Explaining medically unexplained symptoms—models and mechanisms

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Received 21 December 2005; received in revised form 27 March 2006; accepted 27 March 2006

Abstract

We summarize the psychological mechanisms that have been linked to the development and maintenance of medically unexplained symptoms (MUS). Many models postulate that patients with MUS misinterpret physical sensations and show other cognitive abnormalities (e.g., an over-exclusive concept of health) that play a major role in symptom development. While there is strong evidence for the role of cognitive aspects, there is less evidence for their interaction with perceptual features (e.g., perceptual sensitivity, lowered perceptual threshold). Modern neuroimaging techniques show that the expectation of symptoms leads to the activation of brain areas corresponding to symptom perception, while distraction from symptoms reduces brain activity in perception areas. The frequently postulated monocausal organic attribution for physical sensations by patients with MUS needs to be modified, as many patients report multiple symptom attributions, including psychological. Symptom attributions and causal models depend on memorized concepts, and so memory processes need to be investigated in more detail. Aberrations in memory processes not only offer a link to understanding perceptual processes, but are also involved in doctor–patient interaction. This encounter is characterized by unsuccessful medical reassurance, which again involves memory processes. We conclude that psychological mechanisms such as expectation, distraction, and memory processes need to be integrated with biological models to aid understanding of MUS.

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doi:10.1016/j.cpr.2007.07.005
1. Introduction

Medically unexplained symptoms play a major role in most health care systems, and it is dissatisfying that such highly prevalent complaints are considered “unexplained”. This paper aims to summarize the current concepts and mechanisms that underlie physical complaints, to help understand the development and maintenance of symptoms not part of diagnosed medical conditions. We will also discuss the empirical background of these mechanisms. As authors use many different terms for these complaints, we will occasionally provide data from studies using associated diagnoses and concepts, such as somatoform complaints, chronic fatigue syndrome, fibromyalgia, and chronic pain. We will use the terms “somatoform disorders”, “somatization”, and medically unexplained symptoms interchangeably, while focusing on patients with multiple somatic complaints. Conversion and dissociation are not addressed in this review. The major question of the article is, “how can we explain symptoms that are not due to medically recognised diseases?”

In some cases, studies on hypochondriasis might help to understand processes of symptom development and persistence, and are therefore partially included in this overview. However, it should be kept in mind that only a small portion of patients with somatization syndrome report comorbid hypochondriasis (Rief, Heuser, Mayrhuber et al., 1996). Although health anxiety scores are increased in this group, it is still possible that the mechanisms involved in hypochondriasis are typical anxiety processes, and not valid for somatization syndrome. Therefore the results from hypochondriasis studies should be generalized to medically unexplained symptoms with caution.

The list of possible mechanisms that may be involved in the development and maintenance of medically unexplained symptoms (MUS) is overwhelming, and a comprehensive overview would go beyond the space limitations of this journal. Therefore this paper focuses on several specific aspects, without attempting to present an all-embracing overview. First, current models that offer a framework for the discussion of single mechanisms are presented. Then, psychological mechanisms and empirical evidence for the development and maintenance of physical complaints are reported. In this section, we provide data on the relevance of symptom attributions, illness beliefs, attention and perception, expectation and memory, and the role of health anxiety and health worries. Then behavioural aspects, such as health care utilization and illness behaviour, avoidance behaviour and physical deconditioning, reassurance-seeking and the role of doctor-patient interaction are highlighted. Following this, the role of emotion regulation, attachment styles and personality is considered; the role of traumatic experience is addressed in another paper in this issue.

2. Models of medically unexplained symptoms (MUS)

One of the most influential models on multiple unexplained symptoms was first described for hypochondriasis by Barsky & Wyshak (1990). This model focuses on perception and cognition. The authors suggest that hypochondriacs amplify benign somatic sensations and misattribute them to serious diseases. As a consequence, patients focus their attention on bodily processes and experience a broad range of somatic sensations as more intense, more noxious, and more disturbing. This attention-focussing again amplifies the perception of physical signals, thereby forming a vicious circle, as has been described in panic disorder and depression (e.g., Beck, Rush, Shaw, & Emery, 1979; Clark, 1986).
Barsky and others describe this process as somatosensory amplification (see Fig. 1). Although the model has face validity and helps explain processes in simple terms, questions remain. When the model was introduced more than 15 years ago, the empirical data were mainly based on cross-sectional studies using self-rating scales. Moreover, the model was formulated for hypochondriasis, and patients with medically unexplained symptoms only rarely show the full picture of hypochondriasis. Further aspects of the empirical foundation of somatosensory amplification will be discussed later in the article.

Kirmayer and others (Kirmayer & Taillefer, 1997) extended the cognitive-perceptual model by integrating social and forensic aspects (see Fig. 2). The interpretation of physical sensations as a sign of illness leads to help seeking, which can in itself be a source of maintaining factors. Inadequate reassurance or negative doctor-patient interactions can increase the distress associated with symptoms. An interesting part of Kirmayer’s model is the integration of social responses, which include other health care providers, work conditions, insurance, and compensation systems. These social factors can reduce motivation to use self-help strategies and cope with symptoms. Kirmayer’s model offers an integrative and multidimensional approach that adds behavioural and social aspects to the somatosensory amplification process. Other models also emphasize the role of physical deconditioning, avoidance, and physical misconceptions.

Brown (2004) presents another multicomponent model for the development and maintenance of medically unexplained symptoms. In the development of his theory, Brown acknowledges the former concepts of dissociation and conversion, but the central part of his model is cognitive. He proposes that unexplained symptoms constitute an alteration in body image generated by information (“rogue representations”) in the cognitive system. The primary attention system selects rogue representations, which can be any kind of information concerning the nature of physical symptoms. These rogue representations can be acquired from many different sources, including exposure to extraordinary physical states in oneself (e.g., during periods of physical illness, or through traumatic experiences), exposure to physical states in others (e.g., abnormal levels of illness in the family environment), but also through socio-cultural transmission or verbal suggestion. These experiences create memory traces that are functionally similar to those generated when the same symptoms are experienced in the self. The rogue representation selected by the primary attention system, leads to consequences in the secondary attention system, such as selective attention to physical sensations, disease-confirming information and negative affect. These secondary attention processes facilitate re-activation of the rogue representation. Therefore Brown’s model offers a link to both perceptual and memory processes.

The multicomponent models of medically unexplained symptoms acknowledge different risk factors that can contribute to the development and maintenance of complaints. However, it should be kept in mind that the central process is a perceptual one. People have to perceive sensations in order to describe physical complaints. This raises questions about how the perceptual process is constructed. Two models focus on the perception process itself, namely Pennebaker’s model of the psychology of physical symptoms (Pennebaker, 1982), and our signal-filter model (Rief & Barsky, 2005). Both models assume that there is a permanent sensory stimulation, which sends neural impulses to the brain from the periphery of the body. Different organs and body parts as well as the skin continually produce sensory
information that is forwarded to higher cortical structures. The healthy nervous system, however, has learned to filter this “sensory noise”, thus preventing over-stimulation of the upper cortical structures with irrelevant information. This modification of the gate-control theory formulated for chronic pain (Melzack & Wall, 1965) has been adapted for medically unexplained symptoms (MUS). It is proposed that people experience physical complaints if this filtering process is distorted (see Fig. 3). Pennebaker in his work from the beginning of the 80s has shown that the sensory input from the body comes to consciousness if either the sensory signals are amplified, or distracting external stimulation is reduced. While the first increases the sensory input, the second might influence the filter capacity.

The emphasis on basic perceptive processes in medically unexplained symptoms provides the link to psychobiological models of “somatization”. A summary of psychobiological approaches has been published recently (Rief & Barsky, 2005). Psychobiological processes involved in perception and distraction have been examined using neuroimaging techniques, as well as EEG or MEG data (e.g., Bantick et al., 2002; Gordon, Kraiuhin, Kelly, Meares, & Howson, 1986; Hakala et al., 2004, 2002; James, Gordon, Kraiuhin, Howson, and Meares, 1990; James et al., 1987; Lorenz et al., 2005). Psychobiological models for MUS have also been postulated. Dantzer emphasizes the psychoneuroimmune perspective (Dantzer, 2005). Activation of the immune system is typically associated with “feeling sick”, and a behavior pattern that is described as sickness behavior, showing some parallels to the behaviour pattern described for patients with MUS. The group around Hellhammer (Fries, Hesse, Hellhammer, & Hellhammer, 2005) focuses on psychoneuroendocrine aspects. Interactions of the endocrine, the immune and the central nervous system play a major role for pain perception and sickness behavior, and pain perception might be modified to hypo-
as well as hyperalgesia. Current models on MUS should integrate or at least not contradict these biological approaches.

3. Psychological mechanisms

3.1. Cognitive aspects

Most of the models described above focus on the interaction of perceptual and cognitive aspects in the development and maintenance of medically unexplained symptoms (MUS). We will now summarize the empirical evidence for the relevance of cognitive aspects, such as symptom attribution, illness beliefs, attention and perception, expectation and memory bias, as well as health worries, to MUS.

3.1.1. Symptom interpretation and illness beliefs

It is assumed that two cognitive processes are crucial, namely the catastrophizing interpretation of physical symptoms and unhelpful causal explanations for somatic symptoms. Using self-rating scales, it has been shown that patients with hypochondriasis report more catastrophic interpretations of bodily sensations than controls (Barsky et al., 2001; Hitchcock & Mathews, 1992; Marcus, 1999; Marcus & Church, 2003; Smeets, de Jong, & Mayer, 2000). While this association is strongly supported for hypochondriasis, the question remains whether it also holds for patients with multiple somatic complaints. Few studies have investigated catastrophizing cognitions in patients with medically unexplained symptoms without hypochondriasis. In one of our studies (Rief, Hiller, & Margraf, 1998), we showed that not only patients with hypochondriasis, but also patients with somatization syndrome without hypochondriasis, showed increased scores for catastrophizing cognitions associated with bodily perceptions. We also demonstrated that this cognitive style was specific to somatization and hypochondriasis, and was less pronounced in patients with other mental disorders (mainly depression and anxiety).

Further approaches confirm the specificity of over-interpretation of bodily symptoms in patients with hypochondriasis and medically unexplained symptoms. Barsky and others (2001) compared hypochondriacal patients’ appraisal to those of non-hypochondriacal patients from the same primary care setting. The hypochondriacs rated the total risk of developing various medical diseases or being subject to injury as significantly higher than the non-hypochondriacal group. In a non-clinical sample of college students, Marcus and Church (2003) showed that estimates of the likelihood of serious illnesses was best predicted by self-reported hypochondriasis, while other self-report variables (e.g., depression, anxiety, worry, avoidance) did not contribute significantly to this cognitive style. In another study by Marcus (1999), hypochondriacs only demonstrated increased estimates for catastrophic outcomes for major illnesses, while they did not differ from healthy
controls in their estimates for minor illnesses. Although some attempts to show the specificity of this effect have failed (de Jong, Haenen, Schmidt, & Mayer, 1998), overall, the evidence is convincing that patients with hypochondriasis overestimate the likelihood of catastrophic outcomes in medical conditions.

Some studies have addressed the issue of possible consequences of catastrophizing about symptoms. In an experimental approach, pain catastrophizers were compared with non-catastrophizers when receiving low-intensity electrocutaneous stimuli. It was shown that catastrophic thinking enhanced attentional interference immediately after threat stimulus onset. This means that patients with a catastrophizing interpretation of physical sensations have an increased pain perception that is associated with a reduced capacity for distraction. These consequences can play a role in the subsequent process of chronicity (Crombez, Baeyens, & Eelen, 1998).

In a cross-sectional study in the Dutch community, Severeijns, Vlaeyen, and van den Hout (2004) examined predictors of health care use (specialist consultation, use of pain medication, work disability) in 1164 people with musculoskeletal pain. The authors found that pain catastrophizing was an independent predictor of health-care use, even when controlling for other significant predictors, such as pain intensity and the presence of multiple pain locations. Two studies that focused on patients with specific medically unexplained syndromes give further insight to the role of over-interpreting pain and other physical perceptions. Catastrophizing, worry, and other control variables accounted for half of the variance in suffering in patients with irritable bowel syndrome. Pain catastrophizing was found to be a mediator of the relationship between worry and pain suffering (Lackner & Quigley, 2005). The general tendency to worry about health and illness leads to a catastrophizing interpretation of symptoms, if they occur. This interaction is a major predictor of suffering associated with irritable bowel syndrome. Similarly, patients with dizziness and vertigo overestimated the negative consequences of their symptoms, such as falling, fainting, or losing control. These illness beliefs can be modified by therapy (Yardley, Beech, & Weinman, 2001), and a modification of these beliefs is associated with positive outcome.

In summary, overestimation of the association between physical symptoms and negative outcomes is central to most models of medically unexplained symptoms. Empirical investigations have so far focused on people with hypochondriacal tendencies, and there is less evidence for patients with medically unexplained symptoms without hypochondriasis. More experimental studies are needed to investigate the role and consequences of this cognitive style.

3.1.2. Causal attribution and illness beliefs

Most models on medically unexplained symptoms hypothesize that patients with these complaints have a tendency to use medical explanations to account for their symptoms. Many studies on causal illness attributions have examined three factors; organic explanations, psychological explanations, and neutral or neutralizing explanations. When the causal attribution style is investigated in patients with medically unexplained symptoms, the results are less clear than expected. Robbins and Kirmayer (Robbins & Kirmayer, 1991) developed the Symptom Interpretation Questionnaire SIQ, which assesses the three types of causal attributions mentioned above. In family medicine patients, a somatic attribution style was associated with hypochondriasis assessed by the Whiteley Index ($r=0.40$), but more weakly associated with somatic anxiety complaints assessed by the Cognitive–Somatic Anxiety Questionnaire ($r=0.26$). This somatic subscale was primarily associated with a psychological attribution style ($r=0.62$), indicating that somatic complaints associated with anxiety are highly correlated with psychological causal attributions, and less with somatic attributions. In this study, the normalizing attribution style correlated neither with hypochondriasis nor with anxiety-related somatic complaints ($r=0.07$ and $r=0.16$, respectively). Regression analysis confirmed that a psychological attribution style was associated with a history of mental disorders, and negatively associated with a history of physical illness.

A study by our own group (Rief, Nanke, Emmerich, Bender, & Zech, 2004) demonstrated that the association between causal illness attributions and somatoform symptoms is more complex than expected. We investigated 233 primary care patients with MUS and found that most patients reported multiple illness attributions, rather than simplicistic explanations. The more somatoform symptoms patients had, the more explanations in general they considered. Although we found that patients with somatoform symptoms had increased scores for organic illness beliefs, comorbidity with depression and anxiety was associated with more psychological attributions. As depression and anxiety are frequently comorbid with somatoform disorders, psychological illness attributions were prevalent in this patient group, confirming the results above (Robbins & Kirmayer, 1991).

A study with healthy controls confirmed that attribution styles are not uni-dimensional, but rather, people can have two or three very different attribution styles (Lundh & Wangby, 2002). In this study, psychological attributions were associated with a higher degree of somatic complaints and negative affect. Considering these results with those above, the positive association between psychological attributions and somatic complaints only holds for people with negative
affect or depressive symptoms. If the patient has somatic complaints but no mental complaints, there is evidence for a direct relationship between symptoms and organic attributions.

MacLeod, Haynes, and Sensky (1998) confirmed that in a sample of primary care patients, psychological illness attributions were associated with general anxiety, whereas somatic attributions were related specifically to hypochondriasis. Sensky acknowledges different and sometimes contradictory results (Sensky, 1997). He emphasizes that attributions are among the cognitive constructs that make up the individual’s own model of symptoms and illness, and they are therefore crucial for understanding and modification in cognitive therapy. The functionality and dysfunctionality of illness attributions can be very individual. Nevertheless, illness attributions seem to be a stable construct in individuals, as has been shown in a one-year follow-up study in Spain (Garcia-Campayo, Larrubia, Lobo, Pérez-Echeverria, & Campos, 1997).

Different causal attribution styles are not only associated with different syndromes, but also with physical and psychological functioning as assessed by the SF-36. This was shown by Tailliefer, Kirmayer, Robbins, and Lasry (2002) who found that making more somatic attributions was associated with worse physical functioning. Illness attributions also have relevance for the chronicity of complaints. In patients with chronic fatigue syndrome, a prospective study has shown that somatic attributions are associated with symptom severity over time (Schmaling, Fiedelak, Katon, Bader, & Buchwald, 2003). As organic illness attributions showed clear associations with the need for medical investigations and medical treatment, while psychological illness attributions did not (Rief, Nanke et al., 2004), an organic attributional style is not only associated with more healthcare use, but also with the course and outcome of treatments.

In the development and maintenance of symptom attributions, influences of the social network can be crucial. The partners of patients with chronic fatigue syndrome have been shown to endorse somatic attributions for the patients’ symptoms, although they considered other explanations for their own complaints (Butler, Chalder, & Wessely, 2001). Thus symptom attribution styles might be learned and/or reinforced by significant others.

In summary, the relationship between causal illness attributions and medically unexplained symptoms is much more complex than specified in most models. Organic illness attributions do contribute to increased healthcare use. Both increased scores for organic as well as psychological illness explanations can exist in patients with MUS. High scores for psychological illness attributions have been found in MUS patients, particularly those with comorbid anxiety or depressive symptoms.

3.1.3. Health attitudes and other cognitive styles

Barsky and others hypothesized that patients with hypochondriasis have an over-exclusive cognitive concept about good health, and they compared a patient group with hypochondriasis to a non-hypochondriacal group of patients from the same hospital (Barsky, Coeytaux, Sarnie, & Cleary, 1993). With a “Health Norms Sorting Task”, they showed that patients with hypochondriasis believe good health to be relatively symptom-free, and consider more symptoms as indicative of sickness. Such a health concept is irrational, because even healthy bodies produce physical sensations from time to time. However, to our knowledge, this study has not yet been replicated in patients with MUS without hypochondriasis.

Other cognitive styles have also been examined. Patients with somatoform complaints show a stronger self-concept of bodily weakness, again specific to patients with somatoform compared to other mental disorders (Rief, Hiller et al., 1998). Cognitive styles also discriminated patients with chronic fatigue syndrome from depressive patients (Moss-Morris & Petrie, 2001). As will be shown later, behavioral characteristics of MUS seem to be less specific than some of the cognitive features described in this chapter.

3.1.4. Attention and perception

Most models on MUS postulate that selective attention to bodily processes plays a major role in the maintenance of problems. However, before outlining the potential risks of abnormal attention focussing, it should be emphasized that the observation of one’s own body is an evolutionary useful process during health threats. Thus self-attention is usually a helpful process, that only in some extraordinary circumstances yields negative consequences (Cioffi, 1991).

Studies using self-rating scales have shown that patients with somatization and those with hypochondriasis report increased scores for body scanning (Rief, Hiller et al., 1998). This means that people with these disorders observe their bodily processes frequently during the day, in order to detect possible signs of illnesses. A number of experimental studies have tried to investigate this effect in more detail. A frequently used approach is a modified version of the Stroop test. Participants have to name the color of presented words, while the words belong either to a category of body-related words or neutral words. While some studies have found either weak or non-significant effects (e.g.,
(Pincus & Morley, 2001), a recently published study found impressively specific results (Lim & Kim, 2005). The authors compared patients with somatoform disorders, depressive disorders, panic disorder, and healthy controls, showing physical threat words, negative words, and neutral words. They found specific results for depressive patients (cognitive interference for negative words), panic patients (cognitive interference for physical threat words), and somatoform patients (cognitive interference for physical threat and negative words). However, it should be kept in mind that the modified Stroop test assesses cognitive interference, which is not the same as selective attention.

Hypochondriacal patients report more sensations when asked to focus their attention on the body (Schmidt, Wolfs-Takens, Oosterlaan, & van den Hout, 1994). This simple experiment confirms that attention focussing can increase the number of reported physical sensations. This was also shown in a series of studies by Pennebaker (Pennebaker, 1982), who manipulated the degree of attention to internal processes by amplifying body signals. This condition led to higher symptom reports than a distraction condition. In summary, selective attention to bodily processes has been shown to increase the likelihood of symptom reports. Its specific relevance for MUS patients needs to be further investigated.

Another hypothesis is that increased or abnormal ability in proprioception or interoception may be associated with the development of physical complaints. Scholz, Ott, and Sarnoch (2001) used a visual EMG biofeedback task to assess proprioceptive variables in somatoform disorders. Participants had to produce different levels of muscle tension by using visual feedback. The subjects’ task was to bring the needle of the feedback apparatus into a specific area of the display without knowing how high/low this muscle tension was. Afterwards, they had to rate the muscle tension as well as the intensity of the perception. It was found that patients with somatoform disorders demonstrated more precise but not more intense perceptions of muscle tension than did healthy controls. Although this study lacks a clinical control group and a comparison condition, it shows an elegant approach towards investigating proprioception. If patients with MUS perceive physical sensations more precisely, this could lead to increased likelihoods of perceiving even minor physical symptoms, although these differences could also be due to higher distraction by external stimuli in healthy controls.

In tactile sensitivity, no differences between hypochondriacal patients and healthy controls have been found (Haenen, Schmidt, Schoenmakers, & van den Hout, 1997). However, hypochondriacal patients considered themselves more sensitive to benign bodily sensations. It was also found that the intensity of bodily sensations was not associated with electrophysiological changes, even in healthy controls (Steptoe & Noll, 1997). In this study, the subjective rating of bodily sensations was primarily determined by feelings of distress, not by objective physiological activation such as heart rate acceleration. In healthy controls, the perception of tactile sensations not only depended on the intensity of the stimulation, but also on self-control: if stimuli were self-produced, they were rated as less intense. This self-control effect was only found for healthy controls, not for patients with somatoform disorder or fibromyalgia (Karst et al., 2005). The authors conclude that central pain disorders interfere with the correct functioning of the self-monitoring mechanism that normally allows people to distinguish self-produced from externally produced tactile stimuli. If patients with somatoform symptoms react to self-produced stimuli in the same way as externally produced ones, the overall level of perceived bodily stimulation might be increased.

Houtveen, Rietveld, and de Geus (2003) examined the reactions if participants were exposed to symptom-provoking situations, such as mental stress, 5% CO2 breathing, and exercise. Participants high in functional somatic symptoms reported more somatic symptoms at baseline and increased responses to mental stress and CO2 breathing; this reaction was accompanied by higher ratings for tenseness and anxiety.

According to Pennebaker’s approach (1982), people report increased somatic sensations not only if the sensations themselves are more intense, but also if there is a lack of external stimulation. Therefore lack of distraction can also contribute to medically unexplained symptoms. The effect of distraction was tested in patients with hypochondriasis (Haenen, Schmidt, Kroeze, & van den Hout, 1996). The authors found increased symptom reporting when participants were instructed to focus attention to their own body, but did not find a symptom-reducing effect if participants were distracted. Other studies have found that distraction significantly reduces the perceived intensity and unpleasantness of painful stimuli (Lautenbacher, Pauli, Zaudig, & Birbaumer, 1998). This effect has been found in hypochondriacal patients as well as controls. In fact, the pain reducing effect of distraction has not only been found using subjective report measures, but also in brain activation, assessed by functional MRI (Bantick et al., 2002) or PET (Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000). This pain-reducing effect of distraction is more pronounced the more concrete the distraction task is. Only small effects have been found if distraction is only imagined (Johnson, Breakwell, Douglas, & Humphries, 1998). To conclude, distraction has a substantial effect on reducing pain intensity, although the relevance of this effect for functional somatic complaints is unclear.
Some studies that have investigated somatization-like conditions, such as chronic fatigue syndrome, did not find an attention bias towards body-related stimuli, again using Stroop tests (Moss-Morris & Petrie, 2003). However, using self-rating scales, patients with non-cardiac chest pain and patients with somatization syndrome did show increased self-monitoring (Cheng et al., 2003; Rief, Hiller et al., 1998; Rief, Shaw, & Fichter, 1998). Thus if focussed attention to bodily processes is a relevant factor for medically unexplained symptoms (as self-report data suggest), the Stroop test does not show this attention bias reliably, but only in a few studies. As the stimuli in the Stroop test are computer-presented words, the ecological validity to attention to one’s own body might be questionable (see also Kolk, Hanewald, Schagen, & van Wijk, 2002) for the association between physical symptoms and selective attention).

Somatization and depression are frequently correlated, and both conditions seem to be associated with a reduced pain threshold. Therefore Sherman and others (Sherman et al., 2004) investigated whether somatization and depression show comparable associations with pain perception in women with temporomandibular disorders. The authors concluded that somatization and depression are associated with different measures of experimental pain. Somatization may be related to more attentional and perceptual measures of pain, while depression may be related to more behavioral measures of pain. This line of research seems especially important, as different impacts of depression and somatization on pain perception should lead to different approaches in treatment depending on comorbidity with depression. However, these findings have to be replicated with other patients with medically unexplained syndromes.

It has been hypothesized that continuous exposure to pain and physical complaints can lead to a sensitization process. Although sensitization may be a risk factor for the development of medically unexplained symptoms, it seems to be predominantly a maintaining factor. This model of sensitization, as formulated for example by Ursin (1997), also postulates that patients with medically unexplained symptoms show an abnormal sensitivity to sensory input from muscles, the gastrointestinal tract, smell and taste. However, there is little evidence for this assumption, although an older study of Hanback and Revelle (1978) found indices of increased perceptual sensitivity in hypochondriacs. Moreover, the process of sensitization needs to be understood not only as a neural and sensory process, but also as a psychological procedure (which, of course, also has its neurophysiological basis). The repeated experience of pain and complaints can lead to the development of cognitive pain schemata; the more consolidated this schema is, the more frequently it will be triggered from associated stimuli (Pincus & Morley, 2001). Cognitive pain schemata refer to a set of interpretations that are activated by diverging sensations; sensations are interpreted as pain symptoms with associated features and disabilities. This concept of cognitive pain schemata is closely related to Brown’s concept of rogue representations (Brown, 2004), and can be understood as a part of the general symptom memory matrix that is described in the next section.

### 3.1.5. Expectations and memory

Few models of medically unexplained symptoms emphasize the role of expectations. However, it is well established that expectations can substantially influence the intensity of pain symptoms. Experimentally induced pain is experienced as less intense, if low intensity pain stimuli are expected, although high intensity stimuli are applied, and vice versa (Lorenz et al., 2005). In this study, evoked magnetic fields were assessed and possible dipole sources were computed. The contralateral secondary somatosensory cortex (SII) showed variations that were directly dependent on pain intensity as well as expectation. Other regions, such as the caudal anterior cingulate cortex and the posterior cingulate cortex only varied with the intensity of the pain stimulus. The increased activity in the SII-cortex following expected, but not presented high intensity pain stimuli seems especially important, as it underlines the association of expectation with neuronal perception intensity. MUS patients can be hypothesized to have high expectations of experiencing bodily complaints. These expectations can lead to a priming effect for subsequent sensations.

The expectancy effect has been tested using the cold pressure test in combination with a sham stimulator of headache. The sham stimulator produced more headaches if the cold pressure test preceded it than if the cold pressure test was presented afterwards. Thus prior pain experience and expectancy can potentiate each other (Bayer, Coverdale, Chiang, & Bangs, 1997). It has also been found that the pain expectancy effect interacts with the cognitive style of “catastrophizing bodily perceptions”. If participants were catastrophizers, the pain expectancy effect was pronounced, while it was not found in non-catastrophizing participants (Van Damme, Crombez, & Eccleston, 2004).

The expectancy effect has been examined in persons with hypochondriacal attitudes. It was found that the expectancy of a forthcoming pain stimulus reduced the performance of high hypochondriacal subjects, independently of whether the pain was expected immediately or later on. In low hypochondriacal patients, the expectancy of a pain
stimulus interfered with performance only if it was expected immediately, not if it was expected later on (Pauli, Schwenger, Brody, Rau, & Birbaumer, 1993). The influence of expectancy on symptom reporting has been confirmed in other studies (Schmidt et al., 1994).

The expectancy of physical complaints interacts with memory. If more painful events are memorized, more physical complaints will be expected in the future. Therefore a possible memory bias for physical stimuli could be another risk factor for medically unexplained symptoms.

Memory functions in general have been investigated in somatization-associated syndromes but have revealed equivocal results. In a very small sample, somatising patients had lower performance in semantic memory and verbal episodic memory than controls (Niemi, Portin, Aalto, Hakala, & Karlsson, 2002), while other studies have found no difference (Rief, Shaw et al., 1998; Rief, Heitmüller, Reisberg, & Rüddel, 2006). In fibromyalgia, lower scores for verbal recall were associated with depression, which emphasizes the importance of considering comorbid conditions when investigating memory capacity (Sephton et al., 2004). The most striking effect for lower memory capacity was not found for real memory tests, but for subjective ratings of capacity (Glass, Park, Minear, & Crofford, 2005). However, there is some evidence that the experience of pain and complaints does reduce the capacity for memory and attention tasks (Kuhajda, Thom, Klinger, & Rubin, 2002).

In evaluating medically unexplained symptom models, it is especially important to analyze the effects of a memory bias favouring body-related information and pain perception. Lim and Kim (2005) did not find a memory bias for physical threat words in implicit memory tasks, but patients with somatoform disorders showed biases for physical threat words in explicit memory tasks. Another study did not find an explicit memory bias for physically relevant items (Rief, Shaw et al., 1998), while a third study found implicit, but not explicit memory variations in patients with multiple somatic complaints (Martin et al., in press). With hypochondriacal individuals, Brown et al. (1999) unexpectedly found a bias against reporting health-related words, while Pauli and Alpers (2002) found enhanced immediate recall of pain words in patients with somatoform pain disorder and comorbid hypochondriasis.

There is some evidence that patients with MUS do not have problems in memorizing health-related words, but show abnormalities in memorizing the probabilities associated with this information. In a study by Rief and others (Rief et al., 2006) patients with somatization syndrome listened to medical reports and had to remember the doctor’s estimated likelihood for a specific organic explanation for the complaints. Although doctors rejected most of the medical explanations, patients with somatization syndrome remembered increased likelihoods for these medical causes, while healthy controls and clinical controls did not. Thus the memory bias for health-related information does not hold for the information in general, but for the probabilities linked to these events. This is in line with the finding that hypochondriacs are neither immune to reassuring information, nor hypersensitive to alarming information. However, they show a domain-specific bias towards higher estimates of negative outcomes in ambiguous health-related situations (Barsky et al., 2001; Haenen, de Jong, Schmidt, Stevens, & Visser, 2000).

In order to understand possible memory biases, it should be kept in mind that the memorizing process itself is prone to multiple situational influences. Memory for pain can change, depending on the time distance to the pain experience (Christenfeld, 1998). In this experiment, students reported the same pain intensity after a cold pressure test either with or without a distraction condition. However, ten minutes later, students in the distraction condition remembered lower pain intensities than students in the other group. Other studies have shown the “primacy–recency effect” also holds for memory of physical complaints. Colonoscopy was remembered less painful, if the procedure was extended with the tip of the colonoscope remaining in the rectum for a few minutes at the end of the investigation (Redelmeier, Katz, & Kahneman, 2003). The authors’ interpretation is that the latest physical experience of a procedure overwrites the major unpleasant experiences, if the unpleasant experience precedes the less unpleasant sensation. It should be examined in MUS patients whether this overwriting of pain experiences also takes place.

These examples show that the recollection of symptoms is often inaccurate. The perception process is not memorized at it is, rather, the encoding process is influenced by the memory of earlier experiences, expectations, symptom intensity, environmental factors, and other parameters. The development of symptom memories can be associated with cerebral restructurings. This has been shown for single pain symptoms, where already 24 h of pain perception can cause neuronal reorganisation (neural plasticity) that will facilitate and intensify further symptom perceptions (Arnstein, 1997). For the phenomenon of multiple physical complaints, a general symptom memory matrix can be postulated. The perception of one symptom would not only sensitize further perceptions of this unique symptom, but would activate a complete matrix of symptom perception, facilitating the perception of other bodily complaints. In this way, the process of sensitisation described for pain can be postulated to hold true for a general symptom matrix.
For patients with multiple unexplained symptoms, memory errors are especially important in the medical encounter. Salkovskis & Warwick (1986) have postulated that medical reassurance is transformed by hypochondriacal patients, until the memorized doctor’s information confirms their health fears. While shortly after the medical encounter, the doctor’s information is reassuring, hours later the hypochondriacal patient can relapse to concerns and remember the medical information incorrectly (e.g.: doctor: “Cancer is very unlikely in your case”; patient, some hours later: “the doctor said that there is still a likelihood for me of having cancer”). This example points to the interaction of memory distortions and health anxiety. Therefore the next section will deal with the role of illness worry and health anxiety in these patients.

3.1.6. The role of illness worry and health anxiety

In most models of MUS it is hypothesized that the motivational basis for selective attention to bodily processes are illness worries and health anxiety. Therefore these features should be increased in patients with MUS. Moreover, worries about health threats may be a precursor and risk factor for the development of physical complaints.

Fear of illness is a common phenomenon in the general population. More than one-fifth of 40–65 year old Americans are significantly concerned about one of the following illnesses or injury aspects: becoming disabled or impaired, developing a particular illness, becoming mentally ill, sudden catastrophic illness, or the possibility of serious injury. Each of the above mentioned health threats were agreed with by more than 7.5% of the investigated sample. These data are confirmed by a German general population survey investigating more than 2000 representatively selected inhabitants; 8% of the participants reported serious health anxiety (Noyes et al., 2000; Rief, Hessel, & Braehler, 2001). Illness worry in primary care patients was found to be a predictor of bad outcome 5 years later (Jackson & Passamonti, 2005).

Illness worries are increased in patients with somatization syndrome, even in those without comorbid hypochondriasis. Watt and Stewart (2000) related the concept of illness worry to the concept of anxiety sensitivity. In a cross-sectional retrospective study, they found that these features were associated with increased instrumental and vicarious learning experiences related to bodily symptoms. Illness worries, anxiety sensitivity, and symptom reports seem to be related. In chronic fatigue syndrome, illness worry was correlated with somatic attributions, neuroticism, and depression (Taillefer, Kirmayer, Robbins, & Lasry, 2003). However, this was not specific to chronic fatigue patients, but was also found in patients with chronic illnesses.

Processing of different types of illness information (positive, negative, or ambiguous risk for complications) has been investigated using an experimental design. Information about a personal medical condition was provided before people participated in a cold pressure test. In this study, health anxiety was included as a possible predictor. Health anxious individuals displayed the predicted cognitive response (more negative interpretation of the provided information), and behavioural response (increased reassurance seeking). Health anxiety was found to be associated with decreased use of positive somatic monitoring of symptoms, suggesting health anxiety may be associated with failure to engage in protective strategies. In this study, health anxious people did not avoid getting negative information, but they did not make use of positive information adequately (Hadjistavropoulos, Craig, & Hadjistavropoulos, 1998). As health worries appear not only in individuals, but also in societies, Petrie and others (Petrie et al., 2005, 2001) investigated the role of modern health worries. They found that worries such as the contamination of water supply, the depletion of the ozone layer, air pollution, pesticides in food or leakage from microwave ovens are associated with reported somatic symptoms as well as with medical care utilization. Therefore, the authors hypothesize that modern health worries may predict the development of bodily complaints. This hypothesis was tested in a community setting before and after a council pesticide spray programme. Residents in the sprayed area who reported increased modern health worries before the spray campaign reported more somatic complaints afterwards. Thus modern health worries predicted health complaints after exposure to a perceived health threat.

Health worries can be caused by media warnings. This was shown by Winters et al. (2003) comparing one group that received warnings about environmental pollution prior to being exposed to a conditional odor stimulus. The other group received the same exposure, but without warnings about environmental pollution. The authors found that raising environmental awareness through warnings about chemical pollution facilitated the development of subjective health symptoms in response to chemical substances.

To summarize, the role of health anxiety and illness worries as a possible correlate of MUS is well established. Moreover, it has been shown that illness worries can predict the development of health complaints, and are negatively associated with remission in patients with MUS. Experimentally induced illness worries can lead to higher symptom reports.
3.2. Behavioral aspects

Behavioral aspects that may contribute to the development and maintenance of MUS are less clearly integrated into current concepts and models than cognitive and perceptual aspects. However, behavioral features may not only be mere consequences of the disorder, but can also constitute maintaining and even risk factors for its development. The behavioral features have been summarized using the term “abnormal illness behavior” (Mechanic, 1972; Pilowsky, 1969, 1997). One, but only one, aspect of illness behavior is health care use. It has been shown that the different aspects of illness behavior, such as seeking medical investigations, medication and treatment, body scanning, complaining, avoidance behavior, and physical deconditioning are only moderately intercorrelated (Rief, Ihle, & Pilger, 2003). This points to the fact that the individual behavioral features associated with MUS can vary substantially between patients.

Somatization is associated with increased health care costs (Barsky, Orav, & Bates, 2005; Smith, 1994; Smith, Monson, & Ray, 1986). An investigation of more than 1000 patients attending a general medicine clinic as well as some hundred primary care patients, used the “Health Attitude Survey” to assess not only attitudes, but also behavioral aspects of somatization. It was found that somatizing patients showed increased utilization of care, which was comparable to severely ill patients. This was also associated with increased dissatisfaction with care and excessive health worries (Noyes, Langbehn, Happel, Sieren, & Muller, 1999). Frequently, dissatisfaction with care does not lead to cessation of health care seeking, but reinforces the process of seeking better care; a process that increases health care costs.

Fink and others investigated high utilisers of the health care system, and found that about one-fifth of the high utilisers were patients with MUS (Fink, 1992a,b). High frequencies of inpatient admission were associated with mental disorders (adjusted odds ratio = 3.6), especially anxiety, depression, and somatoform disorders (Hansen, Fink, Frydenberg, & Oxhoj, 2002). While these data are based on direct treatment costs, in some countries indirect treatment costs (such as worker compensation, premature retirement etc.) far exceed the direct treatment costs (Hiller, Fichter, & Rief, 2003). As not only somatization, but also depression and anxiety are associated with increased health care use, the question arises whether illness behaviour is specific to one of these syndromes (being apparent in the others because of comorbidity), or whether illness behaviour is an unspecific feature of different psychopathological states (Henningsen, Zimmermann, & Sattel, 2003). In one of our studies, patients with depression could not be differentiated from patients with somatization syndrome on measures of illness behaviour (Rief et al., 2003). Thus illness behaviour in general, and health care use in particular are increased in patients with mental and somatoform disorders. However, in the general population, it has been shown that depression, panic, and somatoform symptoms contribute independently to different aspects of illness behavior (Rief, Martin, Klaiberg, & Brähler, 2005). Therefore the general association between psychopathological states with illness behaviour covers up the specificity of these correlations with sub-features of illness behaviour.

Increased health care use suggests that patients with MUS want something from doctor visits that they are not getting, or that they get only temporarily. One of these aspects is reassurance, which has been postulated to play a major role as a maintaining factor for health anxiety (Salkovskis & Warwick, 1986). These authors emphasize that medical reassurance may have positive short-term effects in reducing health anxiety in hypochondriacs; however, according to the principles of operant learning theory, this effect increases the likelihood of health seeking behaviour, and does not help to reduce health anxiety permanently.

It is widely accepted that medical reassurance can fail (Coia & Morley, 1998; McDonald, Daly, Jelinek, Panetta, & Gutman, 1996). Many doctors assume that explaining that tests have shown no abnormality will sufficiently reassure patients, but this does not work for patients with MUS. Coia and Morley (1998) have shown that patients with high health anxiety scores exhibit only a transient beneficial response to medical reassurance (see also Lucoc, Morley, White, & Peake, 1997). It has been postulated that MUS patients correctly memorized the doctor’s medical explanations in general, but not the likelihood of specific illnesses (Rief et al., 2006). Therefore, usual medical reassurance does not work for patients with MUS. New approaches to reassurance provision in this patient group, and/or the abolition of repeated information, need to be investigated.

The behavioral features of MUS are important because they can be conditioned by positive reinforcement. This has been demonstrated in patients with chronic pain, where the presence of other people increased the likelihood of pain behavior and complaints (Sullivan, Adams, & Sullivan, 2004). In an older study, patients described more complaints if the investigator wore a white coat (Wooley, Blackwell, & Winget, 1978). Thus complaining and other aspects of illness behavior can be reinforced by (expected) positive feedback. Reassurance seeking (from doctors and relatives) can be associated with a negative reinforcement process that maintains health anxieties. These processes demonstrate that illness behavior is not merely a consequence of symptom complaints, but is a mediating factor in symptom
maintenance (see also Cheng, 2000). Consequently, the integration of operant learning principles in the treatment of chronic pain can reduce pain symptoms and pain-associated behavior (Thieme, Gromnica-Ihle, & Flor, 2003). Moreover, illness behaviour can be learned in childhood, as increased rates of health care use in children from parents suffering from somatization disorder have confirmed (Livingston, Witt, & Smith, 1995). However, the overall role of classical and operant conditioning as well as other learning principles in MUS is definitely under-investigated.

Lastly, it has been postulated that avoidance of physical demands can lead to increased body sensitivity and an increased likelihood of experiencing physical symptoms (Rief & Nanke, 1999), as has already been postulated in chronic pain (Asmundson, Norton, & Norton, 1999). Even in subthreshold hypochondriasis, reduced activity levels were reported (Martin & Jacobi, 2006). In this nation-wide study, about 75% of people with hypochondriacal concerns reported less than one hour of physical activity per week, which was significantly different from healthy controls. Avoidance may not only lead to physical deconditioning, but also to interpersonal rewards. To our knowledge, the role of physical deconditioning and avoidance of physical demands in patients with MUS has not been directly investigated, although patients with somatoform symptoms describe reduced activity levels. In patients with chronic fatigue syndrome, physical activity and exercise performance were not different to healthy controls (Bazelmans, Bleijenberg, Van der Meer, & Folgering, 2001). However, the sample size in this study was small (20 subjects per group), and the interaction between physical deconditioning, avoidance behavior, and MUS may be more specific and more individual than postulated in general models. Thus the role of avoidance behavior and physical deconditioning in MUS is unclear.

3.3. Emotional regulation, personality, and attachment

3.3.1. Some comments on alexithymia

Alexithymia represents the most popular emotional regulation approach used to understand MUS. Alexithymia describes the inability to experience and express one’s own feelings, in combination with poor personal imagination, and a technical way of thinking. As alexithymic people do not feel emotions, but only the associated physiological arousal, it has been suggested that the features of emotion-induced physiological activity may be misinterpreted as somatic symptoms (Nemiah, Freyberger, & Sifneos, 1976). The literature on alexithymia is overwhelming, although the major problems are still unsolved: how to assess an ability that does not exist, and how to assess emotions that the person does not feel. Typically, alexithymia is currently assessed with the Toronto Alexithymia Scale TAS (Taylor, Bagby, & Parker, 1992), although a self-rating scale approach to assess alexithymia is questionable. An item-content analysis of the TAS reveals substantial overlap with features of depression and social anxiety. Using the TAS, it has been shown that alexithymic features are increased in patients who experienced traumatic events or body threatening situations (e.g., patients with PTSD, panic disorder, eating disorder; (Bourke, Taylor, Parker, & Bagby, 1992; Krystal, Giller, & Cichetti, 1986; Parker, Taylor, Bagby, & Acklin, 1993; Zeitlin & McNally, 1993; Zeitlin, McNally, & Cassidy, 1993)). Considering this broadly triggered increase of alexithymic features, alexithymia can not only be postulated to be a risk factor for the development of MUS, but also to be a possible coping strategy for people with threatening psychological and physical perceptions.

The association between alexithymia and somatic symptom reporting has been confirmed in some studies (see overview De Gucht & Heiser, 2003). However, when controlling for comorbid depression, the association between alexithymia and somatization sometimes disappears (Rief, Heuser, & Fichter, 1996). Moreover, it has been shown that patients with high scores in the TAS do not use less, but more emotional words; however, they predominantly use negative emotional words, underlining the association of TAS-alexithymia with depression and demoralization. TAS-alexithymia is not only increased in patients with MUS or associated syndromes such as low back pain (Mehling & Krause, 2005), but in most mental disorders. Therefore alexithymia does not seem to be a specific risk factor for somatization, but to be a covariate of mental and psychosomatic disorders in general.

3.3.2. Further aspects of emotion regulation

The role of traumatic experience as a risk factor for the development of somatic complaints and as a influencing factor in emotional regulation has been frequently addressed; some of these aspects are the focus of another article in this special issue and therefore this topic is omitted in this overview.

Somatic complaints are frequently associated with negative affectivity (Watson & Pennebaker, 1989), although the causal relationship is unclear. To help unravel this relationship, an experimental approach used affective pictures before applying a cold pressure task. The results were consistent with the motivational priming model, that unpleasant
affective states enhance pain and that pleasant affective states attenuate it (Meagher, Arnau, & Rhudy, 2001). This has been confirmed by an experiment of Montoya and others (2005) with fibromyalgia patients. The authors used the oddball paradigm and assessed evoked potentials of non-painful somatosensory stimuli, while subjects are either exposed to pleasant or to unpleasant slides. If somatic stimulation took place within an aversive emotional context, abnormal processing of somatosensory information occurred. Compared to patients with pain resulting from identifiable somatic lesions, fibromyalgia patients showed larger P50 and smaller N80 amplitudes when viewing the unpleasant slides. These experiments highlight that negative emotion is not only a consequence of pain, but modulates pain and other somatosensory experience and therefore can be part of a vicious circle.

In another experiment, people with high versus low negative affectivity underwent a gas mixture provocation (with CO2-enriched air), after which subjective complaints were measured (Stegen et al., 1998). In this study, negative affectivity did not predict complaints in response to the gas. The authors suggest that the experimental induction of complaints may largely wipe out differences in attentional and interpretative processes that may mediate the negative affectivity-complaints link. Therefore negative affectivity can be a risk factor for the development of somatic complaints, but other factors can override this effect.

Koh, Kim, Kim, and Park (2005) investigated the relationships between anger expression, depression, and somatic symptoms. Although the data are somewhat inconsistent, the authors interpret the existing literature as confirmation of an association between “anger-out” and depression, while somatoform disorders are more linked to an “anger-in” style. However, the best model fit was found for a model emphasizing the close interrelationship between anger-in and depression, with depression being the major risk factor for somatic symptoms (Bentler’s Comparative Fit Index: 0.98). Although somatoform symptoms seem to have an earlier onset than depressive disorders (Rief, Schaefer, Hiller, & Fichter, 1992), depression and somatization seem to be risk factors for one another. A depressive mood reduces the pain threshold, while somatic complaints increase the risk of developing depressive symptoms.

Some studies have addressed the relationship between medically unexplained symptoms and positive affect or optimism. Fibromyalgia patients show less positive affect, even in longitudinal studies (Zautra et al., 2005). Patients with temporo-mandibular dysfunction and a less optimistic style exhibited lower pain tolerance times and higher pain unpleasantness ratings compared with highly optimistic patients as well as controls (Costello et al., 2002). Optimism was also associated with concentrations of immune parameters (IL-6) and norepinephrine. This study offers links between pain experiences, psychobiological changes, and optimism.

### 3.3.3. Attachment theory

Frequently associated with a psychodynamic understanding of the development of somatoform symptoms, somatization has been linked to theories of early experiences and attachment styles. A review of the literature suggests that somatizing patients display insecure attachment styles, especially the fearful style (Noyes et al., 2003; Stuart & Russell, 1999). The authors hypothesize that this insecure attachment style derives from childhood experiences with care givers. Early exposure to illness also increased the likelihood that anxious attachment behavior was acquired. This insecure attachment style is thought to prime interpersonal interactions in adulthood, including interaction styles with physicians. Somatizers’ interpersonal interactions lead to rejection, which reinforces the belief that he or she will be abandoned (Stuart & Russell, 1999). Investigating patients attending a general medicine clinic, the authors demonstrated that insecure attachment styles were positively correlated with self-reported interpersonal problems, and negatively correlated with patients’ satisfaction with medical care (Noyes et al., 2003). Attachment style, however, is not only correlated with symptom reports, but also with primary care visits and health care costs (Ciechanowski, Walker, Katon, & Russo, 2002). In a large sample of more than 2000 primary care attenders, psychiatric distress, attachment style, and symptom attribution all contributed independently to the presentation of unexplained physical symptoms (Taylor, Mann, White, & Goldberg, 2000).

Attachment theory presents an interesting framework for understanding the communication behavior of patients with MUS. However, it should be kept in mind that most studies so far have been cross-sectional investigations of adults. The theory focuses on early childhood development and can be only scientifically proven with longitudinal studies of young children.

### 3.3.4. Personality

Personality factors are significantly associated with perceptions of poor health. In a representative sample of adults of the United States, openness to experience, extraversion, and conscientiousness were associated with perceptions of
good health, while neuroticism was associated with the perception of poor health (Goodwin & Engstrom, 2002). These associations remain significant after adjustment for age, gender, race, marital status, and education. Therefore it makes sense to investigate personality factors (e.g., using the NEO 5-Factor Inventory) among somatizing patients. As expected, patients with MUS score higher on neuroticism and lower on agreeableness (Noyes et al., 2001). Somatization disorder and MUS in general are also associated with increased base rates of personality disorders. Although sometimes hypothesized, it is not the histrionic personality disorder that is most prevalent in patients with MUS. Patients with MUS show increased rates of fear-avoiding personality disorder, as well as behavioral patterns of distrust and low confidence in others (e.g., schizotype and paranoid personality disorders), and obsessive-compulsive traits (Noyes et al., 2001; Rost, Atkins, Brown, & Smith, 1992). These personality features are in accordance with the frequently described communication problems that these patients have with their relatives and their physicians. Physicians and therapists have to keep in mind that the establishment of a stable relationship needs more effort in patients with MUS (Rief & Nanke, 2004).

4. Integration of evidence-based mechanisms

Most models of medically unexplained symptoms emphasize the role of cognitive factors. There is some evidence that patients with MUS over-interpret physical sensations as possible signs of illnesses. Patients with hypochondriasis have demonstrated an over-exclusive concept of health, although this has not been clearly shown in patients with MUS in general. One aspect of cognitive models for patients with MUS definitely needs to be modified: patients with MUS do not have simplistic, monocular organic explanations for physical sensations, but show a broad variety of causal illness models. It seems that organic causal explanations are over-represented in patients with MUS, and they are also correlated with increased health care use. However, patients with MUS and comorbid mental disorders also have psychological symptom attributions that tend to lie in the background if concurrent organic explanations exist. Current concepts about mechanisms and treatment should be modified to respect these findings.

Selective attention to bodily processes is also postulated to play a major role in MUS. However, the experimental approaches used to assess selective attention in this group are less convincing and mostly limited to the modified Stroop paradigm. The results on selective attention using this paradigm are not as clear as expected. However, some older psychophysiological studies using evoked potentials (Gordon et al., 1986; James et al., 1990, 1987), as well as modern approaches demonstrating the role of selective attention and distraction using fMRI, underline the relevance of this concept for MUS. There is a need for more sophisticated approaches to selective attention to investigate this important link between psychological concepts and sensory processes.

Some newer studies emphasize the role of expectations and memory processes -mechanisms that are not well integrated in current concepts on MUS. The expectation of symptoms activates brain areas that are associated with sensory perception, even if the stimulation is only expected, not provided. This is proof of symptom-corresponding brain activation without external stimulation. Although the results of a possible memory bias are equivocal, it seems that the memorized likelihood of medical explanations for physical complaints is erroneous in these patients. Even if the doctors reject medical explanations for the symptoms completely, patients still remember an increased probability of these medical explanations. This could be one of the reasons why medical reassurance fails and does not show long-term benefits. Non-successful medical reassurance can be a source of problems in the medical encounter, which can lead to unsatisfactory treatment courses for both parties.

Illness worry and health anxiety are further factors that may increase symptom reports. While this has been shown in many studies, it is unclear whether all patients with MUS have increased illness worry and health anxiety. There is clinical evidence that some patients do not show increased scores for health anxiety, although the symptoms persist. However, in the case where health anxiety is a prominent feature of a patient’s syndrome, it plays a clear role in changing symptom perception, symptom attribution, and health care use.

These cognitive features interact with behavioral aspects. The major focus of studies on behavioral aspects so far has been health care use, which is increased in MUS, but also in depression and anxiety disorders. Other behavioral features of MUS are seeking medical reassurance, body scanning, verification of diagnosis, seeking medical treatment and others. These behavioral features show only medium intercorrelations. Thus while some patients with MUS seek diagnosis verification when visiting a doctor, others expect prescription of drugs, and still others expect emotional support for the associated disability. Therefore it is a challenge for the health care system to react differently to these different needs of patients with MUS. If the health care system reacts in a unique way to different needs of patients, increased health care use is partly iatrogenic.
Behavioral aspects are also important in operant conditioning of illness behavior, confirmation of health attitudes, and the development of physical deconditioning. While these aspects could be of major importance for this patient group, their role has been insufficiently investigated in scientific trials.

There is a close interaction between emotional processes and MUS. Negative affectivity is associated with reduced pain thresholds and increased symptom reports. Therefore the high comorbidity between MUS and depression is of major importance. However, whether alexithymia plays a specific role in MUS, or is a general feature of psychopathological states, or is not adequately assessed by existing instruments, is still an open question. Emotion regulation and communication patterns can be the result of former social experiences, which might be associated with specific attachment styles. Most approaches in this area have so far been based on cross-sectional studies; therefore their relevance in the process of symptom development is unclear. An extreme form of emotion regulation is triggered by traumatic experiences. Although not addressed in this paper, some studies indicate that trauma is not only a general factor in the development of psychological problems, but also an additional specific factor in the development of medically unexplained symptoms. Moreover, trauma is also associated with increased health care use, even if no MUS are present.

The psychological mechanisms involved in MUS interact with biological processes that modulate symptom perception, such as HPA axis and immunological activities. Symptom perception is essentially a cerebral process. Therefore, the psychological and biological mechanisms are not competing models, but should be integrated into a comprehensive model of medically unexplained symptoms. Table 1 presents a summary of the psychological mechanisms and some of the psychobiological mechanisms that contribute to our understanding of MUS and are discussed in this article.

Finally, we also have to acknowledge that most studies cited in this paper were either based on the investigation of chronic conditions (e.g., somatization disorder) or on general population data. However, we need more information on

<table>
<thead>
<tr>
<th>Possible precursors of medically unexplained symptoms</th>
<th>Sample reference</th>
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<tr>
<td>Over-exclusive concept of health</td>
<td>Barsky et al. (1993)</td>
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<tr>
<td>Traumatic experiences</td>
<td>Golding (1994)</td>
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<tr>
<td>Family member with chronic illness during childhood</td>
<td>Stuart and Russell (1999)</td>
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<tr>
<td>Attachment style, neuroticism</td>
<td>Noyes et al. (2003)</td>
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<tr>
<td>Former experiences with pain and symptoms</td>
<td>Bayer et al. (1997)</td>
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<td>(Modern) health worries</td>
<td>(Noyes, Carney, Hillis, Jones, &amp; Langbehn, 2005; Petrie et al., 2005; Winters et al., 2003)</td>
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Aspects of symptom development and maintenance

<table>
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<tr>
<th>Mechanism</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Increased awareness of physical sensations; body scanning</td>
<td>Rief, Hiller et al. (1998)</td>
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<tr>
<td>Perception of physical sensations; sensory filtering problems (see EEG studies)</td>
<td>James et al. (1990)</td>
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<td>Attribution of physical sensations as possible illness signs</td>
<td>Hitchcock and Mathews (1992)</td>
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<tr>
<td>Missing distraction</td>
<td>(Bantick et al., 2002; Pennebaker, 1982)</td>
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<tr>
<td>Expectation of physical sensation</td>
<td>Lorenz et al. (2005)</td>
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<td>Generalization of triggering stimuli</td>
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<td>Health anxiety, illness worry</td>
<td>Jackson and Passamonti (2005)</td>
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<td>Erroneous memory for illness probabilities</td>
<td>Riefet al. (2006)</td>
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<tr>
<td>Negative doctor-patient encounter is associated with failing reassurance;</td>
<td>Rief and Nanke (2004)</td>
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<td>dissatisfaction increases health care use</td>
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<tr>
<td>Multiple causal illness beliefs, but organic explanations dominate the scene and predict health care use</td>
<td>Rief, Nanke et al. (2004)</td>
</tr>
<tr>
<td>Partners (and doctors?) confirm organic illness beliefs</td>
<td>Butler et al. (2001)</td>
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<tr>
<td>Operant conditioning of illness behaviour and reassurance seeking</td>
<td>(Salkovskis &amp; Warwick, 1986; Sullivan et al., 2004)</td>
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<tr>
<td>Negative affectivity reduces symptom tolerance</td>
<td>Meagher et al. (2001)</td>
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<tr>
<td>Neural sensitisation, reduced neural filtering, brain plasticity</td>
<td>Basbaum and Jessell (2000)</td>
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<td>Development of &quot;pain and symptom schemata&quot; in the brain</td>
<td>Pineus and Morley (2001)</td>
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<tr>
<td>Chronic stress conditions and immunological aberrations are associated with hyperalgesia and illness behaviour</td>
<td>Fries et al. (2005)</td>
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<tr>
<td>Involvement of the serotonergic system in pain perception</td>
<td>(Basbaum &amp; Jessell, 2000; Rief, Pilger et al., 2004; Russo et al., 2003)</td>
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the process of symptom development and development of chronicity. Therefore incident cases and subthreshold developments should be considered more frequently in scientific trials.

5. Conclusion: strengths and empirical validation of the models

In the light of this overview on empirical data, the different models presented in part two of this article show specific strengths and weaknesses. The strength of Barsky’s model is its simple formulation, and it can even be used to explain the disorder to patients. The basic mechanisms used in this model, such as attention, perception, and attribution processes have some empirical validation, although the model neglects many other well-validated factors, or offers only indirect explanations for them. It is definitely anxiety-focussed, although hypochondriasis and health anxiety are not necessarily associated with MUS. Therefore the model might best fit for anxiety-related symptoms, such as cardiovascular complaints.

Kirmayer’s model extends the pure perception-amplification process described in Barsky’s model, and includes social-interactional factors (help-seeking, social responses, health care regulations and behaviour of health care providers, cultural influences). Moreover, emotional factors (distress, demoralization) are also considered. In contrast to Barsky’s model, people in Kirmayer’s model can only develop MUS with the influence of others, reinforcing their illness behaviour, perception or attribution. At this point, the two models make different predictions. The role of depression and demoralization are important factors to consider, as they perpetuate the perception of physical sensations and pain experiences. A weakness of Kirmayer’s model is its pure descriptive approach. It does not really attempt to explain processes and interactions, but primarily describes them.

Brown’s model and our perception-filtering-model are in line with the findings on the relevance of memory processes and expectation, two empirically well-founded mechanisms not directly included in the other models (although the other models can be easily expanded to include these mechanisms). Further strengths of these two models are their close relationship to the neuronal process of perception. Therefore they offer a link between psychological and psychobiological findings on MUS. Our perception-filter-model makes clear assumptions about the stage where other factors influence the perception process. These assumptions can be further tested using for instance brain imaging techniques. As the model shows parallels to the gate-control-theory formulated for pain, it might best fit pain symptoms, but needs much more empirical foundation.

All models have some weaknesses in common. It seems that the role of organic causal attributions is over-emphasized. This is a prominent feature in some, but not all patients with MUS; other patients suffer from these complaints although they consider many non-organic explanations. Moreover, in some cases rigid organic attributions are a result of doctor-patient-interactions and can be considered a negative consequence, rather than a predisposing factor. And finally, fears about threatening organic origins may be a general feature of humans suffering new symptoms, and not a specific condition of symptom development in MUS.

The dynamics of doctor-patient-interaction need to be further specified. Clearly there are multiple risks of misunderstandings during the medical encounter, but these need to be more specifically understood. The role of coping strategies is also unclear. Receiving news that doctors do not have a remedy for painful symptoms is a challenge to individual and social adaptation processes, and these processes need to be further explored. This overview has summarized the progress we have made towards explaining medically unexplained symptoms, but also highlighted the need for further research.

References


