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CAN NEUROIMAGING HELP US TO UNDERSTAND AND CLASSIFY SOMATOFORM DISORDERS? A SYSTEMATIC AND CRITICAL REVIEW

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Abstract

Objective—Debate about the nature of the somatoform disorders and their current diagnostic classification has been stimulated by the anticipation of new editions of the DSM and ICD diagnostic classifications. In the current paper we systematically review the literature on the neuroimaging of somatoform disorders and related conditions with the aim of addressing two specific questions: Is there evidence of altered neural function or structure that is specifically associated with somatoform disorders? What conclusions can we draw from these findings about the etiology of somatoform disorders?

Methods—Studies reporting neuroimaging findings in patients with a somatoform disorder, or a functional somatic syndrome (such as Fibromyalgia) were found using Pubmed, PsycINFO and EMBASE database searches. Reported structural and functional neuroimaging findings were then extracted to form a narrative review.

Results—A relatively mature literature on symptoms of pain, and less developed literatures on conversion and fatigue symptoms were identified. The available evidence indicates that, when compared to non-clinical groups, somatoform diagnoses are associated with increased activity of limbic regions in response to painful stimuli and a generalized decrease in grey matter density; however methodological considerations restrict the interpretation of these findings.

Conclusions—While the neuroimaging literature has provided evidence about the possible mechanisms underlying somatoform disorders this is not yet sufficient to provide a basis for classification. By adopting a wider variety of experimental designs and a more dynamic approach to diagnosis there is every reason to be hopeful that neuroimaging data will play a significant role in future taxonomies.

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List of Supplemental Digital Content Files:
Supplemental Digital Content 1: PDF.
Supplemental Digital Content 2: PDF.

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Keywords

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Introduction

The somatoform disorders are defined in the ICD10 and DSMIV psychiatric classifications as syndromal conditions characterized by somatic symptoms which cannot be accounted for either by identified disease pathology or by another Axis I psychiatric disorder (1, 2) (Table one). Perhaps confusingly, a parallel and overlapping medical classification of functional somatic syndromes such as fibromyalgia and chronic fatigue syndrome (3) is also in use and largely describes the same patients. The etiology of these conditions is not well understood with the existing diagnostic classifications being based largely on clinical utility. Consequently a range of questions remain outstanding: are these conditions different from malingering? Are they distinct from depression and anxiety? Do they represent many distinct conditions or only one? This ignorance fuels vigorous debate about how best to conceptualize and classify these conditions in the new editions of the ICD and DSM psychiatric diagnostic classifications (4-7). Here we ask what neuroimaging studies might tell us about the nature of these conditions and whether they can inform future diagnostic classification.

What might neuroimaging tell us?

Neuroimaging studies employ a variety of techniques (8) that can tell us about brain anatomy ("structural" techniques such as voxel based morphometery; VBM) or about brain activity ("functional" techniques such functional magnetic resonance imaging; fMRI). Before reviewing what imaging *does* tell us we might usefully ask what *it could* realistically tell us about conditions of unknown etiology, such as the somatoform disorders.

Perhaps the most clinically useful role for neuroimaging is to provide information about whether a disorder is present or not; that is to use neuroimaging as a test to make a diagnosis. Certainly structural imaging currently has a role as a 'negative diagnostic marker' by detecting the *absence* of gross neural pathology in the somatoform disorders. Might neuroimaging also have a role as a 'positive diagnostic marker'? There are some a priori grounds for optimism here as neuroimaging provides precise, quantifiable, multi-dimensional (in three-dimensional space and time) observations that must surely have the potential to add to the clinical observations that currently guide diagnosis. One problem is that the very search for such imaging markers is predicated on the validity of the existing diagnoses; the absence of this, as has been suggested above for somatoform disorders, would seriously undermine the likelihood of discovering such a diagnostic marker. For example, if patients may obtain the diagnostic label of "conversion disorder" as a consequence of a range of different (neural) mechanisms, then simply comparing the neuroimaging data of patients with the diagnosis to those without, is unlikely to reveal any specific 'neural signature' for this diagnosis. A more subtle question asks whether neuroimaging can identify relevant component mental processes associated with the diagnosis, rather than the diagnoses itself. For example might it differentiate conversion disorder (a diagnosis in which symptoms are believed to arise subconsciously) from malingering (in which symptoms are regarded as consciously manufactured) by reliably detecting the component mental process of the intention to deceive? Whilst there has been increased interest in using neuroimaging in this sort of targeted, mind reading role (9), an unequivocal demonstration that it is possible remains elusive, even in a controlled, non-clinical context (e.g. 10, 11-14). Thus while neuroimaging may in principle be able to provide positive diagnostic information for

conditions of unknown etiology, the chance of finding such markers depends critically on the validity of the diagnostic system in use. And whilst this dependence on diagnosis can be sidestepped to some extent by focusing on specific cognitive processes rather than diagnosis, the ability to reliably detect such processes remains to be proven.

A more fundamental approach to neuroimaging explores the etiological mechanisms underlying these conditions, rather than simply describing diagnostic markers. Ultimately, the attraction of such theoretically informed investigation is that it offers a means of transcending the core limitation of current psychiatric practice; etiological ignorance. But there are potential pitfalls in interpretation here also, particularly if neuroimaging data is considered in isolation (15). One is the over-interpretation of differences in neural activation or structure observed between clinical and control groups. While it is tempting to conclude that any such difference must reflect the fundamental abnormalities of brain function which cause the illness, the truth is that they can be interpreted in at least three different ways: as a cause of the illness, as an effect of the illness, or as a compensation for the illness (16). Consequently the way in which neuroimaging data is interpreted is heavily dependent on the model of illness being tested. An important corollary of this is that neuroimaging studies generally provide information about the involvement of a specific neural system in a disorder rather than giving a complete account of the neural abnormalities associated with the disorder. For example, while the demonstration of amygdala hyperactivity to negative information in depression (17, 18) is consistent with both the cognitive models of the illness (19, 20) and with our understanding of the role of the amygdala in cognition (21), it is very unlikely that a hyperactive amygdala is the only neural abnormality associated with depression.

In summary, neuroimaging may be used either to describe or explore psychiatric disorders. When the validity of the diagnoses is questionable, as has been suggested for the somatoform disorders, it seems likely that neuroimaging techniques may most efficiently address questions of taxonomy by exploring the etiology of the disorders.

Aims

In the current review we sought to answer two key questions:

1. Is there evidence of altered neural function or structure that is specifically associated with somatoform disorders?
2. What conclusions can we draw about the etiology of somatoform disorders from these findings?

With these aims in mind we structure the review around the type of symptom (and thus neural system) investigated, rather than around the diagnosis of the patients studied. This strategy allows us to ask whether different diagnoses are associated with abnormalities in similar neural systems. We also include relevant background work from studies of non-clinical populations when they illustrate relevant cognitive neuroanatomical models. We conclude by summarizing the challenges facing the use of neuroimaging techniques in the somatoform disorders and by suggesting strategies by which these challenges may be met.

METHODS

Study Selection

Medline, Embase and Psychinfo databases were searched for relevant articles published between 1960 and 2009. The full search strategy is described in Supplemental Digital Content 1. See Supplemental Digital Content 2 for a flow chart describing the number of records found in the search and final number identified after screening. The great majority of

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the identified publications reported explorations of the neural circuitry involved in one of three symptoms clusters: pain symptoms, loss of motor or sensory function, and fatigue symptoms. We therefore considered each symptom cluster separately. For each we provide a descriptive review of the literature and an analysis of its etiological implications.

Limitations

At the outset, a number of limitations to the current review should be acknowledged. First, although we have systematically searched the literature, the boundaries of the topic are not clear because competing taxonomies are in use (3). As a result, our review incorporates data from patients diagnosed with somatoform diagnoses and also those with only symptoms and those with diagnoses of functional somatic syndromes. Indeed, the use of symptom provocation designs in the functional neuroimaging literature lends itself to the recruitment of patients with a specific symptom rather than a syndromal diagnosis and, as a result, the majority of studies identified in the current review have recruited patients with specific symptoms rather than those with DSM-IV diagnoses. Second we have limited the review to published reports and have not sought to identify unpublished work. Third, as the nature of the data permits only narrative summary, the process of data abstraction from the papers was not done blind to the questions being addressed making bias possible.

RESULTS

Disorders in which pain or discomfort are the primary symptom

Patients with pain attract a range of diagnoses including pain disorder, fibromyalgia (FM), somatization disorder and irritable bowel syndrome (IBS). The relatively high prevalence of these disorders in the general population, the extensive literature on the processing of pain in non-clinical populations and the ease of delivering a controlled painful stimulus during testing have led to a relatively large and sophisticated literature on this topic. The dominant model in pain perception describes a “neuromatrix” (22, 23) which is activated in response to painful stimuli. This matrix includes sensory areas such as somatosensory cortex, limbic regions such as the anterior cingulate cortex (ACC) and insula which are thought to process the emotional aspects of the percept and frontal regions such as the dorsolateral prefrontal cortex (dlPFC) thought to subserve attentional control (24). It has been proposed that the emotional-limbic and attentional-prefrontal systems interact with the sensory-discriminant system and that this interaction can produce a sensitization (or desensitization) to painful stimuli (24). While it is important to be aware that “pain” may incorporate a number of different experiences (e.g. visceral or somatic pain) and that the overlap between the neural structures involved in these experiences is not absolute, there is evidence that a limited set of higher order areas perform similar modulatory functions across pain types (24, 25). Evidence for the higher order modulation of pain perception has been found in studies where neural activation of the ACC, somatosensory and frontal cortices to painful stimuli correlate more strongly with the subjective experience of pain than with the objective intensity of the stimulus whereas activation of ascending sensory regions (e.g. the thalamus) reflects the objective characteristics of the painful stimuli (26). Furthermore, psychological responses to pain such as an increased tendency to catastrophize, which has been proposed as a diagnostic marker of somatoform conditions (27), are associated with increased ACC activity during painful stimulation (28). Lastly, hypnotically suggested pain appears to produce a pattern of brain activation similar to that associated with an actual painful stimulus, indicating that central mechanisms may be sufficient to produce the experience of pain even in the absence of external stimulation (29, 30). In summary, work in non-clinical samples suggests that painful symptoms in the absence of disease may, at least in part, result from aberrant higher order modulation of somatic percepts (31).

Is there any evidence for abnormalities in the activity of these regions in relevant clinical populations? A number of studies, listed in Table 2, have directly compared clinical and control groups during administration of unpleasant stimuli (for recent reviews see also 25, 32).

As can be seen, an overall pattern of increased activation in response to unpleasant stimuli is apparent in the clinical groups, with the ACC and insula cortices being the most commonly identified regions. This observation is supported by the electrophysiological literature in which painful somatic symptoms have been associated with increased sensory evoked potentials in response to aversive stimuli (33), with the sources of these responses being estimated to lie in the anterior cingulate, insula and sensory cortices (34). The increased activity in these limbic areas is consistent with a cognitive model of somatoform disorders (35) which predicts a heightened salience of noxious percepts in these patients. The neuroimaging data therefore provides some support for the contention that medically unexplained pain may reflect abnormalities in the higher order modulation of perception.

Recent studies of patients with somatoform pain disorders have ventured beyond simply studying the response to painful stimuli. Two studies have used suggestion (both with and without hypnosis) to modify the pain experience of patients with fibromyalgia. Both found that activity in a range of pain responsive regions (including the ACC) was influenced by the intervention (36, 37). Similar results have been reported for patients with IBS administered placebo (38), and patients who have repeated administration of the noxious stimuli a number of times over the course of a year (39). By using experimental interventions to alter both neural activity and subjective experience these studies provide corroborative evidence that activity in the identified regions may be causally related to the painful symptoms of patients rather than being merely epiphenomena.

Interestingly depressed patients, who often report somatic complaints, do not seem to show increased activity in these regions during the administration of painful stimuli (40), although they do show increased activity during anticipation of the painful stimuli (41) suggesting that somatoform pain disorders may be differentiated from depression.

A number of studies have investigated the brain neurochemistry of patients with somatoform pain disorders using a range of PET ligands. Evidence from these favors both dopaminergic (42-45) and opioid (46) abnormalities suggesting a possible neurochemical underpinning for the altered functional responses to pain described above.

Other studies (47-59) have used EEG techniques, mainly during sleep, to investigate the electrophysiological abnormalities associated with painful symptoms, particularly in patients with Fibromyalgia. While these studies suggest that abnormalities of sleep architecture are commonly associated with the disorders, it has proven difficult to demonstrate replicable and specific findings.

Lastly, there has been increasing interest in possible structural abnormalities of the brain associated with somatoform pain disorders. It has been suggested that chronic pain syndromes (whether somatoform or not) are associated with decreased grey matter (60), an hypothesis supported by studies of both fibromyalgia (61-64, although see also 65) and IBS (66). The relevance of these findings is supported by the reporting of an association between impaired cognition and decreased grey matter in patients with fibromyalgia (67).

In summary, compared to healthy controls, patients with somatoform pain symptoms show abnormalities of both brain structure and function. The best characterized of these is increased activity in a number of regions of the pain neuromatrix in response to noxious

stimuli. These regions include those believed to be involved in the emotional appraisal of stimuli (ACC, insula).

Disorders in which loss of motor or sensory function is the primary symptom

Loss or excess of motor or sensory function without organic disease may be diagnosed as conversion disorder, a diagnosis currently classified under somatoform disorders in DSMIV. Conversion disorder should be an ideal candidate to investigate using functional imaging as there is an extensive literature on the neural systems involved in motor control and sensation, there are robust electrophysiological techniques which can be used to demonstrate that peripheral aspects of both systems are intact and the relevant neural systems can be readily probed by asking patients to attempt to move a paralyzed limb, or by stimulation of the anesthetic sense. Unfortunately it has been difficult for investigators to recruit sufficient numbers of patients to mount large studies. Consequently the neuroimaging literature on conversion disorder is largely limited to single case studies and small case series. The largest cohort of patients included in a published study so far is twelve. Despite the limited empirical evidence, there is a rich history of theorizing about the etiology of conversion disorders (68, 69). Current models reflect electrophysiological findings that the primary motor (70) and sensory cortices (71, 72) as well as peripheral nervous system function appears to be intact in patients with conversion disorder. By exclusion, therefore, any pathology is presumed to reside in higher order neural systems.

The evidence from functional imaging studies of motor conversion symptoms is summarized in Table 3. All but one of the studies reviewed had insufficient numbers to justify statistical comparison between groups; therefore the differences reported in these studies are from qualitative analysis of activation patterns only. It is difficult to draw any firm conclusions from such analyses. A simple review of the effects reported in each study (see Table 3) does not reveal any strikingly consistent finding. Data from structural imaging studies is even more sparse with only a single study being identified (73). In summary, the available data on motor conversion disorder is interesting but limited.

The results of the studies which have investigated sensory conversion symptoms are summarized in Table 4. Some of these have had sample sizes adequate to permit between group statistical analyses. It is difficult to discern any emerging pattern in the data other than that activation of the relevant sensory cortex is decreased. Given the electrophysiological evidence indicating that sensory evoked potentials are normal in these populations, this finding suggests a modulatory effect on sensory processing occurring after the initial sensory cortical response.

Unfortunately, perhaps the strongest conclusion that can be drawn from the neuroimaging studies of motor and sensory conversion disorder is that the samples studied have been so small that it remains unclear which findings represent signal and which noise.

Disorders in which fatigue is the primary symptom

Fatigue and its syndrome, chronic fatigue syndrome (CFS) presents a different challenge from conversion disorder for those designing neuroimaging studies. Simply put, there is little a priori evidence as to which areas of the brain are most likely to be involved in the sensation of fatigue. Thus while it has proved possible to recruit and study reasonably sized samples of patients, it is less clear which tasks should be completed during imaging and which areas of the brain should be focused on.

Early imaging studies of CFS investigated whether the diagnosis was associated with gross structural abnormalities of the brain. These produced mixed results with some studies suggesting no specific abnormalities (74, 75), while others suggested abnormalities in

subgroups such as those without psychiatric comorbidity (76). More recently the analysis of structural scans has evolved such that statistical inference can be performed on brain structure using a voxelwise approach. One such approach, voxel based morphometery has produced interesting findings in patients with CFS. An initial report of decreased gray matter volume in the dorsolateral prefrontal cortex of patients with CFS (77) was complemented by a report from a different group which reported a global reduction in gray matter volume which correlated with functional status (78). Importantly the authors were then able to demonstrate a small but significant increase in gray matter volume in patients following treatment with cognitive behavioral therapy (CBT) (79).

Early functional neuroimaging studies of resting brain activity in patients with CFS suggested both generalized decreases in cerebral perfusion and localized deficits in the brain stem (80, 81) and possibly ACC (82). There have, however, been no recent replications of this early data. Other functional imaging studies have used a symptom provocation approach. One popular method has been to use a continuous cognitive task (such as adding together sequential digits which are presented every few seconds) which is argued to be "fatiguing". Studies using such methodology have reported increased activation in the cingulate (83), supplemental motor areas, superior parietal cortex (84), medial prefrontal cortex (85), inferior frontal crotex, superior temporal cortex, hippocampus, cerebellum (86), precuneus, lingual gyrus and cerebellum, with decreased activation in dorsolateral PFC (87) and caudate (88). There has been little replication of findings between studies. Finally a single study investigated the authors' hypothesis that CFS was associated with an abnormality of the serotonergic system. Using PET with a specific radioligand for the 5-HT 1a receptor a generalized decrease in binding in patients was demonstrated, particularly in the hippocampus (89).

The electrophysiological investigation of CFS has provided similar results to those found with pain; with relatively nonspecific abnormalities of sleep architecture being reported (90-93).

In summary, a number of different structural and functional approaches have been used to image patients with chronic fatigue. Interpretation of the data they have produced is hampered by the lack of strong a priori predictions about which areas of the brain are likely to be implicated in the production of fatigue. None of the results have been reliably replicated although preliminary evidence does suggest a number of interesting lines of enquiry, with the most compelling data currently available being for a partially reversible decrease of gray matter volume in patients.

Other disorders

Relatively few studies of patients with a diagnosis of "somatization disorder" have been published. These report resting activation (94-96) and structural differences (97) in patients with a range of somatic symptoms, with pain appearing to be the most common. The published studies involve small samples (maximum n=11, with similar cohorts of patients repeatedly analyzed in different studies) so we cannot draw clear conclusion about the patterns of activation associated with this diagnosis.

Body dysmorphic disorder (BDD) is included (controversially) in the somatoform disorders construct. Two structural studies provided no consistent findings when comparing patients with controls (98, 99). A second, fMRI, study demonstrated increased activation in left sided frontal and temporal regions in BDD patients versus controls when a face matching task was completed (100). The neuroimaging literature on BDD must be regarded as preliminary.

COMMENT

In this review we aimed to address two main questions:

(1) Is there evidence of altered neural function or structure specifically associated with somatoform disorders?

A large number of different functional and structural neuroimaging abnormalities have been reported in patients with somatoform symptoms compared to non-clinical controls. In keeping with the neuroimaging literature for other psychiatric disorders, very few of these findings have been reliably replicated, the most convincing exceptions to this rule being an increased activity of limbic structures (insula and ACC) in response to aversive stimuli in patients with pain and decreased gray matter in patients with both pain and fatigue. The great majority of studies published to date have compared patients with a somatoform diagnosis to non-clinical controls. There is therefore little direct evidence to suggest that any of the neuroimaging abnormalities found is specific to the somatoform diagnoses, as opposed to other psychiatric diagnoses such as depression which may present with similar symptoms.

(2) Can we draw any conclusions about the etiology of somatoform disorders from these findings?

For neuroimaging data to provide a meaningful account of pathology; it must be interpreted relative to a model of the condition. In this light the increased ACC and insula activity reported in response to a variety of painful stimuli across a range of functional diagnoses is consistent both with the presumed role of these areas in mediating the emotional response to painful stimuli (24) and with cognitive accounts of functional symptoms which stress the role of increased personal salience of these percepts (35). Further, the finding that common brain regions show increased activity across various diagnoses provides some support for the proposition that similar neural processes may underlie a variety of functional diagnoses (3). However, the evidence that this neuroimaging abnormality reflects a causal illness processes is weak; as we have discussed above, a number of alternative interpretations may account for the association such as the neuroimaging findings representing a consequence or compensation for the illness. It is therefore encouraging that recent studies have used alternative designs such as experimental interventions to alter both cognitive and brain function in patient groups (e.g. hypnosis as used in 36, 37). The demonstration that symptoms covary with brain activity provides better evidence of causality than the simple case-control approach which makes up the majority of the published literature.

Interpretation of the structural change of loss of gray matter associated with symptoms of fatigue and pain is more challenging as it appears that this loss occurs over much of the cortex, rather than being localized to a particular neural system. A possible explanation comes from the animal literature in which environmental enrichment is found to increase neuronal plasticity (101). If correct, this would suggest that loss of gray matter reflects the limiting effects of the illness and is therefore best considered a consequence, rather than a cause of the illness.

In summary, interpretation of the etiological significance, even of the most robust neuroimaging findings described in the current review, requires caution as the methodologies commonly used to date provide only indirect evidence of causality. Encouragingly, experimental approaches which may more directly assess questions of causality are increasingly being employed.

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How might neuroimaging more effectively contribute to our understanding and management of somatoform disorders?

Despite the reservations expressed above and the lack of any clinically useful insights so far, we remain optimistic that neuroimaging may prove useful in developing our understanding of the nature of the somatoform disorders. In order to do so, we believe that it must form part of a concerted approach in which imaging neuroscience has greater interaction with other disciplines. The attempt to isolate a regional abnormality that 'causes' the somatoform disorders is likely to prove fruitless, notably because, as we have pointed out, such regional abnormalities are inherently ambiguous: it cannot be known whether they signify a cause of, a consequence of or a compensation for the disorder. However, this is not to say that they won't offer clues about the underlying pathological processes, clues that may be followed up productively using an iterative approach in which other brain and behavioral observations inform and are informed by functional and structural neuroimaging. A second cause for optimism about the role of neuroimaging in the somatoform disorders comes from other areas of the neuroimaging literature which have overcome many of the difficulties with interpretation we have documented in this review. We therefore conclude by summarizing what we see as the broad challenges facing neuroimaging in somatoform disorders and the ways in which these challenges may be met. We do so, where possible, with reference to the successes of neuroimaging in other psychiatric disorders.

1. Etiology—As we have noted, neuroimaging currently contributes most to the diagnosis of somatoform disorders by excluding other causes of the symptoms. It is to be hoped that the identification of particular disturbances of processing in the brain may offer the clinician a sign to look for, rather than simply one to exclude. But this development will only be possible against the background of useful cognitive models of the disorder. That is, the imaging measure must be testing a hypothesis about a specific process or set of processes whose presence or absence could be invoked to explain the symptoms, an approach which has already achieved some success in cognitive neuroscience (e.g.,102). Encouragingly, there has been an increasing trend for neuroimaging studies of somatoform disorders to utilize experimental interventions in order to assess the role of specific cognitive processes (34, 35). We suggest that such studies are likely to be of increasing importance in elucidating the etiology of the disorders.

2. Diagnosis—Given the widespread acknowledgement that the existing diagnostic systems are unsatisfactory it follows that, especially in the context of traditional case-control methodology, any groupwise difference imaging observation will only reify the diagnostic system that led to grouping in the first place. Clearly, there is a need to adopt more dynamic methods that take into account individual variability and seek to identify both neural commonalities across apparently disparate conditions and neural distinctions between apparently similar conditions. Such an approach has been deployed in depression where it has been suggested that specific symptoms with a known neural architecture, such as anhedonia, offer improved phenotypic definition when compared to clinical diagnosis (103).

3. Prediction—Better diagnostic systems model the real world more accurately than their competitors. This is reflected in the ability of the diagnosis to provide information which predicts prognosis, both with and without treatment. Encouragingly, functional neuroimaging has already been used to predict responsiveness to treatment in a group of depressed patients (104) indicating that, in principle, this is an achievable goal, although it should be noted that even here the neuroimaging outcomes do not differ sufficiently between depressed and control groups to allow the prediction of a given individual's prognosis. If neural observations are to have validity in the setting of somatoform disorders they must be

held to the same requirement, that is, they must predict, at an individual level, the prognosis of the condition as well as informing the choice of treatment.

Conclusion

Neuroimaging studies have begun to delineate the neural processes implicated in the somatoform disorders. By adopting a wider variety of experimental designs and a more dynamic approach to diagnosis there is reason to be hopeful that neuroimaging data will play a significant role in shaping future taxonomies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

5-HT	5 hydroxytryptamine (serotonin)
ACC	anterior cingulate cortex
CBT	cognitive behavioral therapy
CFS	chronic fatigue syndrome
dlPFC	dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
FM	fibromyalgia
fMRI	functional magnetic resonance imaging
IBS	irritable bowel syndrome
ICD	International Classification of Diseases
PET	positron emission tomography
VBM	voxel based morphometery

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Table 1

The somatoform categories described in DSM-IV

Somatization disorder
Undifferentiated somatoform disorder
Conversion disorder
Pain disorder
Hypochondriasis
Body dysmorphic disorder
Somatoform disorder, not otherwise specified

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Table 2

Studies in which patients with medically unexplained symptoms of pain or discomfort are compared to non-clinical control groups. Where both qualitative and quantitative between groups analysis were performed, the quantitative analysis is reported. Broadman areas are those reported in the individual studies or inferred from the co-ordinates of peak voxels when reported

Study	Clinical Diagnosis	N per group	Imaging Modality	Type of Pain	Areas of increased activation in clinical group	Areas of decreased activation in clinical group	Notes
(105)	Atypical Facial Pain	6	PET	Heat	ACC (BA 24)	Left Frontopolar Cortex (BA 10)	No information on the objective intensity of the painful stimuli given in text
(106)	Fibromyalgia	10	SPECT	Pressure (not in scanner)	Nil	Thalamus and Caudate	Pain thresholds assessed outside scanner. No pain administered during scan.
(107)	IBS	6	PET	Rectal Distension	Left Frontopolar cortex (BA10)	ACC (BA 24, 32)	Between group comparisons performed qualitatively.
(108)	IBS	16	fMRI	Rectal Distension	ACC (BA 24)	Nil	
(109)	IBS	12	PET	Rectal Distension	ACC (BA 24)	Orbitofrontal cortex (BA 11); Frontal Pole (BA 10); Putamen; Thalamus	
(31)	Fibromyalgia	16	fMRI	Pressure	Sensory Cortex (BA 2); Insula; Superior Temporal Gyrus (BA 22); ACC (BA 24) ; Precuneus (BA 31); Cerebellum	Left Frontopolar Cortex (BA 10)	
(110)	Chronic Lower Back Pain	16	PET	Heat	Nil	Nil	
(111)	IBS + FM	10	PET	Pressure (somatic) and Rectal Distension	Mid ACC (BA 24/32)	Nil	Comparison performed between patients with IBS and patients with both IBS and FM. Activity in the ACC was greatest for the IBS group during rectal distension and for the IBS+FM group during somatic pressure.
(112)	IBS	9	fMRI	Rectal Distension and Heat	ACC (BA 24); insula; PFC (BA 9)		Pain induced using both rectal distension and cutaneaous heat.
(113)	Chronic Lower Back Pain and Fibromyalgia	11/16	fMRI	Pressure	Bilateral Somatosensory Cortex	Nil	Between group comparisons performed qualitatively.
(114)	IBS	9	fMRI	Rectal Distension	ACC and posterior Cingulate/Precuneus, Bilateral Striatum and Bilateral dlPFC	N/A	Areas of activation inferred from graphical presentation of quantitative between group analysis (no table of activation provided in text). NB majority of paper describes a qualitative analysis.
(115)	IBS	8	fMRI	Rectal Distension	ACC (BA 32), PFC (BA 10)	ACC (BA 24 / 32) PFC (BA 10)	Complex study with small sample size. Three intensities of stimulation were used (subliminal, liminal and supraliminal). Activity in IBS group greater in ACC and PFC

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Study	Clinical Diagnosis	N per group	Imaging Modality	Type of Pain	Areas of increased activation in clinical group	Areas of decreased activation in clinical group	Notes
							during liminal stimulation. ACC activity was greater in the control group during both sub and supraliminal stimulation.
(116)	IBS	7	PET	Rectal Distension	ACC (32/25), Left Amygdala, PFC (BA 9/32)	Dorsal Pons/PAG	In this comparison patients with IBS were compared to patients with quiescent ulcerative colitis.
(117)	IBS	5	PET	Rectal Distension	ACC (BA 32), Parahippocampal gyrus	Nil	Study scanned patients before and after cognitive therapy. The reported regions were those in which activity was reduced by treatment. Extremely small groups used.
(118)	Somatoform Pain Disorder	17	fMRI	Pin Prick	Insula; Dorsomedial PFC (BA 8); Superior Temporal Gyrus (BA 21); Hippocampus; Putamen; Thalamus	Motor Cortex (BA 4)	
(119)	Multiple Chemical Sensitivity	12	PET	Odorant	ACC (BA 24); Precuneus/Cuneus (BA 7,18); Right Right Parahippocampal Gyrus (BA 19)	Amygdala	Noxious stimuli was odorant rather than pain
(120)	Somatoform Pain Disorder	12	fMRI	Heat	Amygdala; Insula; Parahippocampal Gyrus; Primary Sensory Cortex	Orbitofrontal Cortex (BA 11)	
(121)	IBS	15	fMRI	Rectal Distension	ACC (BA 24/32); Insula, Brainstem	Nil	NB Anticipation of cue was associated with decreased deactiviation of amygdala and insula in patients
(122)	Fibromyalgia	18	fMRI	Incision	ACC (BA 24/32); PFC (BA 6/8); Thalamus	Thalamus	Very liberal threshold (P<0.01 uncorrected) used in imaging analysis. An incision was used to induce acute pain.
(123)	Fibromyalgia	16	fMRI	Pressure		ACC (BA 32); Thalamus	Average pressure for control group was approximately twice that for patient group. No description of method for multiple comparison correction given
(124)	Fibromyalgia	9	fMRI	Pressure	ACC (BA 24); Sensory Cortex (BA 4); Insula; Frontal Operculum (BA 44); Basal Ganglia		Novel analysis in which the time course of the neural response is first inferred from the data

NB The study by Bernstein and colleagues (125) which compared patients with IBS and control subjects has been omitted from the table as it employed a particularly unusual statistical approach rendering it difficult to compare with the other papers listed.

IBS=Irritable Bowel Syndrome

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Table 3

Summary of studies which include patients with motor conversion symptoms

Study	Comparison	Control Group	N	Imaging Modality	Areas of increased activation in clinical group	Areas of decreased activation in clinical group	Notes
(126)	Attempted movement vs. rest	None	1	PET	Increased activity in ACC (BA 24/32) and OFC (BA 10)		No statistical analyses performed. Authors note an absence of motor cortex activity
(127)	Resting	None	5	SPECT		Left Temporal and Parietal regions	No statistical analyses performed
(128)	Attempted movement vs. rest	Healthy controls who feigned weakness	2	PET		Left dlPFC (BA 46)	Qualitative between group comparison
(129)	Movement vs. rest and observation of moving hand vs. observation of resting hand	Healthy controls who moved limbs normally	4	fMRI		Motor cortex during movement observation (BA 4)	No differences observed during movement itself. Qualitative comparison between groups
(130)	Attempted movement vs. rest	Healthy controls who feigned weakness	4	fMRI	Frontal (BA 47), striatal and lingual cortex (BA 18)	Motor (BA 4) and OFC (BA 10/46)	Qualitative comparison between groups
(131, 132)	Mental rotation of affected vs. unaffected hand	Within subject analysis—unaffected side acts as control	8	fMRI	Medial frontal (BA 9/11) and superior temporal cortex (BA 22)		Non-parametric statistical analysis performed within subjects
(133)	Go NoGo Task	Healthy controls who feigned weakness	1	fMRI	Ventromedial frontal (BA32/10) and left orbital frontal (BA 47)		Qualitative comparison between groups. Effects reported during movement preparation

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Table 4

Summary of studies of patients with sensory conversion symptoms

Study	Comparison	N	Imaging Modality	Areas of increased activation in clinical group	Areas of decreased activation in clinical group	Notes
(134)	Median nerve stimulation vs. rest	1	SPECT		Contralateral Parietal Lobe	Perfusion abnormality resolved with recovery
(135)	Vibratory tactile stimulation vs. rest	7	SPECT		Contralateral basal ganglia and thalamus	In a subset of 4 patients who recovered the hypoperfusion was found to have resolved and baseline perfusion of the caudate nucleus was found to predict recovery
(136)	Painful and non-painful tactile stimulation of anaesthetic vs. normal limb	4	fMRI	Anterior ACC	PFC, posterior ACC and sensory cortex	Across the group conditions were compared with a qualitative analysis
(137)[a]	Monocular visual stimulation vs. rest.	5	fMRI	Left inferior frontal cortex (BA 47), insula and uncus (BA 34) and bilateral striatum	Visual cortex (BA 17/18) and ACC (BA 25)	A non-clinical control group was also tested allowing a between group analysis.
(138)	Vibratory stimulation of anaesthetic limb vs. bilateral limb stimulation	3	fMRI		Contralateral sensory cortex	Contralateral (to the symptoms) sensory cortex was activated during bilateral stimulation.

[a]All patient groups reported loss of somatic sensation except in which the presenting complaint was unexplained visual loss.