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Trauma and medically unexplained symptoms. Towards an integration of cognitive and neuro-biological accounts

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Citation

Roelofs, K., & Spinhoven, P. (2007). Trauma and medically unexplained symptoms. Towards an integration of cognitive and neuro-biological accounts. *Clinical Psychology Review*, 27, 798-820. doi:10.1016/j.cpr.2007.07.004

Version: Not Applicable (or Unknown)

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Note: To cite this publication please use the final published version (if applicable).

Trauma and medically unexplained symptoms Towards an integration of cognitive and neuro-biological accounts

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Received 31 October 2005; received in revised form 6 March 2006; accepted 6 March 2006

Abstract

Medically unexplained symptoms (MUS) are frequently associated with a history of traumatization. The first purpose of the present review paper was to investigate systematically the evidence for such relation in a subset of clinical samples with MUS presenting with functional somatization: chronic pelvic pain, irritable bowel syndrome and conversion and somatization disorder. The second purpose was to critically review three dominant models explaining the relation between trauma and MUS (i.e. dissociation, conversion and hierarchical cognitive models). The latter model in particular adequately accounts for the non-volitional and non-intentional character of MUS and explains how traumata can affect the development of MUS without assuming that previous trauma is a necessary prerequisite of MUS. The cognitive model, however, lacks integration with current neurobiological findings, indicative of central stress- and central nervous system alterations in MUS. The final purpose of the present paper was, therefore, to review current neurobiological studies focused on trauma and MUS and to formulate a research agenda to integrate these neurobiological developments with cognitive models for MUS.

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1. Introduction

Somatic symptoms are the leading cause of outpatient medical visits. At least 33% of somatic symptoms are medically unexplained (Kroenke, 2003). Medically unexplained symptoms (MUS) constitute an important public health problem that is associated with considerable personal suffering, loss of productivity, and decreased quality of life (Kirmayer, Groleau, Looper, & Dao, 2004). Many patients present with individual somatic symptoms, such as back pain, headache, dizziness, and dyspnoea. Others present with functional syndromes characterized by constellations of somatic symptoms, such as irritable bowel syndrome (IBS) or somatization disorder (SD).

Since the 18th century it has been recognized that MUS may have a psychological origin and already in many early accounts within medicine and psychiatry the experience of potentially traumatic events is mentioned as an important etiological factor in MUS (Shorter, 1992). In this paper we aim to systematically review the empirical evidence of a possible relationship of trauma with MUS and to critically discuss ideas about how exposure to *psychological* trauma may in some way lead to the formation of *somatic* symptoms.

In trying to explain the genesis of MUS a distinction should be drawn among MUS that are: (a) the physiological components of anxiety and depression (presenting somatization); (b) normal bodily sensations or minor pathological events that are misinterpreted as signs of serious illness (hypochondriacal somatization); and (c) subjectively compelling symptoms that cannot be attributed to either physical or psychiatric illness or hypochondriasis (functional somatization) (Kirmayer & Robbins, 1991). For several reasons the current review will primarily focus on the latter type of MUS: functional somatization. Because anxiety and depression are common sequelae of experiencing trauma and because the co-morbidity of MUS with anxiety and depression is very high (Kroenke, 2003), the association of trauma with MUS in the case of ‘presenting somatization’ may be related to the presence of these affective complaints. The concept of ‘hypochondriacal somatization’ predominantly refers to an extreme anxiety for disease, rather than the presence of complaints. It may, moreover, be particularly relevant for MUS occurring after traumatic experiences involving possible exposure to toxic substances, resulting in the attribution of normal and benign physical symptoms to an external, physical cause (Havenaar & Van den Brink, 1997). In sum, presenting and hypochondriacal somatization largely depend on affective complaints or health anxiety. In the case of ‘functional somatization’, however, the association of previous trauma with MUS that are independent of a mental or physical disorder necessitates specific mediational models that can explain the proposed relationship. For these reasons, the link between previous trauma and functional somatization has been, and to a great extent still is, a riddle for which various theoretical models have been proposed, and which will be the primary focus of the present paper. Consequently, the present paper does not involve an exhaustive review of all investigations that study the association of trauma with MUS. The focus of this selected review is more circumscribed and related to the following three aims.

The first purpose of the present review is to investigate whether there is indeed any evidence of a specific relationship of trauma with MUS. For this aim we will review the literature on the association of trauma with MUS in some well-defined patient groups which historically have played a prominent role in the discussions about a possible relationship of trauma with functional somatization (Shorter, 1992). To this end we choose to review the following samples in more detail: chronic pelvic pain (CPP) and irritable bowel syndrome (IBS) (two functional somatic syndromes in which it has long been assumed that childhood sexual abuse may play an aetiological important role), somatization disorder (SD) and conversion disorder (CD) (both historically subsumed under the diagnostic umbrella of hysteria and hypothesized to be related to child sexual abuse as well). The second aim of this paper is to critically review specific mechanisms proposed to explain the relationship of previous trauma with MUS. In this context, three major models (i.e. dissociation, conversion, and hierarchical cognitive models) will be critically discussed. Especially the latter model, which basically integrates existing dissociation and cognitive models, appears to be of specific explanatory value and will be expanded on in the remainder of the paper. Because cognitive models lack integration

with recent neurobiological findings concerning trauma and MUS, the third and last aim of this paper is to review neurobiological stress research indicative of alterations in prefrontal functions and central stress-systems and to integrate this with cognitive accounts of MUS.

2. Review of the empirical evidence on the relationship of trauma with MUS

First, the association of trauma with MUS in chronic pelvic pain (CPP), irritable bowel syndrome (IBS), somatization disorder (SD), and conversion disorder (CD) was investigated. Although it has long been assumed that childhood sexual abuse may play an important role in the genesis of all four disorders, dissociation accounts have prevailed particularly for SD and CD. Given our goal to review the association of trauma with MUS in general and to discuss both dissociative and non-dissociative accounts for such a relationship, the inclusion of two functional somatic syndromes (CPP and IBS) and two presumed ‘dissociative’ somatoform disorders (SD and CD) provided us with a broader and more representative selection of studies on trauma in relation to MUS.

A systematic literature review was performed using the electronic bibliographic databases PsychINFO 1970–2004 and MEDLINE 1970–2004. A computer search was carried out, using a wide range of key words. Reference lists of available reviews and studies were screened as well. Study reports were included if the following inclusion criteria were met: (a) description of a diagnostic procedure to define samples as SD, CD, IBS or CPP; (b) definition of sexual, physical, emotional or psychological abuse or traumatic or major life event; (c) controlled study comparing the prevalence of potentially traumatic/major life events in SD, CD, IBS or CPP with any control group. A total of 33 studies were identified through the combined search strategies and found to be eligible for inclusion in the review. Specific diagnostic groups were used as a basis to categorize the different studies. The first cluster comprised studies in patients with CPP ($n=15$), the second cluster studies in patients with IBS ($n=9$) and the third and last cluster patients with somatization disorder or conversion disorder ($n=9$). Table 1 summarizes the clusters of studies, author and year of the study, specific (control) samples used, measures for trauma/life events and MUS, differences in trauma prevalence between diagnostic groups and any data about the relationship of trauma with MUS. This last point was included to indicate whether the authors also studied the relationship between trauma and the severity of MUS, as well as any variable mediating such a relationship. The findings of this review will be summarized below, for each sub sample separately.

Chronic Pelvic Pain (CPP). Overall, most of the studies within the cluster of CPP clearly show that the rate of physical (5 of the 8 studies) and especially sexual abuse (10 of the 12 studies) is elevated compared to pain free or normal controls. Also, most of the studies show a higher prevalence of (child) sexual abuse in CPP compared to other pain groups (5 of the 7 studies), while with respect to the prevalence of physical abuse no differences between CPP and other pain groups are found (4 of the 6 studies). Moreover, only two studies investigated the association of abuse with duration or severity of MUS, with mixed findings. None of the studies investigated whether the relationship of trauma with MUS could be accounted for by mediating variables such as affective distress or dissociation.

Irritable Bowel Syndrome (IBS). Six of the nine studies within the cluster of IBS showed the rate or severity of physical, and particularly sexual, abuse to be elevated compared to physical pain or pain free control groups. In the few studies in which psychological abuse was measured, its severity was found to be elevated in the IBS groups as well. In four of the six studies in which the relation between abuse and MUS was measured, a significant association between abuse and the severity of MUS was found. In some studies, however, this relation was not specific for the abused functional group but counted also for the control group. Two studies investigated whether mediating variables might account for the relation between abuse and IBS. Whereas Reilly et al. (1999) found no indication of mediation, Salmon, Skaife & Rhodes (2003) identified parenting and somatization as mediating variables in the relation between abuse and IBS.

Conversion/somatization disorders (CD/SD). In all of the nine reviewed studies within this cluster, increased prevalence and/or severity rates of physical or sexual abuse were found compared to organic, psychiatric or healthy controls. In three out of the four studies in which psychological abuse was also taken into account similar increases were found for psychological abuse. In only three studies the relation between abuse variables and MUS variables was investigated and reported. In all of them positive associations between child abuse (in particular physical and psychological) and MUS severity ratings were found. In two of these studies mediating variables were investigated and identified: hypnotic susceptibility, adult life-events, family dysfunction and somatization were found to account for relations between various forms of childhood abuse and conversion symptoms.

In sum, in all of the reviewed subgroups of clinical MUS samples, significantly increased abuse rates have been found. However, fewer than half of the studies investigated whether there was an actual relationship between the abuse and the severity of MUS. In most of these studies such an association was established. Investigations of mediating variables that may account for the relationship between abuse and MUS are extremely scarce in this sample (4 out of 33, of which 3 succeeded in identifying one or more psychological factors that partially mediated the relation between trauma and MUS). All three studies pointed at different mediators (dissociation, emotional distress, hypnotic susceptibility, family dysfunction or somatization). Thus there seems to be a great lack of systematically conducted mediation analyses in these case-controlled studies and the outcomes are too inconsistent to allow for reliable conclusions.

Finally, it should be stressed that the conclusions drawn from this literature review have to be interpreted with care given the non-uniform definitions of abuse, the choice of nonequivalent comparison groups, the differences in the measurement of sexual and physical abuse and the fact that all studies were retrospective. The vast majority of the studies, however, pointed in the same direction, indicating increased abuse rates in clinical samples of MUS compared to organic, psychiatric or healthy control groups.

3. Putative mediators of the relationship of trauma with MUS

As reviewed above, the empirical evidence suggesting a specific relationship of trauma with MUS is quite consistent and shows that for at least a subgroup of persons with MUS (childhood) trauma may have been a risk factor involved in the genesis of MUS. So the question arises how this association can be explained. Three different groups of explanatory models for the pathogenesis and persistence of functional somatization can be discriminated: dissociation, conversion, and hierarchical cognitive models. The origin and development of the respective models will be briefly described followed by a critical discussion of how adequately the models account for the available empirical data on the trauma-related nature, onset and maintenance of MUS and whether they possess desirable characteristics such as theoretical parsimony and specific predictive power.

3.1. Dissociation models

3.1.1. Global description

The dissociation theory of Janet is probably the oldest theoretical account of how individuals exposed to potentially traumatic events may develop MUS. According to Janet (1907) individuals experience a spontaneous narrowing of attention when experiencing traumatic events. The subsequent development of MUS can be attributed to two basic mechanisms both related to attentional narrowing. First, attentional narrowing limits the number of sensory channels that can be attended to simultaneously. This concentration on some sensory channels at the expense of others results in the loss of deliberate attentional control over unattended channels. This distribution of attention may develop into a kind of habitual attentional style. This does not imply however that information in the unattended channel is no longer processed. Janet assumes that, although the individual is unaware of any information in the unattended channel, this information is still processed outside conscious awareness. This dissociated information processing results in so-called negative symptoms. Negative dissociative symptoms refer to apparent losses of function in, for example, memory, motor control or somatosensory awareness.

The second mechanism refers to the activation of memories that have become dissociated from the main autobiographical memory base that underlies the person's sense of identity. Attentional narrowing precludes full awareness of information about the traumatic event and prevents integration of these new memories with the existing personal knowledge base. Because these memories are not integrated with existing knowledge, individuals have no or little control over the activation of these memories. Consequently trauma reminders within the person or external environment can easily trigger these memories. This process results in so-called positive dissociative symptoms. Examples are sensorimotor and affective aspects of reexperienced traumatic events, such as sensory distortions, pain and tics.

It is striking that after a century the theoretical account of Janet is still influential and informs recent theoretical models and therapeutic interventions with respect to MUS. However, although in the original writing of Janet dissociative phenomena also pertained to functions of movement, sensation and perception in most contemporary views of so-called dissociative phenomena, the dissociation of mental functions pertaining to memory, consciousness

Table 1
Summary of studies examining the relation between trauma and MUS in patient samples

Authors	Population	Variables	Group differences in trauma prevalence	Relation trauma severity- MUS
<i>Chronic Pelvic Pain (CPP)</i>				
Bodden-Heidrich, Koppers, Beckmann, Rechenberger, & eBender (1999a,b)	106 CPPS: 100%♀; age=34 36 CVPS (chronic vulvar pain syndrome):100%♀; age=38	Trauma: not specified	SA: CPPS (22%)>CVPS (3%)	Not measured
Collett, Cordle, Stewart, & Jagger (1998)	30 CPP: 100%♀; age=30 30 chronic pain: 100%♀; age=34 30 painfree: 100%♀; age=30	Trauma: adapted self-report questionnaire MUS: somatization scale	SA: CPP (40%)>Chronic pain (17%)=painfree (17%) Severe SA: CPP (27%)>Chronic pain (7%)=painfree (13%) PA: CPP (27%)=chronic pain (20%)=painfree (27%)	Not reported
Ehlert, Heim, & Hellhammer (1999)	16 Idiopathic CPP (ICPP): 100%♀; age=28 10 Abdominal CPP (ACPP): 100%♀; age=29 14 painfree infertile controls:100%♀; age=30	Trauma: SA interview (Russell, 1983), SA/PA questionnaire LE: structured interview MUS: Mehrdimensionale Schmerzskala, screener somatoform symptoms	SA: ICPP (67%)=ACPP (50%)>painfree (21%) PA: ICPP (60%)=ACPP (40%)=painfree (21%) LE (mean): ICPP (6)=ACPP (6)=painfree (5)	Not reported
Harrop-Griffiths, et al. (1988)	25 CPP: 100%♀; age=27 30 laparoscopy controls: 100%♀; age=32	Trauma: SA interview (Russell, 1983) LE: life experiences questionnaire MUS: somatic symptom count	Child SA: CPP (64%)>controls (23%) Adult SA: CPP (48%)>controls (13%) LE (mean): CPP=controls	Not reported
Heim, Ehlert, Hanker, & Hellhammer (1998)	16 CPP: 100%♀; age=28 14 painfree infertile controls:100%♀; age=30	Trauma: SA interview (Russell, 1983), SA/PA questionnaire LE: impact of event scale and structured interview	SA: CPP (67%)>controls (21%) PA: CPP (60%)>controls (21%) Traumatic SA/PA: CPP (47%)>controls (7%)	Not measured
Heim, Ehlert, Hanker, & Hellhammer (1999)	10 CPP+ adhesions: 100%♀; age=29 14 painfree infertile controls:100%♀; age=30	Trauma: SA interview (Russell, 1983), SA/PA questionnaire; LE: structured interview MUS: Mehrdimensionale Schmerzskala	SA: CPP (50%)=controls (21%) PA: CPP (40%)=controls (21%) Traumatic SA/PA: CPP (40%)=controls (7%)	Not reported
Lampe et al. (2000)	36 CPP: 100%♀; age=32 23 CLBP (chronic low back pain): 100%♀; age=41 20 painfree: 100%♀; age=29	Trauma: structured interviews (Russell, 1983) MUS: duration of pain	SA: CPP (36%)=CLBP (17%)>painfree (15%) Child SA: CPP (22%)>CLBP (0%)=painfree (0%) PA: CPP (67%)=CLBP (52%)>painfree (20%) PsyA: CPP (25%)=CLBP (5%)/CPP>painfree >(0%)	Abused subjects same duration of pain as non-abused subjects

Lampe et al. (2003)	43 CPP: 100%♀; age=32	Trauma: structured interview (Russell, 1983)	SA: CPP (28%)=CLBP (21%)=painfree (23%)	Not reported
	40 CLBP (chronic low back pain): 100%♀; age=40	Life-events: inventory of life changing events	Very severe SA: CPP (25%)>CLBP (5%)=painfree (14%)	
	22 painfree controls: 100%♀; age=29	MUS: duration of pain	PA: CPP (63%)=CLBP (45%)>painfree (27%) SLE: CPP (35%)=CLBP (43%)=painfree (50%)	
Rapkin, Kames, Darke, Stampler, & Naliboff (1990)	31 CPP: 100%♀; age=31	Trauma: interview on the occurrence of child and adult PA and SA.	Child PA: CPP (39%)>other pain (18%); Not reported	
	141 Other pain: 100%♀; age=43	MUS: a pain questionnaire	CPP>painfree (9%) Child SA: CPP (19%)=other pain (16%)=painfree (13%)	
	32 painfree controls: 100%♀; age=35		Adult PA: CPP (10%)=other pain (16%)=painfree (3%) Adult SA: CPP (7%)=other pain (8%); CPP=painfree (0%)	
Reed et al. (2000)	18 CPP: 100%♀; age=33	Trauma: unspecified questions	SA: CPP (63%)>vulvodynia (21%)=painfree (26%)	Not reported
	31 vulvodynia: 100%♀; age=43	MUS: Visual Analogue Pain Rating Scale, McGill Pain	PA: CPP (41%)>vulvodynia (6%)=painfree (0%)	
	23 painfree controls: 100%♀; age=42	Questionnaire, Pain Disability Index, Modified Somatic Perception Questionnaire		
Reiter & Gambone (1990)	106 CPP: 100% ♀; age=29	Trauma: unspecified 'detailed questions on sexual histories'	SA: CPP (48%)>Controls (7%)	SA was related to severity of MUS within CPP
	92 painfree controls: 100%♀; age=28	MUS: unspecified 'questions on medical, reproductive, surgical and pain history'		
Walker et al. (1988)	25CPP: 100%♀; age=27	Trauma: unspecified 'structured	Child SA: CPP (64%)>controls (23%)	Not measured
	30 gynecological controls:100%♀; age=32	interview on SA' (Russell, 1983)	Adult SA: CPP (48%)>controls (13%)	
Walker et al. (1995)	50 CPP: 100%♀; age=29	Trauma: structured sexual assault	Any child SA: CPP (58%)>painfree (30%)	Not measured
	50 painfree controls: 100%♀; age=34	interview (Russell, 1983)	Severe child SA: CPP (24%)>painfree (4%) Any Adult SA: CPP (52%)>painfree (26%) Severe Adult SA:CPP (38%)>painfree (18%) Any child SA: CPP (82%)>painfree (43%)	
Walker, Katon, Neraas, Jemelka, & Massoth (1992)	22 CPP: 100%♀; age=28	Trauma: structured sexual assault interview (Russell, 1983)	Severe child SA: CPP (55%)>painfree (5%)	Somatization and dissociation were higher in abused subjects
	21 painfree controls: 100%♀; age=31	MUS: Medical Outcomes Survey, Barsky Amplification Scale		
Walling, O'Hara et al., 1994	64 CPP: 100%♀; age=29	Trauma: structured telephone interview on SA (Russell, 1983) and PA	Major lifetime SA: CPP (53%)>headache (33%); PA but not SA was independently related to the	
Walling, Reiter et al., 1994	42 chronic headache: 100%♀; age=30	MUS: Wahler Physical Symptom Inventory	Child+ adult SA: CPP (16%)>headache (0%); CPP severity of MUS after accounting for socio-	
	46 painfree controls: 100%♀; age=35		Lifetime PA: CPP (50%)>painfree (30%); CPP demographic variables and other forms of abuse	
			Child+ adult PA: CPP (25%)>headache (5%); CPP (25%)>painfree (4%) Major SA/PA: CPP (42%)>headache (19%)=painfree (20%)	

(continued on next page)

Table 1 (continued)

Authors	Population	Variables	Group differences in trauma prevalence	Relation trauma severity- MUS
<i>Irritable Bowel Syndrome (IBS)</i>				
Ali et al. (2000)	25 IBS: 100%♀; age=36 25 Inflammatory Bowel Disease (IBD): 100%♀; age=36	Trauma: PA and SA: 4 specified questions; PsyA: self report questionnaire	Being sexually touched: IBS (44%); IBD (18%) Forced sexually touch another: IBS (22%); IBD (10%) Intercourse: IBS (34%); IBD (14%) PA: IBS (18%); IBD (10%) Severity SA/PA and PsyA: IBS>IBD SA: IBS (32%)>DD (14%)=ophthalmology (13%)=painfree (8%) PA: IBS (21%)>painfree (12%); IBS=DD (22%)=ophthalmology (14%)	Not measured
Delvaux, Denis, & Allemand (1997)	196 IBS: 82%♀; age=41 135 digestive diseases (DD) 46%♀; age=42 200 ophthalmology: 55%♀; age=44 172 painfree controls: 53%♀; age=40	Trauma: questionnaire, including questions on SA and one question on PA.	SA: IBS (32%)>DD (14%)=ophthalmology (13%)=painfree (8%) PA: IBS (21%)>painfree (12%); IBS=DD (22%)=ophthalmology (14%)	Not measured
Heitkemper et al., (2001)	44 IBS 1: 100%♀; age=34 123 IBS 2: 100%♀; age=32 44 painfree controls 1: 100%♀; age=33 42 painfree controls 2: 100%♀; age=32	Trauma: adapted SA, PA interview MUS: Bowel Disease Questionnaire (BDQ), symptom diary; morning cortisol/catecholamine levels (around menstrual cycle)	Child SA: IBS 1,2 (52%,37%)=controls 1,2 (34%, 29%) Child PA: IBS 1,2 (16%, 9%)=controls 1,2 (11%, 5%) Adult SA: IBS2 (50%)=controls2 (55%) Adult PA: IBS2 (7%)=controls2 (2%) IBS 1 and controls 1; no prevalence scores available	IBS women with a history of abuse did not differ from those without abuse with respect to gastrointestinal symptoms, psychological symptoms or physiological arousal indicators.
Hobbis, Turpin, & Read (2002)	50 IBS: 100%♀ 53 chronic idiopathic constipation (CIC): 100%♀ 51 Crohn D:100%♀ 53 painfree controls: 100%♀ age (mean all groups):39	Trauma: abuse history questionnaire and semi-structured interview MUS: General Health Questionnaire (GHQ), a brief measure of psychiatric caseness, bowel disease questionnaire	Questionnaire data: Child SA: CIC(23%)=IBS(26%)=Crohn(24%)=painfree (17%) Adult SA: CIC(34%)=IBS(28%)=Crohn (26%)=painfree (23%) Child PA: CIC(40%)=IBS (54%)=Crohn (61%)=painfree (49%) Adult PA: CIC(55%)=IBS (50%)=Crohn (55%)=painfree (51%) Interview data revealed similar results	Regardless of group, childhood SA and adulthood PA were associated with higher GHQ scores
Reilly, Baker, Rhodes, & Salmon (1999)	Functional groups: 40 IBS: 75%♀, 40 PES: 72.5%♀ Organic groups: 40 Crohn: 50%♀, 40 ES: 60%♀ (Age:functional=organic; Gastrointestinal (GI: IBS,Crohn)>neurological (PES,ES) groups)	Trauma: medical history questionnaire MUS: somatization subscale of the Hopkins Symptom Checklist, Illness Behavior Questionnaire, Medical History Questionnaire	Child SA:IBS (30%); Crohn (8%); PES (33%); ES (15%) Child PA: IBS (45%); Crohn (28%); PES (60%); ES (23%) Adult SA: IBS (30%); Crohn (5%); PES (30%); ES (15%)	In all groups, various forms of abuse were associated with increased somatization, disease concern and disease conviction. Illness orientation and emotional distress were related to both abuse and functional symptoms, but did not mediate the relation between abuse and functional symptoms

Salmon et al. (2003)	64 IBS: 67%♀; age=42 61 physical bowel symptoms: 52%♀; age=38	Trauma: Medical History Questionnaire; Parental Bonding Instrument MUS: Somatization subscale of Hopkins Symptom Checklist	Adult PA: IBS (23%); Crohn (0%); PES (18%); ES (0%) Adult PsyA: IBS (33%); Crohn (8%); PES (5%); ES (13%) Prevalence of all child/adult SA, PA and PsyA: functional groups>organic groups Child SA: IBS (20%)>controls (5%) Child PA: IBS (36%)>controls (13%) Child PsyA: IBS (39%)=controls (31%) Adult SA: IBS (23%)>controls (8%) Adult PA: IBS (0%)=controls (0%) Adult PsyA: IBS (23%)>controls (7%)	Parenting (overprotection) mediated the relation between child PA and IBS and somatization mediated the relation between SA/PsyA and IBS. The relation between Child SA and somatization was mediated by dissociation and the relation between Adult PsyA and somatization by emotional distress. Not Reported
Walker, Gelfand, Gelfand, & Katon (1995)	71 IBS: 85%♀; age=52 40 IBD: 73%♀; age=41	Trauma: Briere Child Maltreatment Interview with additional questions for adult assault. MUS: NIMH diagnostic interview schedule, gastrointestinal (GI) symptom interview, Medical Outcomes Survey	Child rape: IBS (24%)>IBD (8%) Child molestation: IBS (43%)>IBD (18%) Child incest: IBS (17%)=IBD (5%) Child PA: IBS (26%)=IBD (18%) Adult rape: IBS (32%)=IBD (28%) Adult PA: IBS (25%)=IBD (20%) Any SA: IBS (54%)=IBD (42%) Any PA: IBS (42%)=IBD (35%) Severe adult SA: IBS (32%)>IBD (0%)	
Walker, Katon, Roy-Byrne, Jemelka, & Russo (1993)	28 IBS: 79%♀; age=37 19 IBD: 53%♀; age=35	Trauma: structured sexual trauma interview MUS: National Institute of Mental Health Diagnostic Interview Schedule	Any lifetime severe SA: IBS (32%)> IBD (0%) Any lifetime SA: IBS (54%)>IBD (5%) Severe child SA: IBS (11%)=IBD (0%)	Severe SA was associated with greater number of MUS. Severe SA was also more frequently associated with diagnoses of (among others) somatization disorder and functional dyspareunia compared to IBS without severe SA No effect of abuse on sensory thresholds
Whitehead, Crowell, Davidoff, Palsson, & Schuster (1997)	17 IBS with SA 15 IBS no abuse 13 painfree controls with SA 14 painfree controls no abuse (all:100%;age not reported)	Trauma: structured abuse interview, Abuse Severity Index MUS: Cornell Medical Index (somatization); Tests of muscle tone and sensory thresholds	See sample description. Abuse severity index was similar in abused women with and without IBS	

Table 1 (continued)

Authors	Population	Variables	Group differences in trauma prevalence	Relation trauma severity- MUS
<i>Conversion (CD) and Somatization (SD) disorders</i>				
Alper, Devinsky, Perrine, Vazquez, & Luciano, (1993)	71 PES: 73%♀; age=32 140 Complex partial epilepsy (CES): 51%♀; age=32	Trauma: Structured psychiatric interview including abuse history	Child SA: PES (24%)>CES (7%) Child PA: PES (16%)>CES (3%) Child SA/PA: PES (32%)>CES (9%) Severity of SA (not PA): PES>CES SA: PES (54%)>ES (25%)=Psychiatric (32%)	Not measured
Betts & Boden (1992)	113 PES: 85%♀ 215 ES: 61%♀ 130 Psychiatric D: 67%♀ (age not reported)	Trauma: Interview with independent corroboration by relatives or services		Not measured
Binzer & Eisemann (1998)	30 CD: 60%♀; age=39 30 Neurological D: 70%♀; age=34	Trauma: self report measure of perceived parental rearing practices	Child SA: CD (3%)=Neurological (0%) Parental divorce: CD (20%)=Neurological (13%) CD reported less emotional warmth and more rejection	Not measured
Brown, Schrag, & Trimble (2005)	22 SD: 91%♀; age=41 19 Controls with medical symptoms: 68%♀; age=47	Trauma: Childhood Trauma Interview, Family Functioning Scale	Any abuse: SD (96%)=controls (85%) No other prevalence ratings available Severity ratings: SA: SD=controls; PA: SD>controls; PsyA: SD>controls; Neglect: controls>SD	PsyA and PA correlated significantly with the total number of MUS
Kuyk, Spinhoven, Van Emde Boas, & Van Dyck (1999)	65 PES: 77%♀; age=29 94 Temporal Lobe Epilepsy (TLE): 36%♀; age=39 40 Non-TLE 38%♀;age=35	Trauma: Self report trauma questionnaire	SA: PES (33.3%)>TLE (4%)=non-TLE (0%) PA: PES (25.9%)=TLE (6%)=non-TLE (16%) PsyA: PES (37%)=TLE (23%)=non-TLE (24%) AA: PES (44.4%)=TLE (26%)=non-TLE (24%)	Not measured

Morrison (1989)	60 SD 31 affective disorder (AD) (all:100%♀;age not reported)	Trauma+ MUS: Renard Diagnostic Interview	Child SA: SD (55%)> AD (16%)	Not reported
Roelofs et al. (2002, 2005)	54 CD: 83%♀; age=38 50 affective disorder (AD) 82%♀; age=36	Trauma: Structured Trauma Interview LE: questionnaire MUS: number of pseudo neuro-logical symptoms (SCID-I: NOPS); SDQ20: Somatoform Dissociation Questionnaire	Child PA/SA: CD (44%)> AD (24%) Child SA: CD (24%)= AD (14%) Child PA: CD (28%)= AD (20%) Maternal dysfunction: CD (63%)= AD (58%) Paternal dysfunction: CD (50%)= AD (48%) Adult LE (mean and severity): CD= AD Severity: PA; SA; and Incidence of incest: CD> AD Child SA: PES (31%)> ES (16%)	Maternal dysfunction and PA were positively related to the SDQ20 and NOPS, respectively in CD. Hypnotic susceptibility partially mediated the effects between PA and NOPS (Roelofs, 2002). Adult life-events partially mediated the relation between PA/SA and SDQ20 in CD (Roelofs, 2005).
Salmon, Suad, Al- Marzooqi, Baker, & Reilly (2003)	81 PES: 69%♀; age=35 81 ES: 69%♀; age=35	Trauma: Medical History Questionnaire, Parental Bonding Instrument MUS: Somatization subscale of Hopkins Symptom Checklist	Child PA: PES (36%)> ES (21%) Child PsyA: PES (53%)> ES (32%) Adult SA: PES (32%)> ES (15%) Adult PA: PES (14%)> ES (4%) Adult PsyA: PES (31%)= ES (29%)	Only child PsyA uniquely differentiated PES from ES, although its relation to PES was mediated by family dysfunction. Child PsyA, adult PA and adult PsyA were associated with increased somatization. Somatization partly explained the relation of abuse with NES
Litwin & Cardeña (2000)	10 PES: 100%♀; age=31 31 ES: 45%♀; age=35	Trauma: history questions of the dissociative disorders interview schedule (DDIS) MUS: number of attacks	SA (prevalence and duration): PES (60%)> ES (13%)	Not reported

SA =sexual abuse; PA=physical abuse; SA/PA=sexual and/or physical abuse; PsyA=psychological abuse; AA=any abuse; LE=life events; PES: Pseudo-epileptic seizures; ES: epileptic seizures.

and identity is emphasized at the expense of physical forms of dissociation (Nijenhuis, Spinhoven, Vanderlinden, Van Dyck, & Van der Hart, 1998). Moreover although Janet considered dissociation to be an abnormal process provoked by stress in constitutionally weak ‘hysterical’ persons, in contemporary models dissociation is conceptualized as a normal psychological process, i.e. a defense mechanism against the overwhelming feelings provoked by exposure to trauma. The neo-dissociation theory of Hilgard (1977), with its emphasis on dissociation as a fundamental aspect of normal cognitive functioning, has been very influential in this regard. Extending and applying neo-dissociation theory to unexplained neurological symptoms, Kihlstrom (1992) posits a functional dissociation between lower-level implicit information processes and higher-level explicit information processes. A central tenet is that extreme stress can provoke disturbances in higher-level motor and sensory control functions resulting in functional dissociation (i.e. MUS).

3.1.2. Discussion

Empirical support. Both cross-sectional and prospective and longitudinal studies show that overwhelming events may have the potential to induce dissociative experiences (Gershuny & Thayer, 1999), although studies of the link between trauma and dissociative experiences in patients with medically unexplained symptoms are limited in number (Spinhoven et al., 2004). In addition, a number of studies have shown that the level of dissociative experiences tends to be elevated in patients with somatoform disorders (Brown Schrag, & Trimble, 2005) and conversely that patients with dissociative disorders report a high level of MUS (Nijenhuis et al., 1998). Moreover and more specifically, in several studies findings corroborating aspects of a dissociative interpretation of neurological conversion symptoms have been collected. For example, in individuals with unexplained blindness intact visual perception in the absence of visual experience has repeatedly been observed (e.g. Bryant & McConkey, 1989). The view that in somatization and conversion disorders higher-level motor and sensory control functions are disturbed while lower-level control is relatively intact is also supported by several neurophysiological (Fekuda, et al, 1996; Lorenz, Kunze, & Bromm, 1998; Marshall, Halligan, Fink, Wade, & Frackowiak, 1997; Roelofs, De Bruijn, & van Galen, 2006; Tiihonen, Kuikka, Viimaki, Lehtonen, & Partanen, 1995) and neuropsychological studies (Roelofs et al., 2001, 2002, 2003). A functional neuroimaging study by Marshall et al. (1997) for example suggested that unexplained paralysis involves the inhibition of primary motor activity by areas in the prefrontal cortex. These findings fit into the central idea that functional dissociations in information processing may underlie MUS.

Limitations. The first question is whether dissociation models account for the core clinical and research data on MUS. Although dissociation has been put forward as a possible mechanism mediating the relationship between exposure to trauma and MUS almost no studies allowing a mediational analysis have been executed. One study even found that the relationship of dissociation with MUS disappeared after controlling for trauma exposure (Pribor, Yutzy, Dean, & Wetzel, 1993). Moreover, available studies sometimes fail to find elevated levels of dissociation in MUS (e.g., Roelofs et al., 2002). These results indicate that, besides dissociation, different pathogenic mechanisms may be operating in MUS. In addition, it has also been observed that the positive relationship of trauma with dissociation often disappears after controlling for the level of general psychopathology (Spinhoven et al., 2004). These results suggest that dissociation as mostly measured with the Dissociative Experiences Scale (DES) (Bernstein & Putman, 1986) or even the concept itself may be confounded with the general level of psychopathology (van IJzendoorn & Schuengel, 1996). Taken together these findings suggest that dissociative mechanisms might underlie the relation between trauma and MUS in only a subgroup of patients with MUS.

Further considerations limit the dissociation model as an explanatory model. The term dissociation is peculiar in the sense that it can be used descriptively to denote a class of phenomena, but also in a more mechanistic way to denote the mechanisms which are supposed to produce the phenomena in question. It has been noted by several authors that the term dissociation has been increasingly used in such an over-inclusive way that it has lost its explanatory power (e.g. Frankel, 1994). In clinical practice but also in (case) studies the term can refer to almost any symptom involving some loss of control or subjective experience. However, it can be seriously questioned whether phenomena such as depersonalization, derealization, bingeing, etc. are due to the profound alterations in perception, memory and personal identity which are characteristic of dissociation (American Psychiatric Association, 1994). On the other hand it has also been pointed out that the term is now used in an under inclusive way and does not refer to either positive and/or somatoform dissociative phenomena (Van der Hart, Nijenhuis, Steele, & Brown, 2004). Extending the boundaries of the term in this way, however, carries the risk that a still wider array of phenomena (such as intrusive memories) will be called dissociative without sufficient justification.

Recently, Holmes et al. (2005) proposed that in defining dissociation a distinction should be made between ‘detachment’ (i.e. an altered state of consciousness characterized by a sense of separation from the self or the world) and ‘compartmentalization’ (i.e. an inability to deliberately control actions or cognitive processes that would normally be amenable to such control)¹. By delineating compartmentalization as a category of dissociation, this definition brings phenomena such as dissociative amnesia and unexplained neurological/somatic symptoms under one single heading. Although the definition is consistent with Janet’s (1907) original account that conversion symptoms arise from a separation of traumatic material from consciousness, the definition is broader, no longer stipulates that dissociative amnesia or MUS result from trauma exposure and emphasizes functional dissociation of different levels of information processing. However, contemporary dissociation models are still not specific enough to specify when, why and at what level information processing will fail. As will be discussed later, dissociation models could be further specified by being more informed by theory and research from main stream cognitive psychology, such as cognitive hierarchical models (Brown, 2004). Before discussing these cognitive models, we will first briefly describe conversion models that form another category of influential historical theories.

3.2. Conversion models

3.2.1. Global description

Also at the end of the 19th century, Freud, partly as a reaction to the dissociation model of Janet, introduced the concept of conversion. In this view the somatic presentation of problems is considered to be a defense against overwhelming negative emotions. The underlying mechanism of conversion is conceptualized in terms of an energetic model according to which the brain tries to regulate the conscious experience of negative affect by suppressing the conscious recall of painful memories associated with trauma exposure. Although this process of suppression initially protects the person from overwhelming negative affect, neural energy associated with the affect cannot be discharged in the usual fashion. Consequently the energetic balance is compromised and the negative affect is “converted” into somatic symptoms that were present at the time of trauma exposure or are a symbolic representation of it. According to this view a person can express distress by developing MUS without being consciously aware of the negative affect or conflict responsible for it. The primary gain of developing MUS as a defensive reaction is the reduction of anxiety. According to conversion theory this is often expressed as an apparent lack of concern about the somatic symptoms (*la belle indifférence*). Additional benefits resulting from MUS, such as receiving positive outcomes (e.g. attention) or avoiding negative outcomes (e.g. avoidance of work) are seen as a form of secondary gain. In the first versions of his model, Freud regarded conversion as the result of factual early childhood abuse, while in subsequent revisions memories of abuse were seen as reflecting an unresolved unconscious conflict evoked by the repression of sexual fantasies concerning the opposite sex parent.

3.2.2. Discussion

Empirical support. Especially in retrospect it is astonishing how influential the conversion model has been in theorizing about MUS and in shaping the emphasis on repressed emotions in medical practice given the absence of systematically collected data supporting the conversion hypothesis. Although the original ideas about the discharge of psychic energies were discarded long ago, the idea of a kind of conversion of psychic conflicts into somatic symptoms continues to be widely endorsed in some parts of the scientific community and among the lay public.

Limitations. It can be seriously doubted whether conversion models adequately account for the core clinical and research data on MUS as the empirical support for their major assumptions is lacking or weak. As far as primary gain, there are only two group studies testing the assumption that MUS may solve emotional conflict or distress. Both studies claimed that MUS were rated as ‘offering a solution to conflict’ (Raskin, Talbott, & Meyerson, 1966) or ‘serving a defensive and expressive function’ (Bishop & Torch, 1979). However, it remains unclear how the ratings were made,

¹ This concept of compartmentalization stresses the ongoing normal operation of control processes or actions apart from their inaccessibility to volitional control. In principle other syndromes with these features could be included under this concept (such as fugue and Dissociative Identity Disorder (DID)), but the nosological status of these disorders remains controversial and needs further study. From a DID perspective, the non-volitional and non-intentional character of MUS could even be considered to constitute a volitional and intentional action of a dissociative part of the personality, although experienced differently from a first-person perspective. A detailed discussion of the involuntary and non-intentional character of compartmentalization phenomena in MUS and dissociative disorders is beyond the focus of the present article and clearly requires further theoretical elucidation and empirical investigation.

making it hard to judge the validity of these studies (see Brown, 2005). Moreover, when individuals are able to successfully convert psychological distress into somatic symptoms one would expect low levels of psychological distress in MUS. However, this prediction runs counter to the rather robust findings of elevated levels of psychological distress in the majority of persons with MUS (Simon & Von Korff, 1991). Somatic and emotional distress prove to be highly positively correlated rather than inversely correlated as suggested by conversion models (Kroenke, 2003). With regards to ‘la belle indifférence’, an apparent lack of concern about being symptomatic is not only observed in (a minority of) patients with MUS but also in patients with organic disorders (Gould, Miller, & Goldberg, 1986). Studies by Raskin et al. (1966) and Chabrol, Peresson and Clanet (1955) suggested that it may be just as common in organic controls as in patients with MUS. The same holds for the assumption that MUS are maintained by secondary gains. Several studies have shown that secondary gains are important in medical conditions as well (for a review see Brown, 2005). Also the presupposition of psychosocial or emotional precipitants has been criticized because in many individuals with MUS no evidence for such precipitants has been found (see Section 2). Taken together these findings suggest that emotional and motivational factors might contribute to the development of MUS in only a subgroup of patients with MUS.

As a scientific model, the conversion approach has been accused of circular reasoning that seriously undermines the testability of its core assumptions. In the psychoanalytical approach the absence of psychosocial or emotional conflicts can be interpreted as an inability to describe such problems because repression has rendered them unconscious. Especially when the MUS are not seen as a direct expression of such conflicts but as a symbolic manifestation thereof, the model becomes almost immune to falsification. In addition, the concept of repression as a putative mechanism has been criticized. In his well known review of sixty years of research into repression Holmes (1990) concluded that there is no empirical evidence whatsoever for repression in the original Freudian sense of the term.

On the other hand, more recent theories have yielded an alternative account for the unavailability of memories for trauma and concomitant bodily reactions. This idea is, for example, elaborated in emotion-regulation models, in which the tendency to suppress emotional expression or the inability to cognitively elaborate emotional conflicts is stressed (see e.g. Waller & Scheidt, 2006). In these models, instead of a specific relationship of early trauma with MUS, a more specific link of suppression of emotion and inhibition of verbal response to trauma with subsequent somatic distress is hypothesized. Related concepts such as repression-sensitization, ‘alexithymia’ (literally meaning ‘no words for feeling’; Sifneos, 1973), levels of emotional awareness, level of thinking, etc. all refer to the same theme of suppression of emotions or hypocognition of strong emotions. It is assumed that these impairments in emotion regulation will lead to more prolonged emotional arousal and/or strong bodily focus, which in turn will produce higher levels of somatic symptoms and distress. As far as empirical evidence, there are several studies on alexithymia in MUS. Data on the association of early sexual and physical abuse with alexithymia remain inconclusive, however (see Kooiman et al., 2004). Some recent cross-sectional and longitudinal studies in which MUS was diagnosed on the basis of a medical diagnosis and in which anxiety and depression have been considered as possible confounding factors also showed that general alexithymia was not associated with MUS after accounting for negative affect among patients attending an internal medicine outpatient clinic or visiting their primary care physician; in addition, general alexithymia did not predict outcome of MUS during a 6–12 months follow-up (De Gucht, Fischler, & Heiser, 2004a,b; Kooiman, Bolk, Brand, Trijsburg, & Rooijmans, 2000).

In conclusion, with respect to MUS in the form of functional somatization, only dissociation models find solid empirical evidence but omit to specify at what level or stage information processing fails. Such specification could be refined by being more informed by theory and research from main stream cognitive psychology as well as current neurobiological stress research. Moreover, the assumption in contemporary emotion-regulation models that deficits in regulating emotions may result in prolonged physiological reactions or bodily focused attention leading to somatization seems valuable but lacks sufficient empirical support in its current form. Both prolonged physiological activation and bodily focused attention are conceptualized as important mechanisms of MUS in current cognitive hierarchical models discussed below.

3.3. Cognitive hierarchical models

3.3.1. Global description

A recent major development in conceptualizing MUS is the creation of cognitive models (Brown, 2004; Oakley, 1999; Kirmayer & Taillefer, 1997). Most of these models involve a hypothetical integration of previous theories of

MUS and share many similarities with existing dissociation theories. Similar to dissociation theories, functional complaints are, for example, ascribed to functional dissociations between the experience of volition and the control of thought and action (Oakley, 1999; Brown, 2004). The integrated models of Brown and Oakley are, however, more explicitly based on current hierarchical cognitive models of attentional control (e.g. Norman & Shallice, 1986; Shallice & Burgess, 1996). In their model, Norman and Shallice (1986) described a higher-level executive control system, the supervisory attentional system (SAS) that, for the greater part is localized in the prefrontal cortex. It is conceived of as monitoring ongoing activity and modulating behavior when established automatic routines are not sufficient, as, for instance, in novel situations. Automatic routines are in their turn controlled by a hierarchical lower-level control process, involving a series of well-learned behavioral units or schemata that can be activated by environmental and contextual stimuli through a decentralized and semi-autonomous process called “contention scheduling” (see also Shallice & Burgess, 1996). In their models, Oakley (1999) and later Brown (2004) argued that MUS arise when the chronic activation of symptom related ‘mental representations’ stored in memory cause the lower-level attentional selection process of contention scheduling to select inappropriate sensory information or motor programs, resulting in a misinterpretation of the sensory world or a lack of motor activation, respectively.

Although the cognitive models of Oakley and Brown provide a cognitive explanation of how MUS can develop in the absence of a trauma, the model of Brown also explicitly incorporates trauma as an important source in the acquisition of symptom-related representations. Following the cognitive-behavioral tradition, Brown reviews putative predisposing (vulnerabilities), precipitating (antecedents), moderating (maintaining) and consequential (reinforcing) factors in MUS. In the model, the sensory-motor experiences associated with not only physical illness but also potentially traumatic events (e.g. Crimlisk et al., 1998; Fallik & Sigal, 1971) are examples of precipitating factors that may form the basis for symptom-related cognitive representations. For example, the sensory-motor components of defensive reactions during traumatic events, such as freezing (Nijenhuis et al., 1998), analgesia (Nijenhuis, Vanderlinden, & Spinhoven, 1998) or violent motor reactions (Ludwig, 1972) will leave representations in memory. During an overwhelming traumatic experience the normal fear-regulating processes may fail and the SAS may be involved in increasing the salience of the somato-sensory aspects of the trauma by diverting its resources from self-regulation and focusing attention on the body. The retrieval of intense somato-sensory representations associated with a traumatic event is one factor that may account for medically unexplained symptoms (Brown, 2004; Ludwig, 1972; Nijenhuis et al., 1998). Besides direct exposure to physical and emotional states associated with trauma, Brown (2004) distinguishes other types of precipitating factors that may lead to symptom related mental representations, such as indirect exposure to physical states in others, socio-cultural transmission of information about health and illness and verbal suggestion.

As far as moderating factors in the model, attentional processes such as the recurrent reallocation of attention onto symptoms by the SAS is the primary pathogenic factor in the development of symptom chronicity. An important example is self-focused attention. Self-focused attention may lead to increased awareness of bodily sensations and enhanced reports of bodily symptoms. If symptom focused attention is maintained for a long period of time, the activation of symptom related representation may become chronic. Other examples of moderating factors that play a role in the model are illness worry or behavioral responses such as reassurance seeking.

3.3.2. Discussion

Empirical support. An important strength of hierarchical cognitive models above other models of MUS is that they integrate modern insights on attentional information processing with existing dissociation and emotion-regulation models of MUS. As a consequence, the empirical evidence for these models comes from different disciplines. In the past twenty years various series of cognitive experiments have offered support for a hierarchical organization of human attentional control (e.g. Shallice and Burgess, 1996). Moreover, in the section ‘dissociation models’ we have reviewed important support for the assumption that higher and lower level information processing may be dissociated in MUS. Finally, there is good evidence that the direction of attention towards the self may lead to increased reports of subjective physical symptoms (e.g., Pennebaker & Brittingham, 1982; Robbins & Kirmayer, 1986; Robbins & Kirmayer, 1991; Wegner & Guiliano, 1980).

An important strength of hierarchical cognitive models of MUS is that they explain that the symptoms may be generated by psychological mechanisms but are not necessarily produced intentionally. It is also explained why the symptoms are experienced as non-volitional. According to Brown (2004) the experience of volition is associated with operation of the SAS, while the ultimate locus of cognitive and behavioral control occurs with the lower-level control

system where schemata underlying routine action are automatically activated. An important feature of cognitive models in the context of this article is that they provide an explanation of how MUS can develop in the absence of a trauma. On the other hand the previous sections showed that a traumatic history is common in MUS and the cognitive theory of Brown (2004) explicitly incorporates trauma as an important source in the acquisition of symptom-related representations. An advantage of this model is that the development of MUS is described in terms of retrieval of encoded somato-sensory aspects of the trauma and not in terms of a symbolic representation of the underlying dynamics as proposed by the conversion model. Another important aspect of the model is that it offers an explanation of how an overwhelming traumatic experience may lead to a trait-like vulnerability to develop new unexplained symptoms such as those observed in somatization disorder. Brown proposes that focusing attention on the body may become a habitual way of dealing with negative affect and stressful events when other self-regulatory strategies are unavailable.

Limitations. A limitation of Brown's model is that the underlying neurobiological correlates remain implicit. Brown's model is largely based on the work by Norman and Shallice (1986) who localize attentional processes by the SAS in the prefrontal cortex. However, the anatomic correlates of the proposed cognitive processes and the mechanisms by which certain mental representations are "privileged" remain unspecified. Another drawback is that it does not explain how traumatic stress may lead to prefrontal deregulations. Important new insights from neurobiological stress research should be integrated to explain the proposed relations.

4. Towards an integration of neurobiological and cognitive accounts of MUS

Although patients with MUS receive no medical diagnosis that can fully explain their symptoms, several plausible physiological mechanisms by which MUS may be generated have been identified. In general there are two important lines of evidence, namely brain imaging studies, which are strongly indicative of CNS modulation of symptom experience in various somatoform disorders, plus other studies indicating altered responsiveness of central stress systems, in particular the Hypothalamus Pituitary Adrenal (HPA) axis (Heim, Ehler, & Hellhammer, 2000; Kirmayer, Groleau, Looper & Dominice, 2004; Mayer & Collins, 2002; Mayer, Naliboff, Chang, & Coutinho, 2001). Although other physiological alterations are also associated with MUS, such as autonomic nervous system changes, we have chosen to limit the present review to a discussion of alterations in HPA-axis and CNS functions. In the first place, alterations in the glucocorticoid stress system and CNS have recently gained attention in studies on the pathophysiology of MUS. In the second place they are of potential value in explaining how stress and traumatization may be related to the alterations in prefrontal attentional processing, as proposed by hierarchical cognitive models of MUS. As will be indicated, the effects of glucocorticoids involved in the stress response may have great impact on prefrontal functions.

Below, we will first describe a general stress model that has been implicated in a wide range of psychiatric disorders, such as depression and post traumatic stress disorder, and was recently applied in IBS (Mayer et al., 2001). Thereafter we will review the evidence for the changes in the glucocorticoid stress system and central nervous system proposed by Mayer et al. (2001). Whereas Mayer's et al. (2001) model is limited to the case of IBS we will review the evidence for the proposed relations for a broader range of MUS.

Mayer et al. (2001) proposed a model in which alternations in the central stress systems in predisposed individuals are triggered by pathological stressors and play a primary role in the pathophysiology of MUS. The model is largely based on contemporary biological stress theories (McEwen, 1998) that have been implicated in various forms of psychopathology. According to the model the individual's response to stress is generated by a network of integrative brain structures involving sub regions of the hypothalamus (paraventricular nucleus, PVN), amygdala and periaqueductal gray. These structures receive input from visceral and somatic afferents and from cortical structures, in particular the ventral subdivision of the anterior cingulate cortex (ACC) and medial prefrontal (ventromedial and orbitofrontal) cortices. This integrative network provides outputs to the pituitary and to the pontomedullary nuclei. The latter structures respectively mediate the neuroendocrine and autonomic output to the body.

This central stress circuitry is under feedback control via noradrenergic and serotonergic projections from the brainstem and via glucocorticoid pathways, which exert an inhibitory control via glucocorticoid receptors located in the hippocampus and the medial prefrontal cortex (mPFC). The stress response of this central circuitry includes responses of the autonomic nervous system, the HPA-axis, endogenous pain modulatory systems and ascending aminergic pathways.

The individual's stress responsiveness is not only under genetic control but is also influenced by early traumatization and forms of pathological stress, which may result in long lasting and even permanent changes in the

central stress circuitry (e.g. Anisman, Zaharia, Meaney & Merali, 1998; Elzinga, Schmall, Vermetten, van Dyck, & Bremner, 2003; Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; McEwen, 1998; Salpolsky, 1997). These changes may in turn lead to autonomic nervous response changes, neuroendocrine changes, changes in immune and pain modulation, and changes in regional brain activation. Mayer et al. (2001) extensively reviewed the evidence for the proposed relations with respect to IBS. Two aspects of this model in particular (i.e. changes in HPA-axis reactivity and CNS activity, respectively) currently gain great attention in the broader context of various somatoform disorders and will be extracted and reviewed for a wider range of MUS here.

5. A review of neurobiological findings in various MUS samples

Changes in HPA axis reactivity. The model by Mayer et al. (2001) draws significantly from previous studies in patients with PTSD who have been found to show hypocortisolism and increased feedback inhibition of the pituitary–adrenal level of the HPA-axis (Yehuda, Giller, Levengood, Southwick, & Siever, 1995). Also for patients with varying types of MUS, including CPP, IBS, burnout and fibromyalgia, indications for hypocortisolism have been observed (for reviews see Bohmelt, Nater, Franke, Hellhammer, & Ehlert, 2005; Heim et al., 2000). Heim et al. (2000) hypothesized that, due to the lack of the protective properties of cortisol, sustained hypocortisolism may play a causal role in the development of MUS. Hypocortisolism, has however also been observed in healthy individuals living under ongoing stress (for a review see Heim et al., 2000) and it is hard to determine whether it is a cause or consequence of MUS. Moreover, although there are many examples of hypocortisolism associated with CPP, IBS and burnout, there are also examples of increased (Rief, Shaw, & Fichter, 1998) or no (Rief & Auer, 2000) changes in basal cortisol levels in patients with somatization disorder compared to healthy controls. In addition, for patients with conversion disorder decreased suppression of cortisol was found on a dexamethasone suppression test (Tunca et al., 1996). Finally, it should be noted that in patients with PTSD besides low baseline cortisol levels, increased stress induced cortisol levels were found after a psychological stress induction using trauma scripts (Elzinga et al., 2003). Also Heim et al. (2001) studied women with and without a history of childhood abuse and found early abuse to be related to increased neuroendocrine stress-reactivity (adrenocorticotropin: ACTH and cortisol responses) on a psychosocial laboratory stressor. The increased neuroendocrine stress responses were further enhanced when additional trauma was experienced in adulthood. To our knowledge there are no studies using psychological challenge tests in patients with MUS.

Thus, in line with the proposed model there are indeed indications for deregulations of the HPA-axis in patients with various somatoform disorders, although the findings for somatization and conversion disorders in particular, are equivocal. A possible explanation of the contradictory findings may be related to the type of stressor subjects have been exposed to. Unpredictable chronic stress is associated with habituation, whereas single intense stress events may induce sensitization of the HPA-axis (Liberzon, Krstov, & Young, 1997; Yehuda & Antelman, 1993). Other authors suggest that HPA-axis activity in traumatized individuals may change over time. Hellhammer and Wade (1993) and Wang et al. (1996), for example, found that initial HPA-axis hyperactivity was followed by hypoactivity, presumably due to a process of down-regulation of the HPA-axis. It should also be noted that genetic factors play an important role in the proposed models. According to Mayer's model early life stress and severe life-threatening stress may result in permanent changes in the glucocorticoid stress-responsiveness in genetically predisposed individuals. To further examine this hypothesis, future studies also employing psychological challenge tests in patients with MUS are clearly needed.

Finally, there are some indications that the effects of altered HPA-axis functions due to stress may occur via the immune system (e.g. Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Glucocorticoids suppress the production of proinflammatory cytokines that are normally released during stress (e.g. McEwen et al., 1997; Maier & Watkins, 1998). Hypocortisolism may therefore result in increased inflammatory responses in patients with MUS (Heim et al., 2000; Fries, Hesse, Hellhammer, & Hellhammer, 2005). There is indeed increasing evidence that proinflammatory cytokines may exert pain facilitatory effects following their release in the body, brain and spinal cord (for reviews see Watkins & Maier, 2000; Dantzer, 2005). Also, increased cytokines were observed in patients with IBS (O'Mahony et al., 2005), chronic fatigue syndrome (Patarca, 2001) and fibromyalgia (Maes et al., 1999; Thompson & Barkhuizen, 2003). However, other studies indicated unchanged or lower immune activity in chronic fatigue and fibromyalgia (Amel, Kasphipaz, Swinden, Todd, & Powel, 2003; Landis, Lentz, Tsuji, Buchwald, & Shaver, 2004). Interestingly, lower immune (T-cell) activity was also found in abused versus nonabused women (Constantino, Sekula, Rabin, & Stone, 2000). Evaluating these findings, the proposed relation between early abuse, hypocortisolism, increased immune activity and MUS is still uncertain. Also a direct causal link between immune dysfunction and the severity of MUS still

needs to be established. From a recent literature review [Schwetz, Bradesi and Mayer \(2004\)](#), for example, concluded that chronic inflammatory mucosal changes in the gut are not a plausible mechanism to explain the presence of abdominal pain in IBS. Instead, the altered perception of visceral stimuli seemed to play a key role, suggestive of a more pronounced role of central rather than peripheral mechanisms.

In sum, there are indications for deregulations of the HPA-axis in patients with various somatoform disorders. Most studies point at hypocortisolism, although the findings for somatization and conversion disorders in particular, are equivocal. It remains unclear to what extent the effects of altered HPA-axis functions due to stress may occur via the immune system. Finally, it is important to note that the altered HPA-axis functions have been observed in a wide range of psychiatric disorders, including mood (depression), anxiety (post traumatic stress disorder) and somatoform disorders. Although the observed alterations in HPA-axis functioning may be relevant for explaining common mechanisms underlying these forms of psychopathology, they cannot sufficiently explain why a subgroup of patients with altered HPA-axis functions develop functional symptoms such as specific pain responses or functional paralysis. In the next section we will review the evidence for changes in CNS modulation in MUS and investigate whether there is a specific relation with these conditions.

CNS modulation of MUS. A second important factor in the models of [Mayer et al. \(2001\)](#) and [Kirmayer et al. \(2004\)](#) is that the CNS may mediate the effects of psychosocial stress factors on the production of physical symptoms ([Weiner, 1992](#)). Evidence comes from brain imaging studies in various somatoform disorders pointing at altered activation in frontal inhibitory structures such as the ACC and orbitofrontal cortex. Several studies have, for example, shown decreased activity in the ACC in patients with IBS during pain stimulation, which was largely interpreted as a disruption of the normal antinociceptive responses to sensory stimulation such as a failing inhibition of conscious perception of aversive visceral events ([Wilder-Smith et al., 2004](#); [Ringel, et al., 2003](#); [Mayer et al., 2005](#); [Silverman et al., 1997](#)). Interestingly, the absence of normally observed increases in ACC activation to noxious visceral stimuli was found to be strongest in abused patients with IBS, compared to non abused IBS patients and healthy controls ([Ringel et al., 2003](#)). However there are also studies suggesting increased ACC activation in IBS ([Chang et al., 2003](#); [Mertz et al., 2000](#); [Naliboff et al., 2001, 2003](#)). Also in conversion disorder there are studies pointing at increased rather than decreased ACC activity. Simultaneous activation of frontal inhibitory areas and deactivation of primary motor and somatosensory cortex in conversion paralysis ([Marshall et al., 1997](#)), hysterical anesthesia ([Maillis-Gagnon et al., 2003](#); [Tiihonen et al., 1995](#)) and unexplained visual loss ([Werring, Weston, Bullmore, Plant, & Ron, 2004](#)), has been interpreted as indicative of an active inhibition of motor and sensory processing in conversion disorder. Moreover, the findings of a recent ERP study were indicative of hyperactive ACC action monitoring functions playing a part in conversion paralysis ([Roelofs, de Bruijn, & van Galen, 2006](#)). [Vuilleumier et al. \(2001\)](#), however, found no changes in ACC but rather in subcortical regions (thalamus and basal ganglia) during sensory stimulation in CD patients with sensorimotor loss.

In sum, many studies in patients with various MUS suggest a role of the CNS in symptom perception and generation. However the exact features of alterations differ across the various studies and may be largely dependent on the patient and stimulus-response selection. Although most studies in IBS point in the direction of decreased ACC and prefrontal activation, studies in CD point at increased or no changes in ACC and other prefrontal structures. As far as the HPA-axis is concerned, we can similarly conclude that deregulations are common in various MUS. Although most studies in IBS and CPP point in the direction of hypocortisolism, the scarce evidence for CD/SD suggests hypercortisolism. It remains unstudied whether decreased cortisol levels and decreased PFC activation on the one hand and increased cortisol levels and increased PFC activation on the other hand are related.

5.1. Towards an integration

For several reasons it is important to integrate these neurobiological findings with cognitive models of MUS. In the first place, according to the cognitive model of [Brown \(2004\)](#), trauma is predominantly suggested to serve as a *precipitating* factor in the generation of MUS. The above described neurobiological models (e.g. [McEwen, 1998](#)) however explain that early traumatization may also serve as a *predisposing* factor. This factor makes the central stress system more vulnerable to the effects of later stressors that in turn may serve as precipitating factors for symptom onset and also affect symptom manifestation. In the second place, the findings of altered CNS modulation in various forms of MUS may offer an explanation of the failure in SAS (located in the PFC, in particular ACC) modulation of attention to sensory information and stored mental representations in memory. The strong connections between the limbic system and the prefrontal cortex may explain how stress and stress induced cortisol may affect the PFC. However, in both cognitive models of MUS (e.g. [Brown, 2004](#)) and pathophysiological models of MUS (e.g. [Mayer et al., 2001](#);

Kirmayer et al., 2004) it remains largely unclear how psychological stress may affect these prefrontal functions. Whereas Brown (2004) made no predictions in this respect, Mayer et al. (2001) argued that enhanced noradrenalin (NA) release during stress may be associated with the alterations in prefrontal and hippocampal deactivations in IBS. However the mPFC/ACC and hippocampus are targets for the stress hormone cortisol as well (e.g. Cerqueira, Catania, et al., 2005; Cerqueira, Pego, et al., 2005; Meaney & Aitken, 1985; Radley et al., 2004; Sanchez, Young, Plotsky, & Insel, 2000; Wellman, 1993). The findings of two recent human studies suggest that prefrontal functions such as working memory (Elzinga & Roelofs, 2005) and the generation of active approach and avoidance behavior (Roelofs, Elzinga, & Rotteveel, 2005) are impaired during stress, but only when both cortisol levels and NA levels are significantly increased. Thus glucocorticoid stress responsiveness may be an important factor mediating the effects of stress on prefrontal functions. These findings are in line with animal studies showing that (prefrontal generated) active approach and avoidance behavior is diminished and freezing responses are increased in animals with increased HPA-axis stress reactivity (e.g. Nunez et al., 1996). Freezing can be regarded as a form of stress induced behavioral inhibition that resembles the tonic immobility often observed in motor conversion disorder. The findings suggest that especially HPA-axis stress reactivity is important in explaining the relation between early and later traumatic experiences and impaired frontal executive functions that may be implicated in functional motor and sensory complaints.

Future research examining such links between stress and alterations in frontal emotion-regulating functions are of great importance to evaluate the validity of cognitive and emotion regulation theories described earlier. These theories draw significantly on increased attention to bodily sensations and illness related cognitions and indirectly imply a great role for stress on the prefrontal cortex.

6. General conclusions

The first purpose of the present review was to investigate systematically the evidence for the assumed relation between trauma and MUS in a subset of patient samples presenting with functional somatization. Second, we aimed to critically review three dominant models explaining the relation between trauma and MUS (i.e. dissociation, conversion and hierarchical cognitive models). The latter model appeared to be of particular explanatory value and was found to have a firm basis in contemporary information processing theories. Nevertheless, the cognitive model remains unspecified with respect to the neurobiological correlates of the proposed relations between traumatic stress and changes in attentional processing. The final purpose of the present paper was, therefore, to review current neurobiological studies associated with trauma and MUS and to formulate a research agenda to integrate these neurobiological developments with cognitive models for MUS. The following conclusions can be drawn from this investigation.

- 1) Compared to controls, patients with MUS generally report higher trauma rates.
- 2) In the majority of the controlled studies on abuse reports in patients with MUS, the relation between trauma and symptom severity was not measured or reported. In those studies in which it was reported this relation was confirmed for IBS, CD and SD. The findings for CPP were weaker and more ambiguous.
- 3) Only 4 of the presently reviewed 33 controlled studies of trauma in MUS reported a mediation analysis, of which 3 identified one or more psychological factors that (partially) mediated the relation between trauma and MUS. Some mediation analyses did not follow common statistical mediation rules (Baron & Kenny, 1986) and all studies pointed at different mediators (dissociation, emotional distress, hypnotic susceptibility, family dysfunction or somatization). Although the present review was not primarily focused on mediation studies and there may be good mediation analyses in uncontrolled studies that were excluded from the present review due to the lack of group-control, these findings strongly suggest that there is a great lack of systematically conducted mediation studies.
- 4) Hierarchical cognitive theories of MUS form an integration of dissociation, emotion regulation and contemporary information processing theories. They most adequately account for the non-volitional and non-intentional character of MUS and explain how traumata can affect the development of MUS without assuming that previous trauma is a necessary prerequisite of MUS. However, they remain non-specific about the neurobiological correlates of the proposed relations between traumatic stress and changes in attentional processing.
- 5) Neuroendocrinological studies have shown that early traumata can have long lasting effects on the stress-sensitivity of the HPA-axis and that may, specifically in reaction to later stressors, be associated with increased chances of MUS.

6) HPA-axis deregulations are common in various subtypes of MUS. However, most studies in IBS and CPP point in the direction of hypocortisolism, while the scarce evidence for CD/SD points at features of hypercortisolism.

7) Alterations in CNS activations are common in various categories of MUS. Although most studies in IBS point in the direction of decreased ACC and prefrontal activation, studies in CD point at increased or no changes in ACC and other prefrontal structures.

8) These divergent neurobiological findings may support the idea that there are subgroups of MUS that need to be distinguished. There are large differences not only in the manifestation but also in the prevalence of functional complaints. In the general population the incidence and prevalence of functional pain and gastro-intestinal disturbances, for example, is much higher than of pseudo-neurological complaints (Kroenke, 2003). Future studies should be focused more on defining meaningful and empirically validated subgroups of MUS.

9) Finally, it is fruitful to integrate hierarchical cognitive theories with neuro-biological findings in MUS. Such integration leads to specific hypotheses on how traumata and changes in stress-responsiveness affect the changes in attentional functioning proposed by cognitive theories. Recent studies have, for example, shown that the glucocorticoid stress responsiveness greatly affects the impact of stress on prefrontal functions. Moreover, hypotheses can be generated on how increased attention to trauma and bodily cues in turn affects the activity of the central stress circuitry. The present paper offers a first attempt towards an integration between cognitive and neurobiological models for a variety of MUS and stresses the importance of studies in which the effects of stress-induced cortisol on prefrontal executive functions are explored in patients with MUS.

Acknowledgements

This work was supported by a VENI Grant (#451-02-115) from the Netherlands Organization for Scientific Research (NWO) awarded to Dr. K. Roelofs. The authors thank Hanane El Hachoui for helping with the literature search and Bernet Elzinga for her comments on an earlier version of the manuscript.

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