing of their data, and reported no pain or psychiatric disorders, were enrolled in the study as healthy controls.

No other information was collected for individuals who did not meet the selection criteria or failed to complete the questionnaires.

Variables

CPT: Cold pressor test: The CPT [49] is a psychophysical test that measures the pain threshold and tolerance for painful stimulation upon immersion of a subject's hand in a container of water at 0–1 °C. The hand temperature is previously standardized by immersion for 2 min in water at a temperature of 37 °C. The subject is instructed to leave their hand in the ice water until they can no longer tolerate the pain. The time (in seconds) elapsed between the immersion and the first perception of pain and, then, the removal of the hand are used as measures of the subject's pain threshold and tolerance, respectively.

MINI: Mini International Neuropsychiatric Interview (MINI): This a short, structured diagnostic interview constructed according to DSM-IV and ICD-10 criteria. With an administration time of approximately 30 min, the MINI was designed for multicenter clinical trials and epidemiology studies [48]. The Italian version of the MINI-plus used in this research investigates current and lifetime psychiatric disorders, including mood disorders and somatoform disorders [50]. In the presence of more than one psychiatric disorder, for each patient we selected as the main diagnosis the disorder of earliest onset and longest duration. This interview was conducted on the entire sample used in our study (including the healthy control group).

SSAS: Somatosensory amplification scale: This tool quantifies the propensity of a subject to somatosensory amplification, i.e., the tendency to experience intense, noxious and disturbing somatic sensations [1]. It consists of 10 statements scored on a Likert scale (0 = "never" = 1 "a little" 2 = "moderately", 3 = "almost always," 4 = "always"), and the higher the score (maximum 40), the greater the tendency to somatic amplification. This scale has been translated into Italian [51] and previously used in an Italian pain study to assess somatosensory amplification, considered one of the most important factors in pain becoming intractable [52].

Nakao et al. [4] have shown total SSAS scores above 30 in outpatients at a Japanese psychosomatic clinic. Their SSAS scores range from 1–5, whereas we used the original Barsky et al. [1] score, which ranged from 0–4; therefore, a Nakao score of 30 corresponds to a score of 24 according to Barsky et al., 1988 [1].

IPQ: Italian Pain Questionnaire: This tool was constructed ex novo and validated in Italian using the English McGill Pain Questionnaire (MPQ) dimensions and the factorial structure proposed in the original English version; its items are designed to measure four classes, or

dimensions, of pain, namely Sensorial, Affective and Evaluative and Mixed [53]. In this study we used only the first three dimensions. In addition, the subjects' perceived intensity of pain was assessed on a 0–10 NRS (Numerical Rating Scale), on which 0 equals no pain, and 10 the worst pain imaginable.

IBQ: Illness Behavior Questionnaire: The IBQ [54] is a self-assessment questionnaire used to investigate behavior in disease through seven scales, or factors, identified by factor analysis, which respectively measure: 1) General Hypochondriasis (GH), a fearful attitude towards disease, despite an awareness of the disproportionate nature of this concern; 2) Disease Conviction (DC), the conviction of having a physical, rather than mental, disease, and a reluctance to accept any kind of medical reassurance; 3) Psychological Perception vs. Somatic Disease (P/S), a bipolar scale expressing the tendency of the subject to consider the problem from a psychological (higher scores) rather than somatic (lower scores) perspective; 4) Affective Inhibition (AI), the level of disclosure of feelings (especially negative ones); 5) Affective Disturbance (AD), the presence of anxiety, depression and tension; 6) Denial (D), the tendency to deny the stresses of life and ascribe a complaint solely to physical illness; and 7) Irritability (I), an attitude characterized by interpersonal hostility (high scores). The questionnaire also features two subscales for scoring two second-order factors known as Affective State (AS) and Disease Affirmation (DA), respectively. These scores, calculated via dedicated formulas, provide a more global picture of abnormal illness behavior.

Bias

Since FM subjects are predominantly females, gender is the most relevant variable that could lead to bias in the selected sample, as the other groups were more proportionate. However, as we wanted to study the association of somatic amplification with gender, we used a large sample and non-parametric tests (when appropriate) to analyze FM data, and the differences between the groups were corrected for gender.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 21. After application of the Kolmogorov-Smirnov test—which gives details about the Gaussian distribution of the data—the t-test, ANOVA, and Pearson correlation analysis were performed (on global sample and each group). Between-group differences in variables were investigated using chi-squared testing and ANOVA univariate analysis with Bonferroni multiple comparison correction.

To infer the role of global SSAS score as a predictive factor, we used linear regression analysis. The odd's ratio [55] was used to investigate the association of SA with psychiatric disorders and other dichotomous dimensions, dividing the sample into those with a mean SSAS score ≥16 and those below, and plotting them using Forest Plot in Excel. Statistical significance was set at $p<0.05$.

Results

Sociodemographic differences

The sample included 849 subjects: Chronic Pain patients without FM (OCP, n=582), Fibromyalgia patients (FM, n=159), patients with psychiatric disorders (Psy, n=53) and a group of Healthy controls (H, n=55). OCP group diagnoses are described in Table A of the Supplemental Material. Each group differed in several sociodemographic variables (ANOVA and chi-squared analyses) (Table 1). As shown in Table 1, subject groups differed in terms of age, with the OCP group being the oldest and the H group the youngest, and education level, which was lowest in the OCP group and highest in the H group. In addition, the widowed were more prevalent in the OCP and FM groups (11.3 and 7.5%, respectively) as compared to control subjects, 94.5% of whom were single.

ANCOVA revealed that SSAS differences were not influenced by either age (F=0.003), education (F=0.057) or civil status (F=1.82). Only gender influenced differences SSAS score among groups (F=5.82; p=0.016). Splitting subjects based on mean SSAS score (the average SSAS score of the entire sample was 14.65 SD=7.11, with 16 expressing the certainty of having an above average value) into those scoring <16 vs. ≥16, did not reveal any association between SSAS score and gender (logistic regression, Exp(B)=1.25; p=0.21; 95% CI Exp(B)=0.87–1.79).

Relationship between somatosensory amplification and abnormal illness behavior in each group

The Illness Behavior Questionnaire (IBQ) factor scores are reported in Table 1. With exception of Irritability (I) and Affective Inhibition (AI), all other factor scores differed significantly among groups. In particular, General Hypochondriasis (GH) was highest in FM subjects. After Bonferroni correction, there was a significant difference in GH between FM and OCP, with FM with scoring higher (F=8.67; df=3; mean diff=–0.75; p=0.000). All groups displayed statistically significant differences in Disease Conviction (DC) with respect to Healthy (H) subjects. However, there was no difference in DC between OCP and FM, while both FM (DC: F=29.76; df=3; diff: 1.11; p=0.000) and OCP (F=29.76; df=3; diff=0.79; p=0.002) differed from the Psychiatric disorders group (Psy) in DC scores. Psy showed the highest value of Psychological vs. Somatic Focusing dimension (P/S) of the groups (F=6.09; df=3; p=0.000), while FM subjects had statistically significantly higher Affective Disturbance (AD) than the other groups (F=12.81; df=3; p=0.000); H and Psy had the lowest AD scores, and there were no statistically significant differences between the two. The OCP group had the highest score for Denial (D), a statistically significant difference

Table 1: Between-group differences in sociodemographic and clinical variables.

		Healthy			Fibromyalgia			Other chronic pain			Psychiatric					
		n (%)	xM	sD	n (%)	xM	sD	n (%)	xM	sD	n (%)	xM	sD	F/χ2	η2	p
		55			159			582			53					
Age			25.63	2.35		52.84	15.72		54.90	16.78		33.90	11.51	80.74	0.223	0.000
Gender	Males	14(25.5)			19(11.9)			218(37.5)			23(43.4)					
	Females	41(74.5)			149(88.1)			364(62.5)			30(56.6)			41.51		0.000
Education			17.91	1.71		10.03	4.62		9.83	4.77		15.36	3.88	72.50	0.209	0.000
Civil stauts	Single	52(94.5)			30(18.9)			99(17.0)			35(66)					
	Married	3(5.5)			103(64.8)			380(65.4)			16(30.2)					
	Divorced	0			14(8.8)			37(6.4)			2(3.8)					
	Widowed	0			12(7.5)			66(11.3)			0			214.39		0.000
Income	High	6(10.9)			28(17.6)			62(10.7)			9(17)					
	Medium	48(87.2)			124(78)			480(82.5)			40(75.5)					
	Low	1(1.8)			7(4.4)			40(6.9)			4(7.5)			9.83		ns
	Onset of pain (months)					152.17	147.15		80.59	102.15				33.28	0.064	0.000
	Tender points					13.17	3.65		6.89	4.77				134.18	0.336	0.000
CPT	Threshold		14.73	17.39		13.88	14.37		24.00	25.17		21.31	25.06	8.43	0.037	0.000
	Tolerance		54.99	31.32		44.18	33.60		66.92	39.63		67.57	40.97	13.79	0.059	0.000
IPQ	Sensorial					0.43	0.18		0.37	0.29				4.76	0.006	0.02
	Affective					0.47	0.22		0.39	0.29				9.08	0.012	0.003
	Evaluative					0.47	0.24		0.43	0.41				1.17		ns
	Intensity (NRS)					7.37	2.38		7.48	2.37				0.25		ns
IBQ	General hypochondriasis		2.12	2.06		3.54	2.13		2.78	2.0		2.81	1.86	8.67	0.030	0.000
	Disease conviction		1.67	1.33		3.76	1.54		3.43	1.53		2.64	1.75	29.76	0.096	0.000
	Psychological vs somatic focusing		1.83	1.24		1.96	1.16		1.90	1.12		2.60	1.45	6.09	0.021	0.000
	Affective inhibition		2.38	1.45		2.42	1.64		2.27	1.53		2.60	1.47	1.01		ns
	Affective disturbance		2.03	1.60		3.45	1.43		2.75	1.72		2.52	1.58	12.81	0.044	0.000
	Denial		2.30	1.57		2.89	1.66		3.37	1.50		2.60	1.32	13.16	0.045	0.000
	Irritability		2.29	1.24		2.75	1.67		2.38	1.73		2.60	1.43	2.29		ns
SSAS	Total		6.81	6.60		21.11	6.26		13.68	6.06		13.96	6.96	91.97	0.246	0.000

ANOVA univariate analysis, SSAS, Somatosensory amplification scale, global score; IBQ, Illness Behaviour Questionnaire; IPQ, Italian Pain Questionnaire; CPT, Cold Pressor Test.

with all the other groups (F=13.16; df=3; p=0.000). On the whole, FM and OCP groups displayed greater IBQ dimension scores than H and Psy, with the exception of P/S.

Subdividing the entire sample on the basis of the mean SSAS scores, i.e., subjects with scores <16 vs. ≥16, we found a significant difference in IBQ dimensions, as shown in Figure 2. Specifically, subjects with SSAS≥16 scored higher on GH, DC, P/S, AD and Irritability (I) than subjects with SSAS<16. However, when the relationship between SSAS and IBQ dimension scores was studied in more depth, there were differences based on the group investigated.

For example, as shown in Table 2, there was a particularly close association between SSAS score and GH in both OCP and FM subjects. In the OCP group, the SSAS score was strongly correlated with Irritability (I)—a relationship that was not observed in the FM group. In the H group, SSAS score was strongly correlated with the cognitive dimension P/S and Denial (D). There was little correlation between SSAS and IBQ dimension scores in the Psy group (Table 2).

Considering the IBQ dimensions as dependent variables and SSAS score as the independent variable in linear regression analysis, SSAS score appeared to be a positive predictor of GH in the FM, OCP and Psy groups (Table 3). Furthermore, SSAS score was found to be a positive predictor of AD in all groups except H. The relationship between SSAS score and P/S seen in H subjects (Table 2) was confirmed by regression analysis, which showed that SSAS score was a positive predictor of P/S in this group (Table 3).

To confirm the predictive role of SSAS in each group, we investigated the association of IBQ dimension scores (distinguishing into two groups based on mean value) and SSAS score (≥16). As shown in Figure 3, SSAS≥16 was predictive of GH≥3, DC>3 and AD≥3, but only in the OCP group. In fact, FM subjects displayed SSAS scores greater than 16 regardless of the presence of high GH, DC or AD (e.g., SSAS≥16 was associated with 85.7% GH≥3 and 74.1% GH<3; X^2=3.24; p=ns).

Relationship between somatosensory amplification and pain perception in each group

SSAS score was a positive predictor of both the number of tender points (β=0.33; t=5.69; p=0.000) and a longer duration of pain (in months) (β=0.15; t=3.44; p=0.001). Considering the sample as a whole, subjects with SSAS≥16 had greater Affective dimension of clinical pain scores and lower pain threshold (Thr) and tolerance (Tol) than subjects with SSAS<16 (Figure 4). These results are in line with the negative correlation with experimentally induced pain threshold and tolerance in the whole sample shown in Table 2. Considering SSAS score as the independent variable and pain dimensions as dependent variables, we showed that SSAS score was a negative predictor of pain tolerance in all groups with the exception of the healthy control group (Table 4). SSAS score was a negative predictor of Thr only in the OCP group. A high SSAS score predicted high Affective and Evaluative dimension scores and greater pain intensity in the FM group, and high Affective dimension scores in OCP patients (Table 4).

Table 2: Correlation between SSAS and IBQ, IPQ and cold pressure test values.

		Total sample	Healthy	Fibromyalgia	Other chronic pain	Psychiatric
IBQ	General hypochondriasis	0.29****	0.14	0.31****	0.22****	0.29*
	Disease conviction	0.29****	0.32*	0.19*	0.20****	0.24
	Psychological vs. somatic focusing	0.09**	0.67****	0.05	0.06	−0.05
	Affective inhibition	0.04	−0.17	0.07	0.07	−0.15
	Affective disturbance	0.30****	0.17	0.29****	0.21****	0.34*
	Denial	−0.01	0.39***	−0.02	−0.05	−0.15
	Irritability	0.16****	−0.16	0.15	0.16****	0.18
IPQ	Sensorial	0.06		0.13	0.09	
	Affective	0.16****		0.27***	0.10*	
	Evaluative	0.07		0.18*	0.04	
	NRS	0.03		0.31****	−0.02	
CPT	Threshold	−0.17****	−0.09	−0.10	−0.15***	−0.26
	Tolerance	−0.19****	−0.11	−0.17*	−0.11*	−0.33*

IBQ, Illness Behavior Questionnaire; IPQ, Italian Pain Questionnaire; CPT, Cold pressor test, *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Table 3: SSAS as a predictor of IBQ dimensions in each group.

	GH			DC			PSIvsSOM			AD			D			I		
	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p
Healthy				0.32	2.51	0.015	0.67	6.64	0.000				0.39	3.12	0.003			
Fibromyalgia	0.31	4.10	0.000	0.19	2.49	0.014				0.29	3.82	0.000						
Other chronic pain	0.22	5.61	0.000	0.20	5.01	0.000				0.21	5.29	0.000				0.16	3.97	0.000
Psychiatric disordes	0.29	2.16	0.035							0.34	2.60	0.012						

Simple linear regression analysis; SSAS, Somatosensory Amplification Scale, global score; IBQ, Illness Behaviour Questionnaire. GH, General Hypochondriasis; DC, Disease Conviction; PSYvsSOM, Psychological vs. Somatic Focusing; AD, Affective Disturbance; D, Denial; I, Irritability.

Relationship between somatosensory amplification and the presence of psychiatric disorders

As we reported in the inclusion criteria, healthy control subjects had no psychiatric disorders, as assessed via the MINI. In all other subjects (n.794), when, according to the MINI, they showed the presence of more than one psychiatric disorder, we selected that of earlier onset and longer duration as the main diagnosis. As shown in Table 5, the prevalence of subjects without psychiatric disorders in OCP was significantly greater than in FM (OCP 26.3% vs. FM 14.6%). Psy subjects showed a greater prevalence of panic disorder (PD), obsessive compulsive disorder (OCD), eating disorder (Ea) and hypochondriasis (Hy) than FM and OCP subjects (Table 5), while OCP showed a greater prevalence of Pain disorder (Pain) than FM (5.3 vs. 1.9% respectively). FM subjects showed a greater prevalence of somatization disorder than the other two groups of patients.

Exploring the relationship between SSAS score and the presence of psychiatric disorders in each group, we investigated the association with psychiatric disorders and SSAS≥16 using logistic regression analysis. No association was found between psychiatric disorders and high SSAS except that in OCP, in which the SSAS≥16 was a positive predictor of somatization disorder and hypochondriasis, and a negative predictor of the absence of psychiatric disorders (Figure 3). This result was unexpected. In fact, despite the high prevalence of somatization disorder in the FM group, high SSAS scores did not predict somatization disorder in this group.

The role of somatosensory amplification in fibromyalgia

As shown in Table 1, subjects with FM exhibited high SSAS scores (η^2=0.24), as compared to the other groups. No significant differences in SSAS scores were found between the different chronic pain syndromes included in the OCP group. No gender difference was found in SSAS scores in the FM group (Figure 1) (t=0.11; p=0.91). In this group, however, high SSAS score was a predictor of low pain tolerance and high Affective and Evaluative dimensions and intensity of clinical pain (Table 4).

Although FM showed the greatest prevalence of somatization disorders (Table 5), the presence or absence

of somatization disorder was unrelated to high SSAS score (≥16). In contrast, this relationship was observed in the OCP group, in which high SSAS score predicted somatization disorder (Figure 3). As shown in Figure 5, SSAS score was the main predictor of FM, along with GH, DC and AD, independently of each other. On the other hand, our results showed that SSAS≥16 is a negative predictor of OCP (Exp(B)=0.19; p=0.000; 95% CI Exp(B)=0.13–0.27). Thus, SSAS score predicts fibromyalgia but not other forms of chronic pain. However, somatosensory amplification (SA) may be a dimension that can indirectly affect chronic pain, as SSAS score predicted illness behavior and the occurrence of a somatoform disorder.

Table 4: SSAS as a predictor of experimental (CPT) and clinical dimensions of pain (IPQ).

	Threshold			Tolerance		Sensorial			Affective			Evaluative			NRS		
	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p
Healthy																		
Fibromyalgia				−0.17	−2.06	0.041				0.27	3.52	0.001	0.18	2.28	0.024	0.31	4.07	0.000
Other chronic pain	−0.15	−3.22	0.001	−0.11	−2.46	0.014				0.10	2.49	0.013						
Psychiatric disordes				−0.33	−2.41	0.020												

Simple linear regression analysis; SSAS, Somatosensory Amplification Scale score; IPQ, Italian Pain Questionnaire; CPT, cold pressor test.

Discussion

Key results

The main finding of this research was that FM subjects displayed higher somatosensory amplification scores than the other groups, independent of gender, age, education and civil status. Furthermore, SSAS score appears to be a positive associated with the number of tender points and pain persistence.

As regards the etiopathogenesis of CS other than the neurochemical, a biopsychosocial model has been proposed [56]. The high level of SA we observed in fibromyalgic patients may clarify the role of a psychological factor, i.e., somatosensory amplification, in this disease, contributing to the onset of CS and altering pain processing. In fact, as well as increased tender points and pain persistence, our results seem to show that a high level of SA has an effect by reducing tolerance to (experimental) pain and increasing the intensity and affective and evaluative dimensions of pain in FM patients (Table 4).

Our study also reveals that SSAS score is positively associated with general hypochondriasis in subjects with pain or psychiatric disorders, but not in healthy control subjects. This indicates that somatic amplification may be associated with health anxiety, potentially reinforcing symptoms, but only in patients with psychiatric disorders or pain, including fibromyalgia when associated with somatization disorder.

The association of SA and post-traumatic stress disorder (PTSD) showed in previous studies [25, 27] was not confirmed by our research. However, this may be attributable to the specific type of psychiatric assessment we chose; in fact, we elected not to include comorbidities, but to use the first and longest lasting condition as the sole

Table 5: Prevalence of psychiatric disorders (according DSM IV TR criteria) in each group.

	Fibromyalgia		Other chronic pain		Psychiatric D.			
	N	%	N	%	N	%	χ2	p
	159		582		53			
No disorders	23	14.4	153	26.3	0	0	9.63	0.002a
Major depression	24	15.1	93	16	4	7.5	2.67	ns
Dysthymia	6	3.8	15	2.6	0	0	2.23	ns
Bipolar D.	24	15.1	58	10	6	11.3	3.33	ns
Panic D.	19	11.9	41	7	18	34	40.70	0.000
Agoraphobia	0	0	5	0.9	0	0	1.83	ns
Obsessive compulsive D.	10	6.3	25	4.3	7	13.2	8.09	0.017
Post traumatic stress D.	7	4.4	19	3.3	1	1.9	0.88	ns
Social Phobia	1	0.6	8	1.4	0	0	1.27	ns
Generalised anxiety D.	9	5.7	54	9.3	2	3.8	3.64	ns
Substance-related D.	1	0.6	12	2.1	3	5.7	5.12	ns
Eating D.	1	0.6	3	0.5	2	3.8	6.91	0.031
Somatisation D.	26	16.4	40	6.9	4	7.5	14.07	0.007
Hypochondriasis	3	1.9	19	3.3	6	11.3	10.83	0.004
Pain D.	3	1.9	31	5.3	0	0	6.14	0.046a
Body dismorphic D.	1	0.6	2	0.3	0	0	0.48	ns
Suicidal ideation	0	0	3	0.5	0	0	1.09	ns
Dissociative D.	1	0.6	0	0	0	0	0	na
Antisocial personality	0	0	1	0.2	0	0	0	na

D, Disorder; a, considering only the two pain groups; ns, not significant; na, not applicable.

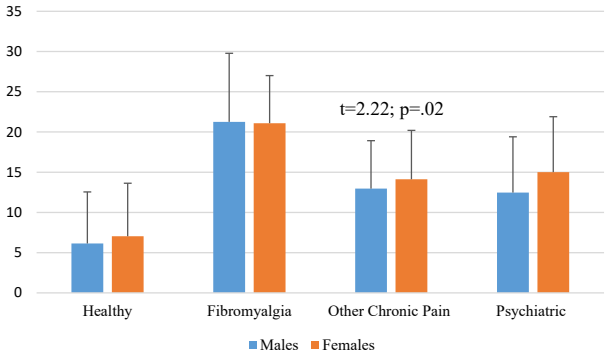

Figure 1: Differences of somatosensory amplification total scoring (SSAS) between gender in each group (t-test analysis).

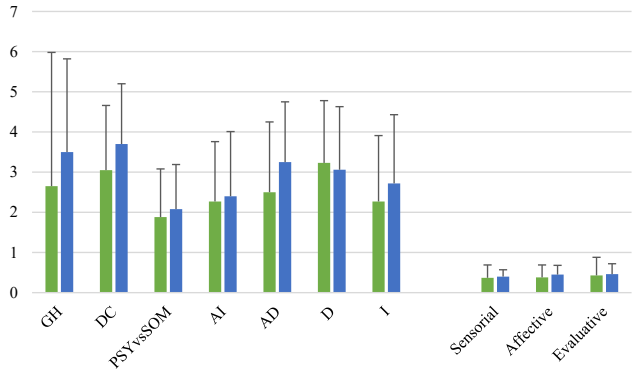

Figure 2: Unpaired t-test of total sample distinguished by mean of the total SSAS <16 (in green) and ≥16 (in blue). *Illness Behaviour Questionnaire* (IBQ): General Hypochondriasis (GH) t=4.14, p=0.000; Disease Conviction (DS): t=5.89; p=0.000; Psychological vs somatic focusing (PSYvsSOM): t=1.95; p=0.05; Affective Inhibition (AI): t=1.25; p: 0.21; Affective Disturbance (AD): t=6.56; p=0.000; Denial (D): t=1.56; p=0.11; Irritability (I): t=3.92; p=0.000. *Italian Pain Questionnaire* (IPQ): Sensorial dimension: t=1.28; p=0.27; Affective dimension: t= 3.47; p=0.001; Evaluative dimension: t=1.07; p=0.28.

main diagnosis. It is therefore probable that only chronic psychiatric disorders emerged more readily, thereby obscuring others.

Another difference we noted between patients and healthy controls regards the potential predisposing role of SA to greater affective disturbance (as per the IBQ), which was observed in FM, OCP and Psy patients (Table 3). This could indicate a neurobiological impairment related to dysfunctional connectivity of the anterior insula, which has been associated with greater SSAS scores found in subjects with FM [57]. The "salience network" (which

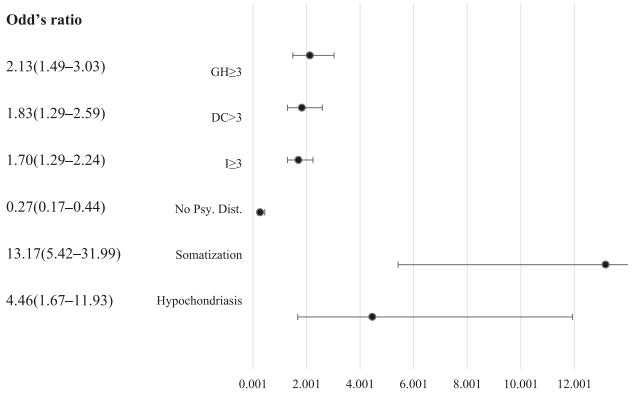

Figure 3: High level of global Somatosensory Amplification Scale (SSAS≥16) score as predictor of GH, General Hypochondriasis≥3; DS, Disease Conviction>3; I, Irritability≥3; Somatization Disorder and Hypochondriasis in the Other Chronic Pain group. Odd's Ratio, using logistic regression analysis.

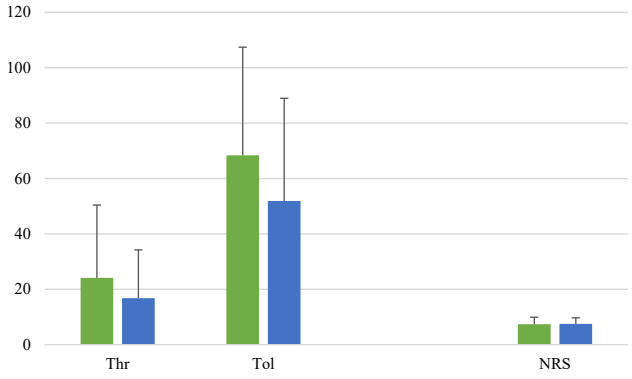

Figure 4: Unpaired t-test of total sample distinguished by mean the total of SSAS <16 (in green) and ≥16 (in blue). *Cold pressor test* (CPT); Threshold (Thr); t=4.14; p=0.000; Tolerance (Tol); t=5.52; p=0.000; *Numerical rating scale* (NRS); t=0.51; p=0.60.

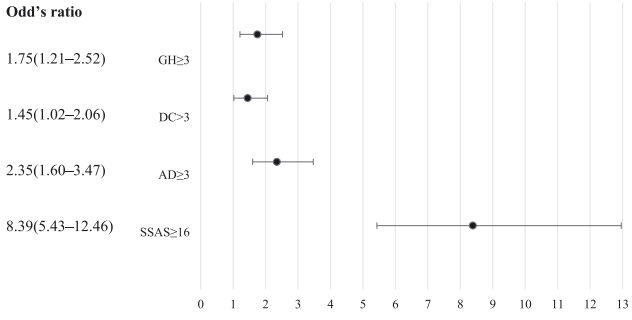

Figure 5: Predictors of Fibromyalgia: General Hypochondriasis (GH) ≥ 3 (mean score of entire sample); Disease Conviction (DC)>3; Affective Disturbance (AD) ≥3; Somatosensory Amplification (SSAS) ≥16 mean score of entire sample.

includes anterior insula function) is also implicated in cognitive deficit in psychiatric disorders [58]. Hence, on the basis of our finding that SSAS score is a positively associated of affective disturbance, we may hypothesize that our patients exhibiting high SA may have a dysfunction in the "salience network", and SA may represent a sign of their disease.

It is also noteworthy that fibromyalgic patients exhibited a greater prevalence of somatization disorder with respect to patients with other forms of chronic pain. This lends weight to the hypothesis that the two functional somatic syndromes might be grouped as a single condition encompassing the medically unexplained somatic symptoms, as recently defined as "bodily distress syndrome" [59]. However, potentially supporting the hypothesis that the two are separate disorders, we found that somatization disorder predicts OCP but not FM, and that a high SSAS score predicts a diagnosis of somatization disorder and hypochondriasis in OCP but not in FM patients. Thus, our finding indicates that somatosensory amplification and somatization disorder are not associated with each other in FM, but are linked in OCP patients, and that somatosensory amplification (i.e., SSAS score) predicts FM, while somatization disorder does not (Figure 5). Therefore, somatization disorder and FM seem to be distinct entities, as postulated by Hauser and Henningsen [34].

Limitations and conclusion

The main limitation of the present study is that it was conducted in subjects with one or more unsuccessful treatment outcomes, which could make it impossible to generalize our results. In addition, a low number of psychiatric patients and healthy subjects were enrolled, owing to the retrospective nature of the study.

That being said, our results appear to show that SA is closely linked to FM, and its presence in FM is independent of both all other dimensions of abnormal illness behavior and the prevalence of somatization disorder. This does not occur in other pain syndromes, in which high SSAS seems to be directly associated with somatization disorder and may predispose individuals to the high levels of hypochondria and disease conviction underlying the diagnosis of somatoform disorders. It is therefore possible that in fibromyalgic patients SA facilitates the development of pain sensitivity, making individuals susceptible to the

onset of amplification in pain, independent of the presence of somatization disorder.

Patients with somatization disorder misinterpret somatic symptoms as a serious physical illness, thereby establishing abnormal illness behavior and an overuse of healthcare. However, our study highlights a dissociation in the fibromyalgic patient between the occurrence of somatic amplification and somatization—considered by Lipowski (1986) [60] to be a borderland between medicine and psychiatry. Nonetheless, the relationship between medically unexplained somatic symptoms and the underlying cognitive aspects of illness behavior is complex and requires further elucidation. Indeed, in the DSM IV-TR [47], the diagnostic criteria for somatization disorder overlapped with those for fibromyalgia, and even the new classification of somatic symptom disorder introduced in the DSM-5 [24] has failed to clarify the elements that distinguish between these two disorders [61].

Another limitation is that the Somatosensory Amplification Scale is a self-report to assess amplification. It remains unclear to what extent this scale captures an underlying mediating process of symptom amplification [62] .

That being said, our results appear to suggest that fibromyalgia is not a somatization disorder, but that instead the two disorders share a common trait, namely somatic amplification. Somatic amplification seems to underlie the health anxiety, disease conviction and affective alterations that predispose to the onset of somatization disorder, which can be associated with various forms of chronic pain. Our results also suggest that somatosensory amplification alone may predispose to fibromyalgia, regardless of the presence of health anxiety, disease conviction and affective disorders. In FM, somatosensory amplification could be a manifestation of central sensitization. Furthermore, our data seem to point to a difference between chronic pain and fibromyalgia in terms of their respective relationships with somatic amplification and the presence or absence of somatization disorder.

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: Being a retrospective study, no Ethics Committee approval was necessary [27]. The study adheres to the STROBE statement guidelines for observational research.

STROBE Appendix

Items
1. a. The title includes the study's design.
b. The abstract contains an informative and balanced summary of what was done and what was found.
2. The background explains the rationale behind the investigation.
3. The aim contains specific objectives formulated following the hypotheses mentioned in the background section.
4. The study is a retrospective observational case-controlled study.
5. In the methods, setting, location, period of recruitment and data collection have been described.
6. The eligibility criteria (inclusion and exclusion criteria) and rationale have been reported for each control and case group of subjects recruited.
7. Diagnostic criteria have been reported for each syndrome explored.
8. Method of assessment has been reported.
9. Bias has been described in a dedicated section.
10. Clinical but not statistical study size has been explained.
11. Each quantitative variable has been described.
12. All statistical methods and subgroup analyzed have been described.
13. Number of participants per each group has been reported.
14. Characteristics of participants have been described and corrected to avoid bias.
15. Description of variables has been reported in a Table.
16. Main results have been described in specific sections. Data have been reported in the tables and each described with the relative effect size. Odd's ratio has been applied.
17. A section of the results of case and the variable differences from the controls have been shown.
18. The key results have been discussed, comparing them with the literature.
19. Limitations and potential bias have been reported.
20. Interpretation and comparison of results with other studies has been done.
21. At the end, the generalizability of the results has been discussed.
22. This study did not have any funding.

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