



The cognitive behavioural model of medically unexplained symptoms: A theoretical and empirical review

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Abstract

The article is a narrative review of the theoretical standing and empirical evidence for the cognitive behavioural model of medically unexplained symptoms (MUS) in general and for chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS) in particular. A literature search of Medline and Psychinfo from 1966 to the present day was conducted using MUS and related terms as search terms. All relevant articles were reviewed. The search was then limited in stages, by cognitive behavioural therapy (CBT), condition, treatment and type of trial. Evidence was found for genetic, neurological, psychophysiological, immunological, personality, attentional, attributional, affective, behavioural, social and inter-personal factors in the onset and maintenance of MUS. The evidence for the contribution of individual factors, and their autopoietic interaction in MUS (as hypothesised by the cognitive behavioural model) is examined. The evidence from the treatment trials of cognitive behavioural therapy for MUS, CFS and IBS is reviewed as an experimental test of the cognitive behavioural models. We conclude that a broadly conceptualized cognitive behavioural model of MUS suggests a novel and plausible mechanism of symptom generation and has heuristic value. We offer suggestions for further research.

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Contents

1.	Introduction: defining terms	0
2.	The model	0
3.	Components of the CBT model for medically unexplained symptoms.	0
3.1.	Predisposing factors.	0
3.1.1.	Genetics and early experience	0
3.1.2.	Neuroticism and somatopsychic distress	0
3.2.	Perpetuating factors	0
3.2.1.	Sensitisation	0
3.2.2.	Attention — cognitive activation and behavioural inhibition	0

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3.2.3.	From attention to attribution and beliefs	0
3.2.4.	Response to illness	0
3.3.	The straws that break the camel’s back — precipitating factors.	0
4.	The coherence of the model	0
5.	Treatment studies	0
5.1.	General MUS	0
5.2.	Chronic fatigue syndrome	0
5.3.	Irritable bowel syndrome	0
6.	Summary, conclusions and recommendations	0
6.1.	The model	0
6.2.	Treatment	0
	References	0

1. Introduction: defining terms

“The term medically unexplained symptoms names a predicament, not a specific disorder” wrote [Kirmayer, Groleau, Loooper, and Dao \(2004\)](#). In the papers we have reviewed it is used in three overlapping ways: (a) to refer to the occurrence of symptoms in the absence of obvious pathology; (b) to refer to individual clinical syndromes such as chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS); (c) to refer to a subset of the DSM-IV somatoform disorders category. Whilst classification remains disputed (for details see the Introduction to this special issue), there is consensus that a cognitive behavioural therapy (CBT) approach offers a useful explanatory model of MUS ([Neimark, Caroff, & Stinnett, 2005](#); [Mai, 2004](#)) and an effective treatment ([Kroneke & Swindle, 2000](#); [Raine et al., 2002](#)). These recent reviews have validated the efficacy of CBT, but there has been less focus on the model on which these treatments are based. This narrative review will focus primarily on the theoretical standing and empirical evidence for the CBT model of MUS, and for the specific CBT models for IBS and CFS. We will then summarise the evidence for its effectiveness as a treatment with a view to how this evidence can contribute to our evaluation of the CBT models. Finally we will suggest areas for further research and development.

For the purposes of our literature search we adopted a broad definition of MUS. We used MUS to refer to itself as a term (“medically unexplained symptoms”), to individual syndromes and to some of the subcategories of somatoform disorder. From somatoform disorders we excluded hypochondriasis, conversion, pain and body dysmorphic disorders. Of the individual syndromes we looked specifically at IBS and CFS. Pain was largely excluded because the scope of the literature would have made the review unwieldy. In addition to the aforementioned subcategories and disorders, we employed the search terms: functional symptoms; functional syndromes; functional illness; functional somatic symptoms; functional somatic syndromes; functional somatic illness and medically unexplained illness. Searches were made of Psychinfo and Medline from 1966 to the present and the Cochrane database. As a first analytic step, we reviewed all the abstracts and reports obtained by using “Medically (near) Unexplained (near) Symptoms” as a search term. We then cross-referenced this and all the above terms with cognitive therapy; behavio(u)r(al) therapy and cognitive behavio(u)r(al). All abstracts were reviewed and this material was used to conduct the narrative review of the CBT model of MUS which forms the bulk of this paper (Sections 2–4). The search was then further limited to meta-analyses, clinical trials, randomised trials, randomised control trials and controlled clinical trials. This review of the clinical trials was performed with particular regard as to how this body of evidence contributed to our understanding of the model (Section 5). Relevant citations from papers identified were followed up and colleagues were asked to identify any other relevant sources.

2. The model

Historically, the classical CBT model of emotional distress as proposed by Beck distinguished between its developmental predispositions and precipitants, and its perpetuating cognitive, behavioural, affective and physiological factors ([Beck, 1976](#)). The CBT model of MUS retains this general structure and its “three Ps”: predisposing, precipitating and perpetuating factors (see for instance [Sharpe, 1995](#); [Suraway, Hackmann, Hawton, & Sharpe, 1995](#); [Richardson & Engel, 2004](#); [Hutton, 2005](#)). Treatment tends to initially focus on the perpetuating cycle, attempting to

dismantle the self maintaining interlock of cognitive, behavioural and physiological responses hypothesised to perpetuate the symptoms. The approach is very similar to Lang, Melamed, and Hart's (1970) three system model of fear maintenance and desensitisation. The *sine qua non* of any CBT model is a vicious circle, the hypothesis that a self perpetuating interaction between different domains maintains symptoms, distress and disability. Irrespective of the symptom type (as Allen, Escobar, Lehrer, Gara, & Woolfolk, 2002, noted, none of the theories are organ specific), the CBT models of MUS, IBS and CFS propose a model of perpetuation that is, to borrow a term from systems theory and cell biology, *autopoietic*.

“Autopoiesis: the process whereby an organization produces itself. An autopoietic organization is an autonomous and self-maintaining unity... The components, through their interaction, generate recursively the same network of processes which produced them” Valera (2005).

The CBT model of perpetuation differs from a more generic biopsychosocial model (see Wade & Halligan, 2004) by proposing a unique autopoietic interaction of cognitive, behavioural and physiological factors for each individual. This model is essentially a hypothesis of a novel mechanism for the generation of physical symptoms in the absence of physical pathology or psychopathology. Several of the papers reviewed here propose such an autopoietic model of symptom perpetuation (Barsky & Borus, 1999; Kolk, Hanewald, Schagen, & Gijsbers van Wijk, 2003; Brown, 2004; Kirmayer et al., 2004; Richardson & Engel, 2004; Rief & Barsky, 2005; Ursin, 2005). All assume that symptoms are generated or maintained not by one specific disease process but by the interaction of factors in distinct domains. Whilst each of these authors give different weights to different domains, some emphasising cognitive process, others physiological, they have in common the implicit notion that a multi-factorial autopoietic cycle lies at the heart of the experience of symptoms. All models which propose such a process will be considered, for the purposes of this review, as examples of the cognitive behavioural model of MUS. In the following, we will first review evidence for the involvement of processes in these separate domains and then turn to look at evidence for their autopoietic interaction in MUS.

3. Components of the CBT model for medically unexplained symptoms

3.1. Predisposing factors

3.1.1. Genetics and early experience

This is one of the least researched parts of the model. There is some evidence for a genetic influence in the development of both unexplained fatigue and somatisation (Kendler et al., 1995; Farmer, Scourfield, Martin, Cardno, & McGuffin, 1999; Hickie, Kirk, & Martin, 1999); however this could simply reflect the expression of an inheritable predisposition to general distress (see Section 3.1.2 below). There is also some evidence that certain types of early childhood environment increase the risk of developing MUS. Hotopf (2003) reported that childhood experience of paternal illness could be a risk factor, and highlights the possibility that vicariously learned illness behaviour could later serve to perpetuate symptoms (see also Hotopf, Wilson-Jones, Mayou, Wadsworth, & Wessely, 2000). This may also explain Fisher and Chalder's (2003) observation that adult CFS sufferers report their parents as having been over-protective; there is some evidence for this learned illness behaviour in IBS (Lackner, 2005). A number of researchers have reported evidence that childhood adversity in the form of physical or sexual abuse is a risk factor for MUS in general (Fiddler, Jackson, Kapur, Wells, & Creed, 2004), IBS (Hazlett-Stevens, Craske, Mayer, Chang, & Naliboff, 2003; Lackner, 2005), CFS (Taylor & Jason, 2001), fibromyalgia (Walker et al., 1997) and somatisation disorder (Morrison, 1989). This may be linked to the sensitisation mechanisms discussed below. The large scale longitudinal studies that would allow for more robust conclusions are lacking.

3.1.2. Neuroticism and somatopsychic distress

Neuroticism (*N*) as a personality trait refers to a stable life long tendency to experience negative affect. Watson and Pennebaker (1989) suggested it be seen not just as psychological trait but as a more general predisposition to experience “somatopsychic distress.” There is good evidence for the lifespan stability of this trait, with a median stability co-efficient for *N* of at least 0.6 (McCrae et al., 2000). There is also good evidence relating *N* to both anxiety and depression (Matthews, Deary, & Whiteman, 2003); to heightened reactivity to stressors (Bolger & Schilling, 1991); to increased incidence of objectively measured negative life events (Magnus, Diener, Fujita, & Pavot, 1993); and to poor prognosis in depression (Surtees & Wainwright, 1996). It is also associated with increased incidence of physical illnesses such as

Asthma (Huovinen, Kaprio, & Koskenvuo, 2001); poorer prognosis following Coronary Heart Disease (CHD) and increased risk of cardiac events (Denollet & Van Heck, 2001); and with the occurrence of multiple physical ailments such as CHD, hypertension and gastro-intestinal illness (Matthews, Yousfi, Schmidt-Rathjens, & Amelang, 2002). *N* emerges from this data as being an important predictor not of specific pathologies, but of a generic vulnerability to physical illness and psychological distress.

Given the above it is hardly surprising to find that high *N* is also associated with MUS. High *N* has been demonstrated in functional dysphonia (Deary, Scott, & Wilson, 1997); in Irritable Bowel Syndrome (Hazlett-Stevens et al., 2003); CFS (Deary, 2001); and in general MUS (Costa & McCrae, 1987; Kirmayer, Robbins, & Paris, 1994; De Gucht, Fischler, & Heiser, 2004a; De Gucht, Fischler, & Heiser, 2004b). The aspects of perfectionism associated with CFS (White & Schweitzer, 2000; Deary, 2001) are the “negative” self critical aspects which are also positively correlated to *N*. Neuroticism could potentially provide a parsimonious explanation of diverse findings. For instance, the genetic component of MUS could be partly explained by *N*, which has a heritability of around 50% (Matthews et al., 2003). The consistently high association between MUS, anxiety and depression could be a manifestation of an underlying tendency to experience somatopsychic distress. Indeed in their meta-analyses of several medically unexplained syndromes and their associated levels of anxiety and depression, Henningsen, Zimmermann, and Sattel (2003) reached just this conclusion (see below).

N is also associated with several mechanisms that the CBT model hypothesises are involved in symptom perpetuation. It is correlated highly with harm-avoidance (Cloninger, 1987); ease of response suggestibility and conditioning to noxious stimuli, and increased generalisation of conditioned response (Van den Bergh, Winters, Devriese, & Van Diest, 2002); increased experience of physical symptoms post vaccination (Petrie, Moss-Morris, Grey, & Shaw, 2004); biased attention to somatic danger signals such as pain or fear (Matthews et al., 2003); compromised immune functioning (Marsland, Cohen, Rabin, & Manuck et al., 2001); increased incidence of negative life events (Magnus et al., 1993; Kendler, Gardner, & Prescott, 2003); and a heightened stress response to adverse life events (Bolger & Schilling, 1991). All of the foregoing factors have been proposed as factors in the precipitation or perpetuation of MUS. *N*, which is higher on average in females than males, might also partly explain the female preponderance of MUS, (see Van Diest et al., 2005, for a full discussion of this.).

Closely linked to this notion of a predisposing “distress proneness” are the associations between MUS, anxiety and depression. Henningsen et al. (2003) found that MUS are consistently positively correlated with high levels of anxiety and depression. They concluded: “In our view, it is most parsimonious to interpret the findings as implying that medically unexplained physical symptoms are best described as constituting one dimension of common distress symptoms and disorders alongside depression and anxiety” (p. 532).

3.2. Perpetuating factors

The CBT model proposes that cognitive and behavioural factors interact with physical factors to produce symptoms (Lang et al., 1970). There has been much promising work in recent years investigating mechanisms other than physical pathology that might be partly responsible for perpetuating MUS.

3.2.1. Sensitisation

Sensitisation refers to the tendency to have a heightened response to stimuli because of prior experience of them. For instance, in animals the prior experience of stressful stimuli lead to increased physiological and behavioural responses to future stressors, and to increased incidence of physical pathology, particularly if the initial stressors were uncontrollable and unpredictable (Overmier & Murison, 2005). Rygh et al. (2005) has studied a specific sensitisation mechanism – long term potentiation (LTP) – in humans. LTP can be induced in pain pathways by prior experience of pain or noxious stimulation which lowers the threshold for future stimulation. Rygh et al. (2005) suggested that central mechanisms such as vigilance and attention, or the effects of anxiety, depression or stress, may dampen inhibition of these pathways, lowering the threshold yet further. This could lead to normally benign sensations being experienced as pain, leading in turn to further sensitisation and vigilance. Here we have the rudiments of an autopoietic mechanism maintaining the experience of pain. LTP also illuminates other findings (e.g. Heim, Ehlert, Hanker, & Hellhammer, 1998) that previous physical trauma leads to increased pain sensitivity. Rygh goes so far as to speculate that in as much as LTP is the cellular substrate of learning and memory, cognitive behavioural therapy works by changing synaptic potentiation in the brain. There is limited evidence for such

sensitisation processes in IBS (see Lackner's (2005) review) and in fatigue patients (Stubhaug, Tveito, Eriksen, & Ursin, 2005).

3.2.1.1. The HPA axis and sensitisation. Physical and emotional stress in humans causes a hormonal cascade beginning in the hypothalamus, passing to the pituitary and ending with the increased production of cortisol from the adrenal cortex. Within this system – the hypothalamus pituitary adrenal axis (HPA axis) – both positive and negative feedback loops exist to regulate the body's response to acute and chronic stress. The HPA axis alters energy metabolism, influences immune functioning and affects both energy and mood with, for instance, high levels of cortisol being consistently found in major depression. Low cortisol has been found in patients with CFS (Roberts, Wessely, Chalder, Papadopoulus, & Cleare, 2004), fibromyalgia and low back pain (Griep et al., 1998) and also in PTSD (Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004). One interpretation is that prolonged activation has led to a “burnout” response and a down regulation of HPA activity in these disorders. This down regulation may lower the threshold for stress sensitivity.

Fries, Hesse, Hellhammer, and Hellhammer (2005) proposed a developmental model along these lines: prolonged stress leads to HPA axis down regulation and reduced cortisol production. This hypocortisolism is marked by a “symptom triad” of pain, fatigue and stress sensitivity. Further, there are indications that lowered cortisol could lead to increased release of inflammatory cytokines, potentially important determinants of the “illness response”, characterised by lassitude and behavioural avoidance. Finally they suggested that hypocortisolism may in fact be an adaptive response that produces stress avoidance, energy conservation and physical recuperation. Dantzer (2005) developed this hypothesis yet further, suggesting that there are two kinds of stress response, one related to anxiety and the other to depression (see also Maier & Watkins, 1998). The latter is the “recuperative system” described above, associated with defensive withdrawal and reduced activity. Dantzer suggested that this essentially adaptive system can become triggered by more generic danger signals and stressors, and can become sensitised to non-pathogenic input, in a way analogous to the fear response in anxiety. He concluded that “all the necessary ingredients are there for a renewed biopsychological approach to somatisation and somatoform disorders” (p. 951).

Cleare (2004) has reviewed the evidence for HPA axis involvement in CFS. Whilst there is evidence for an increased sensitivity to the negative feedback effect of glucocorticoids in the HPA axis, and for reduced ACTH and cortisol responses, there is no obvious HPA axis dysfunction. Rather a varied picture of HPA axis alteration emerges which could have multiple determinants, such as sleep dysregulation, stress, psychiatric co-morbidity etc. Gaab et al. (2005) reported a similarly heterogeneous and inconclusive picture. They suggested, from their research, that their may be “an enhanced perception of cytokine-induced symptoms” possibly due to sensitisation of the HPA axis.

3.2.2. Attention — cognitive activation and behavioural inhibition

Rief and Barsky (2005) acknowledged Dantzer's research but noted that whilst there is some evidence that immune changes can induce behaviour change, it is “unclear whether this causality can also be bi-directional and whether it contributes especially to the development and maintenance of somatoform symptoms in humans.” They observed that the biological findings in patients with MUS are highly varied and do not yet present a consistent and coherent picture. Whilst there is some evidence of increased autonomic arousal and of delayed recovery of the stress response, these findings vary between conditions and between different phases of the same condition. Therefore rather than anchor their explanation to a particular bodily system, Rief and Barsky (2005) proposed a more generic model in which symptoms arise through a two stage process of generation and selection. At the first stage, bodily symptoms may be generated by multiple determinants including over-arousal, chronic stressors, HPA activity, sensitisation etc. At the second stage a hypothetical filter system selects symptoms for conscious attention. This selective process will in turn have multiple determinants: health anxiety, depression, lack of distraction, uncertainty as to origin of symptom etc. These contribute to “faulty filtering” and increased symptom perception. Brown (2004) has suggested a similar model which emphasises the roles of attention, mis-attribution and mis-interpretation in the maintenance of MUS.

It is to this “filter system” that we now turn. It is a notable observation that of all the sensations constantly processed by our bodies, very few reach our conscious attention. Most of the activity of our body is monitored and orchestrated unconsciously by more or less automatic mechanisms. These form the so-called “cognitive unconscious” which is the focus of the rapidly growing body of psychological research and theory known as embodied cognition. Shaun Gallagher's recent book (2005) presents an exhaustive survey and synthesis of this new field of study. One of the key hypotheses of this perspective is that conscious awareness plays very little part in our daily activities. Mostly our body and its processes run

on automatic and remain experientially transparent, passing below the radar of attention. However occasionally physiological or cognitive changes can bring to the foreground processes and sensations that would normally escape notice. “Such hyper-reflection can generate a body image that exaggerates proprioceptive and kinaesthetic sensations, and interferes with the normal functioning of the normally tacit body schema” (p. 205) (Gallagher, 2005).

It is precisely this kind of mechanism that has been suggested to be at work in MUS in conjunction with the sensitisation processes described above. Ursin (2005) noted that “cognitive bias is a higher form of sensitisation... anxious people detect fear related stimuli at a lower threshold than normal controls.” Ursin’s model is based on his notion of a Cognitive Activation System (CAS) which, in response to threat or stress, produces a state of arousal “which is sustained until the source of stress is eliminated” i.e. until some instrumental action is taken to deal with the stressor. This model is similar to Gray’s (1991) Behavioural Inhibition System (BIS) which was proposed to be specifically oriented to aversive, fearful and novel stimuli, producing arousal, behavioural inhibition and selective attention to the stimuli. In both models the first function of the system is to stop other ongoing activity and to re-orientate attention to the threat/stressor/symptom. The arousal, as well as enabling action, acts as a motivational negative reinforcement: the person acts to reduce their aversive state of arousal. These ideas may be of considerable relevance to our understanding of MUS. Prolonged activation of the CAT/BIS could serve to generate symptoms through the physiological processes described above (see also Thayer, Pieper, & Brosschot, 2005). These symptoms in turn may become novel aversive stimuli and thereby produce further arousal. Selective attention is then directed to symptoms and to the thoughts associated with them. A cognitive bias develops for symptoms, further amplifying them which serves to further sensitise “the neural loops supporting cognitive rumination... pain and illness lead to more pain and illness” (Ursin, 2005). These models are notably similar to Barsky and Borus’s (1999) somatosensory amplification and Rief and Nanke’s (1999) cognitive-psychobiological framework.

3.2.2.1. Evidence for attentional processes. The attentional models point to individual differences in attentional biases with respect to threatening stimuli as a factor in MUS. The findings of positive correlations between threat sensitivity, *N*, conditionability, negative affectivity and MUS (MacCleod & Matthews, 1988; Derberry & Reed, 1994; De Gucht et al., 2004b; Petrie et al., 2004) are supportive of this hypothesis. However is there any more direct evidence that attention is a factor? Rief, Hiller, and Margraf (1998) have reviewed some of the literature on cognition and attention. Whilst drawing the conclusion that attention is an important variable, most of the studies linked attention to attribution. Individuals who either perceived themselves as more vulnerable or the symptom as more threatening were more likely to pay attention to the symptoms. Experimentally, attention is a hard variable to isolate. There have been some experimental tests (Pennebaker & Skelton, 1981; Barsky, Goodson, Lane, & Cleary, 1988; Lautenbacher, Pauli, Zaudig, & Birbaumer, 1998) indicating that distraction ameliorates and attention intensifies physical symptoms. Using functional brain imaging Bantick et al. (2002) found that distraction did decrease activity in pain related brain areas.

In CFS a recent trial found that the effect of treatment appeared partly to be attributable to a decreased attention to the symptoms (Moss-Morris, Wash, Tobin, & Baldi, 2005), whilst in IBS Lackner’s (2005) review found some evidence that cognitive processes, such as threat sensitivity, may influence these visceral attentional processes, amplifying pain and normal sensation.

Overall, whilst attention seems to be important it has been hard to isolate this process from attributions, unhelpful illness beliefs, medical uncertainty and other factors which may serve to focus attention onto symptoms. It is to this work that we now turn.

3.2.3. From attention to attribution and beliefs

Kolk et al. (2003) have, in an excellent review, attempted to marshal the data on attention and attribution into a coherent model. Drawing on the work of Pennebaker (1982), Cioffi (1991) and Kirmayer and Taillefer (1997), they have suggested a Symptom Perception Model of MUS, in which negative affectivity, selective attention and somatic attributions are hypothesised as the key factors determining the experience of common physical symptoms. Evidence for the model was obtained by Kolk et al. in a prospective test of 151 patients, one of few attempts to prospectively test a theoretical model and hypothesised inter-relationships between variables.

Other research has studied the relationship of attribution to illness behaviour and outcome (Sensky, MacLeod, & Rigby, 1996; Moss-Morris & Petrie, 2001; Kolk, Schagen, & Hanewald, 2004; Rief, Nanke, Emmerich, Bender, & Zech, 2004; Henningsen, Jakobsen, Shiltenswolf, & Weiss, 2005). There is a broad consensus that making organic illness attributions, lack of normalising attributions and high estimates of personal vulnerability predict increased

symptom experience and illness behaviours such as expression of symptoms and seeking treatment, whereas psychological or mixed somatic and psychological attributions predict better symptom outcomes. Those with more symptoms are more likely to make mixed attributions. A tentative conclusion from the research would be that it is the fixity and exclusivity of somatic attribution, rather than just its type, which contributes to symptom perpetuation.

Kirmayer et al. (2004) adopted a more qualitative approach to attribution and looked at it from the viewpoint of illness narratives — how do people explain symptoms to themselves? This approach is notable for eliciting multifaceted attributions, with individuals from different cultures making sense of their symptoms through complex narratives that involve social, emotional and physical processes. A key finding from their work is that any narrative is better than none; those who could not make sense of their symptoms in some way were the most distressed, and reported the least benefit from the interview process. Kirmayer's work highlighted what Henningsen et al. (2005) also mention in their study: that is the paradox that much research on attribution operationalises the mind/body dichotomy that is otherwise decried by the researchers themselves. Patients are usually divided into psychologisers or somatisers. Whilst patients who are multi-symptomatic tend to make multi-factorial attributions, the current models tend to limit them to just two often mutually exclusive styles. This cognitive bias on the researchers part needs to be challenged in future research.

Illness attributions are often worked out with, or in spite of, the medical profession, and several authors have looked at the part this interaction can play in the development and maintenance of MUS. Simon, VonKorff, Piccinelli, Fullerton, and Ormel (1999), Nimnuan, Hotopf, and Wessely (2000), Dowrick, Ring, Humphries, and Salmon (2004), Gureje (2004) and Salmon, Dowrick, Ring, and Humphries (2004) have all highlighted how a poor or absent relationship with the general practitioner can lead to increased symptom reporting and repeat consultations. Hotopf (2004) has compared the role of doctors in MUS to that of parents of sick children. Both can reinforce unhelpful illness behaviour and symptom interpretations.

Illness related beliefs have also emerged as potentially important factors in the maintenance of symptoms. Deale, Chalder, and Wessely (1998) showed that beliefs about the harmful effects of activity were related to poorer outcome in CFS. The hypothesis from this is that the beliefs inform behaviour, in this case activity avoidance, which in turn affects physiology and symptoms, providing the rudiments of a vicious circle of symptom maintenance. The link between beliefs and behaviour is further evinced in the IBS research (Lackner, 2005) where catastrophic beliefs about symptoms have been shown to contribute to behavioural avoidances and thus, potentially, anxiety and symptom maintenance through operant conditioning. It is to the research on behaviour that we now turn.

3.2.4. *Response to illness*

Several authors have observed that it is not just the illness, but one's response to it that matters. For instance, Candy, Chalder, Cleare, Wessely, and Hotopf (2004) reported that following glandular fever a graded return to activity predicted a lower chance of developing CFS than rest. Hotopf, Noah, and Wessely (1996) found that later fatigue was positively associated with length of convalescence. In a similar study Spence, Moss-Morris, and Chalder (2005) examined coping behaviour in 758 *Campylobacter* patients and found that IBS at 6 months was associated with 'all or nothing' coping behaviour at baseline. As these authors have noted, there is actually relatively little literature concerning illness responses, despite a clinically prevalent belief that 'all or nothing coping' and avoidance behaviours are important in the onset and perpetuation of syndromes such as CFS. In chronic pain avoidance has emerged as equally a potent predictor of disability as pain (Rief & Nanke, 1999). More longitudinal work of this nature is needed to clarify the role of behaviour in the development of MUS.

In the literature it is often difficult to disentangle the factors so far presented: sensitisation, attention, attributions, beliefs and behaviour are theoretically and experimentally difficult to isolate from each other as distinct processes. Sensitisation may be linked to attention which may in turn be informed by beliefs which may affect behaviour, and so on. As such the research offers a kind of de facto support for the *spirit* of the CBT model, which proposes precisely this sort of interaction. However failure to experimentally isolate processes is not equivalent to evidence for their interaction, and more work is needed on both individual factors and their interaction before we can form more definite conclusions.

3.3. *The straws that break the camel's back — precipitating factors*

Finally we turn to the last link in the CBT model, the event or events that are hypothesised as triggering the start of the self-perpetuating cycle we have sketched the evidence for above. The main topic that has been studied here has been

'life events'. This is a field too large to summarize comprehensively, but we can address the key question – do life events precipitate MUS? – with a fairly unequivocal yes. Salit (1997), Chalder (1998), Kroenke, Wood, Mangelsdorff, Meier, and Powell (1998), Theorell, Blomkvist, Lindh, and Evengard (1999) have all reported that major life events are more likely prior to the onset of CFS. Hatcher and House (2003) investigated the role of life events further and repeated the finding that they often precede onset, adding the observations that dilemmas – forced choices between equally undesirable alternatives – appeared to be particularly predictive. Life events have also been found to be important in the onset of chronic pain (Craufurd, Creed, & Jayson, 1990) and IBS (Creed, Craig, & Farmer, 1988). Again, neuroticism is a potential confounding factor as Kendler et al. (2003) and Magnus et al. (1993) found that the occurrence of objectively measured stressful life events are associated with neuroticism.

The effects of life events may be to induce what has been called “prolonged activation” i.e. chronic activation of the physiological stress responses described in Section 3.2.1. The hypothesis is that activation of the stress response over a period of time has neurological, endocrinological, immunological and cardiovascular consequences. Brosschot, Pieper, and Thayer (2005) pointed out that a key element of this process is “perseverative cognition”, that is worry or rumination, which serves to maintain the physiological activation. Whilst the evidence for this mechanism is currently patchy, what there is would fit the model so far presented, of an interaction between environmental, physiological, behavioural and cognitive responses.

4. The coherence of the model

We have reviewed some of the cognitive, behavioural and physiological factors that are thought to contribute to the onset and perpetuation of MUS. Overall, the evidence reflects a welcome move from purely “psychological” models to a more complex multifactorial approach. There is certainly evidence that factors in each domain are associated with MUS. However, the key feature of CBT model is that these individual components become locked into an autopoietic cycle. It is intuitively obvious how this might happen. An innate tendency to somatopsychic distress and ease of distress sensitisation, combined with childhood adversity, increase both the amount of symptoms experienced and lowers the threshold for their detection. Life events and stress lead to physiological changes which produce more symptoms and set up processes of sensitisation and selective attention. This further reduces the threshold of symptom detection. Lack of explanation or advice increases anxiety, symptoms and symptom focus. Stress cues become associated with symptoms through classical conditioning. Avoidance of symptom provocation, and symptom-led activity patterns, lead to further sensitisation through operant conditioning. The prolonged stress of the illness experience itself further activates physiological mechanisms, producing more symptoms, sensitisation, selective attention and avoidance. The individual can thereby become locked into a vicious cycle of symptom maintenance (see Fig. 1).

There are varying degrees of evidence for each of the components of this model. What is lacking is solid proof of their interaction in vicious circles, although all the models reviewed assume this interaction.

The CBT model of CFS (see Suraway et al., 1995; Deary & Chalder, 2006) hypothesises that in vulnerable individuals, such as those who are over-active or under-stress, CFS is precipitated by life events or viruses leading to an autopoietic cycle in which physiological changes, illness beliefs, reduced and inconsistent activity, sleep disturbance, distress, medical uncertainty and lack of guidance interact to maintain symptoms. The evidence supports some of the individual dots in this picture but not yet the lines between them.

According to Lackner (2005), the CBT model of IBS (see Toner et al., 1998; Hutton, 2005; Kennedy et al., 2005) has slightly more coherence and evidence for it than the CFS model, and appears both less controversial and more readily acceptable to patients. IBS perhaps benefits from being largely localised to one organ system, where some of the interactions of physiological and psychosocial processes are better conceptualised and more widely accepted than the more diffuse, complex and idiosyncratic processes that seem to be involved in CFS and general MUS.

What makes the CBT model so difficult to test may also be one of its chief strengths: it is in many ways a meta-model, providing a skeleton structure to join the dots of whatever factors each patient presents. Indeed factors that are neither strictly cognitive nor behavioural, but have been found to be important (for instance social support (Chalder, 1998) or benefit receipt (Bentall, Powell, Nye, Edwards, & Richard, 2002)) can be incorporated into this structure as perpetuating factors. This means that every client will have, in effect, their own model, making the testing of a generic CBT MUS model impossible. Rather, future testing of this model must be of individual factors and of specified interactions between factors, such as HPA axis activity, immune functioning and fatigue. Currently the model is much

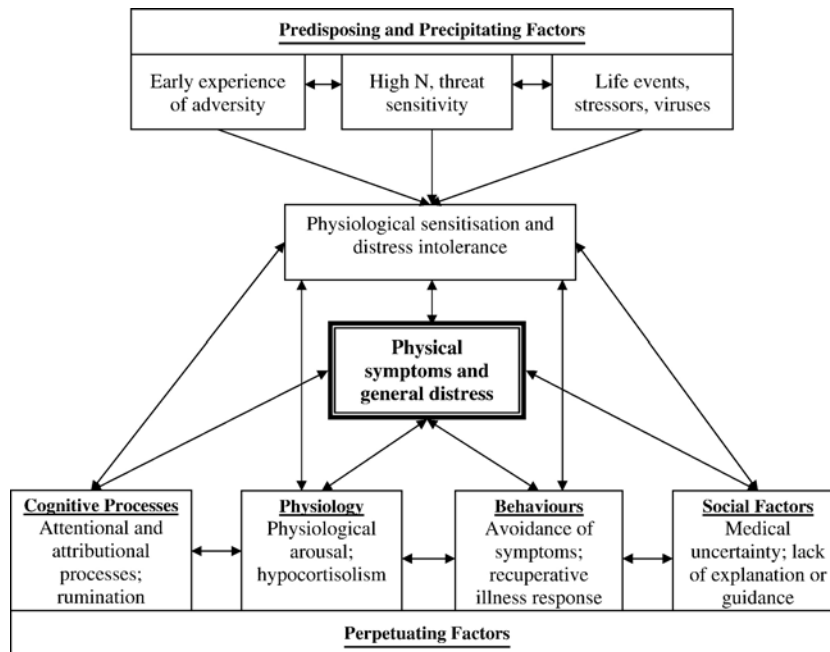


Fig. 1. Expanded CBT model of hypothesised autopoietic cycle of symptom maintenance.

stronger on the individual factors than on their interaction, but overall the evidence does support the more generic conclusion that MUS in general, and IBS and CFS specifically, are multi-factorial conditions caused and perpetuated by several distinct processes. As such the autopoietic explanation of MUS as proposed by the CBT model both fits the current data and could form a theoretically coherent basis for further research. More generally, the research bears out the over-arching CBT hypothesis that the autopoietic interaction of distinct but linked systems could serve to produce physical symptoms in the absence of physical pathology.

5. Treatment studies

The proof of the CBT pudding must, at least in part, be in the treating. Treatment relies on the model to identify the elements maintaining the autopoietic cycles, and to identify what factors made the individual vulnerable in the first place. This is the explicit purpose of the CBT assessment: to form a coherent multi-factorial case conceptualisation that forms the rationale for treatment (see Deary & Chalder, 2006). In CFS inconsistent and reduced activity, disturbed sleep and catastrophic beliefs regarding activity and symptoms are the most commonly identified set of factors and therapeutic targets; in IBS it is catastrophic beliefs, behavioural avoidance and gut symptom intolerance. In as far as these factors are altered in treatment, treatment trials serve as a test of the model, though few have the size or finesse to isolate the “effective ingredients” i.e. to identify which changes in which factors, or their interactions, lead to symptomatic improvement. The purpose of the following review is to summarise the findings of the clinical efficacy of CBT and to see if this casts any light on the standing of the CBT model employed in treatment.

In the last five years four systematic reviews of treatment studies have been published (Kroenke & Swindle, 2000; Allen et al., 2002; Looper & Kirmayer, 2002; Raine et al., 2002) of the MUS literature, each with a slightly different slant. Allen et al. (2002) took the self-declaredly controversial approach of combining all the RCTs of general psychosocial treatments for MUS, IBS, CFS and fibromyalgia into one analysis. Their aggregate analysis found that overall treatment effect sizes are “modest at best” with few intention to treat analyses and very little definition of clinically significant improvement across conditions. Theirs is the most pessimistic analysis, and includes non-CBT therapies. The overall conclusion of the other reviews is for a modest effect size of CBT for MUS, smaller than in anxiety and depressive disorders, but still clinically significant. In the following we will briefly summarise the findings reported in these reviews and also add some notable trials subsequently reported.

5.1. General MUS

Looper and Kirmayer (2002) reported three randomised controlled trials of individual CBT for primary care patients presenting with MUS and concluded that CBT demonstrated a moderate effect size for reduction in somatic symptoms. Two of these studies also reported a significant reduction in psychological distress, one did not. In addition they reported on Hellman, Budd, Borysenko, McClelland, and Benson (1990) randomised study of two CBT groups compared to an attention control group. Both CBT groups produced significant reductions in somatic symptoms and distress, this effect being largest in the group that specifically addressed illness behaviours and beliefs. Kroenke also reported on Lidbeck's (1997) randomised trial of a group treatment in primary care which produced decreased symptom pre-occupation and medication use compared to a waiting list control. There was no observed effect on psychological distress, though in a follow up study Lidbeck et al. (2003) reported that improvement in somatic pre-occupation was maintained and that there was additional reduction in anxiety measures.

Since these reviews were published, other studies have been reported. Larisch, Schweickhardt, Wirsching and Fritzche (2004) studied the effects of a re-attribution intervention delivered by 23 trained GPs, comparing their patient outcomes to 19 untrained GPs. They found no significant impact on psychological symptoms (both Kroneke & Swindle, 2000; Allen et al., 2002 noted this general trend) but some improvement in physical symptoms. Bleichhardt, Timmer, and Rief (2004) and Hiller, Fichter, and Rief (2003) both performed RCTs in tertiary care with CBT having small but significant effects on physical symptoms and HAD scores.

In summary there is evidence for a moderate beneficial effect of CBT for MUS in general. However, the treatments described vary greatly in content, method of delivery and target patient group, so conclusions about the most effective components of treatment and precise mechanisms of change are impossible to draw.

5.2. Chronic fatigue syndrome

Raine et al. (2002) in their review identified eight trials published since 1993. Seven of these were conducted in secondary care, one in primary care. Five were of CBT; three are of what the reviewers called Behaviour Therapy, also known as Graded Exercise Therapy (GET). Three of the CBT trials showed substantial effect of CBT on CFS symptoms, two did not, one of these being the primary care study. All three trials of GET lead to symptomatic and functional improvement, though Wearden et al. (1998) had a smaller improvement and a higher drop out rate. The reviewers concluded that CBT (including GET) was effective in secondary care, but that there was little evidence for CBT in primary care, with only one trial conducted in this context.

Since these reviews were published there have been two further trials of GET in CFS. Moss-Morriss et al. (2005) and Wallman, Morton, Goodman, Grove, and Guilfoyle (2004) both showed clinically significant improvement in CFS patients receiving GET compared to controls, as measured by symptom reports and physical functioning. Edmonds, McGuire, and Price (2004) performed a Cochrane Review of trials of GET for CFS and concluded that GET does lead to significant clinical improvement, but has a higher drop-out rate than comparable treatments. Clarke and White reach a similar conclusion in their survey of the GET trials (Clarke & White, 2005).

Again, it is hard to disentangle the active ingredient in these treatments. The CBT tends to involve pacing, graded increases in activity, sometimes exercise, work on a variety of cognitions including perfectionist beliefs, catastrophic illness beliefs and schema work. The GET trials provide a relatively more focussed intervention, and we could easily conclude that the reversal of de-conditioning is the effective component of this form of treatment. Although seemingly obvious, this is not necessarily true. The Moss-Morriss et al. (2005) GET trial demonstrated that reduced symptom focus partly mediates improvement. We need much larger trials, and more component analyses, before we can draw anything other than the most general conclusion that both behavioural and cognitive interventions achieve moderate clinical improvement in CFS. Overall these trials provide support for the prediction of the CBT model that changing behaviours and cognitions leads to improvement in physical symptoms, implying that the former are instrumental in their perpetuation.

5.3. Irritable bowel syndrome

The Raine et al. (2002) review reported on twelve trials of either Behavioural Therapy or CBT. As for CFS, there were better outcomes from those trials conducted in secondary care, with all studies reporting improvements in both

symptoms and coping. They concluded that although there is some evidence for the effectiveness of CBT, it is mixed, and the strongest evidence is for anti-depressant drugs. Reviewing almost the same trials, Allen et al. (2002) concluded that CBT has only a modest effect. More recently Blanchard (2005) has reviewed the trials and reported a further six. As Blanchard noted, the samples sizes have been small, the results mixed and the treatments heterogeneous. Since this review, a large RCT in primary care has been reported by Kennedy et al. (2005). Patients were randomised to either six sessions of Mebeverine plus CBT or Mebeverine alone. The group who received CBT showed greater improvement in somatic symptoms at six month follow up, but by twelve months this between-group difference was no longer significant. However the CBT group rated themselves as significantly less disabled by symptoms compared to medication only controls, and this difference persisted at twelve month follow up. This trial is notable for both its size, for being in primary care and for its novel method of treatment delivery, using briefly trained non-mental health professionals.

Overall the trials of CBT in IBS paint an inconclusive picture for both the effectiveness of CBT and the validity of the CBT model, the research to date being hampered by being mainly small trials of heterogeneous interventions. As Blanchard (2005) notes, there is equally strong evidence for other psychosocial interventions such as hypnotherapy.

6. Summary, conclusions and recommendations

There is fairly good evidence for the role of the elements of the CBT model in MUS, but less evidence for the patterns of interaction of these elements. There is general evidence that targeting maintaining factors leads to symptom reduction, but only limited evidence for what the key factors or interventions might be. The more vaguely conceptualised and diffuse conditions of general MUS and CFS provide clearer empirical support for CBT treatment than the more coherently conceptualised condition of IBS. However this may be due to the motley nature of interventions tested in the latter, and the preponderance of small trials. Also of note are the mixed findings for reduction in psychological distress. Kroenke and Swindle (2000) concluded that for all MUS, the main effect of CBT was for somatic symptoms (71%) and that psychological distress improved in less than half the studies (46%). This certainly questions the common assumption that improvement in somatic symptoms is caused by improvement in distress.

Given the mixed nature of the interventions, and their relative complexity, the most conservative conclusion from the treatment trials reviewed is that targeting cognitive and behavioural factors can lead to physical symptom improvement. Although this gives support to the overall spirit of the CBT model, we are still some way from pinpointing which interventions and which mechanisms of change are the most important in symptom maintenance and treatment.

6.1. The model

We suggest that we are now at the stage where research should pay more attention to some of the components of the model and to their interaction. Two of the predominant themes to emerge from the theoretical literature are sensitisation and attention. These processes are not necessarily locatable, are poorly understood, and their interaction complex. The psychoneuroendocrinology papers reported here offer some early promise. Brain imaging of symptom experience, informed by theoretical models, is another potentially exciting area for further work. The links so far found between central nervous system processes, such as the HPA axis, and immunological processes are intriguing but far from conclusive; the causal relationships are unclear, as are the nature of the change in these systems in different conditions at different stages. There is however already sufficient data to propose hypotheses about some of the important links, for example, between life events, HPA axis and immune functioning, that could be tested in prospective studies. More speculatively, there are indications of at least two distinct physiological systems at work in MUS, an acute stress system and a recuperation system. Patients or conditions more characterised by anxiety-like responses might have different physiological markers from conditions characterised by withdrawal and lassitude. Whether these constitute distinct systems, and whether there is, as Dantzer (2005) suggests, an isolatable illness response mechanism certainly deserves further investigation. The acknowledgment that the phenomenology reported by patients has a biological substrate will be welcomed by many patients, and is long overdue.

Petrie and Weinman (2003) have called for more attention to be given to symptom appraisal and we would widen this by a calling for more attention to attention in general. The theoretical literature and some of the empirical literature supports this mechanism as being an important part of the cycle maintaining MUS. However there has been relatively

little research on this. Closely related to this is the work on attribution. In future work we need to be measuring not only the nature of the attributions, but also their variety, fixity and exclusivity. In this field a more qualitative, less theory driven approach to attribution assessment, such as Kirmayer et al.'s (2004) might give us more idea of the range and nature of patients versions of their symptoms, rather than trying to corral them into the dichotomy of psychological versus somatic.

The nature of individual differences in susceptibility to MUS would also merit further attention. High neuroticism may offer an underlying common mechanism for distress sensitivity and intolerance which lowers the threshold for symptom detection (both mental and physical), and leads to increased propensity to conditioned responses, more attention to threat stimuli and more avoidant coping. The neuroticism concept captures many of the factors hypothesised to be at work in MUS. This would suggest two further lines of research. Firstly, more examination of the physiological, cognitive and behavioural markers of *N* might give us more insight into the processes at work in MUS. Secondly, longitudinal studies in *N* might give us a clearer idea of what mediates and moderates development of MUS in vulnerable individuals.

The CBT model of MUS offers a previously undescribed illness mechanism maintaining a distinct group of disorders that we might call autopoietic conditions. The fundamental hypothesis underlying the model is that symptoms are maintained by a self-perpetuating, multi-factorial cycle. Treatment is aimed at elaborating the unique inter-play of factors in any given patient and dismantling the autopoietic mechanism by making changes in target areas. In as far as treatment studies are a test of this hypothesis, it has good but at present only indirect support. More direct research support, based on testing this theoretical model of MUS is needed. With inter-plays of cultural, social, cognitive, behavioural, personality and biological factors, these conditions call for a truly multi-disciplinary research programme and a level of inter-disciplinary understanding which is rarely witnessed and technically hard to achieve. Diseases which are confined to one organ system are relatively easy to isolate and study, as reflected in medical and research establishments of increasing specialism. Our understanding of MUS has been hampered by this as each specialism either denies the reality of these conditions or attempts to limit their understanding to its own field. As Rief and Sharpe (2004) suggest, our understanding of MUS calls for a reversal of this trend. We need not only multi-modal treatments, but a research programme that is informed by the knowledge that physical symptoms can be maintained systemically, through the interaction of diverse processes and not just through pathophysiology. This work has barely begun.

6.2. Treatment

Distress intolerance is as a key theme in the CBT model of MUS maintenance. Symptoms are perceived as aversive/threatening, which triggers a physiological response, which serves to maintain avoidance, symptom focus and symptoms. One hypothesis would be that developing the ability to tolerate symptoms whilst not letting them dictate behaviour would be a promising line of enquiry. The so called third wave of CBT, particularly Acceptance and Commitment Therapy (see Hayes, Strosahl, & Wilson, 1999), with its emphasis on distress tolerance and goal maintenance would seem well suited as a paradigm to apply to these conditions, as would the related intervention of mindfulness.

Another approach to treatment that enjoys strong theoretical support but little empirical evidence, lies in the nature of the CBT rationale for treatment. Powell, Nye, and Edwards (2001) “frontloaded” their CFS treatment with a very detailed physiological explanation for symptoms and then used a relatively short GET intervention, which proved comparably effective to longer ones. Several of the papers quoted here show that particular types of illness attributions, particularly very fixed or catastrophic ones, are associated with poor outcome. Kirmayer et al. (2004) reported some explanation is better than none, and that the very process of helping a person construct a narrative in a research interview was beneficial. This component of CBT, constructing a model of the patient's symptoms based on some of the processes described above, could be tested as an intervention in itself. Certainly, spending time constructing a credible treatment rationale is time well spent.

Most GPs want to manage MUS in primary care (Reid, Whooley, Crayford, & Hotopf, 2001), although few feel that there is any effective treatment available. As most of the reviewers have noted, the preponderance of trials of treatment for MUS have been done in secondary care by specialists, mostly in mental health. Very few studies have tested either primary care delivery or training GPs and other non-mental health professionals to deal with MUS. There have been exceptions. Fink, Rosendal, and Toft (2002) have described a GP training course to increase awareness of MUS and its application in a trial (Rosendal, Bro, Fink, Christensen, & Olesen, 2003). Smith et al. (2003) trained practice nurses to treat MUS; Kennedy et al. (2005) used nurses trained in CBT to implement an intervention for IBS in primary care.

There is currently work amongst our team using a similar approach in diabetes, in functional dysphonia and in depression in cancer. Training non mental health professionals to deliver cognitive behavioural treatments for symptoms (both explained and unexplained) would seem to be a promising and cost-effective way forward to target the unmet need in MUS.

With some exceptions, (McCrone, Risdale, Darbishire, & Seed, 2004), we lack good data on cost effectiveness. As trials get larger and move towards primary care, health economics will be vital in assessing the value of these treatments and in assessing the costs versus the benefits of disseminating CBT skills to non-mental health professionals. Certainly, if effective, this would be one way of implementing the “cadre of well trained therapists who are knowledgeable in the principles and practice of CBT” that Mai (2004) recommends be available in primary care.

What about prevention? This work may be far off, but there are some indications of how we could proceed. Prevention is of course predicated on being able to predict increased likelihood of occurrence and we can, to an extent, do this. Individuals who are high *N*, who have experienced childhood adversity or parental illness, who experience a serious virus and/or prolonged life events and stressors, are going to be, the theory and data would suggest, more likely to develop MUS. Longitudinal work, of the kind being conducted in Heidelberg (see Amelang, 1997) studying personality predictors of physical illness would be necessary to see if personality is a genuine marker of vulnerability, and if so to what degree. Hotopf (2004) has drawn our attention to the vital role that both doctors and parents can play in the development, or prevention, of MUS in these vulnerable patients. The right advice derived from a collaboratively constructed model of symptom experience, could be crucial in preventing or ameliorating MUS. In the CBT model, we may just have the means to do this.

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