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Articles

Somatic Symptom Disorder: a narrative review of literature of the last twenty years

Fabrizio Turiaco ^{1*}, Fiammetta Iannuzzo ¹, Abed L. Hadipour ², Gianluca Pandolfo ¹, Maria Rosaria Anna Muscatello ¹, Antonio Bruno ¹

Abstract

Background: according to the DSM-5, somatic symptom disorder (SSD) is characterized by physical symptoms that cause a disruption in patient functioning and by excessive preoccupation about symptoms. There is a high prevalence of SSD in the general population, with a range going from 5 to 7% and with a relevant cost burden for healthcare system. So, it appears useful to know what the state of art regarding this significant problem is.

Methods: the aim of this work is to review studies published in the last twenty years, using Pubmed, Scopus, Cochrane and PsichInfo, as search engines and the following terms: “somatic symptom disorder”, “somatization”, “somatoform disorder”, “medically unexplained symptoms”, “bodily distress syndrome” and “psychosomatic medicine”, linked by the Boolean operator “OR”. Exclusion criteria are studies in languages other than English and French, studies about pediatric population and animals, type of publication other than journal articles.

Results: etiology of SSD is multifactorial, involving internal and external factors. Neuroanatomical studies show the presence of abnormalities in CNS of SSD patients. Assessment still results a problematic field, due to uncertainty of nosography. The therapeutic approach toward SSD can be pharmacological, but also the psychotherapy in its different approaches.

Conclusions: the issue of SSD is complex and needs further investigations. To correctly analyze this phenomenon, it is necessary to consider both psychological and organic factors, being on the base of this disorder. It is worth to develop this research because an improvement of the state of art about this matter could lead to improve the approach to SSD, resulting in better quality of patients’ life.

¹ Psychiatry, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

² Department of Cognitive Science, Education and Cultural Studies, University of Messina, Messina, Italy

E-mail corresponding author: fabrizio.turiaco@gmail.com



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1. Introduction

Somatic symptom disorder (SSD) is one of the most recent diagnostic labeling of a complex nosological phenomenon, that has undergone numerous transformations over time.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), SSD is characterized by preoccupation, with one or more distressing physical symptoms that consequently cause a disruption of normal daily functioning (criterion A), and by thoughts or anxiety about symptoms or excessive energy dedicated to them (criterion B). Worth of noting is that any organic disease explaining the somatic symptom does not exclude the diagnosis of SSD, if the patient's distress and dysfunction referred to the organic disease is too elevated than expectation. A specific symptom does not need to be continuously present, however the condition of being symptomatic must have lasted for at least 6 months (criterion C), (Table 1.) (American Psychiatric Association, 2013; Kurlansik & Maffei, 2016; Rosic et al., 2016).

The main characteristic of this condition is the presence of the so-called medical unexplained physical symptoms (MUPS), also known as Functional Somatic Symptoms (FSS). These are body-referred symptoms, which cannot be explained by an organic damage or by a physiological impairment and influence patients' life from a perceptive and cognitive point of view, generating a different bodily perception that gives negative experience of the self and life, and from a behavioral point of view, leading patients to seek care (Engel et al., 2002; Lacourt et al., 2013).

From the phenomenological point of view, there is a fundamental difference between perception and representation. A distortion in the process of the right attribution of meaning to the bodily perception and to the derived imagines, could be the psychological base of bodily distress syndrome, given that imagines have an active role in exacerbating emotions. (Pappalardo, 2020)

Moreover, it was possible to put in evidence the imagines' role in generating emotions, through the study of oneiric activity of patients affected by SSD, observing that emotional suppression is associated with maladaptive phenomena of somatization and with the recurrence of nightmares, especially in cardiopathic patients (Settineri et al., 2019).

Besides bodily complaints, other characteristics of SSD are a major prevalence in female sex; the common comorbidity with anxiety and depressive disorders, which is higher than in organically explained diseases affecting the same organs (e.g., irritable bowel syndrome vs inflammatory bowel disease); the worsening of the quality of life; and the response to

psychotherapy or psychopharmacological treatments (Barsky & Borus, 1999; Henningsen et al., 2007).

Given the major prevalence in women, some study analyzed the relationship between neuroendocrine factors, as the hormonal changes during menopause and somatic syndrome disorders, highlighting the link between body changes and psychological perception (Conversano et al., 2019).

There is evidence in the literature that FSS has an elevated cost burden on the healthcare system, especially regarding outpatients, who can independently choose when and where to consult a physician or other health provider (Grupp et al., 2017).

Table 1. Characteristics of somatic symptom disorder

Characteristics of somatic symptoms disorder
<ul style="list-style-type: none"> • Presence of not organically explainable symptoms • Negative influence on patient's cognitive and physical perception • Major prevalence in female sex • Often in comorbidity with anxiety and depressive disorders • High-cost burden • Responsivity to psychopharmacological treatment and psychotherapy

Psychiatric or psychological interventions are often not acceptable for most SSD patients since they experience their condition to be a somatic illness rather than a mental problem. Moreover, mental disorders, experienced as “not real”, put the patients under the weight of the stigma generally associated with psychiatry: the tacit consideration that people affected by a mental disorder are no longer able to reason properly and to be aware of them-selves (Sharpe & Carson, 2001).

Patients will be more easily allied with those physicians who provide an organic diagnosis to explain their situation, however this can lead to often harmful consequences such as over-examination, even with invasive procedures, self-treatment, and somatic obsessions that worsen the psychiatric disorder (Greer & Halgin, 2006; Williams et al., 2008). While contested causation of symptoms, especially if it happens collectively involving media and scientific controversy, could severely put at risk the relationship between patient and physician, with the result of a decrease in quality and effectiveness of provided care (Engel et al., 2002).

From a taxonomic point of view, people affected by SSD generally present different symptoms that may be clinically grouped in syndromes such as chronic fatigue syndrome, fibromyalgia, or irritable bowel syndrome (IBS) (Lacourt et al., 2013).

The purpose of the current work was to evaluate of the state of the art about SSD, through a narrative review of the studies published in the last twenty years; to address the multiple factors that can condition the development of this complex disorder, delineating the changes that have occurred in the nosography; to conduce a wide exploration of the therapeutic approaches and to provide a framework in which identifying knowledge gaps and speculate new possible interventions.

2. Method

This article reviews studies published in the last twenty years on the topic of psychosomatic medicine, with attention to those studies related to the SSD diagnostic category.

The selected studies have been identified through research carried out in Pubmed, Scopus, Cochrane and PsichInfo using the following terms: “somatic symptom disorder”, “somatization”, “somatoform disorder”, “medically unexplained symptoms”, “bodily distress syndrome” and “psychosomatic medicine”, linked by the Boolean operator “OR”. Exclusion criteria are studies in languages other than English and French, studies about pediatric population and animals, type of publication other than journal articles.

Table 2. Studies included in the review

Studies included in the review			
Reference	Purpose	Results	Year
(Abbass et al., 2014)	To evaluate the efficacy of STPP in common mental disorders compared with wait-list controls, treatments as usual and minimal contact controls in randomized controlled trials (RCTs).	33 studies involving 2173 participants were included. For general anxiety and depressive symptoms, a greater improvement in the treatment versus the control groups in the short-term and medium-term emerged.	2014
(Albert et al., 2016)	To obtain data on efficacy of AAs as a treatment of anxiety disorder, OCD, and trauma-related disorders to provide	1298 papers were identified, of which 191 were subjected to a full-text review and 56 were included. This systematized review supports the evidence that only a few AAs are effective in a minority of the off-label	2016

	guidance for clinicians on when and which AA to use.	conditions in which they are currently used and confirms that AAs should be used based on a balance between efficacy and side effects, and their own characteristics.	
(American Psychiatric Association, 2013)	<i>The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, is used by clinicians and researcher to diagnose and classify mental disorders.</i>		2013
(Aschbacher et al., 2012)	To investigate whether a personalized system behavioral phenotype of HPA activity relates to disease symptoms, and whether this phenotype reveals disease subtypes of chronic fatigue syndrome (CFS) and/or fibromyalgia (FM).	Patients with functional somatic disorders tend to have nocturnal HPA system dynamics, consistent with a high sensitivity phenotype, in which ACTH-stimulated cortisol secretion is more rapid and/or sustained.	2012
(Bailer et al., 2007)	To examine the 1-year stability of somatic symptoms and idiopathic environmental intolerance (IEI) features in three diagnostic groups: 49 subjects with IEI, 43 subjects with somatoform disorders (SFD) but without IEI, and 54 subjects control group (CG) with neither IEI nor SFD.	IEI and SFD are highly stable conditions. In both SFD and IEI, negative affectivity and the processes of symptom perception, interpretation and attribution contribute substantially to the persistence of typically somatoform symptoms and IEI complaints.	2007
(Budtz-Lilly et al., 2015)	The aim of the present study was to investigate the psychometric properties of the checklist and to test the construct of BDS.	Internal validation analyses revealed acceptable and usable psychometric properties of the BDS checklist.	2015
(Chan et al., 2020)	To develop and validate a comprehensive symptom severity checklist for Functional Gastrointestinal Disorder (FGID) to track symptom profile changes over time.	108 patients completed the FGI-checklist again at follow-up. Exploratory factor analysis identified a 5-factor solution accounting for 66.8% of the total variance. The 5 factors are named Esophageal Syndrome, Reflux Syndrome, Functional Dyspepsia Syndrome, Nausea and Vomiting Syndrome, and Abdominal and Bowel Syndrome. The FGI-checklist total score was correlated with PHQ9 and PHQ15 (all	2020

		p<0.001), which demonstrated good construct validity.	
(Crofford, 2007)	To understand the relationship between violence, stress, and somatic syndromes.	Data suggest that one of the most important health consequences of abuse is an increased prevalence of somatic syndromes characterized by chronic pain, fatigue, and related symptoms.	2007
(Eberhard-Gran et al., 2007)	To study the associations between recent and repetitive exposure to violence and presence of somatic symptoms and diseases in women.	All somatic symptoms, and several diseases, were significantly more common in women exposed to physical and/or sexual violence as compared to nonexposed women.	2007
(Engel et al., 2002)	To review the notion of medical unexplained symptoms (MUPS), the overlap of MUPS with several common but poorly understood symptom syndromes, and the predictable occurrence of MUPS after controversial community, occupational, and military exposures.	Community exposures and occupational illnesses, a context named in the study as “contested causation,” may have an adverse effect on the care of many individuals with MUPS.	2002
(Fink et al., 2007)	To determine whether functional somatic symptoms cluster into distinct syndromes and diagnostic entities.	The study suggests that bodily distress disorder as defined here may unite many of the functional somatic syndromes and some somatoform disorder diagnoses. Bodily distress may be triggered by stress rather than being distinct diseases of noncerebral pathology.	2007
(Frisone et al., 2021)	To examine the clinical instruments useful for evaluating the risk factors and to examine two closely linked dimensions, which may constitute protective factors such as coping strategies and satisfaction.	Many studies used a range of psychodiagnostic tools to measure stress, coping strategies and job satisfaction. However, their integration is necessary to guarantee a complete evaluation protocol.	2021
(Guo et al., 2019)	To present commonalities in medically unexplained symptoms (MUS) across multiple organ systems, including symptoms, aetiological mechanisms, comorbidity with mental health disorders,	There is evidence that an integrated approach might add towards improved MUS care, with implications to reducing the perpetuation of illness, disability, and healthcare utilization.	2019

	symptom burden and impact on quality of life.		
(Henningsen et al., 2007)	To review management for the full variety of functional somatic syndromes (FSS), and give recommendations for a stepped care approach that differentiates between uncomplicated and complicated FSS.	Non-pharmacological treatments involving active participation of patients, such as exercise and psychotherapy, seem to be more effective than those that involve passive physical measures, including injections and operations. Pharmacological agents with CNS action seem to be more consistently effective than drugs aiming at restoration of peripheral physiological dysfunction.	2007
(Henningsen, 2018)	To give an overview of the management of somatic symptom disorder, with a description of the classificatory, epidemiological, and etiological issues and to describe the evidence and practical principles of dealing with these patients who are often seen as “difficult” to treat.	The best-suited approach is stepped care with close cooperation of primary care, a somatic specialist, and mental health care professionals operating on the basis of a biopsychosocial model of integrating somatic as well as psychosocial determinants of distress and therapeutic factors.	2018
(Kallesøe et al., 2016)	To compare the efficacy of group-based ACT with that of enhanced usual care (EUC) in patient diagnosed with the unifying construct of multiorgan bodily distress syndrome (BDS).	Adolescents (15-19 years) with FSS are at risk of continuity of physical problems into adulthood implying reduced quality of life due to potential functional impairment, social withdrawal, lack of education and incapacity to work.	2016
(Kano et al., 2020)	To provide an overview of our brain imaging data on brain-body interactions in one of the most well-known FSS, irritable bowel syndrome (IBS), and discuss the possible development of a brain-based biomarker for FSS.	From brain imaging data, the mPFC/ACC and insula projection to hypothalamus, amygdala, and PAG associated with the ANS and CRH related system as top-down regulation, and cognitive and emotional modulation or discrepancy between subjective sensation and physiological perception can be a possible candidate brain-based biomarker.	2020
(Khalsa et al., 2018)	To evaluate progress in understanding the role of interoception in mental health.	Dysfunction of interoception is increasingly recognized as an important component of different mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic symptom disorders.	2018
(Kingma et al., 2013)	To investigate patient factors that might be	This study suggests that high intelligence, but not high neuroticism, increases the chance of	2013

	important in the process of syndrome labeling.	syndrome labeling in patients with persistent functional somatic symptoms.	
(Kirmayer & Sartorius, 2007)	To review the relevance of cultural models in the generation and amplification of somatic symptoms and syndromes.	The current state of knowledge on social and cultural dimensions of somatic syndromes suggests a typology of forms of psychosomatic and sociosomatic looping that has implications for the nosology of somatoform disorders.	2007
(Kleinstäuber et al., 2014)	To assess the effects of pharmacological interventions for somatoform disorders (specifically somatization disorder, undifferentiated somatoform disorder, somatoform autonomic dysfunction, and pain disorder) in adults.	For each of the comparisons where there were available data on acceptability rates (NGAs versus placebo, NPs versus placebo, TCAs versus other medication, and antidepressants versus a combination of an antidepressant and an antipsychotic), no clear differences between the intervention and comparator were found.	2014
(Kroenke & Rosmalen, 2006)	To highlight an overview of unexplained symptoms and predictors of psychiatric comorbidity in patients with physical symptoms and measuring and managing symptoms.	The article proposes the PHQ scale as a tool to measure patient symptoms and proposes a stepped care approach divided in two phases.	2006
(Kurlansik & Maffei, 2016)	To provide an overview about somatic symptom disorder.	Screening instruments are useful in determining the presence of somatic symptom disorder. Proven treatments include cognitive behavior therapy, mindfulness-based therapy, and pharmacotherapy.	2016
(Lacourt et al., 2013)	To address the lumpers-splitter discussion on functional somatic syndromes by applying means cluster analyses on a heterogeneous sample of persons with unexplained somatic complaints.	The finding of symptom specific patterns in clusters which could not be differentiated on overall symptom severity is in favor of the splitters' view. The finding that all other clusters could be discriminated on overall symptom severity and that the 2-cluster solution had the best fit is in favor of the lumpers' view.	2013
(Liu et al., 2019)	To update and give an overview of the evidence from published literature that focused on the efficacy of cognitive behavior therapy (CBT) in the management of somatoform disorders and medically unexplained	The findings of this systematic review and meta-analysis suggest that CBT is efficacious for somatoform disorders and MUPS in reducing somatic symptoms, anxiety symptoms, depressive symptoms, and improving physical functioning.	2019

	physical symptoms (MUPS).		
(McAndrew et al., 2019)	To review which illness representations are related to outcomes and how they are related.	The results suggest behavioral treatments should focus on reducing threat-related illness representations and negative coping.	2019
(Myles & Merlo, 2021)	The present study was aimed at highlighting the existing relations, the differences and the directions assumed by alexithymic factors and health status in patients affected by psychosomatic conditions.	The analyses demonstrated several significant relationships between alexithymia, psychological outcomes, and physical outcomes, including psychosomatic disorders. In addition, sex differences were found in gastrointestinal outcomes, as well as outcomes related to energy/fatigue and physical functioning.	2021
(Nimnuan et al., 2001)	To establish whether 13 different syndromes are discrete entities.	This study suggests that the existence of distinct functional somatic syndromes (FSSynd) as defined clinically in medicine should be reconsidered.	2001
(Olkin & Sampson, 2001)	Multivariate analysis is conceptualized by tradition as the statistical study of experiments in which multiple measurements are made on each experimental unit and for which the relationship among multivariate measurements and their structure are important to the experiment's understanding.	Multivariate analysis, due to the size and complexity of the underlying data sets, requires much computational effort.	2001
(Pitron et al., 2019)	To explain how the Bayesian model could contribute to understand the cognitive development of somatic symptom disorder.	The Bayesian model of perception is useful to better understand the pathophysiology of somatic symptom disorder and the mechanisms of action of the proposed therapies.	2019
(Rief & Rojas, 2007)	To investigate the stability of somatoform symptoms/disorders.	These results indicate how the classification of somatoform disorders can be improved. Some new diagnostic criteria are suggested that could be considered in the revision of DSM-5.	2007
(Rosendal et al., 2013)	To assess the clinical effectiveness of enhanced care interventions for adults with functional	Enhanced care may have an effect when delivered per protocol to well-defined groups of patients with functional disorders.	2013

	somatic symptoms in primary care.		
(Rosmalen et al., 2011)	The aim of this study was to develop empirically validated criteria for the diagnoses of clinically relevant somatization.	This study in a large population-representative cohort suggests that a simple symptom count can be used as a dimensional diagnosis of somatization. In those instances, in which a categorical diagnosis is preferred, a simple cut-off of four out of 43 functional symptoms best fitted our data.	2011
(Schröder et al., 2012)	To test the efficacy of a cognitive-behavioral therapy (Specialized Treatment for Severe Bodily Distress Syndromes, STreSS) designed for patients with a range of severe functional somatic syndromes.	In the management of functional somatic syndromes, a cognitive-behavioral group treatment was more effective than enhanced usual care.	2012
(Sharpe & Carson, 2001)	To understand causes of somatic symptom disorder.	The study proposes a paradigm shift in which unexplained symptoms are medicalized around the notion of a functional disturbance of the nervous system and treatments currently considered “psychiatric” are integrated into general medical care.	2001
(Sicari, 2019)	The article kicks off from a historical excursus that focuses on the lively debate between Freud and Bleuler, which allows the author to introduce the concept of psychotic disorganization.	It could therefore be said that one of the questions that have arisen around the disorganization and its links with destructiveness is partly illuminated from an economic point of view: the processes of destruction are in fact closely linked to the balance between narcissistic and objective investments.	2019
(Taylor, 2010)	This article briefly reviews some of Nemiah’s conceptual ideas and relates them to several new theories and concepts and findings from empirical research.	His concept of the ‘psychic elaboration’ of emotion is consistent with con-temporary theories of the cognitive processing of emotions that emphasize the importance of imagery and linguistic symbolizations.	2010
(Torres et al., 2021)	To determine the frequency of and risk factors for suicide outcomes in somatic symptom and related disorders and whether any risk was independent of	There exists evidence for an association between somatic symptom and related disorders and suicide outcomes.	2021

	co-occurring mental disorders.		
(van Dessel et al., 2014)	To assess the effects of non-pharmacological interventions for somatoform disorders and MUPS in adults, in comparison with treatment as usual, waiting list controls, attention placebo, psychological placebo, enhanced or structured care, and other psychological or physical therapies.	Compared with usual care or waiting list conditions, CBT reduced somatic symptoms, with a small effect and substantial differences in effects between CBT studies. The effects were durable within and after one year of follow-up. Compared with enhanced or structured care, psychological therapies generally were not more effective for most of the outcomes. Compared with enhanced care, CBT was not more effective.	2014
(Witthöft et al. 2013)	To address the exact latent structure of somatic symptoms.	The findings of both studies help to clarify the latent structure of somatic symptoms in the PHQ-15. The bifactor model outperformed alternative models and demonstrated external validity in predicting IBS.	2013

3. Results

3.1 Lumpers and splitters

Considering the complexity of SSD manifestations, lumping these somatic symptoms in a unique disorder, or splitting them in more syndromes, with their own specific diagnostic criteria deserves some more attention.

Some author cluster symptoms based on their similarities such as pain (back, head, muscles, or joints, etc.), functional disturbance (palpitation, dizziness, etc.) or fatigue. Oftentimes the diagnosis that the patient receives is quite dependent on the specialization of the physician: e.g., the patient could receive a diagnosis of fibromyalgia when visited by a rheumatologist or a diagnosis of post-treatment Lyme disease syndrome if visited by an infectious disease specialist (Nimnuan et al., 2001).

Many patients fulfil criteria for more than one syndrome and many syndromes have overlapping phenomenology, pathophysiology, risk factors, predictors of outcome, and treatment response. It is estimated that this overlap can range from 10% in the general population to 50% in clinical populations (Engel et al., 2002; Henningsen et al., 2007).

Some attempts have been made to resolve the issue, using statistical methods, to assess the so-called “latent structure” of MUPS. This term is used to describe statistical models that try to

explain the variance of a variable, through the individuation of unobservable factors that influence observable ones (Olkin & Sampson, 2001).

Witthöft et al. (2013) tried to find the latent structure of MUS, using 13 items of the patient health questionnaire (PHQ-15), one of the most widely used psychodiagnostic tools. They developed a model consisted of one general factor, in which all the items fitted significantly, and four symptom-specific factors (a gastrointestinal factor, a pain factor, a fatigue factor, and a cardiopulmonary factor). Many of the symptoms show significant fitting in both levels of modeling.

So, it is possible to think that the general factor mainly refers to an affective component associated with symptom experience, pointing out symptom distress variance, whereas the symptom-specific factors are more closely related to the sensory component of the symptom, in a manner just perceived somatically by patient without any negative feeling (Witthöft et al., 2013). Fink et al. (2007) performed a latent class analysis, finding similar results and reporting a cardiopulmonary, a gastrointestinal and a musculoskeletal group of symptoms to derive from a unique pathologic latent phenomenon (Fink et al., 2007).

3.2 Epidemiology

It needs to be stressed that the sampling strategy can influence the data regarding the prevalence of FSS. This is an important point to keep in mind because of the instability of sonographic entities affecting this psychiatric disorder.

The prevalence of somatic symptom disorder and other related disorders is estimated to be 5-7% in the general population and approximately 15% in the primary care population (Rosendal et al., 2013; Torres et al., 2021).

Prevalence of some FSS, such as irritable bowel syndrome, reaches up to 15%, however the diagnostic criteria based on which the data is reported play a decisive role (Henningsen et al., 2007).

3.3 Historical Background

Uterus was the first suspected cause for unexplainable medical symptoms and from here the term “hysterical” symptoms.

As early as the end of 1600, psychological factors began to be considered in the etiology of unexplained symptoms. The positivist culture of 19th century came back to a prevalence of organic explanations of MUS, trying to find the underlying causes, through anatomopathological

studies and creating the term “functional damage” for those cases in whom it was impossible to find an organic lesion. It was only during the 20th century, by the pioneering figures in psychology such as Janet, Freud, Jung, etc. that a psychological foundation for these symptoms was proposed, ruling out the idea of a functional disruption of the central nervous system, in favor of the concept of “psychogenesis”. In particular, the mechanism through which psychological contents could manifest as somatic symptoms was described as somatization (Sharpe & Carson, 2001; Sicari, 2019).

Successively in the neuroanatomical perspective, many researchers such as Cannon in 1928, Papez in 1937 or Maclean in 1949, tried to explain somatic symptoms as a result of the interaction between subcortical brain structures and neocortex or hypothalamus. In the subcortical-neocortex circuit upstream signals would generate the cognitive representation of symptoms, whereas the subcortical-hypothalamus circuit would generate downstream signals that influence the peripheral manifestation of the phenomenon (Kano et al., 2020).

More recently, after the publication of DSM-III, the criteria for diagnosis of somatoform disorder were drawn up and required the presence of 12 symptom for males and 14 for females, that changed to 13 for both sexes in DSM-III-R. The DSM-IV criteria required 8 symptoms in 4 symptom clusters: at least 4 pain symptoms, 2 gastrointestinal, 1 sexual and 1 pseudo-neurological (Rosmalen et al., 2011).

3.4 Etiology and risk factors

Etiology and risk factors of somatic symptom disorder can be divided into external/environmental causes and endogenous (i.e., biological, and psychological causes), obviously influencing each other and giving rise to the complex phenomenon of somatization.

Attachment pattern is one of the most precocious risk factors of SSD. Insecure attachment in adults predicts somatization symptoms: a link between attachment anxiety and anxiety regarding health has been shown (Henningsen, 2018). In addition, difficulties in emotion recognition and control like alexithymia have long been related to different manifestations of bodily distress (Myles & Merlo, 2021; Taylor, 2010).

There is evidence that being a target of sexual assault is related to reproductive and sexual health problems, with a prevalence of history sexual assault being from 26 to 64% in patients complaining about pelvic pain (Eberhard-Gran et al., 2007).

Patients often find the cause of MUPS in significantly stressful or traumatic environmental exposures, even when a direct causal nexus between the stressful event and symptom is not

scientifically demonstrable. Many examples of this could be reported such as veterans developing MUPS after returning from the Gulf War, suggesting the existence of a Gulf War syndrome or soldiers complaining about chronic debilitating physical symptoms after World War I and attributing them to chemical toxic exposures in trenches. After the Vietnam War, veterans sought care for the concern to have been exposed to dioxin. (Engel et al., 2002). Despite this, there is evidence that stress can affect psychological well-being of patients (Frisone et al., 2021).

From a strictly genetic point of view, it has been shown that “high pain sensitivity” (HPS) haplotype of COMT gene, guanine triphosphate (GTP) cyclohydrolase and tetrahydropterin are associated with increased pain sensitivity. Polymorphisms involved in HPA axis function or neurotransmitter systems, including proopiomelanocortin (POMC), nuclear receptor subfamily 3, group C, member 1 (NR3C1), monoamine oxidase A (MAOA), monoamine oxidase B (MAOB), and tryptophan hydroxylase 2 (TPH2) have been identified in patients with chronic fatigue syndrome (Crofford, 2007).

The concept of “interoception” was recently proposed to explain how somatic and psychic functions are linked, indicating the perception of one’s own physiological functions and somatic sensations such as pain, temperature, itch, touch, or visceral sensations. Mood can be a product of our interoceptive activity, which is highly connected with the autonomic nervous system (ANS). Disruption in interoception could thus be the underlying cause of FSS (Figure 1.).

Moreover, a mechanism of central sensitization has been proposed to explain FSS. It would be characterized by hyper-excitability, due to plastic reorganization of synapses of specific central nervous system (CNS) areas, such as limbic lobe, caused by repeated exposure to noxious stimuli. After becoming more sensitive, these structures would contribute to the development of the symptoms mainly characterized by pain, such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome (IBS), temporo-mandibular joint disorder, and tension headache (Kano et al., 2020). Childhood adverse events, social and cultural context, or previous organic diseases (such as gut infections for IBS) may induce epigenetic changes and imbalances in the HPA system and in the immunological system that, co-causing central sensitization, and leading to the development of FSS. The bidirectional link between CNS and peripheral organs through the ANS, means that the peripheral nervous system can influence mood and stress response. Despite high co-morbidity with anxiety, mood disorders and personality disorders, FSS can manifest in the absence of other mental disorders (Guo et al., 2019; Kleinstäuber et al., 2014; Schröder et al., 2012).

The immunological impairment, mentioned above, leads to the production of cytokines, that cause neuroinflammation. This could be the explanation of symptoms reported by patients with functional somatic disorders, such as fatigue, difficulties in concentration, enhanced pain sensitivity and mood symptoms. Regarding the HPA axis, continuous distress can modulate HPA signaling, altering glucocorticoid receptors activity, and causing a chronic inflammatory state (Aschbacher et al., 2012).

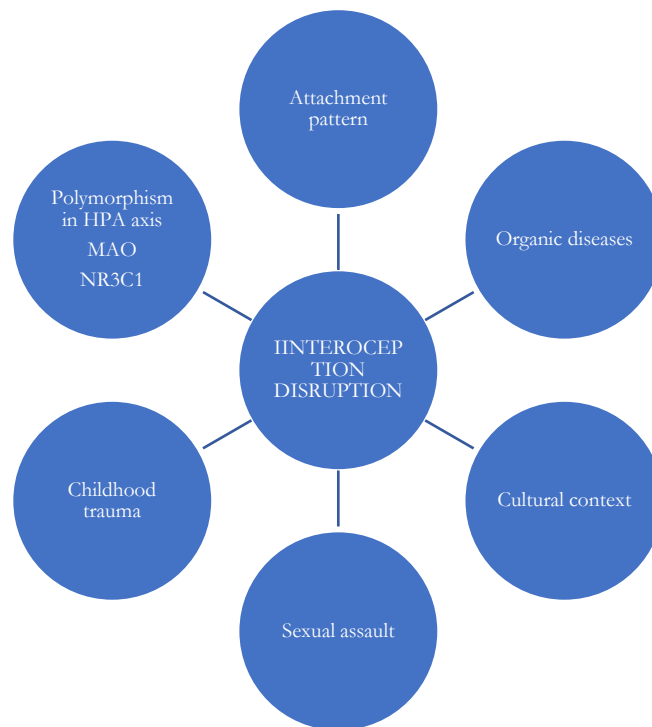


Figure 1. Factors affecting interoception disruption

3.5 Neuroimaging

According to Kano et al. (2020), visceral hypersensitivity is observable in 30 to 40% of IBS patients, in functional dyspepsia, fibromyalgia, and chronic fatigue syndrome.

Similarly, to noxious stimulation, visceral stimulation activates a group of brain areas involved in pain experience including the insula (posterior/middle/anterior), anterior cingulate cortex (ACC; subgenual/pregenual), midcingulate cortex (MCC; anterior/posterior) thalamus and primary somatosensory cortex (SSC). Other areas, not known to directly generate nociceptive input, are also hyperactivated, including the posterior (PCC) and mid-cingulate cortex, ventrolateral prefrontal cortex (PFC), and precuneus and the amygdala, mostly associated with hypervigilance or pain-related fear, are also hyperactivated in this patient. That is why it is possible to think about a hypervigilant state of the brain in patients with IBS, that manifests itself with an abnormal fear in situations that may induce or intensify their symptoms. The

amygdala-periaqueductal gray (PAG) pathway is one of the key descending pain control pathways and the fear of pain may disrupt it. Another important mediator is the corticotropin-releasing factor (CRH) system. In addition to being a hormone, CRH is also a neurotransmitter that stimulates the neurons in medial prefrontal areas, including pACC, in the hippocampus, and in the hypothalamic nuclei. CRH binds CRH1 and CRH2 receptors and there is a high CRH1 receptor expression in the forebrain, subcortical limbic structures, and the amygdala, whereas its expression varies in the hypothalamus, increasing in the case of distress. The CRH1 and CRH2 receptors interact in the myenteric neurons, influencing gut functions such as motility, permeability, and sensitivity. The mPFC/pACC is a system of inhibitory control of the HPA axis, which can be disrupted by increased CRH release in IBS, due to chronic stress, with a consequent upregulation of CRH1 receptors in the pituitary gland. The colorectum motility response to CRH administration is exaggerated in IBS patients, which indicates upregulation of CRH-CRH1 signaling in the colon with an altered brain CRH system. The pACC and aMCC are part of the central autonomic network (CAN) that regulates Autonomic Nervous System (ANS) outputs, through a top-down modulation of visceral nociception. By considering IBS and other FSS as disorders of top-down interaction in the nervous system, it is possible to explain the rise and maintenance of symptoms through impairment of multiple bidirectional feedback loops between the CNS and different organs. Several types of underlying pathologies can produce the same pattern of symptoms that define an FSS. Because of alterations of peripheral functions, brain functions, or brain-periphery interface. So, negative emotions like fear or threat could cause persistent sympathetic activation mediated via projections from mPFC/ACC and/or insula, considered as higher homeostatic regulation regions, on sympathetic effector regions including hypothalamus, amygdala, or PAG. Consequently, somatic symptoms such as diarrhea can occur. In contrast, chronic change of physical conditions could probably result in the dissociation of physical sensation and ability to perceive it correctly, which then may decrease one's belief of mastery over bodily states and increase the loss of control of the bodily state, which may lead to an anxiety state and helplessness (Kano et al., 2020).

3.5 Psychological aspects

It is necessary to adopt a vision that integrates different complex manifestation of FSS, to create or improve the psychological perspective to link the multiple facets of this phenomenon.

Specifically, the model of interoception is to be considered as a combination of the perceptions coming from the peripheral nervous system and predictive mapping generated by expectations

about bodily states, due to probability distributions. According to the inferences based on Bayesian theory, cognitive anticipations contribute to the shape of bodily perceptions, because the nervous system builds a prevision of a possible perception which is considered the most probable, on the basis of the informations it already has. The final perception would be the result of the fusion of the brain's predictive models with the stimuli coming from the periphery. Therefore, the FSS can be supposed to be generated by a disruption of this prevision system (Khalsa et al., 2018; Pitron et al., 2019).

Deepening the subject further, it is possible to describe how the complexity of perceptions is elaborated when it becomes conscious, introducing the concept of illness representation.

These are the ways patients figure out their symptoms and are considered a key to understand MUS, in terms of identity of illness (e.g., I have fibromyalgia), timeline (e.g., I will be affected by it for the rest of my life), causes (e.g., a vaccine caused my symptoms), consequences (e.g., I cannot work), control (e.g., I need to rest), and above all, the emotion status generated by this condition. Illness representations are estimated to explain about 30 to 40% of the variance in MUS health outcomes, such as quality of life. Negative illness representations are related to higher healthcare costs, less patient-provider alliance, and poorer mental and physical health outcomes for patients with SSD and could predict the development of chronic symptoms from acute health episodes. Therefore, cognitive behavioral therapy and reattribution treatment, can change patient's illness representations and improve health outcomes (McAndrew et al., 2019).

Keeping this view, negative illness representations lead to a sense of frustration and hopelessness, setting up a chain reaction until the development of anxiety, depressive disorders, or suicidal ideation.

Lifetime prevalence of suicidal ideation in patients with SSD ranges from 26 to 39%. Studies also found an increased prevalence of suicide attempts in presence of somatic symptom and related disorders, ranging from 13 to 67%. In patients with an elevated risk at baseline, such as those with depression and anxiety, the presence of comorbid somatic symptom and related disorders significantly elevated their risk of suicide attempts, due to the increased feelings of hopelessness and frustration, we talked about, for symptoms that do not have a medically explained etiology. In those patients with depression and anxiety under control, somatic symptoms are still associated with significantly increased risk of suicidality, suggesting that the risk of suicide cannot be explained only by comorbidity with mood and anxiety disorders (Torres et al., 2021).

3.6 Assessment

Complications associated with SSD assessment due to its nosographic uncertainty have been described previously. As of now, there is more than one tool to evaluate FSS, some of which used for specific syndromes, but others used to formulate a general diagnosis of SSD, based on the chosen diagnostic criteria. There are structured interviews like the composite international diagnostic interview (CIDI), structured clinical Interview for DSM-IV (SCID), mini-international neuropsychiatric interview (MINI), schedules for clinical assessment in neuropsychiatry (SCAN) and present state examination (PSE), or standardized questionnaires such as general health question-30 (GHQ-30) or patient health questionnaire (PHQ-15) (Bailer et al., 2007; Kroenke & Rosmalen, 2006; Liu et al., 2019; Witthöft et al., 2013).

Checklists applied in many studies, e.g., PHQ or the symptom checklist (SCL), are based on counting the number of symptoms, but the problem of these methods is that they imply the existence of a general somatization factor, that have not been demonstrated by statistical analysis. The BDS checklist identify distinct patterns of bodily distress syndrome (BDS) which are the cardiopulmonary (CP), gastrointestinal (GI), musculoskeletal (MS), and general symptoms (GS) groups. There must be at least 4 symptoms or more in each symptom group. Patients who meet the criteria in 1 to 3 symptom groups have 'moderate BDS' and patients who meet the criteria in 4 to 5 symptom groups have 'severe BDS' (Budtz-Lilly et al., 2015).

The functional gastrointestinal - checklist (FGID) is a specific tool for the assessment of functional gastrointestinal diseases, evaluating symptoms across time (7-day of recall period) and treatment outcome for the whole digestive tract, covering symptoms in the esophageal, epigastric, and abdominal regions. The FGI-checklist further includes single items to assess global dyspeptic symptom severity, abdominal symptom severity, stool frequency and stool form scale according to Bristol stool scale. Patients express the intensity of their symptoms through a Likert scale indicating 0 if there is no impairment in daily activities, 1 if it is mild, 2 if it is moderate (some daily activities are impaired), and 3 if it is severe (a major part of daily activities are impaired). The items are grouped, following the pathological mechanism of FGID, in esophageal syndrome, reflux syndrome, functional dyspepsia syndrome, nausea and vomiting syndrome, and abdominal and bowel syndrome. This is useful to evaluate overlapping syndromes of FGIDs for better clinical management (Chan et al., 2020).

Finally, the composite international diagnostic interview (CIDI). The CIDI is a fully structured diagnostic interview developed by the World Health Organization for self-administration in

presence of trained interviewers, that investigate the 43 somatic symptoms assessed, asking if the patient has been affected by in the last 12 months (Kingma et al., 2013).

3.7 Treatment

There are two main strategies of treatment for SSD, i.e., psychopharmacologic therapy and psychotherapy used both alone and in combination with each other.

Regarding the first, antidepressants including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), or serotonin antagonist and reuptake inhibitors (SARI) play a key role.

Evidence suggests that in SSD patient there is an increased cortical and subcortical activity that leads to salience dysfunction in response to noxious stimuli. This abnormal brain activity is mediated by serotonin (5-HT) and noradrenaline (NA), therefore the drugs that modulate those neurotransmitters may also be effective in influencing SSD symptoms. Moreover, 5-HT and NA have analgesic properties, inhibiting descending pain pathways, at the level of the spinal cord. In general, antidepressants could have direct effects on the functioning of different organs, for example TCAs that slow gastrointestinal transit, due to the anticholinergic effects, improving diarrhea in IBS. Finally, antidepressants at least targeting the comorbidities that come along with the SSD such as depressive disorders, anxiety disorders, and post-traumatic stress disorder, therefore they improve symptoms burden and reduce functional impairment.

The literature supports the use of antidepressants for the treatment of SSD (Figure 2.). In particular, TCAs showed higher effectiveness in comparison to SSRIs. Among TCAs, Amitriptyline gave the best results for pain, morning stiffness, global improvement, sleep, fatigue, tender point score, and functional symptoms. Among SSRI, fluoxetine demonstrated benefit for pain, functional status, global well-being, sleep, morning stiffness, and tender points. There is no evidence of benefit using mono-amine oxidase inhibitors and bupropion, that should even be avoided (Kurlansik & Maffei, 2016).

Antiepileptic drugs such as pregabalin, or gabapentin, showed efficacy in treating pain-dominated somatoform symptoms such as headache, or neuropathic pain, given their mechanisms of action, which is the modulation of calcium and GABA channels, and to treat comorbidity with anxiety disorders.

There is also some evidence about the efficacy of atypical antipsychotics like olanzapine (Albert et al., 2016; Kleinstäuber et al., 2014).

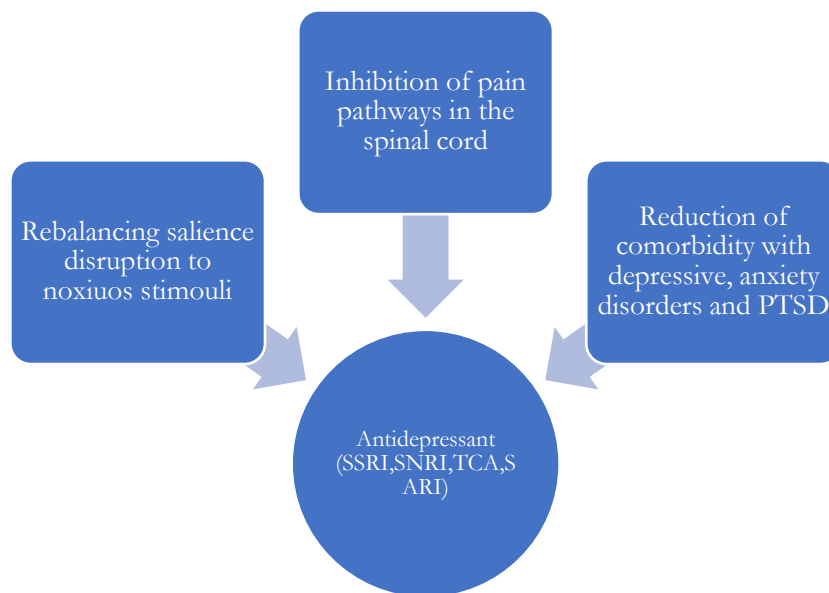


Figure 2. Effects of antidepressants toward SSD

Regarding psychotherapy, it is possible to distinguish three main theoretical orientations: behaviorism, humanistic psychology, and psychodynamic approach.

Common objectives of cognitive-behavioral therapies are time-contingent activity pacing, pleasant activity scheduling, sleep hygiene, assertiveness skills, self-examination for harmful or negative thinking, and structured problem-solving skills (Engel et al., 2002).

To get into the details, there are many types of therapies with different characteristics in theoretical and operative terms, pertaining in their nucleus to one of the three main groups mentioned above. For example, specialized treatment for severe bodily distress syndromes (STreSS) is a CBT-based intervention, composed by nine modules of psychotherapy, each with a duration of 3.5 hour and delivered to groups of patients by two psychiatrists. In a study to test its effectiveness, sessions were given at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16 after randomization (Schröder et al., 2012). For patients with severe functional somatic syndromes combined under the unifying category of multi-organ bodily distress syndrome, the STreSS intervention produced a greater improvement in self-reported physical and social functioning, mental health, physical symptoms, and illness worry than usual care. The treatment effect was maintained at follow-up. These findings suggest patients with the unifying diagnosis of bodily distress syndrome can be treated together regardless of their specific functional SSD diagnosis (Kallesøe et al., 2016).

It is demonstrated that psychotherapies such as cognitive behavioral therapy, hypnotherapy, and mindfulness-based therapy are efficacious for IBS, fibromyalgia, chronic fatigue syndrome, and chronic low-back pain, because of their common psychological characteristics, such as

somatization, conversion (manifesting unconscious internal conflicts with physical symptoms), or depressive and anxiety disorders. It is important to stress that there is evidence that all psychotherapies combined are more effective than usual care or waiting list condition (Kano et al., 2020; van Dessel et al., 2014).

In the metaanalysis conducted by Liu et al. (2019), of 10 studies including 1623 participants, it is showed a significant reduction in the severity of somatic symptoms, with reduction of symptom mean of -1.31 (95% CI: -2.23 to -0.39; $p=0.005$). A subgroup analysis revealed that CBT has statistically reduced somatic symptoms and it was more effective when it was delivered as group therapy (-4.43, 95% CI: -8.47 to -0.39; $p < 0.05$) compared with individual treatment (-1.00, 95% CI: -1.90 to -0.10; $p < 0.05$). The treatment has statistically reduced somatic symptoms if carried out for 12 weeks (-2.28, 95% CI: -4.05 to -0.52; $p < 0.05$), with a duration of sessions of 50 minutes (-1.48, 95% CI: -2.48 to -0.47; $p < 0.01$). CBT has statistically reduced somatic symptoms and was more effective when it emphasized the body-directed technique (-1.70, 95% CI: -2.89 to -0.51; $p < 0.01$) than those did not emphasize it (-0.82, 95% CI: -1.60 to -0.03; $p < 0.05$). In nine studies of the original ten studies analyzed, with a total sample of 1076 participants, CBT has significantly reduced anxiety symptoms, with reduced pooled mean across nine studies of -1.89 (95% CI: -2.91 to -0.86; $p < 0.001$), and depressive symptoms across nine studies, with reduced mean difference of -1.93 (95% CI: -3.56 to -0.3; $p = 0.020$). (Liu et al., 2019)

The common characteristics of psychodynamic approaches are the exploration of defense mechanisms used to avoid distressing thoughts and feelings, that often have their roots in the past and in the cultural environment of the patients. The analysis through the exploration of dreams, imagination, and fantasies of the unconscious world of the patients and how it influences their relationships and their personal realization. Instead, elements that distinguish short-term psychodynamic psychotherapies (STPP) from long-term psychodynamic treatments are the use of selection criteria, time restriction, selection of and adherence to a therapeutic focus, efforts to prevent regression, an active focus on the transference as a template to learn about and activate emotional-relational processes.

The rationale of these treatments is that unconscious impulses and feelings can underpin and perpetuate somatic symptoms, so psychodynamic psychotherapies, with their focus on resolving old psychological wounds and their aversive effects on the whole life of the patient, are used to treat these conditions. Generally, the number of sessions used ranges from 12 to 24. The sessions are face-to-face, weekly, and last about 45 minutes. Many STPP methods use the

triangle of conflict (the link between feelings, anxiety, and defense) and the triangle of person (the link between past, therapist, and current people) as key linkages to examine in the therapeutic process. STPP treatment efforts include interventions falling along a continuum between 'supportive' (such as reassurance and encouragement) and 'expressive' (such as challenge to defenses and elicitation of emotions) elements. Hence, these models can be used with a broad range of people with personality, depressive, and somatic disorders. A metaanalysis of 33 RCTs on STPP, including 2173 participants, shows a modest to large effects compared to controls across a broad range of common mental disorders (Abbass et al., 2014).

4. Discussion

SSD is characterized by not organically explainable symptoms that generate a negative bodily experience negatively affecting the quality of life (American Psychiatric Association, 2013; Lacourt et al., 2013).

The issue of lumping SSD in a unique entity or splitting it in many syndromes, with specific diagnostic criteria is still being discussed (Engel et al., 2002; Henningsen et al., 2007). Considering that SSD is a condition that affects almost the 17% of patients in primary care (Torres et al., 2021), it is essential to broaden our understanding of this condition to find increasingly more effective treatments.

Etiology of SSD is multifactorial, involving external and internal factors, that influence each other. Among the internals, genetics could determine a “high pain sensitivity”, that leads to a major vulnerability to this disorder (Crofford, 2007). Moreover, psychological aspects such attachment style, or social and cultural contexts seem to have a significant role (Henningsen, 2018; Taylor, 2010) as cultural characteristics influence symptoms experience, the attribution of causes, and the extent of disruption in the physiology (Kirmayer & Sartorius, 2007; Rief & Rojas, 2007).

Among the external factors, it is possible to describe the relationship between sexual assault (Golding et al., 1996), other traumatic events, or stressful conditions such as organic diseases, and the development of SSD. It is possible to speculate that all these factors interact also through epigenetic changes.

From a neuroanatomical point of view, many studies provide evidence the presence of different abnormalities in CNS of SSD patients: in particular, in brain areas involved in pain experience such as insula, ACC, thalamus, and somatosensory cortex as well as in brain areas controlling fear and hyperarousal like amygdala and periaqueductal grey (Kano et al., 2020).

Regarding assessment, there are many tools to evaluate SSD, but most of them focus on specific syndromes. When psychodiagnostic tools refer to a general evaluation, they often formulate a mere sum of score of the symptoms. This implies a general somatization factor not statistically validated and, in addition, creates the risks that patient with quite different clinical features have equal total scores (Liu et al., 2019; Withhöft et al., 2013).

The therapeutic approach toward SSD can be pharmacological and is based on the utilization of antidepressant, in particular SSRIs and TCAs, while IMAO are contraindicated. Antiepileptic drugs and antipsychotics have also shown some efficacy (Kleinstäuber et al., 2014; Kurlansik & Maffei, 2016). There is also evidence of efficacy for every type of psychotherapy: psychodynamic, humanistic, and behavioral psychotherapy (Abbass et al., 2014; Liu et al., 2019).

5. Strengths and Limitations

This study has some limitations. First, a narrative review provides less reproducibility than a systematic review, so we could speculate that a further study that reviews literature systematically could be useful. Second, literature shows quite different results about SSD, especially regarding the nosographic classification, so it was not possible to clearly define this issue. The main strength is that this narrative review offers a wide point of view on SSD, from genetics, to neuroimaging, to psychological and cultural aspects, analyzing from different perspectives this complex issue, to get specific focuses through which it is possible to get a track to treat the patients, but also to address the gaps that require further investigations.

6. Conclusions

In conclusion, the issue of SSD is complex and needs further investigations. It is necessary to analyze the psychological and cultural factors that could affect the development of this disorder, trying to melt the knowledge acquired in this field with the organic perspective, that includes the neuroanatomical, psychiatric, and pharmacological research.

It is worth to develop this research because an improvement of the state of art about this matter could lead to overcome the old Cartesian dualistic conception of *res cogitans* and *res extensa*, leading to a real cultural change, that makes it possible to consider life as a unique phenomenon and thus making medicine more human.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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