

Neuroimaging in Somatoform Disorders: A Review



Murad ATMACA

INTRODUCTION

Somatoform disorder is a subtitle of a main diagnosis included in the Fourth Edition Text Revision of The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). The presence of physical signs, which can not be explained by any organic reason based on medical examinations and evaluations, are the basic characteristic of this group of disorders. It is quite common not only in adults, but also in the pediatric population (Kerimoglu and Yalın, 1992; Avcı and Arslan, 1995; Akdemir and Ünal, 2006). Somatoform disorders, particularly somatization disorder and conversion disorder subtypes, are highly prevalent in the Eastern population, although they are not such common in Western populations (Chandrasekaran et al. 1994). As in other mental disorders, its etiopathogenesis remains unclear; likewise, a combination of psychosocial and biological factors seem to cause the development of this disorder. The psychodynamic approach is the oldest and probably the most appreciable theory among those which have tried to explain the event from a psychosocial aspect. According to this theory, emotional problems are replaced by somatic signs via defense mechanisms including denial, displacement and rationalization; thus, somatic sensations are dealt instead of problems that are difficult to overcome (Yücel and Polat 2007). Again, the signs in this model have sometimes been considered as a way to communicate socially, which are exposed to evade responsibility, to express emotions in another way, and to symbolize emotions and beliefs (Yücel and Polat 2007). The cognitive behavioral approach is another psychosocial model and presents an explanation on a quite distinct basis from that of psychodynamic point of view.

The correspondence of the basic A-B-C metaphor of this approach in somatoform disorders is: life events that trigger signs of somatization and accompanying somatic signs and intellectual processes and physical complaints return back as help seeking behaviors depending on the meanings attributed to all of them (Beck 1976). Knowledge concerning the biological basis of somatoform disorders are quite limited (Sağduyu 2001). When comparing somatoform disorders with other mental disorders it is very far behind in terms of neuroscientific data and it can be thought to still be in its infancy. It seems that this results from prejudgement for many years regarding intensive psychosocial, particularly psychodynamic, explanations would be adequate to explain the etiology and that an organic explanation is not necessary; additionally, the disorder is less prevalent in the Western population. Endocrinological studies were the first group of limited neuroscientific studies. Several studies have shown decreased hypothalamo-pituitary-adrenal (HPA) axis activity, which could not be explained medically, in patients with somatic complaints (Ehlert et al. 2001, Parker et al. 2001). Considering increased HPA activity, which is striking in major depressive disorder, this finding claims just the opposite. As evidence about the presence of significant differences in the immune system is increased in patients with somatization syndrome and major depressive disorder, which is directly correlated with HPA axis activity, the notion aforementioned has been established a more concrete basis (Rief et al. 2001).

Neuroimaging studies use various techniques. While some of them reveal information about brain anatomy which is termed "structural brain imaging", some reveal information about the efficacy and activity of the brain, which is termed

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Prof., Firat University School of Medicine Department of Psychiatry, Elazığ, Turkey.

E-mail: matmaca_p@yahoo.com

“functional brain imaging.” The basic role of neuroimaging in clinical use is to go beyond a potential that indicates whether there is a disorder or not; that is to say, to help make a diagnosis. However, rather than having a diagnostic value in mental disorders, primarily in somatoform disorders, it is now used as a negative diagnostic marker in detecting a certain neural pathology as well as in differential diagnosis. Therefore, it seems difficult to specify a “neural sign” for the diagnosis via comparing neuroimaging data of patients who have been diagnosed with “conversion disorder” which developed due to a number of different neural mechanisms, and of a group of subjects that do not have these mechanisms (Browning et al. 2011). However, in any case, it is obvious that there is much work to be done apart from neuroimaging in somatoform disorders, which is still in its infancy in terms of neurobiology. In the present review, a literature overview was performed via Pubmed, Science Citation Index and Science Citation Index-Expanded. We will then discuss the somatoform disorders included in DSM-IV-TR separately and try to provide an overview of the structural and functional imaging findings.

Conversion Disorder

In conversion disorder, symptoms are not required to be developed intentionally, are not to be explained better by a factitious disorder, and cause significant loss of social and occupational ability (Merskey 1995). This disorder is quite common in neurological practice. It has been reported as one of the most common signs encountered in general hospitals with a rate of 1-3% (Marsden 1986). In fact, the relationship between the mind, body and brain have been questioned along with the presence of “hysterical” symptoms. Right hemisphere involvement has been considered based on predominantly left-sided complaints particularly in patients with conversion disorder and motor signs (Stern 1983). Except for a few pilot studies, specific brain signs that accompany conversion symptoms have not been identified. Marshall et al. (1997) performed functional magnetic resonance imaging (fMRI) in a patient with left-sided paralysis without any structural or metabolic neural lesion and detected an increase in orbitofrontal cortex activity, which is responsible for the inhibition of intended movements, by an intentional movement attempt in the involved side. Marshall et al. (1997) speculated that the motor symptoms in conversion disorder in this patient’s case can be explained by the activity of related anatomical regions leading to over-inhibition in specific brain pathways. Spence et al. (2000) reported concomitant distinctive prefrontal cortical signs in patients with hysterical and factitious disorders, who displayed movement disorder as well. While basal ganglia are associated, on one hand, with cognitive and emotional functions, language, attention, functioning memory and motivation, they, on the other hand, are the basic structures in controlling motor functions (Kaji 2001). The basal ganglia are in

close association both with the thalamus and with the motor cortex. On the other hand, many nuclei in the basal ganglia play a key role in the control and arrangement of movements as well as in determining the movements that will continue (Wise et al. 1995). These factors resulted in focusing on subcortical structures, particularly on the thalamus and basal ganglia in conversion disorder. Vuilleumier et al. (2001) performed photon emission computed tomography with technetium 99 in seven patients with conversion disorder, and detected a decrease in regional cerebral flow in the thalamus and basal ganglia of the opposite side of the involved area. They concluded that conversion symptoms might result from functional impairment in the striato-thalamic circuit that controls sensory and motor functions as well as intentional motor behavior. Von Giesen et al. (1994) reported that neglecting the motor aspect of one side of the body is the reflection of impairment in the striato-thalamic pathways, which regulate the intention for preparing and maintaining a movement. Striato-thalamic premotor mechanisms contribute to the intention to initiate a movement and make an effort for this; in this respect, it seems to be in close association with conversion disorder (Gandevia 1987). A neurological functional impairment in these circuits may lead to numerous motor and neuropsychiatric disorders, such as Parkinsonism, chorea and tics, which indicate abnormal cortical control of basal ganglia and thalamic system (Rauch and Savage 1997, Brown and Pluck 2000). In this context, we as well (Atmaca et al. 2006) evaluated the caudate nucleus, thalamus and lentiform nucleus volumes in 12 patients with conversion disorder who presented for the first time and had no history of treatment, and in healthy controls of the same number. No significant difference was identified between the patients and the control groups in terms of intracranial volume, total brain, white matter and grey matter volumes. Nevertheless, the left caudate nucleus and lentiform nucleus ($p < 0.01$ and $p < 0.05$, respectively) and the right caudate nucleus and lentiform nucleus ($p < 0.05$ for both) were significantly smaller in patients with conversion disorder as compared to healthy controls. On the other hand, the right thalamus was significantly smaller in the patient group as compared to healthy controls, whereas the left thalamus was smaller with similar significance. A negative significant correlation was determined between age at the onset of disease, and the left thalamus volume. As a result of this study, we identified significant neuroanatomical changes in the thalamus and basal ganglia of patients with conversion disease as compared to healthy controls. These results may contribute to the development of a new extension, including structural changes of the brain as well, in terms of the biological aspect of conversion disorder and to the psychobiology of the disorder, which has been attempted to be explained only psychodynamically until recent times. Based on the improvement of a chronic conversion disorder, a case report tried to describe the neural circuit of the disorder. A patient, who

was defined as having a four-year hysterical mutism, underwent fMRG while she/he was in an effort to speak and then a psychotherapy program was performed against motivational factors that cause maintenance of mutism (Bryan and Das 2012). The fMRG, which was performed after speaking was completely normal, revealed increased activity in the inferior frontal gyrus (IFG), the median frontal and supplementary areas, and in the temporal and parietal cortexes. On the other hand, increased IFG activity was positively correlated with anterior cingulate activity, but negatively correlated with amygdala activity; as a result, the authors concluded that an impaired connection pattern between the speaking network and the networks that regulate anxiety was responsible from conversion disorder. In a most recent study, Labate et al. (2012) performed comparative whole brain voxel based morphometry and cortical thickness analyses in 20 conversion disorder patients who had pseudo-epileptic seizures and of whom differential diagnoses from epilepsy was made via ictal electroencephalogram (EEG), and 40 healthy controls. They found extensive cortical atrophy in the motor and premotor regions of the right hemisphere and in the bilateral cerebellar hemispheres. Moreover, they reported a significant correlation between atrophy and accompanying depression, and thus, they stated that motor and premotor regions of the right hemisphere and cerebellum might be associated with the pathogenesis of depression and conversion disorder. Again, a recent fMRG study conducted by Voon et al. (2011) in 11 conversion disorder patients and 11 healthy controls matched in terms of age and gender reported decreased activity in the left supplementary motor area (the area known to initiate motor movement) and increased activity in the right amygdala, left anterior insula and bilateral posterior cingulate. As a result, they propounded that negatively affected intention to initiate movement might be responsible for the functional impairment in conversion disorder.

Hypochondriasis

Hypochondriasis is the state of preoccupation about having a serious disease resulting from misinterpretation of stimulations of the body. This preoccupation is required to last for at least six months and to substantially impair public and occupational functions. Preoccupation is maintained despite appropriate medical evaluation and encouragement. The most typical characteristics of the patients include repetitive physical examinations and diagnostic methods and requesting encouragement from the physicians. Moreover, it is observed that they investigate immensely about the disease. As the other somatoform disorders, knowledge about etiopathogenesis of the disease is limited. Data about neuroanatomic changes that play a role in the development of the disease are quite inadequate. Although it is classified in somatoform disorders in DSM-IV-TR, it resembles obsessive compulsive

disorder (OCD), which is an anxiety disorder, with many features such as intrusive thoughts and repetitive controls and is considered within the spectrum called obsessive compulsive spectrum disorder (Barsky 1992). It is known that a group of psychiatric disorders display phenomenological and neurobiological interleaving and take place within this spectrum. These disorders include impulse control disorders, such as Tourette's disorder, autistic disorder, stereotypical movement disorder, body dysmorphic disorder, hypochondriasis, trichotillomania and pathological gambling. A case report demonstrated successful treatment with unilateral anterior thalatomy surgery in a patient with hypochondriasis, who had complaints about internal organs and pain lasting for a long time (Andy 1973). Successful use of the therapy method in hypochondriasis, which is used in therapy-resistant OCD, has been propounded as an additional evidence for the disorder to be considered within OCD spectrum (Martuza et al. 1990). In this context, we performed the first brain volume study in hypochondriac patients focusing on orbito-frontal cortex, thalamus, anterior cingulate cortex and caudate nucleus, which have been studied before and defined as the key brain regions in its neuroanatomy (Atmaca et al. 2010). With this study, we determined that hypochondriac patients have smaller right and left orbito-frontal cortex and a bilateral larger thalamus as compared to the healthy controls. No significant difference was observed in the caudate nucleus or anterior cingulate cortex volumes. Besides, another important finding was the significant correlation between disease duration and volumes of the left thalamus and orbito-frontal cortex. Beyond indicating that the orbito-frontal cortex and thalamus play an important role in the pathophysiology of hypochondriasis, these findings also suggested a neuroanatomic support, which secures the position of the hypochondriasis in obsessive compulsive spectrum disorders. Another study conducted by our group within the context of the question "is hypochondriasis an anxiety disorder" (Olatunji et al. 2009) evaluated hypophysis volume in a group of hypochondriac patients (Atmaca et al. 2010). The study included 20 patients with hypochondriasis and 20 healthy controls. We observed that hypochondriac patients had significantly lower hypophysis volume as compared to healthy controls. These findings were important, revealing the pathophysiological relationships between hypophysis and hypochondriasis. In an fMRI study, Van den Heuvel et al. (2005) investigated blood flow changes in the presence of related adversities (harmonious colors in contrast to inharmonious color, neutral words in contrast to panic-related words, neutral words in contrast to OCD-related words) in patients with OCD, panic disorder, hypochondriasis and healthy controls; they identified increased attention in OCD, panic disorder and hypochondriasis and found that this finding was associated with fronto-striatal and limbic involvement.

Somatization Disorder

Somatization is a subtype of somatoform disorders and begins before the age of 30 years, even in the youth. Its prevalence has been reported to be 0.2-2% in females and lower than 0.2% in males. It is the most common group of somatoform disorders seen in clinical practice. There are limited numbers of studies about the extent of somatization disorders in Turkey. Studies, which evaluated presentation to psychiatry outpatient clinics, reported the prevalence of somatization disorder between 43% and 68% (Ayhan et al. 1988; Oğuzhanoglu et al. 1994). The psychoanalytic approach suggests that somatic signs in somatization disorder allow impulse discharge by means of external reflection of unconscious boredom (Gabbard 1994; Simon 1991). However, biological etiopathogenesis has placed more emphasis on genetics (Tongersen 1986). Neurobiological studies pointed out impairment in the functions related to the differences between auditory evoked potentials of patients with somatization disorder and healthy controls. Based on similar responses given to both relevant and irrelevant stimulations in the patient group, they drew attention to the problems about selective attention (Pennebaker and Watson 1991, Guggenheim 2000). On the other hand, frequent comorbidities in somatization disorder raised the question whether somatization signs might be equivalent to depression (Simon 1991). Neuroradiological research is quite limited. Hakala et al. (2004) compared 10 female patients with somatization and undifferentiated somatoform disorders, and 16 healthy controls and found that the caudate nuclei were significantly larger in the patient group as compared to the healthy controls. Garcia-Campayo et al. (2001) conducted a single photon emission computed tomography (SPECT) study and compared 11 patients with somatization disorder and controls; they found hypoperfusion on SPECT of 7 patients (in the non-dominant hemisphere in 4 and in the bilateral hemispheres in 3 of the patients). In another study, we (Atmaca et al. 2011) evaluated the volumes of the hippocampus and amygdala, which have the closest association with stress and emotion. Compared with controls, the right and left amygdala volumes were significantly lower in the patient group, but there was no difference in terms of hippocampus, total brain, grey and white matter volumes. This finding exposed the pathophysiologic relation between somatization disorder and the amygdala.

Body Dysmorphic Disorder

Currently, body dysmorphic disorders are classified in the somatoform disorders diagnostic group in DSM-IV-TR. Its similar aspects with OCD are being mentioned for a long time. Therefore, it is evaluated in the OCD spectrum disorders together with hypochondriasis, which is another somatoform disorder. In fact, more than a century ago, Morselli (1886) mentioned about obsessional occupations and compulsive

behaviors that define body dysmorphic disorder in today's context. Actually, body dysmorphic disorder resembles OCD in terms of sociodemographic characteristics, family history, underlying neurobiology, concomitant disorders, symptom profile, clinical course and response to selective serotonin reuptake inhibitors, thus, its place in somatoform disorders is being questioned. Neurobiological studies aimed at etiopathogenesis of body dysmorphic disorder are quite limited. As is in other somatoform disorders, neuroimaging studies in body dysmorphic disorder are also limited [^{99m}Tc]. Hexamethylpropylene amine oxime (HMPAO) SPECT research investigated 6 patients with body dysmorphic disorder and reported an association between the disorder and the activity changes in a wide range of brain regions including the parieto-occipital, temporal and frontal regions (Carey et al. 2004). Feusner et al. (2007) performed an fMRI study and asked the patients with body dysmorphic disorder to examine faces in terms of visual recognition and abnormal activation in the inferior frontal gyrus and amygdala of these patients was reported. There are three research studies that performed morphometric investigations. In the first study, Rauch et al. (2003) compared body dysmorphic disorder patients with healthy controls and found caudate nucleus asymmetry on the left side and increased white matter volume. Nonetheless, in their study, 4 of 16 patients had current concomitant disease and half of the patients had lifelong concomitant disease. In the second study, Feusner et al. (2009) examined the volumes of the inferior frontal gyrus, amygdala, caudate nucleus and total grey and white matter; they failed to identify a volume difference between body dysmorphic disorder patients and healthy controls. However, they found a significant correlation between a Body Dysmorphic Disorder version of Yale-Brown Obsession Compulsion Scale (BDD-YBOCS) and the left inferior frontal gyrus ($r=0.69$) and the right amygdala ($r=0.54$). Depending on the relation with OCD, our group (Atmaca et al. 2010a) evaluated the volumes of the anterior cingulate cortex, orbito-frontal cortex, thalamus and caudate nucleus, which are considered as the key regions in OCD, in 12 body dysmorphic disorder patients and in healthy controls of same number. The mean anterior cingulate cortex and orbito-frontal cortex volumes were significantly lower but the mean white matter volume was significantly larger than those of healthy controls. Thalamus volume was almost significantly larger. A negative correlation was found between disease duration and both the right and the left orbito-frontal cortex volumes.

Pain Disorder

Comparing with other somatoform disorders, pain disorder has remained poor in terms of neurobiological research because of being a clinical condition that is most likely to cause a diagnostic paradox. It has been propounded that there is

an interaction between emotional-limbic and attention-pre-frontal systems and the pain-discriminating system and that this interaction influences increased or decreased sensitivity to painful stimulations (Wiech et al. 2008). Increased activation patterns against undesirable stimuli are more frequently encountered in these studies, including the anterior cingulate cortex and insula. This observation has been supported by electrophysiological studies reporting an association between painful somatic complaints and increased sensory evoked potential against irrelevant stimuli arising from the anterior cingulate cortex, insula and sensory cortexes (Diers et al. 2008, Drewes et al. 2005). This increased activity in the limbic regions is associated with an increased danger sensation notion, which is remarkable in this patient group of the cognitive model of somatoform disorders (Brown 2004). Not observing an activity increase in these regions during painful stimuli in depressive patients with somatic complaints is an important finding (Bar et al. 2007). However, such groups of patients show increased activity during expectancy for painful stimulation (Strigo et al. 2008). This does not match with the thought that somatoform pain symptoms are equivalent to depression, which has always been mentioned, but supports that somatoform pain disorder is a clinical entity apart from depression. Studies investigating neurochemical changes of the brain have revealed considerable information. Hagelberg et al. (2003) performed a study in seven patients with atypical facial pain and healthy controls and found that binding to the D2 receptor has been enhanced in the left putamen. It has been reported that chronic painful conditions, whether related or not to somatoform pain, are associated with a decrease in white matter (May 2008) volume. This finding has been demonstrated also in fibromyalgia and restless leg syndromes (Lutz et al. 2008, Davis et al. 2008). This finding is also consistent with the results of a study that associates a decrease in grey matter with impairment in cognitive functions in the patients with fibromyalgia (Park et al. 2001).

DISCUSSION and CONCLUSION

Somatoform disorders are a group of disorders that deserve every effort because of the extent and the functional losses caused by the disorder. Intensive studies on its neurobiological etiopathogenesis are not only inadequate as compared to other psychotic disorders, mood disorders and anxiety disorders, but also provide indirect information. This inadequacy is relevant also for the treatment, and only psychosocial therapies have been considered for the treatment of somatoform disorders. It will be possible for psychopharmacology to find a place only in the presence of underlying strong neurobiological evidence. A question arises at this point: could neuroimaging play a role as a positive diagnostic marker in mental disorders including somatoform disorders? The reason for the current negative answer to this question is the limited number of pre-existing

studies. Neuroanatomic imaging studies, into which our group has contributed, are an important field of study that will pave the way for this subject. However, as was mentioned above, we can say that we are just still in the infancy of discovering the underlying neurobiology of this disorder. This has also been the most important limitation of the present review. Since the data has been quite limited, and there are only one or two studies in related areas of many disorders, this condition does not let us conclude and compare accurately. Nevertheless, neuroanatomic studies have demonstrated significant neuroanatomic and functional differences between patients and healthy controls. Studies comprising both functional and structural imaging, even psychotherapeutic and psychopharmacological therapy effects included, can provide us important data that would be beneficial in the future.

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