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Chapter 8

Joint Hypermobility, Anxiety, and Psychosomatics — The New Neuroconnective Phenotype

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Additional information is available at the end of the chapter

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Abstract

In this chapter, after summarizing the concept and diagnosis of the Joint Hypermobility (Hyperlaxity), we review case control studies in two directions: Anxiety in Joint Hypermobility and Joint Hypermobility in Anxiety disorders, studies in nonclinical samples, review papers, and one incidence study. Collected evidence tends to confirm the strength of the association described two and a half decades ago. Common mechanisms involved include genetics, autonomic nervous system dysfunctions, and interoceptive and exteroceptive processes. Considering clinical and nonclinical data, pathophysiological mechanisms, and present nosological status, we suggest a new Neuroconnective phenotype in which together around a common core Anxiety-Collagen hyperlaxity, it includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses. Somatic illnesses include irritable bowel, dysfunctional esophagus, multiple chemical sensitivity, dizziness or unsteadiness (central vestibular pattern), chronic fatigue, fibromyalgia, glossodynia, vulvodynia, hypothyroidism, asthma, migraine, temporomandibular dysfunction, and intolerances or food and drug hypersensitivity. It is envisaged that new descriptions of anxiety disorders and also of some psychosomatic conditions will emerge and different nosological approaches will be required.

Keywords: Anxiety disorders, joint hypermobility, hyperlaxity, psychosomatic medicine, phobic disorders

1. Introduction

The strong association of a heritable collagen condition and anxiety was an unexpected finding that we first described in 1988 at the Hospital del Mar in Barcelona [1]. Ever since, several clinical and nonclinical researches have been carried out. In this chapter, after summarizing the concept and diagnosis of the Joint Hypermobility (Hyperlaxity), we review case control studies in two directions: Anxiety in Joint Hypermobility and Joint Hypermobility in Anxiety Disorders, studies in nonclinical samples, review papers, and one incidence study. Collected evidence tends to confirm that the association is strong, as described two and a half decades ago. Common mechanisms involved included genetics, autonomic nervous system dysfunctions, and also interoceptive and exteroceptive processes. Considering clinical and nonclinical data, pathophysiological mechanisms, and present nosological status, we suggest a new Neuroconnective phenotype, in which together around a common core Anxiety-Collagen hyperlaxity it includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses. Somatic illnesses include irritable bowel, dysfunctional esophagus, multiple chemical sensitivity, dizziness or unsteadiness (central vestibular pattern), chronic fatigue, fibromyalgia, glossodynia, vulvodynia, hypothyroidism, asthma, migraine, temporomandibular dysfunction, and intolerances or food and drug hypersensitivity. It is envisaged that new descriptions of anxiety disorders and also of some psychosomatic conditions will emerge and different nosological approaches will be required.

Although there is increasing evidence for somatic comorbidity in the major psychiatric conditions, actual psychiatric classifications do not include specific psychiatric illnesses associated to medical conditions other than organic dementias and secondary psychiatric conditions yet. Apparently two main factors concur for this. First, the current nosologies include only two conditions (psychiatric and somatic) when there is a causal connection between them, for instance, organic brain disorder (dementia) with mental symptoms. Along these lines, concepts like vascular depression or even vascular psychiatry are emerging. The reasoning behind this point of view is quite straightforward because it implies the search for etiology and therefore for treatment. Second, there is little evidence of specific somatic signs or conditions in the description of the present psychiatric illnesses. This has reduced the psychiatrists' expectancies to find the coexistence of both other than the secondary psychiatric-somatic comorbidity. There are examples of such comorbid situations like diabetes and schizophrenia already, which some have considered part of the same illness [2]. However the most studied and developed comorbid condition is the joint hypermobility syndrome in anxiety patients. Therefore, there is a need to develop clinical phenotypes containing both psychopathological and somatic features, or even proper psychiatric and somatic conditions. The new phenotype will be built around the core of the association between anxiety disorders (particularly panic, agoraphobia, and social phobia) and the Joint Hypermobility (better Hyperlaxity) syndrome.

The proposed name Neuroconnective to this new phenotype is both comprehensive and specific. It covers the neural component along with the connective dimension of the new phenotype. The prefix neuro- refers to the neural basis of the syndrome, which includes the

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dysfunctional Autonomic Nervous System and also the enhanced "body awareness", including interoception, proprioception, and exteroception. Furthermore and, as a kind of homage, we would like to consider that the prefix neuro- also recalls the concept of neurosis in the nineteenth century which was, just in that period, a comprehensive category that included both mental and extensive physical symptoms at the same level. Concerning "connective", it refers to the relevant value of the heritable disorder of the connective tissue and also to the "connectivity" between systems, between mind and body, and actually as concept. Therefore, on the basis of the collected genetic, neurophysiological, neuroimaging, and most clinical data, several dimensions could be organized together in this neuroconnective model.

2. Historical background of the relationship between joint laxity and anxiety

The relationship between a heritable collagen condition and anxiety was a clinical observation rather than a pathophysiological reasoning. While working at the psychiatric outpatient clinic, we repeatedly found in the medical record of most of our patients suffering from anxiety, a particular rubber stamp: "Hiperlaxitud Articular." This stamp was put there by the rheumatologist, JC Duró, who was using it to systematically collect the criteria for the Joint Hypermobility syndrome described and studied by his mentor, Prof. Rotés. The reiterated coincidence of the two conditions prompted us to study this association in more detail and send a letter to The Lancet [1] with preliminary results.

Considering the high prevalence of mood disorders in patients suffering from collagenosis, psychiatrists had been closer to associate collagen conditions with these autoimmune illnesses like systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), whereas structural collagen disorders (mainly heritable) seemed to be less in mind due to the lack of knowledge of the psychiatric status of these patients [3]. However, there had been scattered observations that pointed in this new direction. In 1957, rheumatologist J. Rotés observed a remarkable degree of nervous tension suffered by patients with hypermobility [4]. To a certain extent, there were some indirect references about the relationship between "visceroptosis," in which viscera displace below their natural position due to ligamental laxity and anxiety/phobias in the classical psychosomatic literature [5]. On the other hand, in 1980, Carlsson and Rundgren [6] found higher hypermobility scores in alcoholic patients compared to controls. Although not mentioned, the case group might have consisted of a high percentage of patients with anxiety.

3. Empirical studies of the link between anxiety and collagen tissue

3.1. General diagnostic criteria of Joint Hypermobility Syndrome

In order to clarify the terminology all along this chapter, we shall use indistinctly Joint Laxity (the original name) and Joint Hypermobility (the given name). Although the second is more

often used in English publications, it in fact refers to a rather unspecific consequence (increased mobility), whereas hyperlaxity refers more correctly to the intrinsic mechanism (increased laxity of fibers).

The condition was described for the first time about 60 years ago when it was properly identified and associated to pathology of the musculoskeletal system [4]. The original name proposed by Rotés was 'Joint Laxity' (Laxité Articulaire) and it was published in a French journal (Revue du Rhumatisme). In 1964, Carter and Wilkinson, also using the name of joint laxity (JL), published a relevant paper in which they proposed some diagnostic criteria [7].

In 1973, after an epidemiological study by Beighton et al. [8] using both joint laxity and joint mobility, the syndrome gained general interest in rheumatology and by then, renamed joint hypermobility (JH), began to be studied in a broader way as a separate entity [9]. Later on, the seminal work of Rodney Grahame was very important to get the Joint Hypermobility Syndrome (JHS) revisited among rheumatologists. He has produced three editions of the Beighton book [10] as well as other books about the topic and also has boosted clinical research on it [11,12]. Another prominent author who has provided insightful clinical descriptions of the JHS is Dr J. Bravo [13].

JHS is an inherited connective tissue disorder associated with a generalized collagen laxity and characterized by an increase of active or passive joint mobility in the absence of another rheumatologic disease. JHS has an estimated prevalence in the general population ranging between 10%–20%, and is one of the hereditary disorders of the connective tissue, which include other conditions such as Ehlers–Danlos syndrome, Marfan syndrome, and ostogenesis imperfecta [10]. In fact, there is an overlap with the Ehlers– Danlos type III. This condition has an autosomal dominant pattern and twin studies showed that genetics accounts for at least 70% of the phenotype variance rather than environmental factors such as training. JHS is more common in childhood and tends to decline when aging. The prevalence is higher in females and probably there are ethnic differences, which suggest genetic variations. JHS is also associated with musculoskeletal dysfunctions, possibly resulting from a glycoprotein deficiency and genetic alterations affecting the formation of collagen, which would explain tissue looseness, prolapsed organs, visceroptoses, pneumothorax, and vulnerability to trauma in these patients.

Clinical features in JHS can be articular or extra-articular and are always related to the connective tissue. Among the best known articular features of JHS are arthralgia, lumbalgia, soft-tissue rheumatism (e.g., epicondylitis, tenosynovitis, bursitis), recurrent dislocations, childhood scoliosis, or rheumatoid arthritis [13,14]. Among the best-known extra-articular features of JHS are hernias, varicose veins, “easy bruising”, keloids, uterine or rectal prolapse, spontaneous pneumothorax, fibromyalgia, dysautonomia, and some other conditions also linked to panic disorder as asthma, mitral valve prolapse, thyroid dysfunction, or irritable bowel syndrome [14,15].

There are several sets of criteria that show minimal variations from the original proposed by Rotés, although new self-assessment questionnaires have been recently added to the assessment methods of JHS [16,17]. A review paper of all the available criteria showed a high degree of agreement among all of them [18]; a more comprehensive set of 10 criteria obtained by cluster analysis was also proposed. However, the most often used are the “Beighton criteria” con-

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verted to a nine point clinical scale by which subjects with a score ≥ 4 are considered as having JH. The condition is characterized through the examination of five body areas, each one receiving a separate score of hyperextension: fifth fingers, thumbs, elbows, knees, and trunk (see Figure 1).

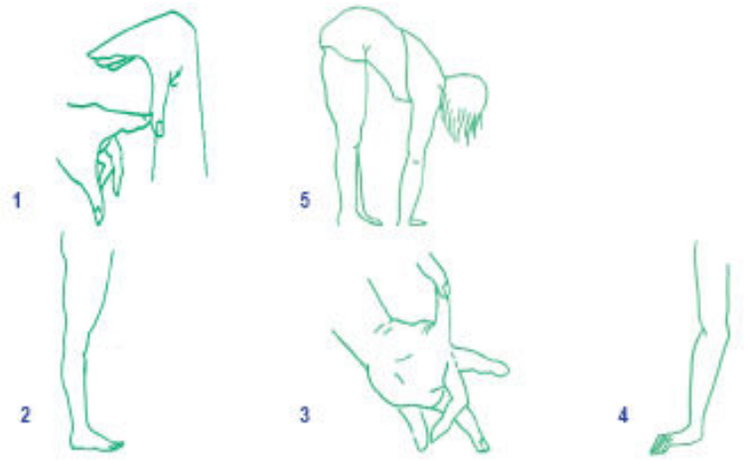

Figure 1. Joint Hypermobility criteria, taken from Beighton P, et al. 1973 [8]. Passive apposition of the thumbs to the flexor aspects of the forearm (one point for each thumb). 1. Hyperextension of the knee beyond 10º (one point for each knee). 2. Passive dorsiflexion of the little fingers beyond 90º (one point for each hand). 3. Hyperextension of the elbows beyond 10º (one point for each elbow). 4. Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor (one point).

In 1992, the Hospital del Mar criteria (Table 1) compiled all the items included in the most clinically used criteria. This new scale showed consistent indicators of reliability, internal consistency, and predictive validity and provided evidence for using different scores according to age and gender [18].

Upper extremities
1. Passive apposition of the thumb to the flexor aspect of the forearm is at a distance of less than 21 mm.
2. The passive dorsiflexion of the fifth finger is 90º or more.
3. The active hyperextension of the elbow is 10º or more.
4. External rotation of the shoulder is up to more than 85º.
Lower extremities. Supine position
5. The passive hip abduction can be taken to an angle of 85º or more.
6. Hypermobility of the rotula.
7. Hypermobility of the ankle and foot.
8. Dorsal flexion of the toe is 90º or more.
Lower extremities. Prone position
9. Hyperflexion of the knee.
10. Ecchymoses.

Table 1. Hospital del Mar criteria for JHS as mentioned in Bulbena A, et al. 1992 [18]. Male patients scoring 4 or more are considered cases; female patients are considered cases with scores 5 or over.

In 2010 Grahame [19] developed the Brighton criteria to replace the Beighton criteria for the joint hypermobility syndrome (JHS). According to these criteria, the syndrome diagnosis is made taking into account the Beighton score and also some other clinical manifestations associated with hypermobility. As it could be expected, the correlation between them is very high. They are seldom used outside of rheumatology. The main sets of criteria are included in Table 2.

Major criteria
1. A Beighton score of 4/9 or more (either currently or historically).
2. *Arthralgia* for longer than 3 months in 4 or more joints.
Minor criteria
3. *Beighton* score of 1, 2, or 3 (0, 1, 2, or 3 *if aged 50 years or older*).
4. *Arthralgia* in 1–3 joints or *lumbalgia* for more than 3 months, spondylosis or spondylolysis/spondylolisthesis.
5. *Dislocation/subluxation* in more than one joint or in one joint in more than one occasion.
6. *Soft tissue rheumatism* in three or more lesions (e.g., epicondylitis, tenosynovitis, bursitis).
7. *Marfanoid Habitus* (tall, slim, span/height ratio "/> 1.03, upper/lower segment ratio < 0.89, arachnodactily).
8. *Abnormal skin:* striae, hyperextensibility, thin skin, or papyraceous scarring.
9. *Eye signs*: drooping eyelids or antimongoloid slant.
10. Varicose veins or hernia or uterine/rectal prolapse.

Table 2. Brighton criteria, taken from Grahame R, et al. 2000 [19]. JHS is diagnosed if the patient presents 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria. 2 minor criteria will be enough when there is a first-degree relative with the syndrome clearly diagnosed. JHS is excluded by the presence of the Marfan or the Ehlers–Danlos Syndrome. The first major criterion and the first minor one exclude each other, as do the second major and the second minor.

The clinical assessment of the joint laxity syndrome is not difficult but examiners should be trained in order to ensure the reliability of the exam. Our group has developed a two-day training course with the support of a CD [20].

3.2. Comorbidity data between anxiety and JHS

Empirical history of the clinical relationship between anxiety disorders and JHS started with a case-control study conducted by our group in 1993, with rheumatologic outpatients with JHS [21]. Diagnoses of panic disorder, agoraphobia, and simple phobia were significantly more frequent among hypermobile patients. There were no significant differences in the diagnoses of generalized anxiety disorder, dysthymia, or major depressive disorder. Around 70% of rheumatologic patients with JHS had some kind of anxiety disorder. However, this only occurred in 22% of controls, a usual figure in chronic patient samples. Cases were 10 times more likely to suffer from anxiety than controls. Specifically, agoraphobia and panic disorders were, respectively, 5 and 7 times more likely (Table 3).

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	% JHS	% Non-JHS	Age-Sex Adjust. Odds Ratio	95 % C. I.
Any Anxiety D.	69,3	22,0	**10.69**	4.80–23.81
Panic D.	34.2	6.8	**6.96**	2.31–20.91
Panic & Agora.	24.6	5.1	**6.40**	1.82–22.43
Simple Phobia	29.8	8.5	**5.77**	2.05–16.24
Agoraphobia	37.7	11.9	**5.08**	2.06–12.49
General.Anx.	10.5	5.1	**2.49**	0.65–9.45
Major Depress.	14.9	3.4	**4.51**	0.99–20.56
Dysthymic D.	7.9	5.1	**2.15**	0.53–8.65

Table 3. Lifetime psychiatric disorders in JHS cases (n=114) and non-JHS controls (n=59) seen at an outpatient rheumatological unit, from Bulbena A, et al. 1993 [21].

For a subsequent second study, conducted to support this hypermobility-anxiety association, outpatients with new diagnoses of panic disorder and/or agoraphobia were examined, as well as nonanxious psychiatric and nonpsychiatric outpatients as control groups [22]. Results showed that JHS was present in almost 70% of anxiety cases, versus slightly over 10% of controls. This meant that cases with panic disorders and/or agoraphobia were 17 times more likely to suffer from JHS. Conclusions were valid for women [OR=23.7; CI95% 10.6–52.9] but also for men [OR=10.5; CI95% 3.0–36.3].

Lumley et al. [23] evaluated the psychosocial functioning in patients suffering from Ehlers–Danlos Syndrome (JHS is considered EDS type III). The sample was selected from an outpatient research clinic and the results showed that EDS type III group had higher scores on anxiety, depression, and interpersonal sensitivity as well as higher scores in the symptomatology checklist and the pain scales.

Other lines of research studied possible specific somatotype characteristics in patients with panic disorder/agoraphobia [24]. Cases with panic and/or agoraphobia from an outpatient mental health clinic were compared to psychiatric and medical controls matched by age and gender. Within the entire sample, the asthenic somatotype was associated with higher JH scores. Interestingly enough, the prevalence of asthenic somatotype was at the same time significantly higher in the panic/agoraphobia group (33.3%) compared to the psychiatric (19.2%) and the medical (18.7%) controls. The authors finally concluded that the relationship between panic disorder and asthenic somatotype might be mediated through JHS.

These results were confirmed by another study carried out by the same group in 2014 [25]. They included 60 patients with Panic and Agoraphobia and 60 controls. The authors found that cases and controls differed in the percentage of ectomorphic subjects: 38.3% of cases and 13.3% of controls were categorized as ectomorphic [χ 2=8.5, df=1, p=0.004]. In order to explore the characteristics associated with the ectomorphic somatotype, the two groups were collapsed into one, and ectomorphic and nonectomorphic subjects were compared. The ectomorphic

group was younger and showed significantly more hypermobility of joints and more prevalence of panic and agoraphobia. Differences in sex, intake of antidepressants, marital status, educational degree, and labour situation were minor and statistically nonsignificant (Table 4). To further clarify the relative value of previously mentioned variables in relation to somatotype, a logistic regression model was constructed with the ectomorphic somatotype as dependent variable and as independent variables, sex, age, and JH. Only the last one was independently associated with the ectomorphic somatotype [OR=3.25, 95% CI: 1.35–7.8, p=0.008]. Therefore, after adjusting for age and sex, ectomorphic somatotype was independently related to JH status (the more hypermobile, the more likely to be ectomorphic).

Characteristics	Ectomorphic group (n=31)	Nonectomorphic group (n=89)	$\chi 2$ / t	p
Female	54.8	48.3	0.17	.677
Age	29.2	32.2	1.98	.050
Antidepressants	41.9	30.3	0.92	.338
Single	67.7	51.7	1.80	.180
High educated	22.6	43.8	3.53	.060
Employed	93.5	97.8	0.29	.588
Panic	64.5	41.6	3.98	**.046**
Agoraphobia	64.5	32.6	8.43	**.004**
JH status	45.2	20.2	6.09	**.014**

Table 4. Comparison of subjects with and without ectomorphic somatotype (according to the Heath-Carter method). All characteristics are expressed in %, except age expressed in mean (S.D.).

Later on, this association was studied in the general population. A two-phase cross-sectional epidemiological study was carried out in a rural town in order to establish lifetime risk for anxiety and affective disorders in subjects affected with JHS. A sample of 1,305 individuals was examined at baseline and over 500 were subsequently subjected to follow-up in a two-stage epidemiological study. Hypermobile patients were six times more likely to suffer from agoraphobia (OR 5.9; CI 95% 3 to 11.7), eight times more likely to suffer from social phobia (OR 7.8; CI 95% 2.4 to 24.8), and eight times more likely to suffer from panic disorder (OR 8.2, CI 95% 3.4 to 19.7) than non-JHS patients. Results were valid for males and females. No differences were found for other anxiety disorders or mood disorders [26].

In the same sample of general population, it was also found that hypermobiles had significantly higher scores in fear and phobia scales, strenghtening the hypothesis that intensity of fears is greater in subjects with JHS [27]. We assessed fear intensity and frequency using a modified version of the Fear Survey Schedule (FSS-III). When the groups with and without joint hypermobility were compared, the mean total scores for both genders were significantly higher for the hypermobile group. These results showed that the association of JHS and phobic

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anxiety is sustained for intense fears and might represent a susceptibility factor for these anxiety conditions.

The same design was replicated in 2011 in a sample of 150 nonclinical students [28]. Severe fears and daily consumption of cigarettes, alcohol, coffee, and chocolate were compared with the hypermobility scores. We found significant differences when comparing severe fears between the groups with and without hypermobility (7.6 vs. 11; p = 0.001). The frequency of chocolate intake was also significantly higher among subjects with joint hypermobility (31.2% vs. 51.2%; p = 0.038). No significant differences were found regarding cigarette (19.5% vs. 19.3%), alcohol (36.6% vs. 34.9%), and coffee (46.3% vs. 35.8%) consumption. These patterns of consumption may, therefore, be interpreted as self-treatment attempts of subsyndromal anxiety in hypermobile subjects.

In 2004, our group also assessed a nonclinical sample of subjects employed in the same company (N=526) [29]. Subjects with JHS had significantly higher scores in STAI trait anxiety [female average: 16.5 vs. 11; p<0.001] [male average: 13 vs. 11; p<0.03]. STAI state anxiety scores were also higher among hypermobile subjects, although not significantly (Figure 2).

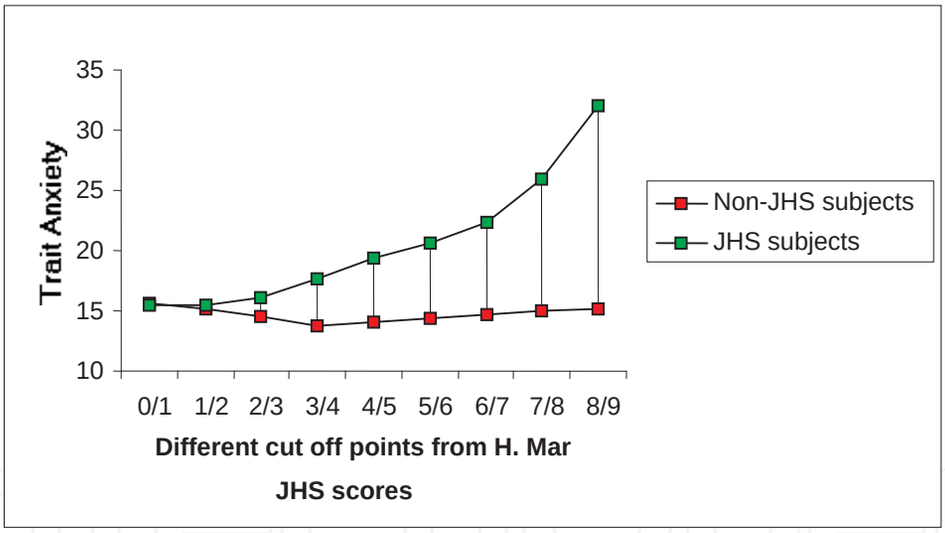

Figure 2. STAI trait anxiety scores (range: 0–60) in 203 women with or without joint hypermobility according to all possible cutoff scores on the Hospital del Mar hypermobility criteria. From Bulbena A, et al. 2004 [29].

Joint hypermobility has also been assessed in relation to psychoactive substances. Baeza-Velasco [30] designed a cross sectional study in college students to assess the use of alcohol and tobacco. The odds of being assessed with JH were greater in those who consumed tobacco and alcohol. Women with JH had higher levels of state anxiety and used emotion-focused coping (i.e., efforts to regulate affect) more than any other coping strategies to deal with stress.

The first structural neuroimaging study on the association was published in 2012 evaluating regional cerebral grey matter in regards to hypermobility status in 72 healthy volunteers [31].

Interestingly enough, bilateral amygdala volume was higher in the hypermobile group. Their findings linked hypermobility to the structural integrity of a brain center implicated in normal and abnormal emotions and physiological responses.

In 2005, we studied schizophrenic outpatients (N=124) with the hypothesis that anxiety disorders mediated by JHS were not symptoms but an independent comorbid entity in schizophrenic patients [32, 33]. Joint Hypermobility was noticeably more likely among panic disorder/phobia-clustered schizophrenic patients than among the noncomorbid group (OR = 9.35; IC = 95% [3.85–22.73]; $p<0.0001$). The cluster panic disorder/phobia had higher scores in fear scales and schizophrenia positive symptom scales. We are now performing a voxel-based morphometric study in order to examine brain structure, comparing magnetic resonance images of 20 schizophrenic-anxious patients and 20 schizophrenic patients. The preliminary results indicated gray matter volume differences in the schizophrenic-anxiety group in the dorsolateral prefrontal cortex related to the interaction between both conditions. Our findings suggest that the schizophrenic-anxiety group is characterized by specific neural abnormalities that cannot be explained by the presence of schizophrenia or anxiety, but by their conjunction, and this might result in a certain symptomatology [34].

The relationship between social phobia and height was studied through a cross sectional study to explore the frequency of social phobia as well as a heritable disorder of the connective tissue (HDCT) in tall people [35]. One hundred and fifty eight subjects with heights greater than 180 cm in females and 190 cm in males were included in the study; social phobia and HDCT were highly prevalent in tall subjects. JHS was associated with greater prevalence of social phobia symptoms.

The association between anxiety disorders and JHS was also assessed in a sample of university students from Chile [36]. Fifty university students with JH and 50 controls were selected to participate in this case control study. The JH group had higher use of antidepressants and anxiolytics compared to the controls. They also exhibited greater anxiety background, anxiety symptoms, and psychosomatic complaints. A similar study was carried out by Baeza-Velasco et al. in a group of undergraduates in a French university [37]. The aim of the study was to explore the Joint Hypermobility Syndrome (JHS) in the university students and also to assess a possible relationship between this collagen condition and certain psychological variables. Three hundred and sixty five undergraduates from a French University were included in the study and the researchers found that JH was present in almost 40% of the sample and it was also associated with higher levels of somatosensory amplification as well as higher scores in depression and general anxiety in females.

After a number of significant cross-sectional studies we conducted a prospective incidence analysis that assesses whether JHS could be a risk factor in developing anxiety conditions [38]. We sought to determine the cumulative incidence of anxiety disorders in a cohort of young subjects recruited from the general population who had not developed any type of anxiety condition up to the moment; consequently a scheduled 15-year follow-up covering subjects from late adolescence to adulthood was planned. The total population sample was 1,305 subjects, and in order to observe the development of anxiety disorders during the 15-year study period, only the lower age segment (at that time subjects aged between 16 and 20) included in

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the town's municipal registry was invited to participate. We sought to describe the occurrence of new cases of anxiety disorders during the study period, therefore the exclusion criterion for the study was having already had an anxiety disorder at baseline examination. At baseline, 158 subjects were screened for participation in the study, and after the 15-year follow-up the final sample comprised 137 subjects (86.7% retention rate). Results showed that cumulative incidence of panic/agoraphobia at follow-up was significantly higher for the JHS group (41.4%) than for the control group (1.9%) with relative risk of 22.3 (CI 95% 4.6–108.7), p<0.0001, (NNT 3, CI 95% 2.9–2.3). Incidence of social phobia (RR=6.52; CI 95% 1.7–24.2; p<0.001) and simple phobia (RR=3.31; CI 95% 1.1–9.6; p=0.02) was also significantly higher for the JHS group (Table 5). Moreover, anxiolytic drug use was nearly fourfold higher among JHS subjects compared to non-JHS.

Total Sample **n = 137**	JHS Status						
	JHS present *n* = 29		JHS absent *n* = 108		*RR*	**95% CI**	*P*
	n	%	*n*	%			
Anxiety Disorders							
Panic/Agoraphobia	12	41.4	2	1.9	22.3	(4.6 to 108.7)	0.0001***
Social Phobia	7	24.1	4	3.7	6.5	(1.7 to 24.2)	0.001*
Simple Phobia	8	27.6	9	8.3	3.3	(1.1 to 9.6)	0.02*
GAD	7	24.1	9	8.3	2.9	(0.97 to 8.62)	0.14 ns
Other Disorders							
Depression/Dysthymia	7	24.1	7	6.48	3.7	(1.2 to 11.7)	0.15 ns

JHS, Joint Hypermobility Syndrome according to Beighton criteria assessed at baseline.

GAD, Generalized Anxiety Disorder

Statistical significance: * p<0.05, ** p<0.001, *** p<0.0001, ns: non significant.

Table 5. Incident cases and relative risk after 15 years of follow-up according to JHS status. Taken from Bulbena A, et al. 2011 [38].

Nevertheless, some studies failed to find a significant correlation between panic disorder and JH. The study by Benjamin et al. was carried out in Israel on 101 patients with patient disorder and 39 controls [39]. The authors also attempted to examine the possible association between reactivity to carbon dioxide and JH. The rate of JH did not differ between the cases and controls neither between JH and carbon dioxide responses. However they used the crude number of hyperlax joints instead of the scoring method, which carries the cutoff point to the extreme of the distribution and therefore is not fully comparable to the rest of studies. On the other hand, the instruments used to assess anxiety in these patients (the self-rating scale of the National

Institute of Mental Health, DSM IV panic symptoms scores and 100mm visual analogue scales of anxiety) are uncommon and could explain the results of the study.

Gulpek et al. designed a study to test the association between JHS and panic disorder and also to determine whether mitral valve prolapse (MVP) accounts for or changes this association [40]. The sample consisted of 115 subjects that were divided in 3 groups. The first group (n=42) included patients with PD and MVP, the second group (n=35) consisted of patients with PD and without MVP and the third group (n=38) had patients with MVP and no psychiatric diagnosis. No significant differences were found in prevalence or severity of JH between groups according to Beighton criteria scoring. However, JH was present in 59.5% of the panic disorder patients with mitral valve prolapse, and 52.6% of the control subjects. Compared to other studies, the prevalence of JH in the control group was never found as high as in this study. Since the prevalence of JH was higher in patients with PD and MVP (59.5%), authors suggested that MVP affects the prevalence of JH in PD. The prevalence of panic disorder was also higher in the JH compared to controls.

Another research group from Turkey studied the relationship between thorax deformity, anxiety, and joint hypermobility. Fifty-two males with thorax deformity and 40 healthy controls from a general outpatient medical clinic were selected to participate in the study [41]. Twenty patients (40%) from the cases group met criteria for JH and those subjects had significantly higher scores in the anxiety scales, particularly in panic disorder. All the cases (with and without JH) had higher anxiety scores compared to controls.

Ercolani and his team designed a study to assess the psychological features of the joint hypermobility syndrome [42]. They recruited 30 JH subjects and two control groups; 25 healthy subjects and 30 fibromyalgia patients. JH group showed significant psychological distress and increased frequency and intensity of somatic symptoms compared to both control groups. A work from another Spanish group [43] has shown again a high prevalence of JHS (61.8%) among panic subjects compared with 10.9% in the healthy control group and 9% in the psychiatric control group. Interestingly, these authors found an intermediate figure among subjects suffering from fibromyalgia (25.4%).

One recent study provided insight about the importance of autonomic symptoms the hypermobility type of Ehlers–Danlos syndrome (EDS) [44]. They included 80 patients with EDS JH, as well as 11 patients with classical EDS (cEDS), seven with vascular EDS (vEDS), 38 with Fibromyalgia and 43 healthy controls. The total autonomic symptom burden was higher in EDS JH (57.9 ± 21.57) than in the other groups but comparable to FM (53.8 ± 19.85). They concluded that joint hypermobility and neuropathy may play a role in the development of autonomic symptoms. In the same line of research, another study described the lived experience of EDS JH and the impact of the symptoms in the daily functioning [45]. The most frequent physical symptoms were joint pain (99%), hypermobility (99%), and limb pain (91%). They also reported a high frequency of other conditions including chronic fatigue (82%), anxiety (73%), depression (69%), and fibromyalgia (42%). These studies are summarized in Table 6.

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CLINICAL STUDIES

STUDY (author/year/country)	DESIGN	SETTING	SAMPLE	VARIABLES STUDIED	MAIN RESULTS
Bulbena* 1988 [1] Bulbena* 1993. [21] Spain	Case Control	Rheumatology outpatient clinic	114 JH 59 controls	Anxiety: HAD-A EPQ, SCID III JH: Beighton	Significant association between JH and PD/A [OR 10.7 (4.8-23.8)] and simple phobia [OR 5.8 (2.0-16.20]. No association with GAD [OR 2.5 (0.6-9.4)] JH patient with MVP do not present with more anxiety
Martin-Santos* 1998. [22]Spain	Case Control	Outpatient psychiatric and medical clinic	99 newly diagnosed PD/A 99 psychiatric controls 64 medical controls	Anxiety; HAM A/D, SCID III JH: Beighton Other: ECHO,	JH found on 67.7% of patients with anxiety [OR 18.6 (8.6-40.5)] (10.1% in psychiatric and 12.5% in medical control).
Lumley 1994. [23] USA	Case Control	Outpatient research clinic	21 EDS III/JH 20 controls (other EDS)	Anxiety: HAM-A JH: EDS subtypes	EDS III (JH) higher scores on anxiety, depression and interpersonal sensitivity and greater scores on symptomatology and pain.
Bulbena* 1996. [24] Spain	Case Control	Outpatient mental/medicine clinic	99 PD/A 99 psychiatric controls 64 medical controls	Anxiety JH: Beighton Other: *Quetelet index*	Significant correlation between asthenic somatotype and PD/A [OR 2.23] PD/A & asthenic somatotype may be medication through JH
Pailhez* 2014 [25]	Case Control	Outpatient clinic	60 PD/A 60 controls	Anxiety: JH: Other: somatotype, sociodemographic	Ectomorphic somatotype was independently related to JH status [OR = 3.25, 95% CI 1.35-7.8, p = 0.008].
Benjamin 2001 [39] Israel	Case Control	Anxiety outpatient clinic	101 PD/A 30 healthy controls	Anxiety: NIMH, PSS, VAS 100mm JH: Beighton	JH = in both groups No association between carbon dioxide response and JH
Gulpek 2004 [40] Turkey	Case Control	Outpatient psychiatric clinic	36 PD/A 42 PD/A + MVP 38 MVP	Anxiety: SCID IV JH Beighton Other: ECHO	JH= 3 groups PD/A higher JH MVP may affect JH prevalence in PD
Gulsun 2007 [41] Turkey	Case Control	Outpatient clinic	52 Thorax deformity 40 controls	Anxiety: SCID, HAM-A, JH: Beighton Other: Thorax diameter	21 patients with TD had JH + (40%) JH group had higher anxiety scores (specially PD). TD group higher anxiety scores (JH + and -)
Ercolani 2008 [42] Italy	Case Control	General outpatient	JH 30 30 control Fibromyalgia	Anxiety: DSM IV JH: Beighton	JH group showed psychological distress and increased frequency and intensity of somatic symptoms
		medical clinic	25 healthy control	Others: SCL-90-R, IBQ, SQ, FSF	
Garcia-Campayo 2010. [43] Spain	Case Control	Primary care clinic	55 PD/A 55 psychiatric controls 55 Fibromyalgia controls 55 healthy control	Anxiety: PAS, STAI JH: Beighton Other: SPPI	Prevalence of JH in PD was higher than in controls Prevalence of JH in PD 61.8% Significant correlation between PAS scores and Beighton criteria
De Wandele 2014 [44] Belgium	Case Control	Outpatient clinic	80 EDS-JH 11 classic EDS 7 vascular EDS 38 Fibromyalgia 43 controls	Anxiety: HADS JH: GHQ Others: ASP, QOL, SF 36, GHQ, fatigue checklist, Baecke Physical Activity	The total autonomic symptom burden was higher in EDS-HT (57.9 ± 21.57) than in the other groups but comparable to FM (53.8 ± 19.85)
Murray 2013 USA [45]	cross-sectional	Outpatient clinic	466 adults with EDS JH	237 online survey	High frequency of chronic fatigue (82%), anxiety (73%), depression (69%), and fibromyalgia (42%) among EDS JH

NONCLINICAL STUDIES

STUDY (author/year/country)	DESIGN	SETTING	SAMPLE	VARIABLES STUDIED	MAIN RESULTS
Bulbena* 2004 [26] Spain	Cross sectional	General population	1305 subjects	Anxiety: JH: Beighton MVP	Significant association between JH and PD/A [OR 10.7 (4.8-23.8)] and simple phobia [OR 5.8 (2.0-16.20]. JH patient with MVP do not present with more anxiety
Bulbena* 2004 [29] Spain	Cross sectional	Medical department of an auditing consultancy	526 subjects	Anxiety: STAI JH: Hospital del Mar	Males and females with JHS significantly higher trait anxiety scores (median scores 11 p< 0.05 and 17 p<0.001). Both trait and state anxiety showed significant correlations with JHS (Spearman's rho, 0.10–0.16; P<0.05).
Bulbena* 2006 [27] Spain	Cross sectional	General population	1305 subjects	Anxiety: FSS JH: Beighton	JH group higher fear scores and higher intensity of fears The association of JH and phobic anxiety might represent a susceptibility factor for these anxiety conditions.
Baeza-Velasco* 2009 [35] France	Cross sectional	Internet survey in tall subjects (>180cm females and >190cm males)	158 subjects	Anxiety: LSAS JH: Beighton	High rate of JH and social phobia in tall subjects JH greater social phobia symptoms
Baeza-Velasco* 2010 [36] Chile	Case control	University students	50 JH 50 Control	Anxiety: HADS, LSAS JH:	JH group had higher use of antidepressants and anxiolytics compared to the controls. They also exhibited greater anxiety background, anxiety symptoms and psychosomatic complaints

Baeza-Velasco* 2011 [37] France	Cross sectional	University students	365 subjects	Anxiety: HADS, LSAS JH: Beighton	JH was associated with higher levels of somatosensory amplification as well was higher scores in depression and general anxiety females.
Pailhez* 2011 [28] Spain	Cross sectional	High school students	150 subjects	Anxiety: FSS JH: Hackim & Grahame Others: chocolate rate	Higher fear scores in JH Frequency of chocolate intake higher in JH
Bulbena* 2011 [38] Spain	Cohort study	General population	137 subjects followed 15 years	Anxiety: SCID, STAI, ASI, FSS JH: Beighton, Hospital del Mar Other: GHQ 28	JH RR: PD/A: 22 (5-109) Social phobia: 6.5 (1.7-24.2) Simple phobia: 3.3 (1.1-9.6) GAD: 2.9 (0.97-8.6) JH score higher in social dysfunction subscale and other use of anxiolytics; - Concordance between Beighton scale and Brighton (Kappa=0.91) and Hospital del Mar (Kappa=0.61)
Baeza-Velasco* 2014 [30] France	Cross-sectional	College students	305 females	Anxiety: STAI JH: self administered JH Other: alcohol, cigarettes	More tobacco and alcohol if JHS JH higher scores on state anxiety
Eccles 2012 [31] UK	Cross sectional	General population	72 healthy volunteers	Anxiety: BAI JH: Beighton Other: Brain MRI, PBPQ	Amygdala volume greater in JH JH higher scores in interoceptive sensitivity an anxiety JH linked to brain center implicated with emotions and physiological responses,

Abbreviations

HADS Hospital anxiety and depression scale
ASI: anxiety severity index
EPQ: Eysenck Personality questionnaires
SCID: Structured clinical interview for DSM
HAM: Hamilton anxiety and depression scale
ECHO: echocardiogram
EDS: Ehlers Danlos syndrome
NIMH: self-rating scale of mental symptoms
PSS: Panic symptom scale checklist

VAS: Visual analog scale of anxiety
SCL-90: Symptom checklist 90 R
IBQ: Illness behaviour questionnaire
SQ: Symptom questionnaire
FSF: Function symptoms frequency
PAS: Panic and agoraphobia scale
STAI: state trait anxiety inventory
SPPI: Standardized polyvalent psychiatric interview
LSAS: Liebowitz social anxiety scale
ASP: autonomic symptom profile
QOL: quality of life scale
SF-96: checklist of individual strength
FSS: fear survey schedule
GHQ: general health questionnaire
BAI; Beck anxiety inventory
SSAS Somatosensory amplification scale
PBPQ: Porges body perception questionnaire

Table 6. Characteristics of the clinical and nonclinical studies on the association between joint hypermobility and anxiety. (*) Although most of papers come from the same research group, there is no study duplication. Only Bulbena et al. [26] and Bulbena et al. [27] are extracting results from the same sample but they deal with different variables.

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4. The role of psychosomatic mechanisms involved

Once the link between anxiety and the joint laxity syndrome has been established and its association achieved validity and clinical utility, their common etiological and pathophysiological mechanisms ought to be identified. Concerning the etiology and the origin of this "new" revealed condition, so far, only the common genetic linkage has been partially proven. The fact that both conditions (anxiety disorders and joint hyperlaxity syndrome) are highly heritable provides a high likelihood to the genetic etiological pathway. In our first genetic study [46] using pedigree analysis we found duplication in chromosome 15 (15q24-q26 named "DUP25"), which appeared to be present in subjects with both conditions. Although replication studies by other research groups failed to confirm this particular duplication, recent studies of the same chromosome showed complex mental and somatic clinical conditions and also relevant clues for both, anxiety (among other features) and morphological anomalies, either in deletion studies [47] or in supernumerary chromosome markers study [48]. Furthermore, heritability is very often found in both types of patients. It is estimated to be at least 40% in anxiety patients [49] whereas 65% of the hypermobile subjects have at least one first-degree relative suffering from the same condition albeit often goes unnoticed.

In regards to the possible pathophysiology of the link JHS-Anxiety, there are two main sources of evidence. The first source is the so-called dysautonomia, a "blanket term" type of disorder, which has been related to both conditions that controversial but successful concept collects a combination of autonomic disorders, and very often, just collections of anxiety symptoms that are simply named differently [50]. On the other hand, the joint hypermobility syndrome has also been repeatedly related to dysautonomia [51, 52].

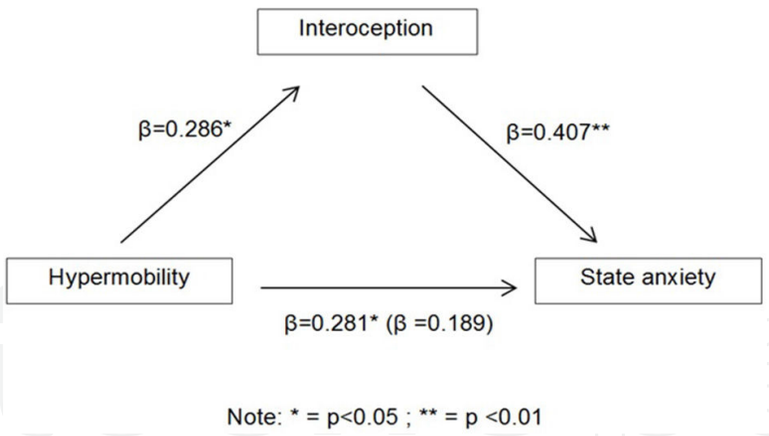

Figure 3. Schematic showing the regression coefficients, with the coefficients (β) for the effect of hypermobility on state anxiety with the latter (when entering interoception into the model) in parentheses.

The second source of evidence for common mechanisms is body awareness, particularly interoception processing. Working together with Prof. Critchley and his group of the Brighton & Sussex Universities, we could confirm a significant correlation between state anxiety score and joint hypermobility [53]. Interoceptive accuracy was associated with both state anxiety and hypermobility and was formally shown to mediate the relationship between these two conditions (Figure 3). Hypermobile participants, when compared to nonhypermobile, displayed heightened neural reactivity to sad and angry scenes in the brain regions implicated

in anxiety states, notably in the insular cortex. These findings highlight the dependence of emotional state on bodily context and increase our understanding of the mechanisms through which vulnerability to anxiety disorders arises in people bearing a heritable variant of collagen.

5. The Neuroconnective Phenotype as a new psychosomatic phenotype

When talking about phenotypes in psychiatry, authors tend to include only behavioral and psychopathological traits which again, represents a bias against somatic or body characteristics. Along the first part of the twentieth century, one classic part of the clinical assessment that is currently neglected was the somatotype (i.e., Leptosomatic, Pyknic, and Athletic) after the contributions of Sheldon and Kretschmer. Nevertheless nowadays, somatotype is being used in other areas of medicine away from psychiatry, notably in Sports medicine. Our group carried out several studies assessing somatotype in psychiatric samples in which we could replicate twice the finding of the association of ectomorphic features with both Anxiety and Joint hypermobility [24,25].

The neuroconnective model is reflected in Figure 4 in which together around a common core Anxiety-Collagen hyperlaxity it includes five dimensions that allows minor overlap: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses.

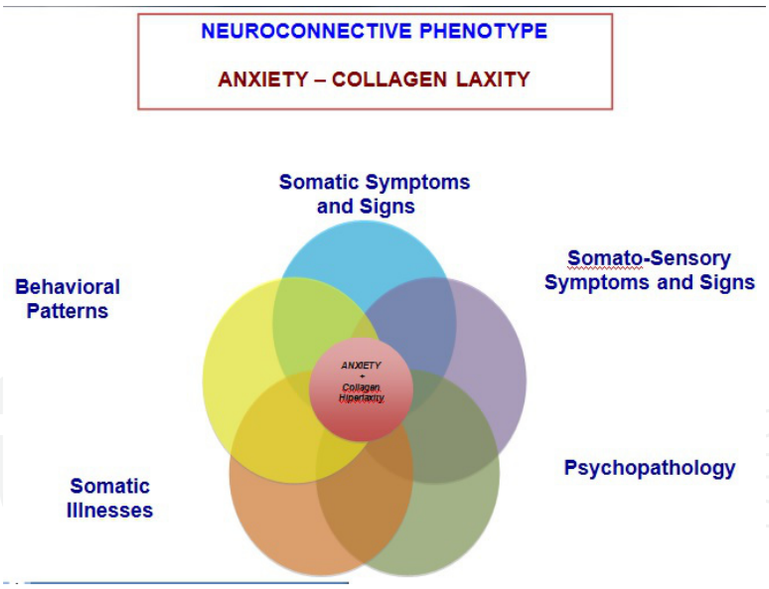

Figure 4. Neuroconnective model of anxiety-collagen laxity.

Two components appear in the core. The first is anxiety and includes any lifetime presence of panic, agoraphobia, specific, and social phobia. Generalized anxiety should be considered when it has reached great severity or when is a residual state of any of the previous disorders. The second component of the core is the Joint Hyperlaxity (hypermobility) Syndrome, which could also be classified as Ehlers–Danlos type III among the hereditary disorders of the connective tissue.

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There is a common characteristic of the components of this core, as very often both go unnoticed and undiagnosed. The failure and delay in the initial treatment contact in patients with anxiety disorders is much higher and longer than in mood disorders [54]. On the other hand, the diagnosis of the joint hypermobility syndrome is very often neglected unless there are articular complaints such as pain or collateral manifestations such as sprains or repeated twisted joints. Except for somatic illnesses, which will be dealt with in the next section, we will only summarize the main characteristics of each dimension, without going into detail.

Behavioral dimensions are patterns of defensive mechanisms often identifiable at the extreme of a continuous axis. They include active flight or fight (hypervisibility), passive flight or fight (hypovisibility), trophotropism (increased appetite, sleep, social withdrawal, and rest), ergotropism (decreased appetite, weight, but increased activity, and aggressiveness), overcontrol (ritualism, compulsions), addictions (alcohol and other nonchemical), Restriction (avoidance of spaces, people, activities or delayed use of time, i.e., procrastination), and dependency (of people, spaces, activities).

Somatic symptoms include dysautonomia, asthenic somatotype, dark or "blue" sclera, easy bruising (especially in women), eczemas, esophageal dyskinesia, sprains and dislocations, visceroptosis, prolapses, allergies, dyspareunia, and hypertrophic scars or keloids.

Somatosensory symptoms include increased olfactory sensitivity (especially for negative odors), difficulties in eye contact and sensitivity to some luminous stimuli, dizziness (unsteadiness), sighing, dyspnea, dysphagia or choking, palpitations, urologic and vaginal pains (dynias), joint pain (especially cervical or lumbar) and intolerances, or enhanced sensitivities to weather, drugs (particularly psychotropic), chemicals, heat, or cold.

Psychopathology includes increased exteroception (e.g., meteorosensibility); increased interoception (visceral-body); increased and distorted proprioception; and depersonalization; high loss of sensitivity; anticipatory anxiety; high positive confrontation (high ability to deal with real acute problems); fear of annihilation or neutralization; fear of rejection, abandonment, or neglect; amplification or exaggeration; and denial or avoidance. This dimension would include fears and phobias including fear of medication (side effects or addiction), fear of illness or hypochondriasis, and mood disorder (depression and hypomanic states).

Finally, somatic illnesses include irritable bowel, dysfunctional esophagus, multiple chemical sensitivity, dizziness or unsteadiness (central vestibular pattern), chronic fatigue, fibromyalgia, glossodynia, vulvodynia, hypothyroidism, asthma, migraine, temporomandibular dysfunction, and intolerances or food and drug hypersensitivity.

6. Anxiety disorders do relate to some somatic illnesses: measuring medical conditions in anxiety patients

Patients with anxiety disorders often complain of somatic features, especially cardiac (tachycardia, chest pain), gastrointestinal (epigastric pain), and neurological complaints (headaches, dizziness, or presyncope), in emergencies and primary services [55–57]. This clinical phenom-

enon helped to deepen into the study of differential diagnoses: are they symptoms of the primary anxiety disorder or are they symptoms of a comorbid physical illness? [58–60]. Besides, more recent research suggests a strong association between anxiety disorders and somatic conditions, although some authors emphasize the huge amount of published research about somatic conditions and depression in contrast to a few studies about the same relationship with anxiety disorders [61–63]. Furthermore, results from the National Comorbidity Survey-Replication (NCS-R) showed that various anxiety disorders had equal or greater association than depression with four chronic physical disorders (hypertension, arthritis, asthma, and ulcers) [64].

The more recent review articles about this relationship are organized according to medical illness specifically associated to anxiety disorders in several descriptive and analytical studies with clinical samples [55,56,62,65,66]. These reviews often include the following somatic conditions: irritable bowel syndrome, asthma, cardiovascular disease, cancer, chronic pain, vestibular and thyroid dysfunction, chronic obstructive pulmonary disease, and mitral valve prolapse. Among the main general conclusions of these reviews are the following: 1) emerging evidence about the bidirectional relationship between anxiety disorders and medical illness suggests that they may be as important as depression [62]; 2) such associations provide important clues for the understanding of the neurobiology of anxiety disorders [55]; and 3) such associations are greater for panic disorder [56, 65], worsening its identification, presentation, and treatment [66].

Despite the significant prognostic and therapeutic implications derived from the comorbidity between mental disorders and medical conditions [55, 62], there is a lack of measuring instruments designed to quantify the physical health and disease in the psychiatric population. Obviously, the use of these instruments in clinical settings is virtually absent. Our group has recently developed a scale (TOPYPS scale) designed to detect and measure functional and organic diseases to be used especially in psychiatric but also in general population.

SIRSs are obtained according to the following criteria:*

Score	Limitation of activity	Treatment	Prognostic	Some examples
0	None	None	Good or mild	Absence of pathology
1	Mild	Not necessary	Mild or moderate	Skin diseases, hemorrhoids, herniae
2	Moderate	Necessary	Moderate	Some cases of diabetes, hypertension, ischemic cardiomyopathy, anxiety disorder
3	Severe	Essential (life risk)	Severe	Some cases of ischemic cardiomyopathy, heart failure, stroke, schizophrenia

*Score SIRS according to the most severe criterion

Figure 5. Criteria for obtaining the SIRS scores in each body system section.

TOPYPS yields a Cumulative Illness Rating Scale (CIRS), and detects, as well, with a high index of suspicion some functional diseases (allergies, migraine, tension-type headache, mitral valve

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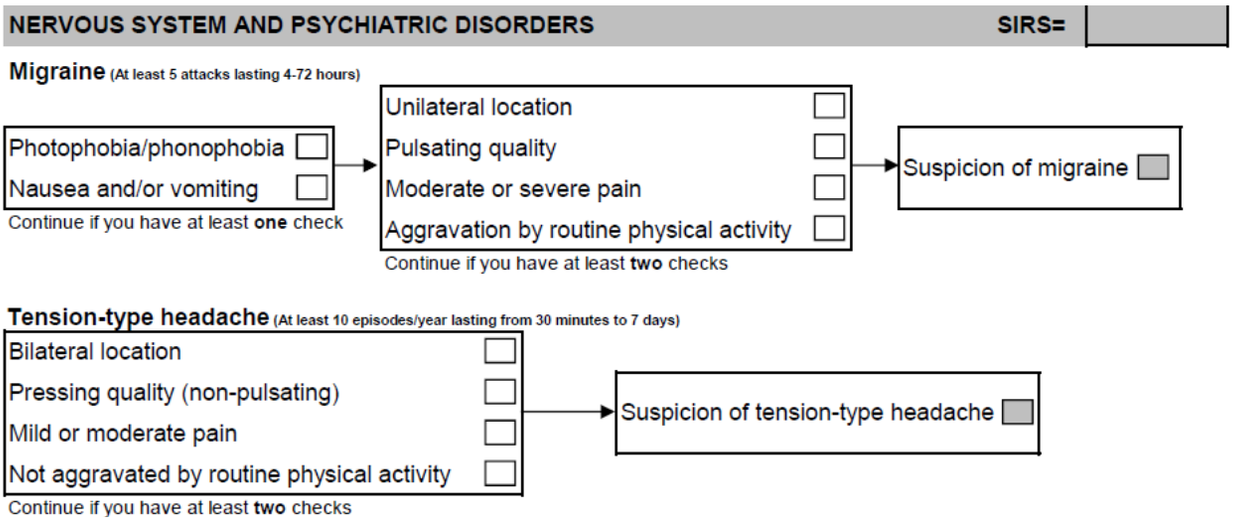

Figure 6. Example of the nervous system and psychiatric disorders section. It collects diagnostic criteria for migraine and tension-type headache.

prolapse syndrome, interstitial cystitis, sexual dysfunction, dyspepsia, functional esophageal disorder, irritable bowel syndrome, fibromyalgia, chronic fatigue, and temporomandibular joint dysfunction) by an interview according to standard diagnostic criteria. TOPYPS has six sections: 1) respiratory, eyes, ears, skin, and annexes; 2) neurological and psychiatric; 3) cardiovascular; 4) genitourinary; 5) digestive, endocrine, and metabolic; 6) musculoskeletal; each one yielding a Specific Illness Rating Scale (SIRS) scored 0–3 according to Figure 5. Figures 6 and 7 are examples of some sections (*the full version of the scale can be requested to the authors by e-mail*). CIRS is obtained at the end by the total sum of the SIRS scores in each section, rated either absent (0 points), mild (1–6), moderate (7–12), or severe (13–18).

The TOPYPS scale was administered to 67 adults randomly chosen from a primary care setting and displayed good psychometrical properties in a Spanish population [67]. Repeatability (test-retest) in each of the six sections (Kappa index) was between 0.72 (musculoskeletal) and 0.968 (respiratory), with an overall average of 0.823 (calculated in all volunteers on two occasions one week apart). Inter-rater agreement was also at its lowest value in the musculoskeletal (0.6) whereas the highest was in the respiratory section (0.78), with an overall average of 0.703. As for the total score, an intraclass correlation index of 0.923 and 0.858 was obtained for the intra- and inter-rater agreement, respectively. Validity was also acceptable (correlation coefficients between 0.726 and 1) according to the correlation of clinical assessments (gold standard) with the SIRS scores in each body system section of TOPYPS. A remarkable degree of agreement (Cohen's kappa between 0.548 and 1) between clinical assessments and diagnostic suspicion of functional diseases according to the scale was also observed. Validity was analysed by comparing the results with the clinical examination performed by two different specialists in general practice. This examination included both the application of the diagnostic criteria for the various functional diseases and the use of a clinical classification based on the same parameters of CIRS ("Gold Standard"). Therefore, TOPYPS scale appears as a suitable tool to detect and measure functional and organic diseases in general population. Our group

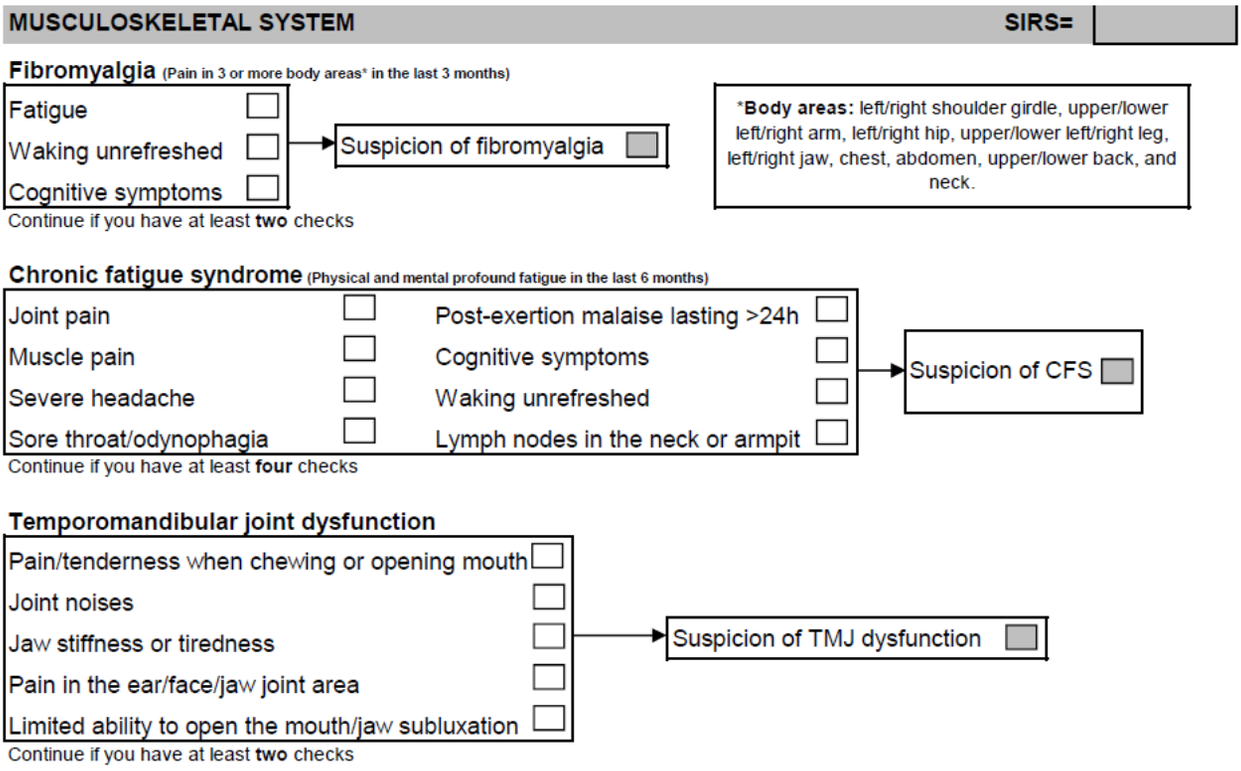

Figure 7. Example of the *musculoskeletal system* section. It collects diagnostic criteria for fibromyalgia, chronic fatigue syndrome and temporomandibular joint dysfunction.

is now actively working on evaluating if patients with panic and/or phobic disorders have a greater burden of somatic conditions than control groups with depressive disorder and with no mental illness.

7. Conclusions

Finally, a number of conclusions can be made after more than 30 years of active research and clinical work in this field. The well-established association between a collagen condition and anxiety has opened new ways to clinical and basic research. Most probably, new forms of psychosomatic conditions will emerge and different nosological approaches will be required. The Neuroconnective model is a proposal under research that may be useful for clinical practice. Nevertheless, new basic and clinical research on this reviewed association is mandatory because it might open new ways to assess, to understand, and to treat our patients.

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