Psychobiological perspectives on somatoform disorders

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Summary Common physical symptoms such as abdominal pain, headache, back pain and dizziness play a major role for the health care system. Existing models for the development and maintenance of these symptoms emphasize a vicious circle with cognitive-perceptual, behavioral, and psychobiological components. In this manuscript, we present examples of psychobiological factors that might contribute to somatoform disorders. We emphasize that somatoform symptoms are not strictly mental events, but are associated with a diversity of biological processes. The possible role of the endocrine and immune system, amino acids and neurotransmitters, but also physiological activation and cerebral activity is exemplified. These approaches are categorized using a model of perception and filtering of bodily signals. Studies are needed that combine the investigation of different biological systems with assessments of psychological variables in longitudinal trials, but also experimental investigations in humans examining the interaction of behavior changes, biological variations, and body perception are still rare.

Abdominal pain, bloating, dizziness, chest pain, pelvic pain, intolerance of food, palpitations or joint pains are common symptoms and typical reasons for doctor visits. Some of these symptoms have base rates of more than 30% in the general population (Rief et al., 2001a). Although the probability of remittance is substantial for individual symptoms, many affected people have multiple symptoms which tend to be persistent (Kroenke and Mangelsdorff, 1989). The health care impact of these syndromes is substantial (Smith et al., 1986; Barsky et al., 2001). A diversity of diagnoses and labels have been suggested for these complaints, e.g. unexplained physical symptoms, subjective health complaints, as well as fibromyalgia, chronic fatigue syndrome, or multiple chemical sensitivity syndrome show associations with these complaints. Therefore, we will refer to these disorders with the term 'somatoform-associated disorders'. However, the focus of this article will be on research using the
DSM-IV concept of somatoform disorders. The most expensive subgroup of patients with somatoform disorders are those with multiple and persisting complaints. DSM-IV suggests the diagnosis somatization disorder for patients with at least eight symptoms from four body sites; a total list of 33 somatic symptoms is suggested to be typical for somatization disorder. We will refer to the list of these 33 symptoms as 'somatoform symptoms'. As the criteria for somatization disorder are very exclusive and do not represent the majority of patients with multiple somatic complaints, subsyndromal classification for these patients have been suggested. In most of our studies, we included patients with at least eight symptoms from the list of 33 somatoform symptoms, but not necessarily fulfilling all criteria for somatization disorder. We will use the term 'somatization syndrome’ for this subgroup. This implies that not all patients with multiple physical complaints or with subjective health complaints are included in this subgroup, but only those with bodily symptoms from the somatization disorder symptom list, which cannot be attributed to typical medical conditions. While somatization disorder and somatization syndrome are sub-diagnoses of the general category 'somatoform disorders', this general category also includes other diagnoses such as hypochondriasis, conversion disorder, pain disorder, or body dysmorphic disorder.

Most models of somatoform symptoms emphasize the interaction of cognitive and perceptual processes with behavioral, affective, and biological changes. Although there is evidence that all of these features contribute to the perception of physical complaints, somatoform disorders are frequently misunderstood as mere cognitive-attributional phenomenon. In this article, we will therefore review the literature suggesting that biological factors play a role in the development and maintenance of somatoform symptoms. As space limitations do not allow a comprehensive literature review, we will present just a few examples highlighting biological components of the disorder. These findings will be discussed in light of the cognitive activation theory and sensitization model published in this journal (Ursin and Eriksen, 2004). Finally, we will conclude with suggestions for further psychobiological research.

DSM-IV somatoform disorders are characterized by bodily complaints that cannot be completely attributed to known physical conditions. However, as already outlined elsewhere (Sharpe and Bass, 1992), this does not mean that these symptoms are without physiological covariates. Although there may not be evidence of discrete organic pathology, demonstrable physiological changes can still increase the risk of development and maintenance of physical complaints.

In many of the studies included, the specificity of the findings is unclear, since anxiety, traumatization and depression can also be associated with biological changes, and frequently occur in conjunction with somatoform symptoms.

1. Somatoform symptoms are not 'unfounded’—Some biological correlates

1.1. Autonomic physiological arousal

Somatoform symptoms could in theory result from heightened physiological activity. Increased physiological activation increases the likelihood of perception and misattribution of bodily signals. Although it is evident that perception is substantially influenced by psychological factors, physiological activation of variables such as heart rate or others could still play an independent role (Wientjes and Grossman, 1994). Empirical investigation of this basic hypothesis is less frequent than expected. In Pennebaker’s model (Pennebaker, 1982), the perception of physical symptoms is determined by the intensity of the interoceptive signal itself divided by the intensity of external stimulation ('distraction'). This model would suggest a direct relationship between the intensity of physiological signals and the severity of somatoform symptoms. Physiological hyperreactivity would therefore be a risk factor for the development of physical symptoms.

In a study by our group (Rief and Auer, 2001), the psychophysiological reactivity of patients with multiple somatoform symptoms was assessed during relaxation and mental distress. As mental stressor, the span of apprehension test which requires continuous attentional processing was used. This is a choice-reaction time task with visual stimuli including differing numbers of distracting elements. For most physiological signals included in this study (such as muscular reactivity, cutaneous responses, peripheral circulation), no significant differences between healthy controls and patients with somatization syndrome were found. In healthy controls, the change from attention tasks to rest periods was associated with a substantial decrease in heart rate activity ('recovery response'). This reduction of physiological activity after mentally distressing tasks was not found in patients with somatization syndrome. This effect was not determined by depression or anxiety.
To summarize the results on autonomic physiological activity, we can conclude that only few studies have addressed this question so far. Only small differences have been found, although there is some consistency indicating the involvement of the cardiovascular system. Therefore, it would be interesting to combine these approaches with the assessment of heart beat perception, as has been done for panic disorder (Barsky et al., 1994; Ehlers et al., 1995).

1.2. The endocrine system

The endocrine system, in particular the hypothalamic-pituitary-adrenal axis (HPA), is activated by stress and also influences pain perception. Stress and pain perception are both relevant to somatoform disorders.

Amongst the hormones of the HPA-axis, cortisol has been investigated the most. However, the results are equivocal. Some authors emphasize the comparability with posttraumatic stress disorders (Heim et al., 2000), finding that distressed patients with ‘unexplained’ physical symptoms showed a tendency for hypocortisolism. Other studies have found normal or even increased concentrations for free cortisol (Rief et al., 1998; Rief and Auer, 2000), although we controlled for depression. Some authors argue that the activity of the HPA-axis changes depending on the time line of the stressors (Gaab et al., 2002), with different HPA-axis-activities to acute versus long-lasting chronic stress. These variations might interact with changes of symptom and pain perception, with hyperalgesia during acute stress, but hyperalgesia following chronic states of distress (Pruessner et al., 1999). In another study, Gaab and others confirmed normal cortisol concentrations in somatoform-associated disorders (chronic fatigue syndrome), but found evidence for enhanced glucocorticoid sensitivity with in vitro dexamethasone stimulation (Gaab et al., 2003).

We can conclude that the relevance of the HPA-axis for the somatization syndrome is still unclear. HPA-activity definitely plays a role; however, this role might be unspecific, course depending, and multi-directional. The results for cortisol, either nonstimulated or stimulated, do not allow a final interpretation of its relevance in somatoform disorders.

1.3. Somatoform symptoms and immunology

Immune stimulation seems to activate both analgesia and hyperalgesia circuitry (Watkins and Maier, 2000). Some immune parameters seem to be associated with the subjective feeling of being ill. Lekander and others (Lekander et al., 2004) demonstrated that there is a correlation between self-rated health and levels of circulating cytokines. However, the confounding effect of on-going diseases is unclear in this study.

Activation of the immune system seems to induce behavior patterns that are similar to the illness behavior seen in depression and somatization. Dantzer and his group investigated the effect of injecting the proinflammatory cytokine IL-1 into the brain of rats, and they could show that this induces sickness behavior such as social withdrawal, reduction of physical activity, and others (Dantzer et al., 1998; see also Vollmer-Conna, 2001). These results suggest that in some cases, immune changes can induce behavior changes that are relevant for somatization syndrome. However, it remains unclear whether this causality can also be bi-directional, and whether it contributes especially to the development and maintenance of somatoform symptoms in humans.

In depressed people, higher concentrations of parameters of the proinflammatory system have been described. In prior work, we were able to confirm increased concentrations of soluble CD8-T-Lymphocytes in depressives, but the concentrations for patients with somatization syndrome were decreased (Rief et al., 2001b). Also the concentrations of interleukin-6 as one of the major cytokines confirmed reduced proinflammatory capacity in patients with somatoform disorders.

To summarize the immunological findings, it is possible that depression and somatization, although they co-occur frequently, may be associated with different biological concomitants. However, these results have to be further confirmed.

1.4. Monoamino acids, neurotransmitters

Serotonin plays a major role in various pain conditions, such as migraine. Serotonin-associated disorders such as depression are typically associated with altered pain perception thresholds. However, this is not the only rationale for investigating amino acids in somatoform disorders. Physical weakness, bodily exhaustion, and fatigue are not only possibly triggered by the central nervous system, but can also have peripheral sources, such as energy metabolism in the muscles.

We could demonstrate that the concentration of branched chain amino acids BCA (such as valine, leucine, isoleucine) differs among patients with somatization syndrome, depressives and controls, W. Rief, A.J. Barsky998
with reduced concentrations in both clinical groups, which were however more pronounced in somatization than in depression (Rief et al., 2004). These amino acids are not only competing with other amino acids (such as tryptophan) at the blood-brain barrier, but are also relevant for the energy metabolism in the muscles; therefore this might be a correlate of the subjective feeling of weakness which is a typical symptom not only of somatization syndrome, but also of somatoform-associated disorders such as chronic fatigue syndrome. For the neurotransmitter-relevant monoamino acids thyrosine and tryptophan, we found only specific effects for tryptophan indicating the relevance of the serotonergic system in somatoform disorders. Schwartz and others (Schwartz et al., 1999) found that low levels of 5-HIAA and tryptophan were related to higher pain scores in fibromyalgia patients, a result that might be relevant to somatization syndrome. Moreover, there was a tendency of higher pain scores to be related to higher serum concentrations of the neuropeptide substance P, pointing to the antagonism of substance P and the serotonergic system in nociception.

Therefore investigations of monoamino acids indicate the involvement of the serotonergic system, while the relevance of the noradrenergic system is unclear. One finding also indicates changes of the muscle metabolism, but this finding requires replication.

1.5. Brain mechanisms

The conscious perception of symptoms takes place in the brain. Evoked potentials reflect both attention and filtering processes. Modern brain imaging techniques have been widely used in pain research, but few studies involve somatoform disorder patients. In pain research, the existence of a 'pain matrix' including structures of the spinal cord, brainstem, hypothalamus, amygdala/hippocampus, prefrontal and cingulated cortex, as well as thalamus and somatosensory cortices is widely accepted (Jones et al., 2003). It can be expected that at least some of these areas are also involved in the perception of somatoform symptoms.

Attention and perception processes in somatization disorder have been studied using EEG evoked potentials (Gordon et al., 1986; James et al., 1990). The results indicated increased N1-components and decreased mismatch negativity in somatization disorder, facts that might correspond to deficits in filtering processes.

Modern brain imaging techniques are only beginning to be applied to the somatoform symptoms. It can be expected that somatosensory areas are involved, but also both prefrontal and right parietal regions are thought to be components of a distributed neural network that integrates processes of attention and awareness. Hakala and colleagues (Hakala et al., 2002) compared PET-results of 10 women with multiple somatoform symptoms to healthy controls. They found lower glucose metabolism rates in both caudate nuclei, left putamen, and right precentral gyrus. The patients also showed bilateral enlargement of caudate nuclei volumes (Hakala et al., 2004). Abnormalities of the caudate nuclei have also been found for body dysmorphic disorder (Rauch et al., 2003). However, the specificity of these findings remains unclear. Brain imaging techniques in somatoform disorders have also been used in patients with conversion symptoms. Altered somatosensory-evoked responses in specific forebrain areas have been described (Mailis-Gagnon et al., 2003), as well as decreased regional blood flow in the thalamus and basal ganglia contralateral to the sensorimotor deficit (Vuilleumier et al., 2001).

Experimental fMRI studies provide perhaps one of the most exciting insights into brain processes involved in the maintenance of chronic complaints. The effect of distraction on pain perception was demonstrated by Bantick et al., who found that distraction leads to reduced activity in pain-associated centers (Bantick et al., 2002), again supporting a signal-filter-model as presented below.

To conclude, brain research on somatoform disorders is at its earliest inception. Although differences in the caudate nuclei have been described in some studies, the specificity of these findings is unclear.

2. A signal-filtering model of somatoform symptoms

Somatoform disorders can be understood as disorders in the perception of bodily signals. Therefore, all biological approaches have to be discussed in light of their possible influence on the perception of bodily signals. To facilitate this process, we will present a simplified model consisting of signal development, filtering, and perception.

We assume that most body parts send sensory signals to the brain. Due to neural filtering processes, most of these signals do not come to consciousness in healthy people. This is also the
basis of the gate-control-theory in pain research. In somatoform disorders, physical sensations are perceived and interfere with planned behavior and intentional thinking. Consequently, reasons for these (mis-)perceptions can be either amplified sensory signals (e.g. strong sensory input), reduced filtering capacities, or further factors influencing the strength of the signal or the capacity of sensory filters (e.g. selective attention because of health anxiety, immunological changes during infections; see Figure 1).

In the model in Figure 1, possible psychobiological and psychological influences in somatoform disorders are grouped to signal amplifying versus filtering reduction effects. The recently published more general cognitive activation theory of stress (Eriksen and Ursin, 2004) can be combined easily with this signal-filter-model of somatoform symptoms. The primary stress response leads to an activation, which increases physiological signals. In most people, this does not lead to prompt symptom perception, as most distressing situations offer substantial distraction. Only when the situational distraction ends and the physiological activation continues does the risk for the perception of bodily signals increase. This is especially the case in chronic states of distress. As Ursin and Eriksen point out, only sustained high arousal levels constitute a potential health risk.

In somatoform disorders, sensitization might play also a role (Ursin, 1997). Sensitization describes the fact that same signals can lead to more and more amplified perceptions. Although the bodily signal may continue to be of minor amplitude, it might be perceived as more and more intense. The repeated perception of physical signals in combination with uncertainty about the origin of the sensations can hinder the habituation that would ordinarily be expected. The cognitive component of this model has already been well-described in the somatosensory amplification model (Barsky, 1992), but sensitization also refers to a neuronal process.

In sum, somatoform symptoms have biological components that have an important role in creating a vicious circle together with cognitive, behavioral, and emotional features. However, most of the studies cited above have specific short-comings, e.g. most are cross-sectional in nature. Therefore, these results do not allow any conclusions regarding the sequence and time-line of the single components during development and persistence. We will continue with suggestions for future psychobiological research.

3. Psychobiological research in somatoform disorders—what should be the next steps?

3.1. Replication and extension of existing approaches

It is evident that many of the findings cited above should be replicated before further interpretation.
They present exciting options, but are not comprehensive and should therefore be extended.

3.2. Examination of covariation of different features, longitudinal studies

We know more and more about components of somatoform symptoms, but little about their interaction, sequences, etc. although all vicious circle models include assumptions about it. In addition to biological features, behavioral components (such as reduction of physical activity, health care use, social withdrawal, self-examination), cognitive attributions, and affective components (e.g. demoralization, alexithymia) should be considered. Therefore, the next step would be to assess these variables longitudinally, and to analyze covariations of patterns of change.

3.3. Experimental biological approaches

Experimental animal studies helped us to understand biological processes and interactions. To close the gap between basic biological research and clinical phenomena such as somatoform symptoms, psychobiological experiments in humans are necessary. These experiments can either vary psychological features (e.g. behavioral components, cognitive attribution, selective attention) and assess their biological consequences, or vice versa influence the biological systems (e.g. through biochemical stimulation) and assess the psychological outcome.

3.4. What happens in the brain of patients with somatoform disorders?

Somatoform disorders cannot exist without brain activity. Functional MRI, however can be only as good as the experimental paradigms used to provoke different disorder-relevant brain conditions; therefore better psychological paradigms comparing different, but repeatable conditions are needed; in some first approaches, modified Stroop-tasks have been used, but their effects have been equivocal, and approaches modifying symptom intensity would be preferable. Although fMRI techniques are currently popular, the advantages of other brain activity assessments (e.g. EEG, ERPs, EMG) allowing detailed time-line analyses should also be considered.

References


