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de Vroege, Lars

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Lars de Vroege

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Diagnostic assessment and clinical characteristics of patients suffering from Somatic Symptom and Related Disorders

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Promotores:	Prof. dr. C.M. van der Feltz-Cornelis (Tilburg University) Prof. dr. K. Sijtsma (Tilburg University)
Copromotor:	Dr. W.H.M. Emons (Tilburg University)
Promotiecommissie:	Prof. dr. A.J.L.M. van Balkom (EMGO VUmc) Prof. dr. J.K.L. Denollet (Tilburg University) Prof. dr. B. Sabbe (Universiteit Antwerpen) Prof. dr. E.J.A. Scherder (Vrije Universiteit Amsterdam) Dr. E.P.M. Brouwers (Tilburg University)

Paranimfen:	C. de Vroege, MSc E. de Heer, MSc

Contents

Introduction and outline of the PhD dissertation

This chapter is partly based on:

De Vroege, L., Khasho, D., Foruz, A., & Van der Feltz-Cornelis, C.M. (2017). Cognitive rehabilitation treatment for mental slowness in conversion disorder: A case report. *Cogent Psychology,* 4: 1348328.

Introduction

During an intake at the Clinical Centre of Excellence for Body, Mind, and Health (CLGG), GGz Breburg in Tilburg, the Netherlands, a 54-year old woman described her symptoms. She explains that a few months ago, after recently having experienced a high workload, she experienced a significant amount of stress and also suffered from physical symptoms, such as fatigue, heart palpitations, and blurred vision. She attributed these symptoms to stress. However, the next morning her face was drooping, her tongue felt numb, and she stuttered if she tried to speak. A cerebrovascular accident was suspected; hence, extensive neurological examination was performed. However, the examination did not yield a neurological explanation, and she was told that the symptoms were just 'in her head'. She was sent home without treatment. Her symptoms persisted and in addition, she started to experience headaches and neurocognitive symptoms, which were primarily memory problems. A second neurological assessment did not yield abnormalities, and she was referred to CLGG.

During the intake, the woman said she forgot more things than she was used to, and could not remember conversations. During intake, several instruments were used to assess her symptoms. A physical examination yielded no abnormalities. The results of psychological assessment by means of questionnaires, suggested she was depressed (Patient-Health Questionnaire-9, PHQ-9; Kroenke, Spitzer, & Williams, 2001; PHQ-9 score equal to 11), experienced pain (Brief Pain Inventory, BPI; Tan, Jensen, Thornby, & Shanti, 2004; BPI score equal to 5), had physical symptoms (Physical Symptom Checklist, PSC; Van Hemert, 2003; PSC score equal to 85), but did not report anxiety symptoms (General-Anxiety Disorder-7, GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006; GAD-7 equal to 5). A neuropsychological assessment (NPA) showed impaired functioning within the domains of memory, which primarily concerned information processing speed, immediate recall and delayed recall. This finding confirmed her subjective memory problems. A psychiatric examination confirmed that she suffered from a conversion disorder, one of the disorders amongst Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (American Psychiatric Association (APA), 2013) somatic symptom disorders and related disorders (SSRD). The diagnosis was explained to the patient, and she agreed to undergo treatment.

First, the woman underwent cognitive behavioral treatment (CBT), which is the preferential treatment according to the multidisciplinary guideline. However, she suffered so much from subjective cognitive symptoms that she was unable to remember the appointments and to perform the assignments for CBT, which resulted in serious non-adherence to treatment. Hence, CBT was stopped and Cognitive Rehabilitation Treatment (CRT) was

started to improve her neurocognitive symptoms. She improved and both her cognitive and her physical symptoms went in remission. However, although this is good news we realized that the whole trajectory of her illness, from first neurological examination until remission of symptoms and end of treatment, took four years while only one year was needed for treatment. Three quarters of the trajectory were used for diagnosis. This case emphasizes the need for diagnostic strategies enabling us to understand somatically unexplained symptoms to offer patients an effective treatment. Furthermore, this case highlights the importance of a wide scope of such assessments. Medically unexplainable symptoms (MUS) comprise more than merely physical symptoms, the diagnostic information provided by current questionnaires may be limited, and (neuro) psychological aspects might be as important to tailor the treatment to the specific needs of patients. This calls for multidisciplinary diagnostic assessments to account for the complexity of SSRD.

This introductory chapter is organized as follows. First, classifications of SSRD are discussed. Second, theories on the development of MUS are briefly discussed with respect to the aim of this PhD dissertation. Third, an overview of assessment tools used so far is provided, and neurocognitive functioning in relation to mental and physical disorders is discussed. This introductory chapter ends with the objectives and an outline of this PhD dissertation.

Unexplainable physical symptoms

Classifications of unexplained physical symptoms

MUS, somatoform disorders and somatization are amongst terminologies that have been used throughout the years for patients that experience significant impairment due to symptoms that could not be explained or not completely explained by a medical disease. These symptoms occur frequently and form a burden for patients, their families, and their doctors. The symptoms present themselves in many health care settings and are associated with substantial work dysfunctioning (Escobar et al., 1987; Rask et al., 2015). A common requirement for classification of MUS used to be that medical doctors were unable to provide a physical explanation for the physical symptoms. This was also the main criterion of the somatoform disorders section in the fourth edition of the DSM-IV text revision (DSM-IV-TR) (APA, 2000). This classification required the absence of a medical explanation for the symptom that was persistent for at least six months and caused significant impairment or distress in functioning. However, the criterion *absence of a medical explanation* has often been criticized (Rief & Martin, 2014; Sykes, 2012), because it is hard to determine if a symptom is medically unexplainable (Barsky, 2016). Doctors often disagree, confusing the

patient. Moreover, critics argue that individual colleagues may experience problems communicating mental problems as medically unexplainable to patients (Frances, 2013). Patients may consider the diagnosis of mental causes insulting, thus causing stress, and stress can provoke many of the symptoms that are candidates for MUS. Stress also accounts as a medical explanation (Kirmayer, Groleau, Looper, & Dominicé, 2004).

In general, somatization, which is *the tendency to experience or express psychological stress as somatic symptoms* (Lipowski, 1968), is considered a mechanism that occurs after stress exposure (Van der Feltz-Cornelis, 2015). Several suggestions were done (Van der Feltz-Cornelis & Van Balkom, 2010) to revise the somatoform disorder classification as mentioned in the DSM-IV-TR (APA, 2000). Furthermore, the classifications of the DSM-IV-TR were found difficult to use in clinical practice. Likewise, SSRD classifies psychological phenomena related to physical symptoms, such as excessive thoughts about pain, which is the so-called B-criterion. Recently, the Somatic Symptom Disorder-B criteria scale (SSD-12) was developed (Toussaint et al., 2016). The SSD-12 is a self-report questionnaire and aims to assess criterion B of the Somatic Symptom Disorder (SSD). SSD is one of the classifications within SSRD (APA, 2013).

Because of these criticisms, the section of somatoform disorders was changed into SSRD in the DSM-5 (APA, 2013). In most cases, this change does not require the absence of a medical explanation. All of the disorders included in the SSRD classification share one prominent feature, which is experiencing somatic symptoms that are associated with significant distress (APA, 2013). In the section of SSD, three criteria are incorporated that resemble the feeling of distress: criterion A, presence of one or more somatic symptoms, which are perceived as very distressing or result in disruption of functioning; criterion B, presence of abnormal, excessive, disproportionate, and maladaptive thoughts, behaviors or feelings related to the symptoms; and criterion C, persistence of the symptoms for at least six months (APA, 2013). The other categories of SSRD are illness anxiety disorder, conversion disorder, factitious disorder, psychological factors affecting other medical conditions, other specified somatic symptoms and related disorders, and unspecified somatic symptoms and related disorders (APA, 2013).

Theoretical models of unexplainable physical symptoms

The focus of classification thus changed from the presence of MUS to coping with somatic symptoms rather than searching for their cause (Barsky, 2016; Rief & Martin, 2014). This shift of focus with respect to classification requires a shift of the diagnostic approach and a different explanation of the symptoms to the patients. Because of the recent

introduction of the DSM-5, this PhD dissertation uses the DSM-IV-TR classification of *somatoform disorders* (APA, 2000), the DSM-5 classification *SSRD* (APA, 2013), and somatization (Lipowski, 1968). Hence, some new theoretical models to explain the onset and the prolongation of unexplainable physical symptoms and models that are relevant to this new development are briefly discussed here.

Mayou, Bass, and Sharpe (1995) describe an explanatory model in which previous experiences with diseases, personality characteristics, emotional states, and psychiatric vulnerability determine how the symptoms are interpreted (Mayou et al., 1995). Robbins and Kirmayer (1991) describe the relationship between cognitive processes and illness behavior in another way (Robbins & Kirmayer, 1991). Physiological changes result in specific physical reactions (e.g., fast heartbeat). These reactions often co-occur with emotions, such as depression or anxiety (e.g., fastened heartbeat). Some individuals misinterpret these physical sensations resulting in enlarged symptoms, known as somatosensory amplification. Somatosensory amplification is a tendency to perceive normal visceral and somatic sensations as disturbing and impairing (Barsky, Wyshak, & Klerman, 1990). The two models share one common feature, which is that not the symptoms themselves but their interpretation is key to the experience of impairing physical symptoms. These models suggest a vicious circle in which emotions and behavior, influence the experience of physical symptoms.

A third model pertains to the relationship between somatization and stressful life events (Van der Feltz-Cornelis, 2015). Stress can lead to MUS (Kirmayer et al., 2004). Stress causes the release of cortisol, a stress hormone that the adrenal cortex produces. Cortisol is released when the pituitary signals by using the adrenocorticotrophic hormone (ACTH). The hypothalamus influences the production of ACTH. The hypothalamus assesses our inner state and combines this assessment with external input (e.g., combining fear with pain). When the hypothalamus senses stress, corticotropine releasing hormone is released and ACTH and cortisol are produced. This is the stress-hormone system, also known as the hypothalamic-pituitary-adrenal axis. Cortisol triggers behavior and decreases pain, leading to an adaptively favorable reaction (Selye, 1950). However, in case of chronic stress, the neural networks in the hippocampus, amygdala, and prefrontal cortex change under the influence of stress (McEwen, 2007; McEwen & Lasley, 2002). Furthermore, usually the hippocampus controls the level of stress but in case of prolonged exposure to stress, this reaction does not occur. This phenomenon leads to atrophy of neurons in the hippocampus and the amygdala. These two brain areas are involved in several neurocognitive processes and may be related to the concentration and memory problems (Squire & Cave, 1991) patients often mention. It is thus

plausible that patients suffering from SSRD, which we assume are exposed to (prolonged) stress, experience neurocognitive problems. Neurocognitive functioning is a characteristic that is present in these patients. However, as far as we know, no studies have explored neurocognitive functioning in patients suffering from SSRD.

Assessment of somatic symptoms and related disorders

In clinical practice, clinicians assess psychological and physical symptoms in different ways. They may use psychiatric and physical examinations, (semi)structured interviews and other psychodiagnostic tests administered by psychologists, neuropsychological and other psychodiagnostic tests administered by trained psychologists, or self-report questionnaires. In general, a psychiatric examination is considered as the gold standard. If such a consultation is impossible, clinicians can revert to (semi) structured diagnostic interviews for DSM disorders such as the Structured Clinical Interview (CIDI) for DSM-IV Axis I Disorders (First & Gibbon, 2004), the Schedules for Clinical Assessment in Neuropsychiatry (Rijnders et al., 2000) or the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). However, for SSRD, so far structured interviews are unavailable. The reason is that theoretical models so far focused mostly on the psychological aspects of SSRD, such as emotions, cognitions and behavior, but until recently, the diagnostic classification focused mainly on establishing if the MUS were medically explainable. This proved to be a fruitless endeavor that did not explore the patient characteristics relevant for treatment, often not leading to treatment, and was illustrated by the individual case described at the beginning of this chapter.

Another possibility to assess symptoms is by means of self-report questionnaires, which can be used for different purposes such as to screen, to determine symptom severity, or to classify (Hiller & Janca, 2003). Examples of such measures include the Whiteley Index (Pilowsky, 1967) and the Illness Attitude Scale (Kellner, 1987) for assessing hypochondriasis, the PSC (Van Hemert, 2003; Van Hemert, De Waal, & Van Rood, 2004) and the Patient Health Questionnaire-15 (PHQ-15; Kroenke, Spitzer, & Williams, 2002) for assessing severity of physical symptoms. The PHQ-15 claims to enable assessment of somatoform disorders, and it is the questionnaire most often used for assessing somatic symptoms and screening for somatoform disorders (Kroenke, Spitzer, Williams, & Löwe, 2010). However, the PHQ-15 does not differentiate between MUS and medically explained symptoms (Körber, Frieser, Steinbrecher, & Hiller, 2011), and even though the questionnaire is validated, it is only moderately reliable for detection of individual differences with respect to somatoform disorders in primary care (Van Ravesteijn et al., 2009). The 4-Dimensional

Symptom Questionnaire (4DSQ; Terluin, Rhenen, Schaufeli, & De Haan, 2004) contains a somatization subscale that has been validated (Braam et al., 2009; Koorevaar, Terluin, Van't Riet, Madden, & Bulstra, 2015; Terluin et al., 2006). These questionnaires mainly focus on physical symptoms. One can argue whether these kinds of questions capture the full spectrum of unexplained physical symptoms and whether they are suitable for screening for these kinds of symptoms. This PhD dissertation explores the validity of both the PHQ-15 and the 4DSQ somatization subscale in the occupational health care setting.

However, the PHQ-15 measures somatic symptoms, not the misinterpretation of bodily symptoms. A construct that may be relevant here is alexithymia. Nemiah and Sifneos (1970) defined alexithymia as the inability to interpret, talk about, or describe emotions. Patients suffering from a somatoform disorder are prone to express emotions by means of physical symptoms (Van Dijke et al., 2013) rather than identifying and verbalizing emotions (De Gucht & Heiser, 2003; Lieberman, 2007; Luyten, van Houdenhove, Lemma, Target, & Fonagy, 2012). According to Taylor (1984), this is a feature of alexithymia. The expression of emotions through physical distress (Wearden, Cook, & Vaughan-Jones, 2003) induces a vicious circle in which emotions are expressed through physical distress, and the physical distress in turn leads to enhanced emotions, which further increases physical distress. In this way, individuals are unable to regulate emotional reactions and distress (Lane, 2008). One can argue that such a characteristic is related to criterion B of SSRD. Thus, alexithymia is an interesting construct to explore in patients suffering from SSRD, and its assessment may help to recognize somatic symptom disorders.

Other personality constructs are relevant to explore, because comorbid personality disorders are reported frequently in somatoform disorders (Bass & Murphy, 1995; Fink & Schröder, 2010). For instance, somatization was associated with higher level of neuroticism (De Gucht & Heiser, 2003), and lower level of extraversion and conscientiousness (Van Dijk et al., 2016). Another study reported that negative affect determined the number of symptoms reported (De Gucht, Fischler, & Heiser, 2004). Because affect and emotion regulation are pivotal in the development of somatoform disorders (Waller & Scheidt, 2006), a personality construct that also includes maladaptive affect regulation is worthwhile to explore in patients suffering from SSRD. Such a construct is type D (distressed) personality. Several characteristics of individuals with alexithymia reflect the type D personality profile (Topciu et al., 2009). Type D personality is thought to consist of 'not the experience of negative emotions per se, but rather the chronic psychological distress that results from holding back negative emotions' (Denollet, Sys, & Brutsaert, 1995) and was first suggested in studies

among cardiovascular patients (Pedersen & Denollet, 2003). Individuals characterized by type D personality tend to withhold negative emotions from others. More specifically, the type D personality construct combines two traits, social inhibition and negative affectivity. Social inhibition refers to the tendency to suppress the expression of emotions and behaviors in social interactions (Denollet, 2005). Negative affectivity refers to the experience of negative emotions across situations and time (Denollet, 2005). These two aspects of type D personality can be measured by means of the type D personality scale (DS14), which measures both negative affectivity and social inhibition (Denollet, 2005).

Aims and outline

This PhD dissertation aims to contribute to the solution of several problems with respect to the diagnostic assessment of patients suffering from SSRD and to explore the clinical characteristics of patients suffering from SSRD. The research was done in a specialty mental health institution and occupational health-care setting. Depending on the setting, patients suffering from SSRD may have different characteristics. This PhD dissertation comprises three parts.

Part one consists of chapters 1, 2, 3, and 4, and is titled 'Diagnostic assessment and clinical characteristics'. Chapters 1 and 2 adopt the DSM-IV-TR line of thought, assuming that the key feature of MUS is that they are medically unexplained, and explores the use of two questionnaires that assess somatoform disorder. The validity of the PHQ-15 and the 4DSQ Somatization subscale was investigated in the occupational health care setting. Both instruments are frequently used to assess MUS, and mainly measure physical symptoms to explore if they enable the occupational physician to screen for somatoform disorder. Chapters 1 and 2 present the results.

In chapter 3, alexithymia is investigated in the general population and in patients suffering from SSRD because alexithymia may be a feature of patients suffering from SSRD. In particular, chapter 3 reports the validity of the Bermond-Vorst Alexithymia Questionnaire in the Dutch general population ($N = 974$) and provides normative data for assessing alexithymia in SSRD samples. Chapter 4 focuses on neurocognitive symptomatology in patients suffering from SSRD and discusses the clinical implications. Patients often report neurocognitive problems in the clinic and if patients experience significant memory problems, a cognitive behavioral therapy might not be efficient. This chapter explores neurocognitive functioning in patients suffering from SSRD ($N = 201$) in the Clinical Centre of Excellence for Body, Mind, and Health, across a broad range of neurocognitive domains.

Part two consists of chapters 5 and 6 and is titled ‘Treatment outcomes in relation to clinical characteristics’. Chapters 5 and 6 focus on alexithymia and Type D personality, respectively, because these characteristics are considered to play a pivotal role in the etiology of somatoform disorders or SSRD. Clinically, these characteristics are highly relevant, because if a patient is unaware of his or her feelings and somehow cannot express them, physical symptoms or misinterpretation of symptoms can occur. If an association of alexithymia or type D personality with treatment outcome is present, the characteristic or both characteristics would be clinically relevant and should be explored during the diagnostic assessment of patients suffering from SSRD. The information collected should be used for designing the treatment. Chapter 5 explores the association of alexithymia with treatment outcome in patients suffering from SSRD (N = 234). Chapter 6 discusses the association of type D personality with treatment outcome in patients suffering from SSRD (N = 230). Finally, the epilogue summarizes the findings, strengths and limitations of this PhD dissertation and implications for future research are discussed.

Part one
Diagnostic assessment and clinical characteristics

Chapter 1

Validation of the PHQ-15 for somatoform disorder in the occupational health care setting

This chapter is based on:

De Vroege, L., Hoedeman, R., Nuyen, J., Sijtsma, K., & Van der Feltz-Cornelis, C.M. (2012). Validation of the PHQ-15 for somatoform disorder in the occupational health care setting. *Journal of Occupational Rehabilitation*, *22,* 51-58.

Abstract

Within the occupational health (OH) setting, somatoform disorders are a frequent cause of sick leave. Few validated screening questionnaires for these disorders are available. The aim of this study is to validate the Patient Health Questionnaire-15 (PHQ-15) in the OH setting. In a cross-sectional study of 236 sick listed employees, we studied the performance of the PHQ-15 in comparison with the Mini International Neuropsychiatric Interview (MINI) as golden reference standard. We approached employees who were sick listed for a period longer than six weeks and shorter than two years for participation. This study was conducted on one location of a large OH service in the Netherlands, serving companies with more than 500 employees. All employees who returned the PHQ-15 were invited for the MINI interview. Specificity and sensitivity were calculated to determine the optimal cut point. A receiver operating characteristic (ROC) was constructed and 95% confidence intervals (95% CI) were calculated for validation scores. A total of 107 patients consented to participate in the MINI interview. A non-response analysis showed no significant differences between groups. According to the MINI, the prevalence of somatoform disorders was 21.5%, and the most frequently found disorder was a pain disorder. The PHQ-15 had an optimal cut point of 10 (i.e., patients scoring 10 or higher (≥ 10) were most likely to suffer from a somatoform disorder), with specificity and sensitivity equal to 70.2% (95% CI*:* (59.8%; 79.0%)) and 52.2% (95% CI: (33.0%; 70.8%)), respectively. ROC showed an area under the curve of 0.63 (*SE* = 0.07, 95% CI: (0.50; 0.76)). The PHQ-15 shows moderate sensitivity but limited efficiency, has a cut point of 10, and can be a useful questionnaire in the OH setting.

Validation of the PHQ-15 for somatoform disorder in the occupational health care setting

Medically unexplained symptoms (MUS) and somatoform disorders occur frequently in sick listed employees in the workplace (Shima & Satoh, 2006). In this article, the term somatoform disorders is used when satisfying the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) category. MUS entail the complaints of a somatoform disorder or complaints that do not yet satisfy the criteria for a somatoform disorder. Frequently occurring somatoform disorders include pain disorders, which include pain involving physical factors and pain involving psychological factors.

Previous studies reported a prevalence of MUS in the occupational health (OH) setting ranging from 10% to 16% (De Waal, Arnold, Eekhog, & Van Hemert, 2004; Hoedeman, Krol, Blankenstein, Koopmans, & Groothoff, 2009; Shima & Satoh, 2006) and MUS often coincided with mental disorders such as depressive or anxiety disorders. In addition, there are indications that somatoform disorders are often presented as musculoskeletal symptoms, inhibiting work functioning (De Waal et al., 2004; Leiknes, Finset, Moum, & Sandanger, 2007; Mergl et al., 2007; Van der Feltz-Cornelis, Meeuwissen, De Jong, Hoedeman, & Elfeddali, 2007). To offer patients a suitable treatment, timely recognition is crucial. However, in the OH setting, somatoform disorders are often not recognized (Van der Feltz-Cornelis et al., 2007). A proper screening tool might be useful to improve recognition of somatoform disorders in the OH setting. The use of a routine screener such as the Patient Health Questionnaire-15 (PHQ-15) could be very useful for the occupational health physician (OHP) to identify patients who are in need of appropriate treatment. In the Netherlands, a multidisciplinary guideline for evidence-based treatment of somatoform disorders was recently published, which advocates the use of screeners like the PHQ-15 (Van der Feltz-Cornelis, Swinkels, Blankenstein, Hoedeman, & Keuter, 2010).

In this study, the Dutch version of the PHQ-15 was chosen for validation as a screener in the OH setting. The PHQ-15 is the somatic symptom severity scale of the PHQ, which is a short, self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) developed by Kroenke et al. (2002). The PHQ-15 consists of a list of 15 somatic symptoms. In a validation study within a primary care setting situated in Germany, higher scores on the PHQ-15 were strongly associated with functional impairment, disability, and health care use (Mergl et al., 2007). In the Netherlands, in two studies focusing on sick listed employees in the OH setting, higher scores on the PHQ-15 were associated with more disability, longer sickness absence and higher health-related job loss (Hoedeman et al., 2009; Van der Feltz-

Cornelis et al., 2007). In a recent review of studies in primary care, the PHQ-15 was found to be equally effective or superior to other brief measures for assessing somatic symptoms and screening for somatoform disorders. The PHQ-15 uses cut points of 5, 10, and 15 representing mild, moderate and severe symptom levels (Kroenke et al., 2002). However, a validation of the PHQ-15 in the OH setting was not yet performed. Van Ravesteijn et al. (2009) validated the Dutch version of the PHQ-15 for the primary care setting. We expected the PHQ-15 to be a valid instrument for the OH setting. The aim of this study was to validate the PHQ-15 in the OH setting by comparing the PHQ-15 with the MINI International Neuropsychiatric Interview (MINI; this is a short neuropsychiatric interview (Sheehan et al., 1998), see section 2.7), which is considered as the gold standard.

Method

The validation study of the PHQ-15 was performed as part of a cross-sectional survey to assess the prevalence of severe MUS and psychiatric comorbidity in a sick-listed population (Hoedeman et al., 2009), and to validate several questionnaires against the MINI. Validation of the PHQ-15 is reported here. The Medical Ethics Committee of the University Medical Center in Groningen approved of the study.

Participants

A total of 776 employees who were sick listed for a period longer than six weeks and shorter than two years were approached to participate in the study when they were visiting their OHP at a large OH service (i.e., ArboNed, Corporate Accounts) in the Netherlands. In particular, patients were recruited from April 2006 until December 2007 from one location of ArboNed, which serves companies with more than 500 employees. Individuals unable to fill out the questionnaires (due to insufficient mastery of the Dutch language) and persons with psychotic symptoms or at increased risk for suicide were excluded from the study.

Data collection design

Across a period of six weeks, 12 OHPs were asked to select a four-hour consultation session every week on the same day. The practice assistants in the administrative section of the OH service were instructed to invite all sick-listed employees, who had an appointment for this session, to participate in the study. The employees who volunteered to participate received the research questionnaires (including the PHQ-15) and an informed consent form one week before the actual consultation, or later if they received the invitation after that time. The OHPs were not involved in the selection of the patients. The questionnaires were sent to the Trimbos-institute (Netherlands Institute of Mental Health and Addiction). After receipt, a Trimbos-institute research assistant contacted the employee by telephone for the MINI

interview. To assess the validity of the PHQ-15, we invited all patients who returned the PHQ-15 (N = 172) for a MINI-interview within two weeks after receiving the PHQ-15. The interviewer did not know the results of the PHQ-15 and did not know the patient. This procedure is described more extensively elsewhere (Hoedeman et al., 2009).

Figure 1 shows a flowchart of the study. Of the 776 sick listed employees who were approached to fill out the PHQ-15, 172 (22.1%) returned the questionnaire. Eventually we analysed the data of 107 persons for whom we obtained both a PHQ-15 score and a MINI classification; this is 13.7% of the persons who were initially approached to participate for informed consent. In nine cases (8%), a psychiatrist was consulted regarding uncertainty about the patient suffering from pain syndrome or from medically explained pain without psychological factors. Among these nine cases, five were considered medically unexplained and were included as pain disorder; four were assigned to the 'No somatoform disorder' group. CFC was the consulting psychiatrist.

Table 1 shows the MINI classifications. In the subsample (n =107), 84 patients did not fulfill diagnostic criteria and were not classified with a somatoform disorder according to the MINI interview (i.e., the "MINI No-somatoform disorder group"), and 23 fulfilled classification criteria for somatoform disorders (i.e., the "MINI somatoform disorder group"); this is a prevalence of 21.5%. Amongst the somatoform disorders, pain disorders were the most prevalent (47.8%, n = 11). The next most frequent somatoform disorder was chronic fatigue (21.7%, n = 5), followed by Irritable Bowel Syndrome (IBS) (8.7%, n = 2) and undifferentiated somatoform disorder (13.0%, n = 3). Conversion (4.3%, n = 1) and somatoform disorder (4.3%, n = 1) were rare.

Assessment

Socio-demographic variables, depression, anxiety, distress, and MUS were assessed.

Objectives

Primary objective was to validate the PHQ-15 for detecting somatoform disorders in the OH setting by using the MINI as gold standard.

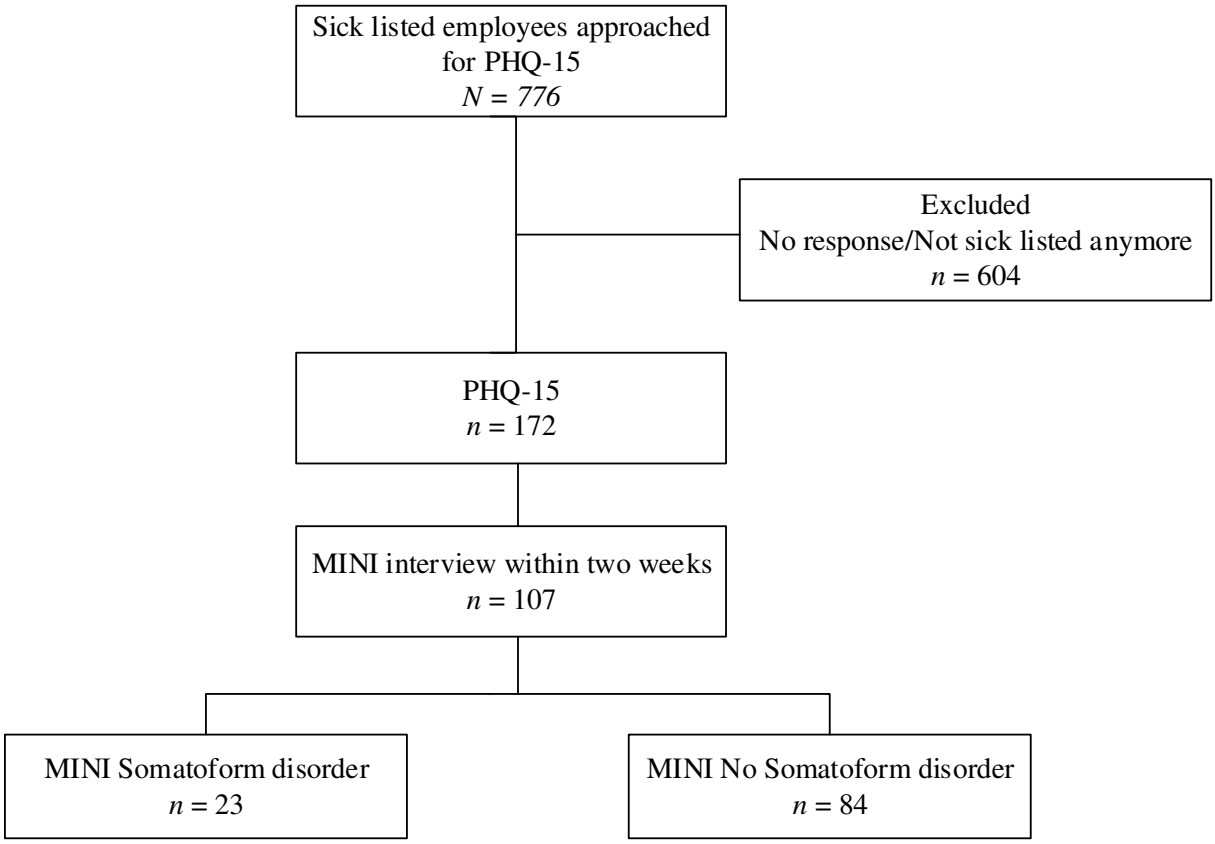


Figure 1. Report of the number of participants during the course of our study.

Table 1
Disorder classifications and PHQ-15 scores

MINI classification	Somatoform disorder according to MINI (*n* = 23)
	n
Pain disorder	8
Pain disorder RSI	1
Undif. cardiac pain	1
Fibromyalgia	1
Undif. chronic fatigue	5
Undifferentiated IBS	2
Undif. Somatoform	3
Conversion Disorder	1
Somatoform disorder	1

Abbreviations: Undif: Undifferentiated, IBS: Irritable Bowel Syndrome, RSI: Repetitive Strain Injury, soma. dis.: somatoform disorder.

The PHQ-15

The PHQ-15 is the somatic subscale of the PHQ. It comprises almost all physical symptoms in the outpatient setting (Kroenke, Spitzer, Williams, & Löwe, 2010). The PHQ-15 contains 15 items, 13 of which use a 3-point response scale, with ordered response categories labeled 'not bothered at all' (0 points), 'bothered a little' (1 point) and 'bothered a lot' (2 points). The remaining two items consist of questions about 'feeling tired or having little

energy' and 'trouble sleeping', which are contained in the depression module of the PHQ. Scores for these two questions can be 0, 1, 2 or 3 points, depending on the patient's response, which is 'not at all', 'several days', 'more than half the days' or 'nearly every day'. Before adding these item scores to the total score based on the other 13 items in the PHQ-15, responses to the two questions obtained from the depression module were re-scored as described by Kroenke et al. ('not at all' received 0 points, 'several days' 1 point and 'more than half of the days' or 'nearly every day' 2 points) (Kroenke et al., 2010).

MINI interview

The MINI interview was used as the gold standard in this study. Based on the DSM-IV criteria, Sheehan et al. (1998) developed this interview. The MINI is used to diagnose and classify somatoform disorders, and is often used in the clinic. A trained research assistant of the Trimbos-institute conducted the MINI interview by telephone. The research assistant did not know the patient, nor knew she the results of the PHQ-15. Patients were asked about physical symptoms during the previous period (ranging from the past two weeks to six months) (Sheehan et al., 1998).

Clinical appraisal in case of doubt regarding status of physical symptoms

In case of uncertainty after the MINI interview whether patients were suffering from a medically explained or unexplained condition or pain symptom, a psychiatrist was consulted. The consulting psychiatrist was CFC. The psychiatrist was consulted on nine occasions, because of uncertainty about whether the sick listed employee suffered from a pain syndrome or from medically unexplained pain. Five of these nine cases were eventually diagnosed having MUS and were included as pain disorder. The other four patients were assigned to the MINI No Somatoform disorder group.

Analysis

Construct validity. First, the mean PHQ-15 scores were calculated for patients who, according to the MINI, suffered from somatoform disorders and for subjects who did not. Also, demographic characteristics of both groups were recorded. Significance of differences was established by means of chi-square tests and *t*-tests. Cohen's *d* was calculated as a measure for the effect size (Cohen, 1992). We expected that the PHQ-15 scores were higher in the MINI Somatoform disorder group compared to the MINI No Somatoform disorder group. We used the "known groups" method (DeVellis, 2016) for validation of the PHQ-15. In particular, we expected that the PHQ-15 scores were higher in the MINI Somatoform disorder group compared to the MINI No Somatoform disorder group. Empirical support of this hypothesis supports the construct validity of the PHQ-15.

Diagnostic validity. For clinical diagnosis, a test needs to be sensitive enough to detect the relevant problem if it is present (and therefore avoid many false negative results), but specific enough to keep the number of false positives as low as possible. Therefore, to assess the diagnostic validity of the PHQ-15, based on the sum score of the PHQ-15, the sensitivity, the specificity, the positive predictive values (PPV) and the negative predictive value (NPV) (i.e., the proportion of positive test results that are true positives and the proportion of negative test results that are true negatives, respectively) and efficiency were calculated (Offringa & Assendelft, 2008). Table 2 shows the formulas used to calculate the validation quantities (including an example of the calculations at this study's optimal cut point of 10). Youden's *J* (Youden, 1950) was computed to express the optimal balance between sensitivity and specificity. If *J* reaches the maximum value, the cut point is considered optimal. A receiver operating characteristic (ROC) was calculated to explore diagnostic performance. By plotting the true positive rate (sensitivity) against the false positive rate (1-specificity), an area under the curve (AUC) was calculated to explore diagnostic performance.

Sensitivity, specificity, predictive values, and efficiency are subject to sampling error. Because the validation quantities were based on small samples, the need for reporting a measure of precision is obvious (Offringa & Assendelft, 2008). By using 95% confidence intervals (95% CIs), the precision of all validation scores for each cut point was estimated. The 95% CIs were calculated following the method by Agresti and Coull (1998). SPSS v15 (IBM Corp., 2006) was used for the statistical analyses.

Table 2
Illustration of computation of screening statistics using the MINI as gold standard

Variable	Positive MINI	Negative MINI	Total
Positive PHQ-15	a (12)	b (25)	a+b (37)
Negative PHQ-15	c (11)	d (59)	c+d (70)
Total	a+c (23)	b+d (84)	a+b+c+d (107)

Variable	Formula	
Sensitivity	a / (a + c)	(12/23=.521)
Specificity	d / (b + d)	(59/84=.702)
Negative predictive value (NPV)	d / (c + d)	(59/70=.843)
Positive predictive value (PVV)	a / (a + b)	(12/37=.324)
Efficiency	(a + d) / (a + b + c + d)	(71/107=.664)
Youden's *J*	sens + spec – 1	(.52+.70–1=.22)

Adapted from: Offringa & Assendelft(Offringa & Assendelft, 2008).
Note: In between brackets example values at the optimal cut point of 10 of the PHQ-15.

Sensitivity analysis. In total, 604 employees did not respond or were not sick listed anymore after sending the questionnaires including the PHQ-15. Unfortunately, we had no access to the baseline characteristics of these respondents, thus rendering a sensitivity analysis impossible. However, background information was available for the 65 employees who returned the PHQ-15 but could not be reached for the MINI interview within the planned timeframe of two weeks. Because this might pose a risk of bias, differences between the employees who returned the PHQ-15 but could not be reached for the MINI interview and the MINI interviewees, were tested with respect to demographic characteristics. In all analyses, two-tailed testing was used with .05 significance levels.

Results

Sample sizes

Table 2 shows the sample sizes used for the computation of the diagnostic indicators; see the denominator of the formulas. Computation of the 95% CIs for the sensitivity and the specificity was based on subsample sizes equal to 23 and 84, respectively. The sample sizes used for the computation of the NPV and PPV varied, because with the cut point the number of negatives and positives varies with the cut score. Consequently, cut points at the extremes of the scale sample sizes may become too small to calculate accurate 95% CIs for the NPVs and the PPVs. Based on Agresti and Coull (1998, p. 120) we therefore only report 95% CIs when sample sizes were at least 15. Efficiency estimates and CIs were based on the total sample (n = 107).

Non-response analysis

Of the 172 persons who returned PHQ-15 questionnaires, 107 patients subsequently underwent the MINI interview, while 65 did not. PHQ-15 scores, demographic characteristics, gender, marital status, age and level of education did not differ significantly between responders and non-responders.

Demographic characteristics

None of the demographic characteristics showed a significant difference between the MINI Somatoform disorder group and the MINI No Somatoform disorder group, suggesting absence of bias. The sample consisted of 53 male (49.5%) patients. The mean age was 47.9 years (SD = 9.8). A percentage of 13.1% (n = 14) of the patients reported they were single, 74.8% (n = 80) reported they were living together or were married and 12.1% (n = 13) said to be divorced or be widow/widower. A total of 31.8% (n = 34) patients finished education at low level, 38.3% (n = 41) at middle-high level and 29.9% (n = 32) at high level.

Before sick leave, patients on average worked 4.2 days (*SD* = 1.2) per week, which corresponds to 30.3 hours (*SD* = 11.2) per week. Almost all patients (98.1%) reported they were in paid employment. A percentage of 12.1% of the patients fulfilled an executive function and 64.5% declared to be wage earner. All employees included in the study were sick listed during the study.

Mean scores on PHQ-15

The mean PHQ-15 score in the total sample was 8.3 (*SD* = 4.6; range 1—22). The means (*Mean* (*M*)) in the MINI Somatoform disorder group equaled 10.1 (*SD* = 5.5, range 1—22) and the mean in the MINI No Somatoform disorder group equaled 7.8 (*SD* = 4.1; range 1—19) and differed significantly ($p = 0.030$, $d = 0.52$), giving some evidence of the construct validity of the PHQ-15.

Classification accuracy

Table 3 includes for every possible cut point the sensitivity, the specificity and the corresponding 95% CIs. Table 4 shows the PPV, the NPV, the efficiency and the 95% CIs. A cut point of 6 resulted in high sensitivity (82.6%), but unacceptable low specificity (34.5%). For the cut point of 12, high specificity (82.1%) but low sensitivity (34.8%) were found. A cut point of 10 resulted in a sensitivity of 52.2% and a specificity of 70.2%; and a PPV of 34.4%, a NPV of 84.3% and efficiency of 66.4%. A cut point of 10 also produced the highest value of Youden's *J* (.22). The corresponding 95% CI for the sensitivity was (33.0%; 70.8%) and for the specificity, it was (59.8%; 79.0%). The corresponding 95% CI for the PPV was (19.6%; 48.5%), for the NPV, it was (74.0%; 91.0%) and for the efficiency, it was (57.0%; 74.6%) (see Table 3 and Table 4).

Table 3
Sensitivity, specificity and 95% CIs of the PHQ-15

Score of the PHQ-15	Number of patients	Positive MINI	Sens.	95% CI	Spec.	95% CI
0	0	0	100.0	85.7-100.0	0.0	0.0-4.4
1	2	1	100.0	85.7-100.0	0.0	0.0-4.4
2	5	0	95.7	79.0-99.2	1.2	0.2-6.4
3	7	1	95.7	79.0-99.2	7.1	3.3-14.7
4	6	1	91.3	73.2-97.6	14.3	8.4-23.3
5	13	1	87.0	67.9-95.5	20.2	13.0-30.0
6	13	3	82.6	62.9-93.0	34.5	25.2-45.2
7	9	2	69.6	49.1-84.4	46.4	36.2-57.0
8	7	1	60.9	40.8-77.8	54.8	44.1-65.0
9	8	1	56.5	36.8-74.4	61.9	51.2-81.6
10	10	3	52.2	33.0-70.8	70.2	59.8-79.0
11	4	1	39.1	22.2-59.2	78.6	68.7-86.0
12	2	1	34.8	18.8-55.1	82.1	72.6-88.9
13	5	1	30.4	15.6-50.9	83.3	74.0-89.8
14	8	3	26.1	12.6-46.5	88.1	79.5-93.4
15	1	0	13.0	4.5-32.1	94.1	86.8-97.4
16	0	0	13.0	4.5-32.1	95.2	88.4-98.1
17	2	0	13.0	4.5-32.1	95.2	88.4-98.1
18	1	1	13.0	4.5-32.1	97.6	91.7-99.3
19	2	0	8.7	2.4-26.8	97.6	91.7-99.3
20	0	0	8.7	2.4-26.8	100	95.6-100
21	0	0	8.7	2.4-26.8	100.0	95.6-100.0
22	2	2	8.7	2.4-26.8	100.0	95.6-100.0
23	0	0	0.0	0.0-14.3	100.0	95.6-100.0

Abbreviations: PHQ-15: Patient Health Questionnaire-15, MINI: Mini International Neuropsychiatric Interview, Sens.: Sensitivity, Spec.: Specificity, 95% CI: 95% confidence interval.
Note: specificity, sensitivity and 95% CIs are presented in percentages. From scores ≥23 Sens. and Spec. are not reported because of reaching minimum and maximum values, respectively.

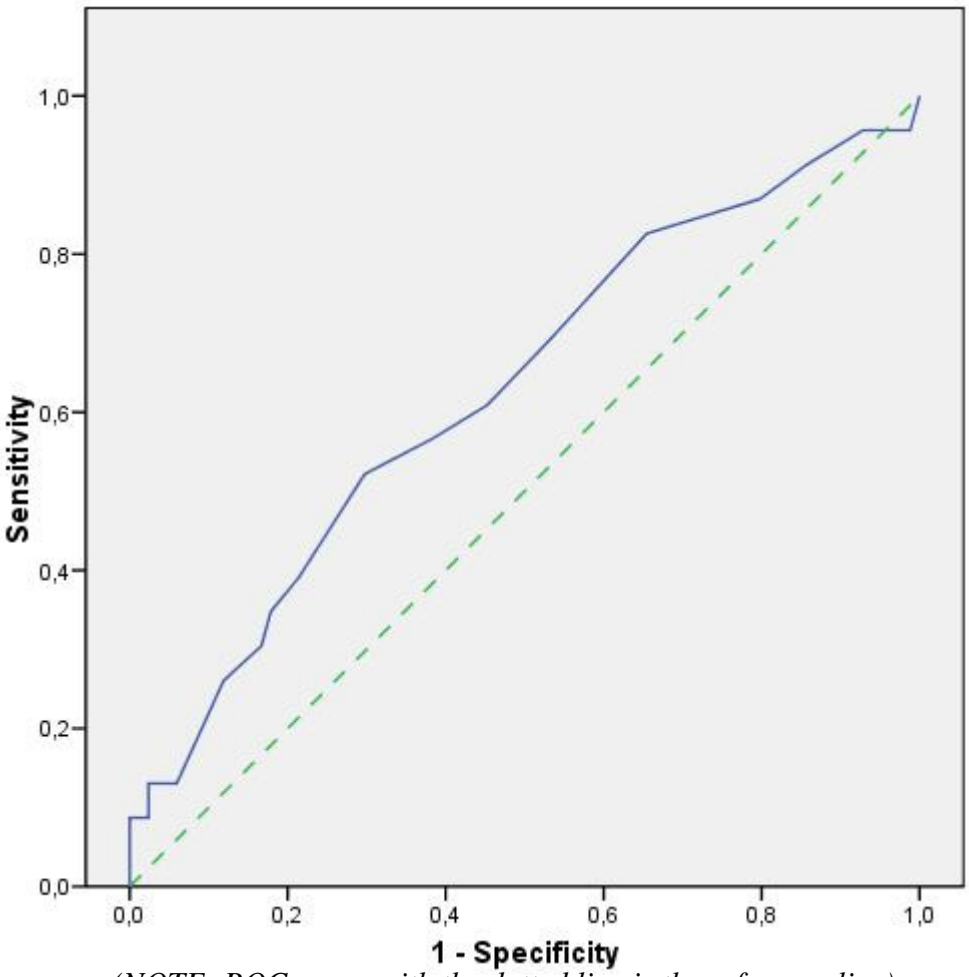
Table 4
Sensitivity, specificity and 95% CIs of the PHQ-15

Score of the PHQ-15	PPV	95% CI	NPV	95% CI	Eff.	95% CI
0	21.5	14.8-30.2	---	---	21.5	14.8-30.2
1	21.5	14.8-30.2	---	---	21.5	14.8-30.2
2	21.0	14.3-29.7	50.0	---	21.5	14.8-30.2
3	22.0	15.0-31.1	85.7	---	26.2	18.8-35.2
4	22.6	15.3-32.1	85.7	---	30.8	22.9-40.1
5	23.0	15.4-32.9	85.0	64.0-94.8	34.6	26.2-44.0
6	25.7	17.1-36.7	87.9	72.7-95.2	44.9	35.8-54.3
7	26.2	16.8-38.4	84.8	71.8-92.4	51.4	42.1-60.7
8	26.9	16.8-40.3	83.6	71.7-91.1	56.1	46.6-65.1
9	28.9	17.7-43.4	83.9	72.8-91.0	60.8	51.3-69.5
10	34.4	19.6-48.5	84.3	74.0-91.0	66.4	57.0-74.6
11	33.3	18.6-52.2	82.5	72.7-89.3	70.1	60.9-78.0
12	34.8	18.8-55.1	82.1	72.6-88.9	72.0	62.8-79.6
13	33.3	17.2-54.6	81.4	71.9-88.2	72.0	62.8-79.6
14	37.5	18.5-61.4	81.3	72.1-88.0	74.8	65.8-82.0
15	37.5	---	79.8	70.9-86.5	76.6	67.8-83.6
16	42.9	---	80.0	71.1-86.7	77.6	68.8-84.4
17	42.9	---	80.0	71.1-86.7	77.6	68.8-84.4
18	60.0	---	80.4	71.7-86.9	79.4	70.8-86.0
19	50.0	---	79.6	70.8-86.3	78.5	69.8-85.2
20	100.0	---	80.0	71.4-86.5	80.4	71.9-86.8
21	100.0	---	80.0	71.4-86.5	80.4	71.9-86.8
22	100.0	---	80.0	71.4-86.5	80.4	71.9-86.8
23	---	---	78.5	69.8-85.2	78.5	69.8-85.2

Abbreviations: PHQ-15: Patient Health Questionnaire-15, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Eff.: Efficiency, 95% CI: 95% confidence interval.
Note: PPV, NPV, efficiency and 95% CIs are presented in percentages. From scores >22 PPV reached maximum values. 95% CIs for NPVs and PPVs based on less than 15 observations are not reported.

ROC analysis

Figure 2 shows the ROC for the PHQ-15 versus the MINI as gold standard. The AUC of the PHQ-15 was 0.63 (*Standard Error* = 0.07; 95% CI: (0.50; 0.76)).



(NOTE: ROC-curve with the dotted line is the reference line)

Figure 2. ROC curve for PHQ-15 versus the MINI interview.

Discussion

In this study, in a sick listed population, 23 out of 107 sick listed employees were classified with a somatoform disorder according to the MINI interview, which is a prevalence of 21.5%. This prevalence is higher than the prevalence found by Hoedeman et al. (2009), in a comparable sick listed population. The explanation may be that Hoedeman et al. used a cut point of 15 or more on the PHQ-15 to diagnose somatoform disorder; given the present findings, using such a high cut point results in missing a substantial number of cases of somatoform disorders in the OH setting (i.e., low sensitivity). Given the findings from the MINI and given comparable PHQ-15 mean scores (M = 9.8, SD = 5.4) in Hoedeman et al.'s

study and ours (M = 10.1, SD = 5.5), a cut point of 15 may be unnecessarily high to detect somatoform disorders by means of the PHQ-15 in the OH setting.

In the primary care population, Van Ravesteijn et al. (2009) found a mean PHQ-15 score of 6.1 (SD = 5.3). The difference between primary care patients and sick-listed patients may explain the lower mean scores in the Van Ravesteijn et al. study; not all primary care patients suffering from MUS have such strong degrees of job dysfunction that they are sick listed. Consequently, the sample in this study in the OH setting suffers from more serious dysfunction than the primary care sample of Van Ravesteijn et al. (2009).

The MINI classifications showed that the most prevalent somatoform disorders in this sick listed population are pain disorder (48%) and chronic fatigue (22%). This finding corroborates the findings of Nimnuan, Rabe-Hesketh, Wessely, and Hotopf (2001) who established that pain and fatigue were MUS that could be found in many somatoform disorders. Furthermore, in this study, IBS occurred but less frequently than reported in previous studies (El-Serag, 2003). This corroborates the findings of Fink, Toft, Hansen, Ørnbøl, and Olesen (2007), who also found IBS to be one of the three most frequent MUS in a primary care population. Apparently, these are the most relevant symptoms in MUS in the sick listed population as well, although prevalence rates for IBS are lower here than in the study of Fink et al. The explanation may be that although pain and fatigue are strongly associated with dysfunction at work and thus with being on sick leave, IBS may not be so disabling in employees in general that it leads to sick leave.

An optimal balance between sensitivity and specificity was reached at a cut point of 10, which yields a sensitivity of 52.2% and a specificity of 70.2%. The validity of the PHQ-15 as a screening instrument for assessing somatoform disorders in the OH setting, can be considered low (Fischer, Bachmann, & Jaeschke, 2003) to moderate (Jones & Athanasiou, 2005). Furthermore, ROC analysis showed an AUC of 0.63, which can be considered suboptimal.

As far as we know, a screener for somatoform disorders with more than moderate validity is unavailable. Our analyses suggest that sick-listed employees without somatoform disorders have scores on the PHQ-15 of at least 5, which Kroenke et al. (2010) consider mildly severe somatic symptoms; however, in this study the mean score on the PHQ-15 was significantly lower than in the group classified by the MINI as having a somatoform disorder. MUS is associated with poor prognosis and physicians in OH often fail to recognize MUS which may be due to the lack of better screeners for somatoform disorders. Moreover, the frequency of MUS is associated with poor prognosis, high medical consumption, and longer

sickness absence (Hoedeman et al., 2009). Van der Feltz-Cornelis et al. (2010) reported that adequate recognition and treatment can speed up Return to Work (RTW) considerably. Therefore, the use of the PHQ-15 as a screener to detect somatoform disorders may still be of high clinical relevance.

The cut point of 10 is higher than the cut point reported in the primary care study of Van Ravesteijn et al. (2009). However, Van Ravesteijn et al. studied the validity of the PHQ-15 using the Structured Clinical Interview for DSM Disorders as gold standard instead of the MINI. They reported a sensitivity of 78% and a specificity of 71% at the optimal cut point of 6. The sample of Van Ravesteijn et al. (2009) came from a high-risk primary care population with patients known to suffer from MUS, frequent attendees to the general practitioner and patients suffering from mental health problems. The difference between primary care patients and sick-listed patients may explain the lower cut point in the Van Ravesteijn et al. study. Probably, the PHQ-15 can be used with a lower cut point in patients in primary care. However, in the OH setting, in a sample of sick listed employees with a longer duration of sickness, absence and thus a negative selection of employees with symptoms (most sick-listed employees return to work with a shorter duration of sickness absence than 2 weeks), the optimal cut point of 10 is more appropriate to use. Our study supports this conclusion.

Non-response analysis showed no evidence for selectivity within our sample. In this study, we provided confidence intervals for sensitivity, specificity, NPV, PPV, and efficiency. The sample size was rather small and therefore the intervals are wide. For instance, at the optimal cut point of 10 the 95% CI for sensitivity (52.2%) ranged from 33.0% to 70.8%, and for specificity (70.2%) it ranged from 59.8% to 79.0%. The 95% CI of sensitivity includes values smaller than 50%, which reflect worse levels of sensitivity than diagnosing persons by chance. Therefore, our results do not allow precise conclusions about the sensitivity or the specificity at the population level and caution should be exercised when generalizing sample results to the population.

The findings suggest that the PHQ-15 may be used as a screener in the OH setting, to alert the OHP to the possibility of somatoform disorders. Due to the low efficiency of the instrument, it may be best to apply the screener in high-risk groups. Previous studies suggested that patients in the primary care setting with more than four to six symptoms were more often disabled (Escobar, Waitzkin, Silver, Gara, & Holman, 1998). Frequent doctor visits were also associated with disability. Furthermore, research in the OH setting showed that such high-risk groups might be those with many MUS (Jackson & Passamonti, 2005), may be older employees (Nieuwenhuijsen, Verbeek, De Boer, Blonk, & Van Dijk, 2006),

have high medical consumption (Escobar et al., 1998; Jackson & Passamonti, 2005) and report to be severely disabled (Kroenke et al., 1997). Also, for sick-listed employees with depression or anxiety disorder it was shown (Nieuwenhuijsen et al., 2006) that higher age and negative expectation of the employee (Hoedeman, Blankenstein, Krol, Koopmans, & Groothoff, 2010) (regarding duration of sickness absence) contributed to longer duration of sickness absence. Maybe high age and employees' negative expectations should also be an indication to screen for MUS using the PHQ-15. Although the PHQ-15 might not be helpful enough as a stand-alone screener, it may be useful for screening high-risk groups. The multidisciplinary guideline for MUS and somatoform disorder (Bosma & Kessels, 2002) or the Dutch multidisciplinairy guideline might be useful to provide the OHP with evidence-based treatment options.

Occupational rehabilitation for employees with somatoform disorders could be improved by applying rules for management and communication. Evidence (Hoedeman et al., 2010) is indirect as effectivity was shown in primary care, after establishing the diagnosis by psychiatric screening; and further investigation of the effectivity in the sick-listed population is needed, but in primary care these interventions showed improvement of functioning and reduction of medical consumption. If the process of RTW in employees with somatoform disorders is hampered, referral to cognitive behavioral therapy or multidisciplinary treatment with graded activity and cognitive behavioral therapy is indicated. These treatments have shown to be effective for the outcome of functioning (Henningsen, Zipfel, & Herzog, 2007).

Further research is needed to validate the PHQ-15 in groups running a high risk of somatoform disorder. Furthermore, comorbid depressive and anxiety disorder in somatoform disorders may influence the low to moderate efficiency of the PHQ-15. Comorbidity is highly prevalent (Van der Feltz-Cornelis & Van Balkom, 2010) and has a negative influence on the course of disease as well as treatment outcome (Huijbregts et al., 2010; Huijbregts et al., 2010). In this study, the MINI interview did not reveal comorbid conditions. However, more research is needed to study this possibility and its implications for the validity of the PHQ-15 for this patient group.

Strengths and limitations of the study were the following. A return rate for a mail questionnaire of 22.1% is commonly found but it is a small percentage. Another limitation is that not all patients who filled out the questionnaire also consented to the MINI interview; 62% did (n = 107). Nonresponse was probably due to the eligible persons being approached twice, once for the mail questionnaire, and again for the MINI interview. However, a non-response analysis did not show significant differences between responders and non-

responders at least in terms of demographic characteristics. The reported health reasons for being sick-listed in this study are unknown. In a comparable population with a random sample of Dutch employees being sick-listed between three weeks and two years (Hoedeman et al., 2009), the OHP diagnoses were realized for 40% mental, 30% musculoskeletal and for 30% other disorders.

The application of the MINI interview to diagnose somatoform disorders as gold standard is a strength of this study. For example, in another validation study that reported high reliability, convergent validity, and discriminant validity for the PHQ-15, the PHQ-15 was compared with the outcomes on the 20-item Short-Form General Health Survey as gold standard (Kroenke et al., 2010). We compared the PHQ-15 to the valid MINI. Another strength of the study is that sick listed employees were approached by questionnaire, thus eliminating selection bias by the OHP. Our study is also the first to validate the PHQ-15 in the OH Setting.

To conclude, the PHQ-15 has reasonable sensitivity but limited efficiency. The best choice for a cut point was 10. Due to its adequate sensitivity, the PHQ-15 can be used as a screener for somatoform disorders in the OH setting, in particular in high-risk groups. Further validation studies of the PHQ-15 based on larger sample sizes are needed.

Chapter 2

Validation of the 4DSQ somatization subscale in the occupational health care setting as a screener

This chapter is based on:

De Vroege, L., Emons, W.H.M., Sijtsma, K., Hoedeman, R., & Van der Feltz-Cornelis, C.M. (2015). Validation of the 4DSQ Somatization subscale in the occupational health care setting as a screener. *Journal of Occupational Rehabilitation*, *25*(1), 105-115.

Abstract

Somatoform disorders (physical symptoms without medical explanation that cause dysfunction) are prevalent in the occupational health (OH) care setting and are associated with functional impairment and absenteeism. Availability of psychometric instruments aimed at assessing somatoform disorders is limited. In the OH setting, so far only the Patient-Health-Questionnaire 15 has been validated as screener for somatoform disorder, and has been shown to have moderate validity. The 4-Dimensional Symptom Questionnaire (4DSQ) is frequently used in the OH setting but the Somatization subscale is not validated yet. The aim of this study is to validate the 4DSQ Somatization subscale as screener for the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) somatoform disorder in the OH setting by using the Mini International Neuropsychiatric Interview (MINI) as gold standard. Employees absent from work due to physical symptoms, for a period longer than 6 weeks and shorter than 2 years, were asked to participate in this study. They filled out the 4DSQ and underwent a MINI interview by telephone for DSM-IV classification. Specificity and sensitivity scores were calculated for all possible cut-off scores and a receiver operator curve was computed for the Somatization subscale. 95% confidence intervals (95% CIs) were calculated for sensitivity and specificity. The Somatization subscale of the 4DSQ has an optimal cut point of 9, with specificity and sensitivity equal to 64.3% (95% CI: (53.6%; 73.7%)) and 60.9% (95% CI: (40.8%; 77.8%)), respectively. Receiver operator curves showed an area under the curve equal to 0.61 (*Standard Error* = 0.07; 95% CI: (0.48; 0.75)) for the Somatization subscale of the 4DSQ. We conclude that the 4DSQ Somatization subscale is a questionnaire of moderate sensitivity and specificity.

Validation of the 4DSQ somatization subscale in the occupational health care setting as a screener

Somatoform disorders refer to physical symptoms without medical explanation despite proper medical examination (De Waal et al., 2004), and cause dysfunction (American Psychiatric Association (APA), 2000). In the occupational health (OH) setting somatoform disorders are common, prevalence rates range from 15% to well over 20% (De Vroege, Hoedeman, Nuyen, Sijtsma, & Van der Feltz-Cornelis, 2012; Hoedeman et al., 2009), and are associated with disability (Hoedeman et al., 2009; Vlasveld et al., 2012) and absenteeism (Vlasveld et al., 2012); hence, it is expected that Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV somatoform disorder may frequently occur in sick listed employees that present themselves with physical symptoms. Vlasveld et al. (2012) suggested that occupational physicians (OPs) need to be aware of the possibility of somatoform disorders since these disorders are associated with long-term absenteeism. Early identification and treatment may promote well-being and return to work (Van der Feltz-Cornelis et al., 2010). However, recognition of somatoform disorder by the OP in case of presentation with physical symptoms in sick listed employees is low (Hoedeman et al., 2009; Terluin et al., 2006; Van der Feltz-Cornelis et al., 2007). OPs therefore might benefit from a screening instrument for somatoform disorder that is easily applicable in their particular setting.

This study aims at establishing the validity of the Dutch version of the 4-dimensional Symptom Questionnaire (4DSQ) Somatization subscale in the OH setting using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) as gold standard. So far, only the Patient-Health-Questionnaire 15 (PHQ-15), a screener for somatoform disorder, has been validated for the OH setting (De Vroege et al., 2012). In view of the moderate sensitivity (56.5%) and specificity (61.9%) of the PHQ-15 (De Vroege et al., 2012), evaluation of possible alternative screeners for the OH setting is highly relevant. Such an alternative could be the Somatization subscale of the 4DSQ (Terluin, 1996; Terluin et al., 2006), which exists of four subscales: Somatization, Distress, Anxiety and Depression. The complete 4DSQ has been validated for the primary care setting in 2006 (Terluin et al., 2006), but only the Distress subscale has been validated for the OH setting (Braam et al., 2009; Terluin et al., 2004). The Somatization subscale of the 4DSQ has not been validated for the OH setting.

Method

Participants

In total, 776 consecutive employees sick listed for physical symptoms for a period longer than 6 weeks and shorter than 2 years, who visited their OP were approached at a large OH service in the Netherlands (i.e., ArboNed), Corporate Accounts, from April 2006 until December 2007. These consecutive employees were recruited at one location of ArboNed, serving profit and non-profit companies with more than 500 employees working in the center of the Netherlands, serving a total of 1 million employees. Exclusion criteria were: individuals unable to fill out the questionnaires (due to deficient mastery of the Dutch language) and participants presenting themselves with psychotic symptoms or increased risk for suicide.

During a period of six weeks, 12 OPs were asked to organize a four-hour consultation session weekly on the same day. Practice assistants in the OH service were instructed to invite all sick listed employees with physical symptoms who had an appointment for this session to participate in the study. The consecutive sick listed employees who were approached (N = 776), received the questionnaires, including the 4DSQ, and an informed consent form one week before the actual consultation. The OPs were not involved in the selection of the participants. All employees who returned the questionnaires (including the 4DSQ) and gave informed consent (n = 172) were contacted for the MINI interview by telephone within two weeks after having received the 4DSQ. The interviewer did not know the scores on the 4DSQ.

In total, 107 of the employees could be reached by phone within this timeframe. They all completed the MINI. This corresponds to 13.7% of the 776 employees who were initially approached to participate.

According to the MINI interview, 84 out of these 107 employees (78.5%) did not comply with diagnostic criteria of somatoform disorder and were assigned to the "MINI No somatoform disorder" group. The other 23 participants (21.5%) complied with the criteria of somatoform disorder and were assigned to the "MINI Somatoform disorder" group. Figure 1 represents the flowchart of the study. Table 1 shows the different MINI classifications. The total sample used for analysis included 107 participants. The Medical Ethics Committee of the University Medical Center in Groningen approved of the study.

Clinical appraisal in case of doubt regarding status of physical symptoms

In case of uncertainty about participants' suffering from a medically explained or unexplained condition or pain symptom after the MINI interview, we consulted the psychiatrist. The psychiatrist was consulted in nine cases regarding uncertainty about the sick listed employee suffering from either a pain syndrome or from medically unexplained pain. Of these nine cases, five were eventually considered medically unexplained and were included as pain disorder; the remaining four participants were assigned to the 'MINI No Somatoform disorder' group.

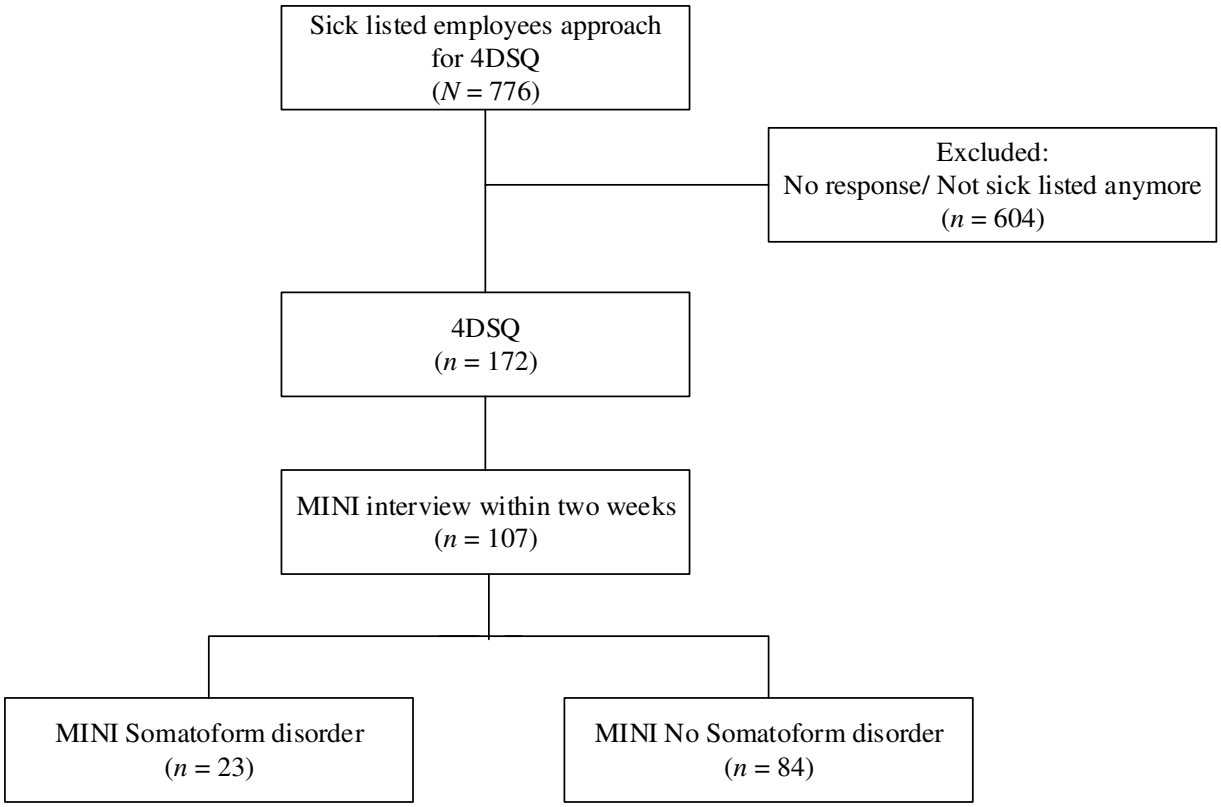


Figure 1. Flowchart of patients in the study.

Table 1
Classifications in the MINI somatoform disorder group

MINI classification	Somatoform disorder according to MINI *(n = 23)*
	n
Pain disorder	8
Pain disorder RSI	1
Undiff. cardiac pain	1
Undiff. som. dis. Fibromyalgia	1
Undiff. chronic fatigue	5
Undiff. IBS	2
Undiff. soma. dis.	3
Conversion Disorder	1
Somatoform disorder	1

Abbreviations: Undif: Undifferentiated, IBS: Irritable Bowel Syndrome, RSI: Repetitive Strain Injury, soma. dis.: somatoform disorder.

Assessment

Socio-demographic characteristics, depression, anxiety, distress, and somatoform disorder were assessed in this study. The latter four characteristics were assessed by means of the 4DSQ. Somatoform disorders were also assessed by means of the MINI. The latter served as the gold standard.

Objectives

The primary objective was to validate the 4DSQ Somatization subscale for detecting somatoform disorders in the OH setting using the MINI as gold standard.

The 4DSQ

The 4DSQ is a 50-item Dutch language self-report questionnaire, in which the questions are formulated comparable to those asked in general practice. The questions are concerned with the past week. The 4DSQ was developed to assess somatization, distress, anxiety and depression (Terluin, 1996; Terluin et al., 2006). The 50 items of the 4DSQ are distributed across the Somatization, Distress, Anxiety, and Depression subscales. The Somatization subscale contains 16 items and has a score range of 0 to 32 points; the Distress subscale consists of 16 items (score range: 0—32); the Anxiety subscale consists of 12 items (score range: 0—24); and the Depression subscale consists of 6 items (score range: 0—12) (Terluin et al., 2006). In this study, all 4DSQ subscales were assessed but only the Somatization subscale was validated. Response categories for the items within this subscale are 'no', 'sometimes', 'regularly', 'often', and 'very often or constantly'. Following the original scoring method (Terluin, 1996), responses are scored with 0 points for 'no', 1 point for

'sometimes' and 2 points for the other three response options (scores on the Somatization subscale range from 0 to 32 points). The reason for scoring the items this way is to offset extreme answer tendencies (Terluin, 1996). Table 2 shows the questions of the 4DSQ Somatization subscale.

MINI interview

The MINI interview was due to be performed within two weeks after the return of the 4DSQ questionnaire. The section on somatoform disorder of the MINI interview was used as the gold standard for classification of DSM-IV somatoform disorder. Based on DSM-IV criteria, Sheehan et al. (1998) developed this interview, which is often used in clinical practice. A blinded and trained research assistant conducted these interviews by telephone. Participants were asked about their physical symptoms during the past period ranging from two weeks up to six months (Sheehan et al., 1998).

Analysis

Construct validity. First, mean scores on the 4DSQ Somatization subscale were computed for sick listed employees who suffered from somatoform disorders according to the MINI, and also for sick listed employees who did not suffer from somatoform disorders and of whom physical symptoms could be medically explained. Significance of differences was established by means of chi-square tests and *t*-tests. Cohen's *d* was used as a measure for the effect size. We expected that the average 4DSQ Somatization subscale scores were higher in the MINI Somatoform disorder group than the MINI No Somatoform disorder group, which will support the construct validity of the scale. In this way, the subscale is validated using the "known groups" method (DeVellis, 2016).

Diagnostic validity. For clinical diagnosis, a screener needs to be sensitive enough to detect the relevant problem if it is present; that is, sensitivity needs to be as high as possible. Therefore, false negative results need to be limited. A test also needs to be specific enough, thus be capable of correctly identifying healthy people, to keep the number of false positives as low as possible. To assess the diagnostic validity of the 4DSQ Somatization subscale, based on the sum score of the 4DSQ Somatization subscale the sensitivity, the specificity and the positive and negative predictive values (i.e., the proportion of positive test results that are true positives and the proportion of negative test results that are true negatives, respectively) were calculated for all possible cut points ranging from 0 to 32. To evaluate the diagnostic performance of the 4DSQ Somatization subscale, sensitivity, specificity, predictive values, and efficiency (defined as the total percentage of correct diagnoses) were established for different cut points (Offringa & Assendelft, 2008) (see Table 3 for an explanation of how to

compute these statistics, including example calculations at this study's optimal cut point of 9). To find the optimal balance between sensitivity and specificity we also computed Youden's *J* (Youden, 1950), which summarizes the sensitivity and specificity. The optimal cut point is the value for which *J* reaches its maximum. This procedure ensured the determination of an optimal cut point. A receiver operating characteristic (ROC) was calculated to explore diagnostic performance. An area under the curve (AUC) was also calculated to explore diagnostic performance by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity).

In sample data, sensitivity, specificity, predictive values, and efficiency are subject to sampling error. Therefore, 95% confidence intervals (95% CIs) were used to assess the precision of the sensitivity, specificity, predictive values and efficiency estimates for each cut point. Because sensitivity and specificity estimates were based on small samples, reporting 95% CIs is of great merit (Offringa & Assendelft, 2008). 95% CIs were computed using the method suggested by Agresti and Coull (1998). The Statistical Package for the Social Sciences version 19 (IBM Corp., 2010) was used for the statistical analyses.

Sensitivity analysis. A total of 604 employees did not respond or were not sick listed anymore after sending the questionnaires including the 4DSQ. We had no access to the baseline characteristics of these respondents rendering a sensitivity analysis impossible. Of the 65 employees who returned the 4DSQ that could not be reached for the MINI interview within the envisioned timeframe of two weeks, these data were available. As this might pose a risk of bias, possible differences in demographic characteristics of those 65 employees and the MINI interviewees were tested for significance.

Table 2
Items of the 4-Dimensional Symptom Questionnaire (4DSQ) somatization subscale

Somatization subscale	No	Sometimes	Regularly	Often	Very often or constantly
During the past week, did you suffer from:					
1. dizziness or feeling light-headed					
2. painful muscles?					
3. fainting?					
4. neck pain?					
5. back pain?					
6. excessive perspiration?					
7. palpitations?					
8. headaches?					
9. a bloated feeling in the abdomen?					
10. blurred vision or spots in front of your eyes?					
11. shortness of breath?					
12. nausea or an upset stomach?					
13. pain in the abdomen or stomach area?					
14. tingling in the fingers?					
15. pressure or a tight feeling in the chest?					
16. pain in the chest?					

Table 3
Illustration of computation of screening statistics using MINI as gold standard

	Positive MINI	Negative MINI	Total
Positive 4DSQ somscale	a (14)	b (30)	a+b (44)
Negative 4DSQ somscale	c (9)	d (54)	c+d (63)
Total	a+c (23)	b+d (84)	a+b+c+d (107)

Variable	Formula	
Sensitivity	a / (a + c)	(14/23=.609)
Specificity	d / (b + d)	(54/84=.643)
Negative predictive value (NPV)	d / (c + d)	(54/63=.857)
Positive predictive value (PVV)	a / (a + b)	(14/44=.318)
Efficiency	(a + d) / (a + b + c + d)	(68/107=.636)
Youden's *J*	sens + spec – 1	(.61+.64–1=.25)

Note: Adapted from: Offringa & Assendelft(Offringa & Assendelft, 2008). In between brackets example values at the optimal cut point of 9 for the 4DSQ somscale.

Results

Sample sizes

The sample sizes used for the computation of the diagnostic indicators are given by the denominators in the formulas in Table 3. Hence, computation of the 95% CIs for the sensitivity and specificity was based on subsample sizes equal to 23 and 84, respectively. Because the number of negatives and positives varies with the cut score, the sample sizes used for the computation of the NPV and PPV varies with the cut point as well. As a result, for cut points at the extremes of the scale sample sizes may become too small to obtain accurate 95% CIs for the NPVs and PPVs. Therefore, based on Agresti and Coull (1998, p. 120), we only report the corresponding 95% CIs when sample sizes were at least 15. Efficiency estimates and CIs were based on the total sample, thus using a sample size of 107.

Sensitivity analysis

Comparative analysis showed that 4DSQ scores, demographic characteristics, gender, marital status, age and level of education did not differ significantly between the 65 employees who could not be reached within the envisioned two weeks for MINI interview and the MINI interviewees. Therefore, there was no indication for a risk of bias. See Table 4 for details.

Demographic characteristics

None of the demographic characteristics differed significantly between the MINI Somatoform disorder group and the MINI No Somatoform disorder group. The total sample comprised 53 (49.5%) male participants. The mean age was 47.9 (*SD* = 9.8). Fourteen participants (13.1%) reported they were single, 80 (74.8%) lived together or were married, and thirteen (12.1%) said they were divorced or widow/widower. Thirty-four participants (31.8%) finished an education at low level, 41 (38.3%) at middle high level and 32 (29.9%) at high level.

Before being sick listed, participants worked on average 4.2 days (*SD* = 1.2) per week, for 30.3 hours (*SD* = 11.2) per week. 105 participants (98.1%) reported they enjoyed paid employment. Of the 107 participants, 13 (12.1%) fulfilled an executive function and 69 (64.5%) declared to be wage earner. All participants were sick listed during the study.

Table 4
Sensitivity analysis

Characteristics	MINI (n = 107)*	No MINI (n = 65)*	
	M (SD)/ n (%)	*M (SD)/ n (%)*	*p*
Age	46.1 (9.9)*1	46.2 (11.3)*1	.947
Gender			.159
♀	52 (48.6%)	25 (38.5%)	
♂	53 (49.5%)	40 (61.5%)	
Missing	2		
Marital status			.341
Single	14 (13.1%)	15 (23.1%)	
Married	80 (74.8%)	45 (69.2%)	
Divorced	10 (9.4%)	4 (6.2%)	
Widow(er)	3 (2.8%)	1 (1.5%)	
Educational level			.141
Low level	34 (31.8%)	15 (23.1%)	
Middle level	49 (45.8%)	31 (47.7%)	
High level	24 (22.4%)	19 (29.2%)	
Average number of work days*2	4.2 (1.2)	4.4 (0.8)	.185
Average hours of work a week*2	30.3 (11.2)	32.3 (9.6)	.241
Executive function			.255
Yes	13 (12.2%)	12 (18.5%)	
No	94 (87.8%)	53 (81.5%)	
Wage earner			.135
Yes	69 (64.5%)	49 (75.4%)	
No	38 (35.5%)	16 (24.6%)	
Somatization subscale	11.2 (13.5)	10.6 (8.5)	.411
Distress subscale	14.3 (12.8)	16.8 (19.9)	.373
Depression subscale	1.8 (3.4)	3.4 (6.6)	.064
Anxiety subscale	2.4 (4.3)	6.1 (14.6)	.054

Abbreviations: M: Mean, SD: standard deviation.
Note: * = MINI group comprises sick listed employees who could be reached for the MINI interview, the No MINI group could not be reached for this interview. *1 = birthdates of two participants are missing. *2 = before being sick listed.

Mean scores on the 4DSQ subscales

Table 5 shows the mean scores, denoted *M*, of the four subscales of the 4DSQ for the MINI Somatoform disorder group and the MINI No Somatoform disorder group. Only the mean scores on the Somatization subscale and the Distress subscale differed significantly between the two groups (p = 0.045 and p = 0.026, respectively). The mean score on the Somatization subscale within the MINI Somatoform disorder group was 10.9 (*SD* = 7.6, range = 1—28) and within the MINI No Somatoform disorder group the mean score was 7.9 (*SD* = 5.8, range = 0—26), which according to Cohen (1992) indicates a medium effect (d =

0.48). This result supports the construct validity of the Somatization subscale. Also, the mean scores on the Distress subscale differed significantly between the MINI Somatoform disorder group (M = 14.8, SD = 7.7 and range = 3—30) and the MINI No Somatoform disorder group (M = 10.4, SD = 8.5 and range = 0—29) with medium effect (d = 0.52) (Cohen, 1992). The mean scores on the Depression and Anxiety subscales were low in both groups.

Table 5
Mean scores on the 4DSQ and the subscales of the 4DSQ

4DSQ subscales	MINI Somatoform disorder group (n = 23)	MINI No somatoform group (n = 84)		
	M (SD)	*M (SD)*	*p*	*d*
Somatization subscale	10.9 (7.6)	7.9 (5.8)	0.045	.48
Range	1—28	0—26		
Distress subscale	14.8 (7.7)	10.4 (8.5)	0.026	.52
Range	3—30	0—29		
Depression subscale	2.1 (2.7)	1.4 (2.4)	0.259	.28
Range	0—10	0—9		
Anxiety subscale	2.1 (3.5)	2.2 (3.7)	0.916	.03
Range	0—14	0—20		

Abbreviations: M: Mean, SD: standard deviation.
Note: numbers are displayed as Mean (Standard Deviation).

Classification accuracy and optimal cutoff scores

Table 6 presents for every possible cut point the estimated values and corresponding 95% CIs for the sensitivity and specificity. Table 7 includes for every possible cut point the predictive values for both positive predictive value and negative predictive value (PPV, NPV), efficiency, together with the 95% CIs.

A cut point of 6 resulted in high sensitivity (69.6%), but unacceptable low specificity (36.9%). For cut point equal to 10, a specificity of 67.9% was found, but this resulted in unsatisfactory low sensitivity (47.8%). A cut point of 9 seemed to produce the best balance between sensitivity and specificity, which resulted in a sensitivity of 60.9% and a specificity of 64.3%; and NPV of 85.7%, PPV of 31.8%, and efficiency of 63.6%. Cut point 9 produced the highest value of Youden's index J across all possible cut points. The corresponding 95% CI for the sensitivity was (40.8%; 77.8%), and for the specificity it was (53.6%; 73.7%). The corresponding 95% CI for PPV at cut point 9 was (20.0%; 46.6%), for the NPV (75.0%; 92.3%) and for the efficiency (54.1%; 72.1%) (see Table 6 and Table 7).

Table 6
Sensitivity, specificity and 95% confidence intervals of the 4DSQ somatization subscale

Score 4DSQ somatization subscale	Number of participants	Positive MINI	Sens.	95% CI	Spec.	95% CI
0	6	0	100.0	85.7-100.0	0.0	0.0-4.4
1	4	1	100.0	85.7-100.0	7.1	0.0-14.7
2	9	2	95.7	79.0-99.2	10.7	5.7-19.1
3	6	0	87.0	67.9-95.5	19.1	12.1-28.7
4	7	2	87.0	67.9-95.5	26.2	18.0-36.5
5	6	2	78.3	58.1-90.3	32.1	23.1-42.7
6	10	2	69.6	49.1-84.4	36.9	27.4-47.6
7	4	0	60.9	40.8-77.8	46.4	36.1-57.0
8	11	0	60.9	40.8-77.8	51.2	40.7-61.6
9	6	3	60.9	40.8-77.8	64.3	53.6-73.7
10	5	1	47.8	29.2-67.0	67.9	57.3-76.9
11	4	1	43.5	25.6-63.2	72.6	61.8-80.6
12	2	0	39.1	22.2-59.2	76.2	66.1-84.0
13	7	3	39.1	22.2-59.2	78.6	68.7-86.0
14	0	0	26.1	12.6-46.5	83.3	74.0-89.8
15	6	1	26.1	12.6-46.5	83.3	74.0-89.8
16	1	0	21.7	9.7-41.9	89.3	80.9-94.3
17	2	0	21.7	9.7-41.9	90.5	82.3-85.1
18	2	1	21.7	9.7-41.9	92.9	85.3-96.7
19	1	0	17.4	7.0-37.1	94.1	86.8-97.4
20	1	0	17.4	7.0-37.1	95.2	88.4-98.1
21	1	1	17.4	7.0-37.1	96.4	90.0-98.8
22	2	0	13.0	4.5-32.1	96.4	90.0-98.8
23	1	1	13.0	4.5-32.1	98.8	93.6-99.8
24	1	1	8.7	2.4-26.8	98.8	93.6-99.8
25	0	0	4.4	0.8-21.0	98.8	93.6-99.8
26	1	0	4.4	0.8-21.0	98.8	93.6-99.8
27	0	0	4.4	0.8-21.0	100	95.6-100.0
28	1	1	4.4	0.8-21.0	100	95.6-100.0
29*	0	0	0	0.0-14.3	100	95.6-100.0

Abbreviations: 4DSQ: 4-Dimensional Symptom Questionnaire, MINI: MINI International Neuropsychiatric Interview, Sens.: Sensitivity, Spec.: Specificity, 95% CI:, 95% confidence interval.
Note: specificity, sensitivity and 95% CIs are presented in percentages. From scores >29 Sens. and Spec. are not reported because of reaching minimum and maximum values, respectively.

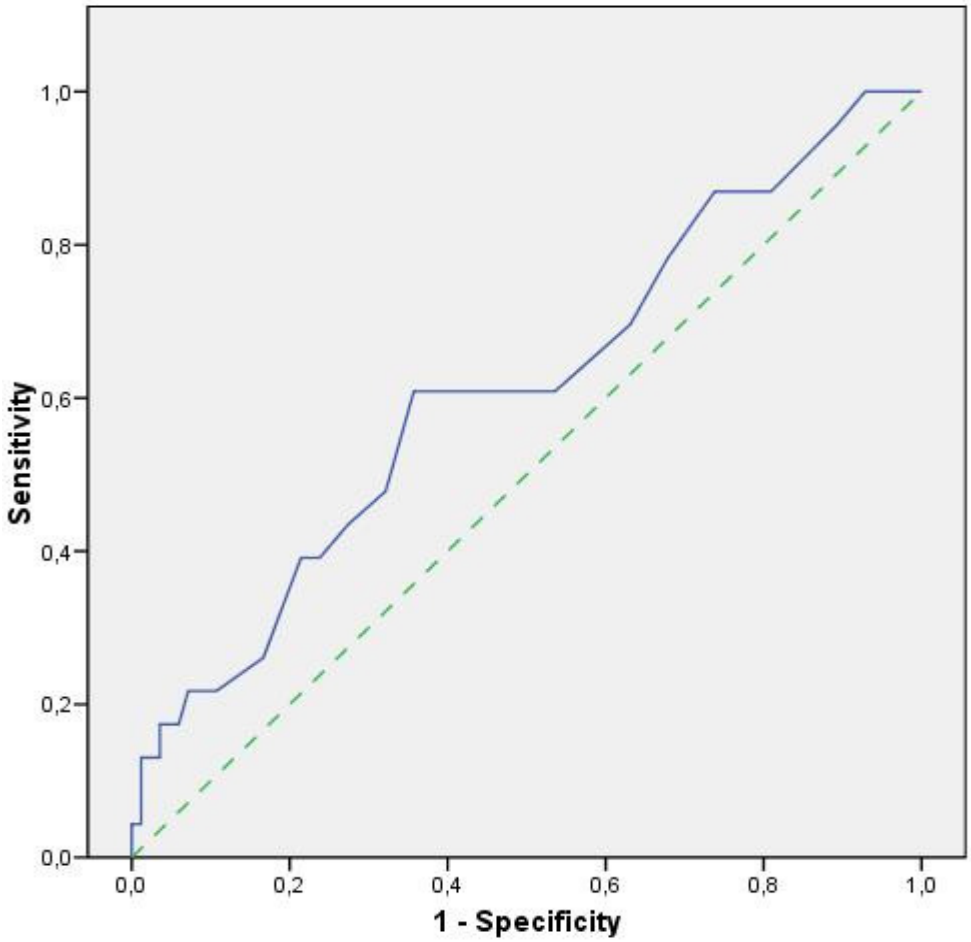
Table 7
PPV, NPV, efficiency and 95% confidence intervals of the 4DSQ somatization subscale

Score 4DSQ somatization subscale	PPV	95% CI	NPV	95% CI	Eff.	95% CI
0	21.5	14.8-30.2	---	---	21.5	14.8-30.2
1	22.8	15.7-31.9	100.0	---	27.1	19.6-36.2
2	22.7	15.5-32.0	90.0	---	29.0	21.2-38.2
3	22.7	15.2-32.5	84.2	62.4-94.5	33.6	25.4-43.0
4	24.4	16.4-34.7	88.0	70.0-95.8	39.3	30.5-48.7
5	24.0	15.8-34.8	84.4	68.3-93.1	42.1	33.1-51.5
6	23.2	26.5-48.7	81.6	66.6-90.8	43.9	34.9-53.4
7	23.7	14.7-36.0	81.3	68.1-89.8	49.5	40.3-58.9
8	25.5	15.8-38.3	82.7	70.3-90.6	53.3	43.9-62.5
9	31.8	20.0-46.6	85.7	75.0-92.3	63.6	54.1-72.1
10	29.0	17.0-44.8	82.6	72.0-89.8	63.6	54.1-72.1
11	30.3	55.7-84.9	82.4	72.2-89.4	66.4	57.0-74.6
12	31.0	17.3-49.2	82.1	72.1-89.0	68.2	58.9-76.3
13	33.3	18.6-52.2	82.5	72.7-89.3	70.1	60.8-78.0
14	30.0	14.6-51.9	80.5	70.9-87.4	71.0	61.8-78.8
15	30.0	14.6-51.9	80.5	70..9-87.4	71.0	61.8-78.8
16	35.7	---	80.7	71.5-87.4	74.8	65.8-82.0
17	38.5	---	80.9	71.8-87.5	75.7	66.8-82.9
18	45.5	---	81.3	72.3-87.8	77.6	68.8-84.4
19	44.4	---	80.6	71.7-87.2	77.6	68.8-84.4
20	50.0	---	80.8	72.0-87.4	78.5	69.8-85.2
21	57.1	---	81.0	72.2-87.5	79.4	70.8-86.0
22	50.0	---	80.2	71.4-86.8	78.5	69.8-85.2
23	75.0	---	80.6	71.9-87.1	80.4	71.9-86.8
24	66.7	---	79.8	71.1-86.4	79.4	70.8-86.0
25	50.0	---	79.1	70.3-85.7	78.5	69.8-85.2
26	50.0	---	79.1	70.3-87.7	78.5	69.8-85.2
27	100.0	---	79.3	70.6-85.9	79.4	70.8-86.0
28	100.0	---	79.3	70.6-85.9	79.4	70.8-86.0
29*	---	---	78.5	69.8-85.2	78.5	69.8-85.2

Abbreviations: 4DSQ: 4-Dimensional Symptom Questionnaire, PPV: Positive Predictive Value, 95% CI: 95% confidence interval, NPV: Negative Predictive Value, Eff.: Efficiency.
Note: PPV, NPV, efficiency and 95% CIs are presented in percentages, '---' represent divided by 0 error. From scores >28 PPV reached maximum values. 95% CIs for NPVs and PPVs based on less than 15 observations are not reported.

ROC analysis

Figure 2 shows the ROC curve for the 4DSQ Somatization subscale versus the MINI as gold standard. The AUC of the Somatization subscale of the 4DSQ was 0.61 (*Standard Error* = 0.07; 95% CI: (0.48; 0.75)).



(NOTE: ROC-curve with the dotted line being the reference line)

Figure 2. ROC curve for the somatization subscale of the 4DSQ versus MINI.

Discussion

This is the first validation study of the Somatization subscale of the 4DSQ administered to sick listed employees presenting themselves with physical symptoms in the OH setting. Our data showed significantly different mean scores on the Somatization subscale, with the MINI Somatoform disorder group having a mean equal to 10.9 and the MINI No Somatoform disorder group having a mean equal to 7.9. The means are higher than 7.6, which was the mean attained with patients suffering from somatoform disorders in the primary care setting (Hoedeman et al., 2009; Terluin et al., 2006). In fact, mean scores on all subscales of the 4DSQ were higher with sick listed employees. This difference suggests that compared to

primary care, in the OH setting sick listed employees present themselves to the OP with more severe complaints. These complaints ultimately lead to functional impairment and sick leave. Hoedeman et al. (2009) found similar results.

An optimal combination of sensitivity and specificity was achieved at a cut point of 9. In terms of predictive validity, these findings are rather disappointing; based on these findings, the validity of this screening instrument in the OH setting can be considered low (Fischer, Bachmann, & Jaeschke, 2003) to moderate (Jones & Athanasiou, 2005). ROC analysis shows an AUC of 0.61, which according to common rules of thumb (in general, AUC > 0.75 is considered large, following the guidelines of more commonly effect size estimates such as Cohen's *d* by Cohen, 1988 and Cohen, 1992) is not optimal either. However, the 4DSQ does perform slightly better than the PHQ-15 that had a sensitivity of 56.5% and a specificity of 61.9% in this sample (De Vroege et al., 2012), but differences are within the 95% CI and may be ignored.

We provided 95% CIs for sensitivity, specificity, NPV, PPV and efficiency. Because groups of participants with MINI Somatoform symptoms and MINI No Somatoform symptoms were small, the intervals are rather wide. In particular, at the optimal cut off of 9, the 95% CI for sensitivity (sample value 60.9%) ranged from 40.8% to 77.8%. The interval also includes values smaller than 50%, which reflect sensitivity levels that are actually worse than diagnosing persons by flipping a fair coin. The 95% CI for specificity ranges from 53.6% to 73.7%. These results show that our sample size does not allow precise conclusions about sensitivity and specificity at the population level. Caution should be exercised in generalizing the sample results.

This study is the first to address classification results for the Somatization subscale of the 4DSQ in the OH setting, meanwhile using the MINI interview as gold standard to diagnose somatoform disorders. Furthermore, sick listed employees received questionnaires by mail without prior selection. In this way selection bias by OPs was eliminated. 95% CIs allowed an estimation of the degree of precision of the results, thus providing the reader with information on the generalizability of the outcomes to the population level. The optimal cut point lies between total scores 6 and 10, and given the sample information the best choice is 9.

A limitation of the study is the low return rate of 22.1%. Of this 22.1%, for logistical reasons 38% could not have the MINI interview within two weeks. Another limitation of the study is the small number of subjects, which limits the precision of the results. In order to give an impression of the level of uncertainty of results, 95% CIs were calculated.

Duration of sick leave might have contributed to the findings of this study as well. Unfortunately, data regarding duration of sick leave were not obtained. In addition, selecting employees who were on sick leave for a period of longer than six weeks and shorter than two years might have influenced the sensitivity and specificity and explain differences with other studies since they used a different time period (Braam et al., 2009). However, in this study we used this specific time period, bearing in mind the period ranging from two weeks up to six months used in the MINI. To conclude, we recruited employees sick listed for a period longer than six weeks and shorter than two years, used the 4DSQ to let them rapport physical symptoms within the past weeks and used the MINI interview, asking about physical symptoms in the past two weeks up to six months. These differences in time periods might have contributed to the reported moderate sensitivity and specificity in this study. Unfortunately, a gold standard which covers the same time period as the screener under study does not exist.

Because some sick listed employees could not be reached within the envisioned period for the diagnostic interview, our sample might have been biased. However, for the relevant background variables, no significant differences were found between the group that could be reached within the envisioned period, and the group that could not be reached. Thus we assume that the 107 interviewees constituted a random subsample of all 172 respondents.

Our findings suggest that the 4DSQ Somatization subscale can be used as a screener in the OH setting to alert the OP of the possibility of somatoform disorders. However, given the NPV (85.7%) and PPV (31.8%) at cut point 9, clinicians should be aware of the rather high chance of false positives. Especially since PPV is rather low, the possibility of false positives is realistic. One can conclude that in addition to diagnosis based on the 4DSQ Somatization subscale further complementary diagnostic evaluation for somatoform disorder is necessary.

Subsequently, psychiatric consultation and/or liaison consultation of a psychiatrist can serve as a next step in the diagnostic process, especially since somatoform disorders predict poor prognosis (Hoedeman et al., 2010) even without psychiatric co-morbidity (Barsky, Orav, & Bates, 2005; Harris, Orav, Bates, & Barsky, 2009; Olde Hartman et al., 2009). Furthermore, sick listed employees who present themselves in the general practice with somatoform disorders can also benefit from the use of the 4DSQ as a diagnostic tool and psychiatric consultation and/or liaison (Van der Feltz-Cornelis et al., 2010; Van der Feltz-Cornelis, Van Oppen, Adèr, & Van Dyck, 2006). In this way, sick listed employees with somatoform disorder may earlier receive appropriate care, leading to a tailor-made treatment procedure ranging from cognitive behavioral therapy, medication or use of the

multidisciplinary guidelines (Van der Feltz-Cornelis, Hoedeman, Keuter, & Swinkels, 2012). These implications lead to satisfactory recognition and treatment, which can effectively accelerate return to work (Van der Feltz-Cornelis et al., 2010).

Further development of screening instruments for somatoform disorders in the OH setting is needed. Also, validation research on the Somatization subscale of the 4DSQ for somatoform disorders in larger samples in the OH setting is necessary and should take duration of sick leave into account. Because of these limitations replication studies in larger samples are needed.

To conclude, we found that the 4DSQ Somatization subscale has moderate sensitivity and specificity, limiting the usefulness of the 4DSQ Somatization subscale as a screener for somatoform disorders in the OH setting. Given the high prevalence of somatoform disorders in the OH setting, and because so far screeners for somatoform disorders have not been found to possess more than moderate validity (De Vroege et al., 2012), the establishment of a suitable cut point of the 4DSQ Somatization subscale is of clinical relevance. However, clinicians need to be aware of the rather high chance of false positives. Further research using larger samples are needed to study the diagnostic performance of screeners for somatoform disorders in the OH setting, especially since we found that the uncertainty of classification results in a small sample is considerable.

Chapter 3

Psychometric properties of the Bermond-Vorst Alexithymia Questionnaire (BVAQ) in the general population and a clinical population

This chapter is based on:

De Vroege, L., Emons, W.H.M., Sijtsma, K., & Van der Feltz-Cornelis, C.M. (under review). Psychometric properties of the Bermond-Vorst Alexithymia Questionnaire (BVAQ) in the general population and a clinical population.

Abstract

The Bermond-Vorst Alexithymia Questionnaire (BVAQ) has been validated in student samples and small clinical samples but not in the general population; thus, representative general-population norms are lacking. We examined the factor structure of the BVAQ in Longitudinal Internet Studies for the Social Sciences panel data from the Dutch general population (N = 974). Factor analyses revealed a first-order five-factor model and a second-order two-factor model. However, in the second-order model, the factor interpreted as analyzing ability loaded on both the affective factor and the cognitive factor. Further analyses showed that the first-order test scores are more reliable than the second-order test scores. External and construct validity was addressed by comparing BVAQ scores with a clinical sample of patients suffering from somatic symptom and related disorder (SSRD) (N = 235). BVAQ scores differed significantly between the general population and patients suffering from SSRD, suggesting acceptable construct validity. Age was positively associated with alexithymia. Males showed higher levels of alexithymia.

Psychometric properties of the Bermond-Vorst Alexithymia Questionnaire (BVAQ) in the general population and a clinical population

Sifneos (1973) introduced the terminology of alexithymia to describe emotional deficiencies in patients suffering from classic psychosomatic disorders and epilepsy (MacLean, 1949; Nemiah & Sifneos, 1970). These patients were unaware of their feelings and their unawareness was accompanied by an inability to fantasize about their inner thoughts, feelings, and attitudes. Alexithymia has been linked to neurobiological and neuropsychological characteristics such as functioning of the "visceral" or "limbic" brain (e.g., MacLean (1949)). Furthermore, alexithymia has been associated with somatization (Kellner, 1990; Rief & Broadbent, 2007), somatoform disorder (Waller & Scheidt, 2006), and psychosomatic symptoms (Taylor, Bagby, & Parker, 1999). Emotional deficiencies were found to have a negative impact on one's health and were a potential obstacle for successful psychological treatment (Lumley, Neely, & Burger, 2007). This renders alexithymia important in research on understanding the onset and progress of medically unexplained symptoms and to further improve the effectiveness of psychotherapeutic interventions.

The conceptualization of alexithymia is ongoing and several questionnaires have been developed to assess alexithymia: the two most frequently used questionnaires are the Bermond-Vorst Alexithymia Questionnaire (BVAQ; Vorst & Bermond, 2001) and the twenty-item Toronto Alexithymia Scale (TAS-20; Bagby, Parker, & Taylor, 1994). Both questionnaires are self-report measures and both have good reliability (Bermond, Oosterveld, & Vorst, 2014). The TAS-20 operationalizes alexithymia as a constellation of three cognitive factors: difficulty identifying feelings, difficulty describing feelings, and external-oriented thinking. However, the TAS does not cover fantasizing, which Bagby et al. (2009) and Bermond et al. (2014) conceived as another essential feature of alexithymia. The absence of fantasizing motivated Bagby and colleagues to develop the Toronto Structured Interview for Alexithymia (TSIA; Bagby, Taylor, Parker, & Dickens, 2006), which also measures fantasizing.

The BVAQ uses a more comprehensive definition of alexithymia by operationalizing alexithymia as a constellation of five basic factors: ability to fantasize and fantasize about virtual matters (fantasizing), ability to identify emotions (identifying), looking for an explanation of emotional reactions (analyzing), ability to describe and/or communicate about emotional reactions (verbalizing), and ability to be emotionally aroused (emotionalizing). The inclusion of emotionalizing as a distinctive factor is a crucial difference between the BVAQ

and the TSIA and the TAS-20. Figure 1 shows the conceptualization of alexithymia for the BVAQ, the TSIA, and the TAS-20.

According to Vorst and Bermond (2001), emotionalizing refers to the degree of emotional arousal by emotion-inducing events. However, considering emotionalizing as an aspect of alexithymia is subject to debate (Bagby, Taylor, Quilty, & Parker, 2007), because emotionalizing might not describe differences in awareness of feelings but rather differences in physiological arousal (Bagby et al., 2009). The BVAQ enables the clinician to assess both cognitive and affective aspects of alexithymia, whereas the TAS-20 only provides information about cognitive factors. Hence, the BVAQ provides clinicians with clinically relevant information. Therefore, in this study we focus on the psychometric properties of the BVAQ.

Internal validity of the BVAQ

For justifiable use of the BVAQ, both in research and clinical settings, it is important that its psychometric properties are well understood. Although the factorial structure and the psychometric properties of the BVAQ have been the subject of several studies (e.g., Bagby et al. (2009); Bekker, Bachrach, and Croon (2007); Bermond et al. (2007)), six potential issues necessitate further research: a) indeterminacy of the BVAQ's factor structure, b) use of inadequate groups such as student samples, c) use of small sample sizes, d) invalid respondent answers due to lack of motivation to fill out the BVAQ, e) lack of comparison of the BVAQ between groups with expected different alexithymia levels, and f) factor structures for indicative and counter-indicative items.

Several studies replicated the first-order five-factor structure of the BVAQ, including the factors identifying, verbalizing, analyzing, fantasizing, and emotionalizing (e.g., Bagby et al. (2009); Bekker et al. (2007); Bermond et al. (2007); Deborde et al. (2007); Vorst and Bermond (2001)), but Hornsveld and Kraaimaat (2012) found poor fit. Bermond et al. (2007) reduced the five factors to two second-order factors, representing a cognitive dimension and an affective dimension. These two second-order factors were obtained using principal component analysis (PCA) followed by both orthogonal (varimax) and oblique (oblimin) rotation and were corroborated by findings in neuropsychological research (Bermond, Vorst, & Moormann, 2006). Other studies were unable to replicate the second-order factors (Bagby et al., 2009) or the affective dimension (Bekker et al., 2007). Hence, our study aims at addressing internal validity by exploring the first-order and second-order factor structure of the BVAQ using exploratory factor analyses (EFA).

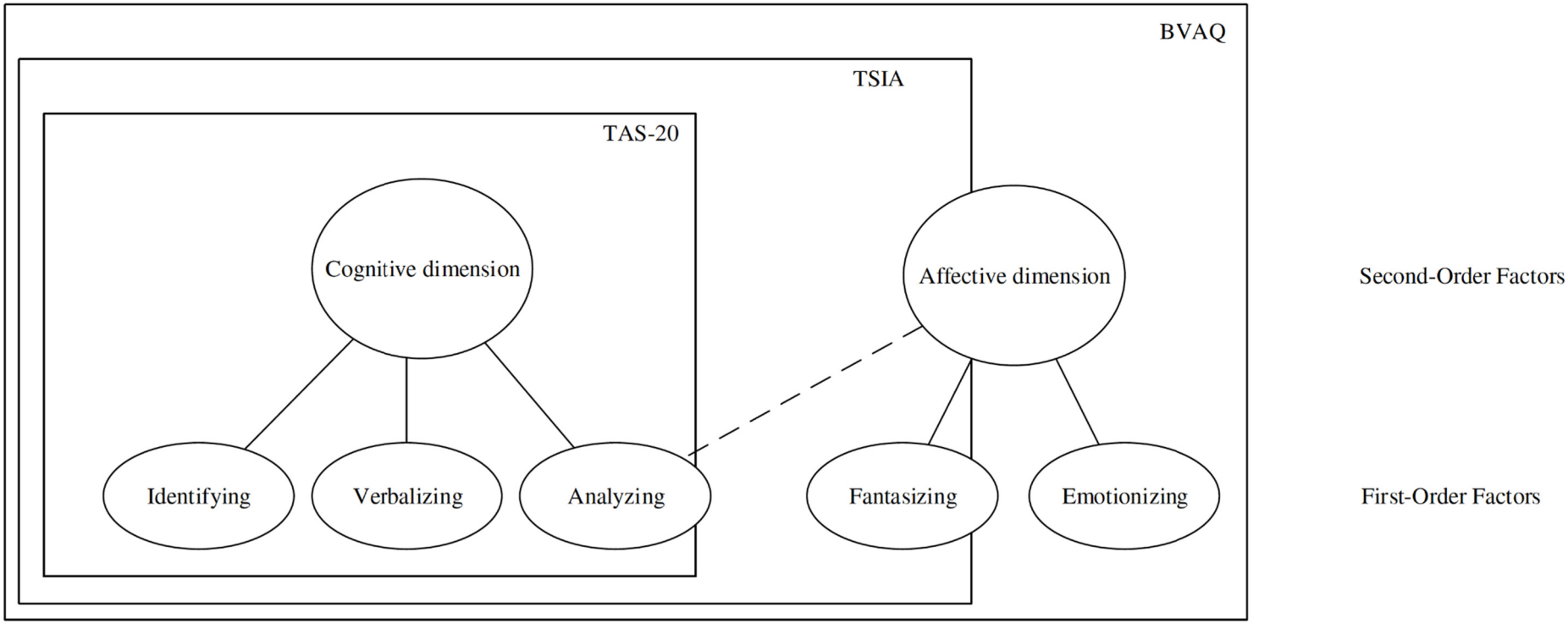


Figure 1. Visualization of the different conceptualizations of alexithymia and the position of the different questionnaires.

External validity

Different explanations may be given for the ambiguity in the first-order and the second-order factor structures, some of which pertain to the external validity of the BVAQ. Most studies used small clinical samples or student samples, usually psychology students, and may have played a role in ambiguous findings regarding factor structure so far. Student samples cannot be considered to adequately represent the populations of interest, such as the general population or clinical populations. Another problem is that PCA or EFA using small samples may be overly sensitive to sampling fluctuation (Pett, Lackey, & Sullivan, 2003), limiting the generalizability of the sample results to the population. Sample size limitations were rarely recognized in the literature. Hence, in this study we used a large sample and we explored the external validity of the BVAQ in several ways.

Ecological validity

In this study, we used panel data from a large sample from the general population. A disadvantage of panel data is that respondents complete the questionnaire under artificial conditions, because the outcomes of the BVAQ are not the respondent's interest. As a result, respondents may not be motivated to complete the selected questionnaires (thus inducing selection bias), complete the questionnaire randomly, or tend to give only extreme responses (i.e., either 1 or 5 scores). This might result in data having questionable validity that provide a biased picture of the questionnaire's ecological validity. Invalid data may also explain ambiguous factor-analysis results. Person-fit analysis (Meijer & Sijtsma, 2001) may signal traitedness for a limited number of respondents, thus casting doubt on the validity of their data (Reise & Waller, 1993).

Construct validity, differences between populations

The BVAQ renders assessing differences between alexithymia scores obtained from different populations possible. Differences are likely to be found between the general population and patients suffering from somatic symptom and related disorder (SSRD) (American Psychiatric Association (APA), 2013) which replaced the somatoform disorders (APA, 2000). Somatoform disorders were related with alexithymia, and we expect that the same relationship exists for patients suffering from SSRD. Therefore, for investigating construct validity, medical patients suffering from a high expected likelihood to suffer from alexithymia were included in the study. We anticipated that these patients scored higher on alexithymia than non-patients. Previous studies suggest that alexithymia mediated effectiveness of psychotherapy (Ogrodniczuk, Piper, & Joyce, 2011). Patients were recruited from a specialty mental health outpatient clinic for patients suffering from SSRD. The data

were collected during intake for treatment, hence patients might be more honest with respect to their possible alexithymia symptoms than people from the general population who were investigated without personal treatment objective. Observed mean differences in BVAQ scores between the general population and SSRD patients provide further evidence of the questionnaire's construct validity.

Construct validity, indicative and counter-indicative items

Another validity issue with the BVAQ is the use of indicative and counter-indicative items. Questionnaires containing indicative and counter-indicative items, in the literature often referred to as balanced scales (e.g., Vigneau and Cormier (2008)), may reveal additional factors related to response styles, or additional factors may arise because positively and negatively worded items might tap slightly different attributes, thus limiting construct validity. Subtle differences between subpopulations with respect to interpretation of indicative and counter-indicative items might also explain differences between the factorial structures found in different BVAQ studies. Interpretation differences have received little attention so far. To further understand the possible wording effects and possible implications for using the BVAQ in clinical practice, we performed two EFAs, one for the indicative items (i.e., *I find it difficult to express my feelings verbally*) and one for the counter-indicative items (i.e., *I often use my imagination*).

Scoring

BVAQ item scores may be added to obtain test scores for items loading on the first-order factors, the second-order factors, and for all the items in the questionnaire. In general, sum scores are more reliable when the number of items grows larger, but when additional items tap different traits, the conceptual interpretation of the scores may be less clear. For example, total BVAQ scores are most reliable but equal scores might reflect different alexithymia profiles, thus hampering the clinical interpretation of total scores. Therefore, sum scores have to be based on subsets of items allowing a clear interpretation. Vorst and Bermond (2001) advocated the use of second-order BVAQ scores, because these scores preserve about 70% of the variance of the first-order scores and maintain a clear meaning. Researchers and clinicians may want to use first-order scores to investigate how different alexithymia aspects correlate with other variables, but then the question arises whether first-order scores have additional value compared to second-order scores. Reise, Bonifay, and Haviland (2013) showed that under certain conditions total scores on a multi-factor questionnaire may provide more-reliable information about specific trait aspects than scores based on single factors. We compared the psychometric properties of sum scores based on

first-order factors and second-order factors, including sum-score reliability, and explored whether or not first-order test scores were more reliable than the second-order test scores.

Finally, we provided norms based on normative data from the general population to enhance the interpretation of individual BVAQ sum scores. Because in former studies results regarding gender and age differences were ambiguous (Salminen, Saarijärvi, Äärelä, Toikka, & Kauhanen, 1999; Vorst & Bermond, 2001), we explored gender and age differences with respect to the BVAQ.

Method

Participants

General population sample. Data were used from the Longitudinal Internet Studies for the Social Sciences (LISS) panel (www.lissdata.nl) collected by CentERdata (Tilburg University, The Netherlands). The LISS panel constitutes a representative panel sample of 7,000 Dutch-speaking adults from the general population, permanently residing in the Netherlands, who participate in monthly internet surveys. The panel was created using a sample of households drawn from the population register. Households without access to the internet were provided with a computer and an internet connection. Relevant ethical safeguards were met with respect to the participant's confidentiality and consent. Detailed information about the LISS panel is provided in Scherpenzeel, Das, Ester, and Kaczmirek (2011).

For this study, a random sample of 1,434 panel members from the LISS panel were invited by email to complete an online questionnaire that included the BVAQ, but 335 respondents (23.4%) did not respond. Thirteen participants (1.2%) started filling out the BVAQ but did not complete the survey and were considered as non-responders. Hence 1,086 (75.7%) participants completed the questionnaire. Table 1 shows the sample characteristics of both responders (47% males and 53% females) and non-responders (44.8% males and 55.2% females). Men were on average older than woman ($t(972) = -2.95, p = .003, d = 0.19$). Responders were significantly older (mean difference = 12.3, $t(1432) = 12.72, p < .001$, $d = 0.78$), better educated ($p = .03, V = .10$) and more often engaged in a relationship ($p < .001, V = .20$) than non-responders. Figure 2 shows how the final sample was obtained. The Dutch version of the BVAQ was digitalized and propounded to the LISS panel. After data collection, the raw data were transformed following the scoring syntax suggested by Vorst and Bermond (2001).

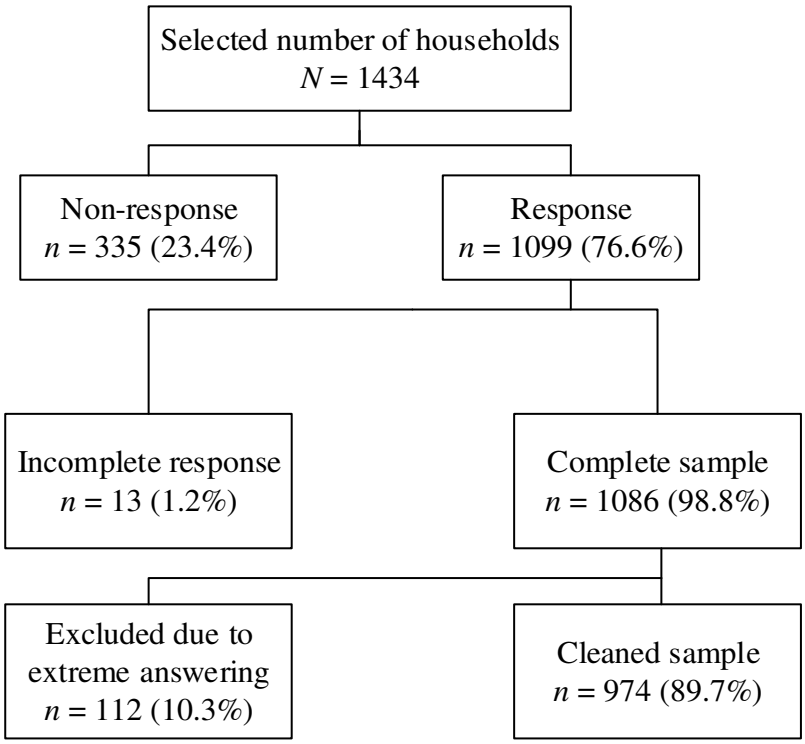


Figure 2. Overview of sample composition general population.

Outpatient clinic sample. A sample of patients suffering from SSRD ($N = 235$) was used for external validation. All patients referred to the Clinical Centre of Excellence for Body, Mind, and Health situated in Tilburg, The Netherlands were included. The BVAQ was self-administered during the standard intake procedure. The Commission of Scientific Research of GGz Breburg approved to conduct this study (file number: CWO 2014-09). Patients gave consent to make use of their intake data for scientific research purposes.

Table 1
Socio-demographic characteristics of the study sample and the non-responders

Characteristic	Study sample			Gender differences		Non-responders	Differences between study sample and non-responders	
	Total *N* =974 *M (SD)/ n ((%)*	Men *n* = 458 *M (SD)/ n ((%)*	Women *n* = 516 *M (SD)/ n ((%)*	*p*	Effect size	*n* = 348 *M (SD)/ n ((%)*	*p*	Effect size
Gender							.47	.02[c]
Men	47.0%	---	---			156 (44.8)		
Women	53.0%	---	---			192 (55.2)		
Age (M)	50.4	52.1	48.8	.003	.19[a]	37.7	<.001	.78[a]
(SD)	17.2	17.4	16.9			15.4		
(range)	18-89	18-89	18-87			16-80		
Educational level[*]				.09	.10[b]		.03	.10[b]
Low (1-4)	284 (%)	125 (%)	159 (%)			102 (29.3)		
Medium (5)	211 (%)	107 (%)	104(%)			84 (24.1)		
High (6-7)	479 (9%)	226 (%)	253 (%)			161(46.3)		
Marital status				.27	.06[b]		<.001	.20[b]
Married	522 (53.6%)	254 (55.5%)	268 (51.9%)			133 (38.2)		
Divorced	104 (10.7%)	46 (10.0%)	58 (11.2%)			29 (8.3)		
Widow(er)	54 (5.5%)	19 (4.1%)	35 (6.8%)			7 (2.0)		
Never	294 (30.2%)	139 (30.3%)	156 (30.0%)			179 (51.4)		

[*] Based on the Verhage coding, which includes seven levels ranging from low (levels 1 through 4), medium (level 5) and high (levels 6-7) (Verhage, 1964).
[a] Cohen's *d*
[b] Cramer's *V*
[c] Phi
Note: non-responders did not complete the survey.

Instrument

Bermond-Vorst Alexithymia Questionnaire (BVAQ). Alexithymia was measured by means of the Dutch BVAQ. The BVAQ comprises 40 items; half of the items is alexithymia indicative and the other half is counter-indicative. Respondents rated their answer on a 5-point Likert scale ranging from "*this definitely applies*" to "*this in no way applies*". All items were scored 1 through 5 such that higher scores reflect higher levels of alexithymia (Vorst & Bermond, 2001). The questionnaire comprises five subscales, which are identifying, verbalizing, analyzing, fantasizing, and emotionalizing, each in accordance with the five-factor model of alexithymia (Vorst & Bermond, 2001). Given item scores ranging from 1 to 5, the first-order test scores range from 8 to 40. Test scores on the cognitive factor were obtained by adding the total scores on the subscales identifying, analyzing and verbalizing, meaning that test scores can range from 24 through 120. Test scores of the affective factor were obtained by adding the total scores on the subscales emotionalizing and fantasizing, thus producing test scores ranging from 16 through 80. Hence, high cognitive test scores represent problems with respect to the conscious experience of arousal accompanying emotions and high affective test scores reflect difficulties with respect to emotionalizing and fantasizing.

Data analysis

Internal validity. Validity was investigated in a series of analyses. Because data were collected in low-stakes conditions, some respondents may not have been motivated to complete questionnaires seriously. Others may have used idiosyncratic response styles. Resulting aberrant item-response patterns were identified using person-fit analysis (Meijer & Sijtsma, 2001). Aberrant patterns were removed from the sample prior to EFA to obtain a sample without invalid item-response patterns. For person-fit analysis, we used the average normed number of Guttman errors (denoted G_N) (Emons, 2008) across the subscales. Statistic G_N can assume values between 0 (perfect fit) and 1 (extreme misfit). Following Emons, Sijtsma, and Meijer (2005), we removed the highest 10% of the cases, which amounts to removing cases whose G_N value was above 0.326. This cutoff is consistent with cutoffs suggested by Emons (2008), based on simulations. This results in two (overlapping) samples, the complete sample and the cleaned sample.

EFA was done as follows. First, we used parallel analysis (Horn, 1965) in combination with minimum rank factor analysis (MRFA; ten Berge & Kiers, 1991; Timmerman & Lorenzo-Seva, 2011) to determine the number of common factors. Like any factor-analysis approach, MRFA maximizes the item communalities given the number of factors (ten Berge & Kiers, 1991), but MRFA does this such that the reduced correlation matrix is statistically

correct. Therefore, MRFA allows valid estimates of the explained common variance (ECV) (Ferrando & Lorenzo-Seva, 2013), which expresses the proportion of common variance explained by the hypothesized factors. Parallel analysis compares the percentage of variance explained by the factors with the percentage of variance explained by the same number of factors resulting from randomly generated data. In total, 500 random correlation matrices were generated by means of permutation of the raw data and subsequently analyzed by means of MRFA. Factors were considered meaningful if the percentage of variance these factors explained exceeded the percentage of variance the random-data factors explained. Because the BVAQ comprises ordinal items, showing both positive and negative skew, some also showing excessive kurtosis, factor analysis of the polychoric correlation matrix was preferred (Muthen & Kaplan, 1992). Parallel analysis was conducted by means of the free software program FACTOR version 10.3.01 (Lorenzo-Seva & Ferrando, 2006).

Once the number of factors was determined, we investigated the factor structure using the configuration of the factor loadings. Promax rotation (Gorsuch, 1983) was used to obtain the final rotated factor loadings. The presence of second-order factors was investigated by factor analyzing the correlations between the first factors obtained using the first-order factor model. The final factor solution was again obtained using promax rotation. The final structures were inspected for adherence to a simple structure (Gorsuch, 1983) and compared with the factorial structure Vorst and Bermond (2001) found. EFAs were run in MPLUS7.1, using weighted least squares means and variance adjusted estimation (Muthén & Muthén, 2007) and R-package Psych (Revelle, 2015).

Total-score reliability is commonly examined using coefficient alpha (Cronbach, 1951). The accompanying 95% confidence intervals (CIs) of coefficient alpha were obtained using the method of Feldt, Woodruff, and Salih (1987), which is available in the R-package cocron (Diedenhofen, 2016).

Construct and external validity. To examine construct validity, we ran EFAs separately for the indicative and for the counter-indicative items. EFAs were run in MPLUS7.1 using weighted least squares means and variance adjusted estimation (Muthén & Muthén, 2007) and R-package Psych (Revelle, 2015) in R (R Core Team, 2014).

To examine external validity, we compared the BVAQ scores of the general population with the scores of SSRD patients to explore the degree to which the BVAQ discriminates between groups. Independent sample *t*-tests were done to compare the first-order and second-order BVAQ scores and Cohen's *d* estimated effect size.

Scoring. To examine whether first-order test scores provided additional diagnostic information about the first-order factors that is more reliable than the information provided by the aggregated total scores, we used Haberman's procedure (Haberman, 2008). This procedure uses the proportional reduction in mean squared errors (PRMSE). The PRSME is conceptually similar to the reliability, and for first-order test scores the PRMSE is equivalent to coefficient alpha. Large PRMSEs are desirable. PRMSEs were obtained using the R-package sirt (Robitzsch, 2016) in R (R Core Team, 2014).

Because of the expected differences between gender groups and age groups with respect to alexithymia, it might be useful to have separate norms for males and females and for different age groups. We first examined the relationship of gender and age with alexithymia to decide if separate norms for men and women and different age groups were needed. In case gender or age was associated with alexithymia, we used regression analysis to derive normative data (e.g., Oosterhuis, Van der Ark, and Sijtsma (2016)). This was done as follows. First, we regressed BVAQ scores on gender and age using a linear model with main effects only. The regression model provides estimates of mean BVAQ score as a function of gender and age. Second, for each respondent i we computed a standardized residual (e_i); that is, e_i = observed test score – expected test score, based on the estimated regression model. The distribution of the residuals served as normative reference distribution. The residuals were standardized using $\frac{e_i}{S_{e_i}}$ in which S_{e_i} is the standard deviation (*SD*). The standardized residual indicates the relative position of the individual's score with respect to the mean in the population of persons having the same gender and the same age. To facilitate the interpretation of the standardized residuals, we converted standardized residuals to percentile values by means of the standard normal cumulative distribution. Model assumptions were tested by means of graphical inspection of the residuals. Analyses were done in Statistical Package for the Social Sciences for Windows version 22.0 (IBM Corp., 2011).

Results

Comparison of the background characteristics in the original sample and the cleaned sample did not show any differences. Inspection of the misfitting cases showed unsystematic patterns. Six respondents scored '3' on all items, suggesting they did not seriously fill out the BVAQ. Consequently, they were considered as cases showing extreme response styles. The corresponding data records were removed from the sample, thus producing a cleaned sample of 974 participants to be used for EFA.

Factor structure

Parallel analysis suggested five common factors. Model fit of the first-order five-factor model was acceptable (Comparative Fit Index = .94; Root Mean Square Error of Approximation = .046; Root Mean Square of the Residuals = 0.032). The first-order five-factor model explained 45.7% of the total variance and 68.3% of the common variance. Extracting a sixth factor only marginally improved the explained common variance to 71.7%, thus accounting for only a small proportion of common variance between the items. Therefore, we retained five first-order factors for further analysis.

Table 2 (columns 2 – 12) shows the standardized factor loadings for the first-order five-factor model and promax rotated factors, for the full sample and the cleaned sample (only loadings above 0.3 are reported). In both samples, the loadings approximated a simple structure (e.g., Gorsuch (1983, p. 178); that is, for each factor at least a few items only loaded predominantly on that specific factor. However, the pattern of loadings differed from the postulated five-factor structure (Vorst & Bermond, 2001), and results differed between the complete sample and the cleaned sample. Based on the literature (Bermond et al., 2007; Vorst & Bermond, 2001), we initially labelled the factors as follows: verbalizing (F1), fantasizing (F2), identifying (F3), emotionalizing (F4), and analyzing (F5).

Comparison of the factor loadings between the full sample and the cleaned sample showed few notable differences. Deletion of the aberrant item-score patterns removed the cross loadings for items in the subscales verbalizing and fantasizing. In the complete sample, the identifying items 8, 18, 23, and 33 loaded on analyzing instead of identifying, but in the cleaned sample, all items loaded on the postulated factors, with low cross loadings for items 13 and 28 on analyzing. Interestingly, these items are the counter-indicative items, and the results suggest that these items are indicators of analyzing rather than identifying. In the complete sample, the factor loadings showed an unsystematic pattern. In the cleaned sample, the indicative items (10, 20, 30, and 40) loaded on the postulated factor but only item 40 had a substantial loading (> .60), two items (25 and 35) had weak cross loadings on other factors, and the other items (5 and 15) loaded on none of the factors. Hence, the subscale analyzing could not be replicated in the complete and the cleaned sample.

Table 2

Standardized factor loadings of the five factor model for complete and cleaned sample (i.e., without aberrant response patterns). Items are listed in clusters according to the subscales as suggested by Vorst and Bermond's subscales. Only loadings of .3 or higher are reported

	Complete sample					Cleaned sample				
	F_1	F_2	F_3	F_4	F_5	F_1	F_2	F_3	F_4	F_5
Items from Vorst and Bermond's subscale verbalizing										
i1	.61				.30	.72				
i6	.63					.63				
i11	.71					.73				
i16	.58					.61				
i21	.44				.30	.51				
i26	.62					.61				
i31	.65		.34			.65				
i36	.45					.51				
Items from Vorst and Bermond's subscale fantasizing										
i2		.35			-.34		.40			
i7		.67					.70			
i12		.77					.77			
i17		.56					.57			
i22		.87					.89			
i27		.77					.77			
i32		.64					.67			
i37		.51					.58			
Items from Vorst and Bermond's subscale identifying										
i3			.55					.48		
i8					.59			.58		
i13			.59					.54		.34
i18					.64			.66		
i23					.59			.62		
i28			.68					.60		.37
i33					.68			.65		
i38			.64					.62		
Items from Vorst and Bermond's subscale emotionalizing										
i4				.48					.47	
i9				.70					.75	
i14				.60					.57	
i19				.35	-.49			-.33	.30	.31
i24				.51	.39			.31	.51	
i29				.59	-.41				.55	
i34				.55					.54	
i39				.70					.72	
Items from Vorst and Bermond's subscale analyzing										
i5					.36					
i10			.40							.41
i15										
i20			.50							.49
i25					.38			.39		
i30			.45	.30						.42
i35				.49					.41	
i40			.54							.63

Note: F_1 represents 'verbalizing, F_2 represents 'fantasizing, F_3 represents 'identifying', F_4 represents 'emotionalizing, and F_5 represents 'analyzing.

Table 3 shows the estimated factor correlations and the second-order factor structure based on the estimated factor correlations, in both the complete and the cleaned sample. Results for verbalizing, fantasizing, identifying, and emotionalizing were consistent across different EFAs, corroborating the presence of a cognitive and an affective domain within the BVAQ. The affective dimension emotionalizing showed a substantive cross loading with the cognitive dimension in the complete sample but not in the cleaned sample. Results for analyzing were ambiguous.

Reliability

Table 4 (column 3) shows coefficient alpha and corresponding 95% CIs for the first-order test scores, and the second-order test scores. Coefficient alpha ranged from .75 to .89. PRMSEs for the first-order test scores (column 4) were higher than the PRMSE for the second-order test scores or total scores (column 5). Table 4 (column 2) also shows the range of item-rest correlations of the items constituting the first-order test scores and the second-order test scores in the general population. Item-rest correlations suggested adequate assignment of the individual items to the subscales. These results also showed that some items are weak indicators of the general attribute of alexithymia. In particular, item 2 (*Before I fall asleep, I imagine all kinds of events, encounters and conversations*), item 5 (*I hardly ever consider my feelings*) and 15 (*When I feel uncomfortable, I will not trouble myself even more by asking myself why*) are weak indicators.

Table 3

Correlations between the first-order factors of the five-factor model and standardized second-order factor loadings in the cleaned sample

	Estimated inter-factor correlations					Second-order factor loadings	
Subscales of the BVAQ	Verbalizing	Fantasizing	Identifying	Emotionalizing	Analyzing	G1	G2
All items (complete sample)							
Verbalizing	1.00					.83	
Fantasizing	.16	1.00					.85
Identifying	.47	.08	1.00			.79	
Emotionalizing	.25	.31	.14	1.00		.34	.76
Analyzing	.52	.31	.49	.46	1.00	.82	.47
All items (cleaned sample)							
Verbalizing	1.00					.51	
Fantasizing	.21	1.00					.62
Identifying	.45	.02	1.00			.80	
Emotionalizing	.33	.39	.15	1.00			.66
Analyzing	.23	.32	.11	.36	1.00		.53
Indicative items (cleaned sample)							
Verbalizing	1.00					.57	
Fantasizing	.23	1.00					.76
Identifying	.45	.09	1.00			.73	
Emotionalizing	.41	.41	.20	1.00			.58
Analyzing	.51	.49	.42	.52	1.00	.60	.37
Counter-indicative items (cleaned sample)							
Verbalizing	1.00					.59	
Fantasizing	.09	1.00					.45
Identifying	.39	-.03	1.00			.74	
Emotionalizing	.12	.31	.05	1.00			.70
Analyzing	.48	.20	.50	.41	1.00	.75	(.29)

Note: G1 represents the cognitive factor and G2 represents the affective factor.

External validity

Table 5 shows results for EFAs for the indicative and the counter-indicative items. For both sets of items, the five-factor model fitted the data well and all items loaded on the corresponding factor. Cross loadings were absent. These results suggest that the items can be clustered into subscales as intended, but the counter-indicative items of analyzing may represent a slightly different conceptualization than the indicative items. Figure 3 shows a visualization of the factor structure for the indicative and the counter-indicative items.

Table 4
Reliability and additional values (PRMSEs) of the first-order and second-order scores of the BVAQ (results obtained in the total sample)

Subscales	Range item-rest score correlations	Coefficient alpha (95% CI)	PRMSE	
			First-order scores	Total score
First-Order Scores:				
Emotionalizing	.31-.55	.75 (.73-.77)	.75	.53
Fantasizing	.35-.70	.82 (.80-.84)	.82	.68
Identifying	.39-.55	.79 (.77-.81)	.79	.65
Analyzing	.39-.60	.80 (.78-.82)	.80	.68
Verbalizing	.39-.64	.83 (.81-.85)	.83	.71
Second-Order Scores:				
Cognitive dimension	.30-.63	.89 (.88-.90)	.89	.74
Affective dimension	.27-.58	.82 (.80-.84)	.81	.57

Abbreviations: 95% CI: 95% confidence interval, PRMSE: Proportional reduction in Mean Squared Error, BVAQ: Bermond-Vorst Alexithymia Questionnaire.
Note: Range Item-Rest Score Correlations, Coefficient Alpha, and PRMSE were calculated for the general population (Total sample).

Table 5

Standardized factor loadings of the five factor model in the LISS panel data of the cleaned sample for the indicative items and counter-indicative items. Only loadings of .3 or higher are reported

	Indicative items						Counter-indicative items				
	F_1	F_2	F_3	F_4	F_5		F_1	F_2	F_3	F_4	F_5
Items from Vorst and Bermond's subscale verbalizing											
Items						Items					
i1	.68					i6	.63				
i11	.69					i16	.65				
i21	.49					i26	.64				
i36	.48					i31	.66				
Items from Vorst and Bermond's subscale fantasizing											
Items						Items					
i7		.74				i2		.45			
i17		.53				i12		.77			
i22		.92				i27		.77			
i32		.65				i37		.55			
Items from Vorst and Bermond's subscale identifying											
Items						Items					
i8			.60			i3			.60		
i18			.60			i13			.49		
i23			.65			i28			.79		
i33			.69			i38			.59		
Items from Vorst and Bermond's subscale emotionalizing											
Items						Items					
i4				.50		i14				.59	
i9				.63		i19				.53	
i24				.50		i29				.75	
i34				.59		i39				.69	
Items from Vorst and Bermond's subscale analyzing											
Items						Items					
i5					.35	i10					.51
i15					.39	i20					.68
i25					.59	i30					.52
i35					.60	i40					.80

Note: F_1 represents 'verbalizing, F_2 represents 'fantasizing, F_3 represents 'identifying', F_4 represents 'emotionalizing, and F_5 represents 'analyzing.

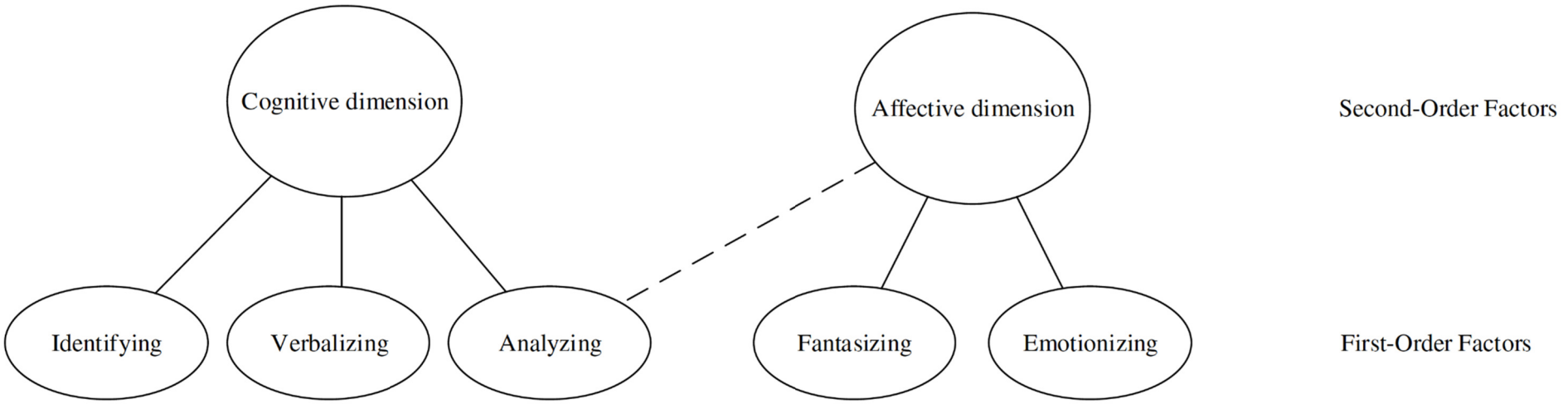


Figure 3. Second-order factor structure of the BVAQ based on EFA on the indicative items and on the counter-indicative items (cleaned sample).

Table 3 also shows estimated factor correlations and the second-order factor structure based on the estimated factor correlations for indicative and counter-indicative items. Correlations of analyzing with the other factors were lower when analyzing all 40 items together than for indicative and counter-indicative items separately. The different factor correlations for indicative and counter-indicative items might also explain the differences between the second-order factor structures. Results suggest that indicative and counter-indicative analyzing items refer to slightly different attributes, which is obscured when analyzing all items together.

Scoring

Table 6 (columns 2—5) shows the means and SDs of the first-order test scores and the second-order test scores for the SSRD sample and for the general-population sample. Table 6 (columns 6—7) also shows the *p*-values and Cohen's *d* for the comparison between the SSRD sample and the general-population sample. The mean scores of emotionalizing ($p < .001$, $d = .57$) and the affective dimension ($p = .003$, $d = .22$) were significantly higher in the general-population sample. The mean scores on identifying ($p < .001$, $d = -.57$), verbalizing ($p < .001$, $d = -.35$), and the cognitive dimension ($p < .001$, $d = -.33$) were significantly lower in the general-population sample than the SSRD sample.

Inspection of the residuals suggested that BVAQ total scores were linearly related to age and that heteroscedasticity was absent. Table 7 (columns 2 - 4) shows the estimated unstandardized regression coefficients for predicting first-order test scores and second-order test scores from age and gender. Age and gender explained 2% (identifying) to 15% (emotionalizing) of the variance of the first-order test scores (Table 7, column 5), which amounts to small to medium effects according to Cohen's (1988, p. 413) rules of thumb. Except for fantasizing, a significant effect of gender was found for the other subscales. Significant effects of age were found for the subscales fantasizing, analyzing, and the affective factor. To gauge the practical importance of age given the estimated regression model, we looked at differences between predicted scores for the youngest and the oldest respondents. The predicted score of 18 year-old males equaled 46.9, whereas the predicted score for an 89 year-old male equaled 53.3, which represents a score difference of 6.4 units. Based on the distribution of the residuals (i.e., $SD = 8.84$; see Table 7), a score difference of 6.4 units amounts to Cohen's *d* of .73 (6.4/8.84), meaning a large effect size. Therefore, it is important to control for age.

Table 7 (columns 6—8) also describes the distribution of the residuals (i.e., SD, skewness and kurtosis). In all models, residuals were obtained for the model including both age and gender as predictors. The residuals were normally distributed. The coefficients in Table 7 can be used to norm scores that take age and gender differences into account. An Excel template for this purpose is available upon request from the corresponding author as well as norm tables for each age and gender group.

Table 6

Descriptive statistics, of the first-order and second-order scores of the BVAQ (results obtained in the total sample), descriptive statistics for the SSRD sample (N = 234) and statistical comparison between SSRD sample and general population of BVAQ scores

Subscales	Descriptive statistics (SSRD sample)		Descriptive statistics (general population)		BVAQ scores comparison	
	M	*SD*	*M*	*SD*	*p*	*d*
First-order scores:						
Emotionalizing	18.8	5.2	21.7	5.1	<.001	.57
Fantasizing	26.8	6.9	25.8	6.4	.056	-.15
Identifying	22.1	7.0	18.9	5.2	<.001	-.57
Analyzing	19.6	6.0	20.4	5.3	.065	.15
Verbalizing	25.4	8.3	23.1	6.0	<.001	-.35
Second-order scores:						
Cognitive dimension	67.1	17.6	62.3	13.4	<.001	-.33
Affective dimension	45.5	8.9	47.5	9.3	.003	.22

Abbreviations: SSRD: Somatic Symptom and Related Disorder, BVAQ: Bermond-Vorst Alexithymia Questionnaire.

Table 7

Multiple regression analysis predicting first-order scores or second-order scores from age and gender, and distribution of the residuals

Multiple regression analysis					Distribution of residuals		
BVAQ score	Regression effect (*B*)[a]			*R*-square	SD	Kurtosis	Skewness
	Constant	Gender[b]	Age				
Emotionalizing	24.07 (0.50)	**-4.00** (0.30)	-0.01 (0.01)	.15	4.66	-0.12	0.07
Fantasizing	21.20 (0.67)	-0.63 (0.40)	**0.10** (0.01)	.08	6.17	-0.22	-0.16
Identifying	18.93 (0.55)	**-1.36** (0.33)	0.01 (0.01)	.02	5.12	-0.14	0.04
Analyzing	19.89 (0.55)	**-2.33** (0.33)	**0.03** (0.01)	.07	5.08	0.12	0.02
Verbalizing	24.67 (0.63)	**-2.59** (0.38)	0.00 (0.01)	.05	5.81	-0.32	0.10
Cognitive dimension	63.50 (1.40)	**-6.28** (0.84)	0.04 (0.02)	.06	12.94	0.14	-0.14
Affective dimension	45.27 (0.96)	**-4.63** (0.57)	**0.09** (0.02)	.10	8.84	0.07	-0.09

[a]Unstandardized partial regression coefficients (standard error in parentheses).

[b]Reference category is men

Note: Estimated regression coefficients printed in boldface are significant at the 1% level.

Discussion

This study was the first to validate the BVAQ for the general population. Aberrant item responses due to extreme responders were removed prior to the EFA in an effort to better validate the BVAQ factor structure. Removal of aberrant item-response patterns produced a factor structure that was consistent with the conceptualization of alexithymia. This study showed that person-fit analysis may contribute to a better understanding of the factor structure.

The results suggest that items indicative of analyzing represent a conceptually different attribute than counter-indicative items. A competing explanation for different results might be the wording of the items. For example, indicative items are phrased in terms of 'unclear' whereas counter-indicative items are phrased in terms of 'understand'. Such small differences may invoke different cognitive processes, rendering responses that represent different attributes. Because this was the first study in the general population, it is unclear whether such wording effects are typical of the general population or whether these results also generalize to other populations. This is a topic for future research. Because the results showed a clear difference with respect to the second-order factor structure for the indicative and the counter-indicative items, and because analyzing ability also loaded on the affective factor instead of only on the cognitive factor, our analysis of indicative and counter-indicative items may explain why construct validity of the BVAQ was found suboptimal in earlier studies.

We found that the BVAQ is a reliable instrument. Additional analyses showed that when scores are aggregated to second-order test scores, reliable information about the constituent components is lost. Consequently, this study provided support for the use of first-order test scores to provide diagnostic information for understanding alexithymia at a more detailed level. Because first-order test scores have additional value with respect to second-order test scores, clinicians and researchers should better rely on the first-order test scores for a clinical judgement.

This was also the first study that compared alexithymia scores in the general population and in a patient population suffering from SSRD, that, we hypothesized, would have more difficulty expressing their feelings and thoughts about their symptoms. Consequently, they were expected to score higher on an alexithymia scale than the general population. Another possibility was that patients gave a more involved opinion about their symptoms, because the data were collected in connection with their intake for treatment. We checked the likelihood of these alternative explanations. Because higher scores of alexithymia were found in the SSRD group, support for construct validity was found.

Regression analyses of alexithymia on age and gender corroborated the trends found in other studies. Males had higher mean alexithymia scores than women and a positive effect of age was found, similar to findings in studies using clinical populations (e.g., Franz et al. (2008); Joukamaa, Saarijärvi, Muuriaisniemi, and Salokangas (1996); Mattila et al. (2008); Pasini, Delle Chiaie, Seripa, and Ciani (1992); Salminen et al. (1999)). Caution should be exercised drawing conclusions about within-person change in alexithymia over time based on cross-sectional data. Individuals in varying cohorts may grow up in different social contexts, which may produce between-person variation in mean alexithymia across age groups, while alexithymia remains stable within persons. Longitudinal data are needed to study within- and between-person differences in alexithymia over time while controlling for physical conditions. This is a topic for future research.

Normative data were reported, both unconditional and conditional on age and gender. Both types of norms have practical value, but should be used carefully. When using age and gender-specific norms, one implicitly assumes that gender and age differences in alexithymia are related to contextual and not the construct itself. Contextual factors may include social environment and time-specific social norms. For example, two persons with the same BVAQ scores but of different age may not be conceived as equally alexithymic because the older person grew up in times where it was socially not that well accepted to talk about emotions while the younger person is more used to it. Likewise, a male and female having the same BVAQ scores may not be equally alexithymic because the female may have learned to express their emotions when she was young while the male did not. Hence, gender differences results from social norms and not the trait itself and this effect should be partialled out when comparing BVAQ scores between males and females. However, in the clinical practice, where the BVAQ is used for screening and treatment decisions, one may not want to treat males and females with the same BVAQ total scores differently. In such cases, clinicians can use the unconditional scores. We may notice that screening using unconditional norms may result in different prevalence rates for males and females or across age cohorts, while prevalence rates will be the same when using conditional norms.

Previous studies showed a relationship between alexithymia and distress (Barbosa et al., 2011; Castelli et al., 2012; Evren, Evren, & Guler, 2006; Lumley et al., 2011; Malt, Olafsson, Lund, & Ursin, 2002; Van Middendorp et al., 2008). Distress can be an outcome or a determinant of alexithymia (Margalit, Har, Brill, & Vatine, 2014), but this topic did not receive much attention yet. Tominaga, Choi, Nagoshi, Wada, and Fukui (2014) suggested that alexithymia hampers the successful regulation of negative affect and leads to increased

distress. Distress also has been shown to coincide with alexithymia as a state-dependent phenomenon (Haviland, Shaw, Cummings, & MacMurray, 1988; Honkalampi, Hintikka, Saarinen, Lehtonen, & Viinamäki, 2000). Because the role of distress for alexithymia is unclear, future studies may address this topic.

Significant differences were found between responders and non-responders with respect to age, educational level, and marital status. Because age is associated with alexithymia, caution should be exercised when generalizing results to the general population. Another limitation involves the use of panel data. However, we corrected for extreme responders to mitigate this limitation. One can argue that the use of the BVAQ is not preferred, because the majority of the alexithymia research studies used the TAS-20. The TAS-20 is limited with regard to measuring alexithymia. First, fantasizing, which is an important factor of alexithymia (Bagby et al., 2009; Bermond et al., 2014), is not in this questionnaire. Second, the absence of fantasizing in the TAS-20 even motivated the authors of the TAS-20 to develop a structured interview, which allows the measurement of fantasizing (Bagby et al., 2005). Third, a recent study reported that the subscale external oriented thinking of the TAS-20 has weak psychometric properties in the group of younger adolescents (Craparo, Faraci, & Gori, 2015). Bagby, Ayearst, Morariu, Watters, and Taylor (2014) corroborated this result, and concluded that the psychometric properties of the external oriented thinking subscale are poorer than those of identifying and describing feelings. Taken this information into account, we consider the BVAQ a more reliable and elaborate measure for alexithymia.

As far as we know, this was the first study exploring the BVAQ factor structure in the general population, taking external validity into account, and comparing the general population with a patient population expected to score higher on alexithymia. Hence, the norms provided by this study can provide clinicians with a valuable tool for assessing alexithymia in the clinic.

Chapter 4

Neurocognitive dysfunctioning of patients suffering from somatic symptom and related disorders: a cross-sectional clinical study of the impact of comorbid depression and anxiety

This chapter is based on:

De Vroege, L., Timmermans, A., Kop, W.J., & Van der Feltz-Cornelis, C.M. (2017). Neurocognitive dysfunctioning and the impact of comorbid depression and anxiety in patients with somatic symptom and related disorders: a cross-sectional clinical study. *Psychological Medicine,* 1-11 [Epub ahead of print].

Abstract

The prevalence and severity of neurocognitive dysfunctioning of patients suffering from somatic symptoms and related disorders (SSRD) is unknown. Furthermore, as far as we know, the influence of comorbid depression and anxiety on neurocognitive dysfunctioning of patients suffering from SSRD has not been studied yet. This study examines neurocognitive dysfunctioning of patients suffering from SSRD and explores if comorbid depression and anxiety is associated with specific neurocognitive dysfunction. Cross-sectional study with consecutive patients suffering from SSRD visiting an outpatient specialty mental health care Centre of Excellence for SSRD. Extensive neuropsychological assessment and assessment of depression and anxiety symptom levels using the Patient-Health-Questionnaire-9 and General Anxiety Disorder questionnaire-7 at intake. Multivariate analysis was performed. The study sample consisted of 201 SSRD patients (mean age = 43 years, *standard deviation* = 13); 37.8% were male. Neurocognitive dysfunction in the domains information processing speed, sustained and divided attention, working memory, verbal and visual memory were reported. Comorbid depression and anxiety occurred frequently (75.1% and 65.7%, respectively). Neurocognitive dysfunction was associated with comorbid depression but not with comorbid anxiety. Poor neurocognitive performance of patients suffering from SSRD is common and worsens in case of comorbid depression. This may explain treatment dropout of SSRD patients from neurocognitive behavioral therapy. Research on novel interventions is needed targeting neurocognitive functioning of SSRD patients, particularly those suffering from comorbid depression.

Neurocognitive dysfunctioning of patients suffering from somatic symptom and related disorders: a cross-sectional clinical study of the impact of comorbid depression and anxiety

Somatic symptom and related disorders (SSRD) are characterized by somatic symptoms that are associated with significant distress and impairment (American Psychiatric Association (APA), 2013). SSRD constitutes a new category in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (APA, 2013) and replaces the previous diagnostic classification of somatoform disorders that was used in the DSM-IV-TR (APA, 2000). SSRD differs from somatoform disorders in the numbers of disorders and subcategories. The category of SSRD consists of illness anxiety disorder, conversion disorder, factitious disorder, somatic symptom disorder, psychological factors affecting other medical conditions, unspecified somatic symptom and related disorder, and other specified somatic symptom and related disorder (APA, 2013). The criterion of somatoform disorder according to the DSM-IV-TR which stated that physical symptoms had to be medically unexplainable, was disposed because it was hard to determine whether or not a symptom in fact is medically unexplainable (Barsky, 2016). Therefore, several suggestions for changing the classification were made (Van der Feltz-Cornelis & Van Balkom, 2010) and the focus of the definition of SSRD changed towards coping with physical symptoms rather than searching for their cause (Barsky, 2016; Rief & Martin, 2014). Because of its recent introduction and the conceptual differences with somatoform disorders, studies of patients suffering from SSRD are scarce, and results from previous studies that focused on somatoform disorders are not necessarily generalizable to the SSRD population. As a result, little is known about SSRD patients, in particular regarding neurocognitive functioning.

Previous research has shown that neurocognitive dysfunctioning of patients suffering from late-life somatic symptom disorder is common (Inamura et al., 2015). However, the details regarding neurocognitive dysfunctioning of SSRD patients are unknown. Because studies about the neurocognitive profile of adults suffering from SSRD are unavailable, a brief summary of neurocognitive profiles of somatoform disorders is given. In particular, results from studies on neurocognitive dysfunctioning of patients suffering from somatoform disorders suggest impaired functioning of (working) memory (Al-Adawi, Al-Zakwani, Obeid, & Zaidan, 2010; Brown, Nicholson, Aybek, Kanaan, & David, 2014; Demir, Celikel, Taycan, & Etikan, 2013; Grace, Nielson, Hopkins, & Berg, 1999; Luerding, Weigand, Bogdahn, & Schmidt-Wilcke, 2008; Niemi, Portin, Aalto, Hakala, & Karlsson, 2002), executive functioning (Al-Adawi et al., 2010; Brown et al., 2014; Demir et al., 2013), attention and

concentration (Demir et al., 2013; Grace et al., 1999; Niemi et al., 2002), and visuospatial functioning (Demir et al., 2013; Niemi et al., 2002). However, different studies identified different impaired cognitive domains. Furthermore, most studies have not adjusted for important confounding variables such as comorbid depression, were based on small samples, or focused on only a limited number of neurocognitive domains. In addition, studies did not include symptom validity tests in the neurocognitive test battery they used, such as a test assessing presence of malingering. Therefore, results of previous studies about neurocognitive dysfunctioning of patients suffering from somatoform disorders should be interpreted cautiously.

Research has shown that the prevalence of comorbid depression in patients with medically unexplained physical symptoms (13.5%), medically explained physical symptoms (7.4%), and medically explained symptoms combined with unexplained physical symptoms (10.9%) is higher than the prevalence of depression in patients without physical symptoms (5.1%) (Van Eck van der Sluijs et al., 2015). However, the influence of comorbid depression on neurocognitive dysfunctioning of SSRD patients so far has not been explored.

Patients with a depressive disorder showed increased neurocognitive impairment across multiple domains, such as attention (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Rock, Roiser, Riedel, & Blackwell, 2014), information processing speed (Bennabi, Vandel, Papaxanthis, Pozzo, & Haffen, 2013; Lee et al., 2012; Tsourtos, Thompson, & Stough, 2002), memory (Lee et al., 2012; Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011; Rock et al., 2014), and executive functioning (Lee et al., 2012; Murrough et al., 2011; Rock et al., 2014; Snyder, 2013). Furthermore, neurocognitive dysfunctioning has been reported to be proportional to the severity of the depressive disorder (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008; Wang et al., 2006). Anxiety is also associated with neurocognitive dysfunctioning (Castaneda et al., 2008; Tempesta et al., 2013), such as impairment of executive functioning, memory, attention, and learning (de Geus, Denys, Sitskoorn, & Westenberg, 2007; Harkin & Kessler, 2011; Polak, Witteveen, Reitsma, & Olff, 2012; Tempesta, Mazza, Iaria, De Gennaro, & Ferrara, 2012).

The association of comorbid depression and anxiety on neurocognitive functioning of SSRD patients so far has not been explored. If SSRD, depression, and anxiety independently would have a negative influence on neurocognitive functioning, then it is plausible that comorbid depression and anxiety in SSRD patients impairs neurocognitive dysfunctioning. Hence, a comparison between the neurocognitive profile of SSRD patients with and without comorbid depression and anxiety would have substantial clinical relevance. The comparison

may not only increase insight into the disorder but might also suggest new treatment options, which increase effectivity and lead to faster reduction of symptoms and better coping with SSRD. However, until now, studies exploring cognitive dysfunction and the impact of comorbid depression and anxiety of SSRD patients are lacking.

This study had two objectives. The first objective was to establish the prevalence and severity of neurocognitive dysfunctioning, comorbid depression and comorbid anxiety disorder in SSRD patients. We hypothesized that, compared to the most recent norms, SSRD patients show extensive neurocognitive dysfunctioning within the domains of attention and concentration, information processing speed, memory, and executive functioning. The second objective was to evaluate whether comorbid depression and anxiety in SSRD adversely affect neurocognitive functioning. We hypothesized that neurocognitive functioning is poorer for patients suffering from comorbid depression (SSRD+D) and comorbid anxiety (SSRD+A) than for patients without comorbid depression (SSRD-D) and anxiety (SSRD-A). Specifically, we expected that patients with SSRD+D and patients with SSRD+A show more severe impairment in the domains of attention and concentration, information processing speed, memory, and executive functioning.

Method

Study design

A cross-sectional design was used to address the study aims.

Setting and participants

Consecutive outpatients (N = 250) older than 18 years, referred to Clinical Centre of Excellence for Body, Mind and Health (Dutch abbreviation: CLGG), at specialty mental health institution GGz Breburg, Tilburg, the Netherlands, participated in this study. For all patients referred to CLGG, we evaluated the inclusion and exclusion criteria before intake. Patients were excluded if they (a) were engaged in personal or professional injury procedures, (b) had an intelligence quotient (IQ) below 80, (c) had a threatening suicide risk, or (d) suffered from substance abuse. During intake, IQ is assessed using screeners, which may lead to inclusions of patients with an IQ below 80. For this study, we explored possible effects of IQ to decide whether to exclude them for further analyses. Patients referred to CLGG filled out questionnaires as part of routine clinical care (i.e., routine outcome monitoring (ROM)) before intake at CLGG (Van der Feltz-Cornelis et al., 2014). The standard intake procedure at CLGG includes a neuropsychological assessment (NPA) and a Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) of which the data are used in this study.

Figure 1 shows a flowchart of the patients included in this study. A total of 250 consecutive patients referred to CLGG between September 2013 and April 2016 were included. A total of 11 patients did not have a SSRD diagnosis, 2 patients did not completed ROM at intake, and 24 patients did not complete the NPA. 48 patients of the 213 patients that completed a NPA were not assessed with a symptom validity test. A total of 165 patients were tested with a symptom validity test of which 12 were suspected of malingering and excluded from the study sample. This resulted in a total sample of 201 patients.

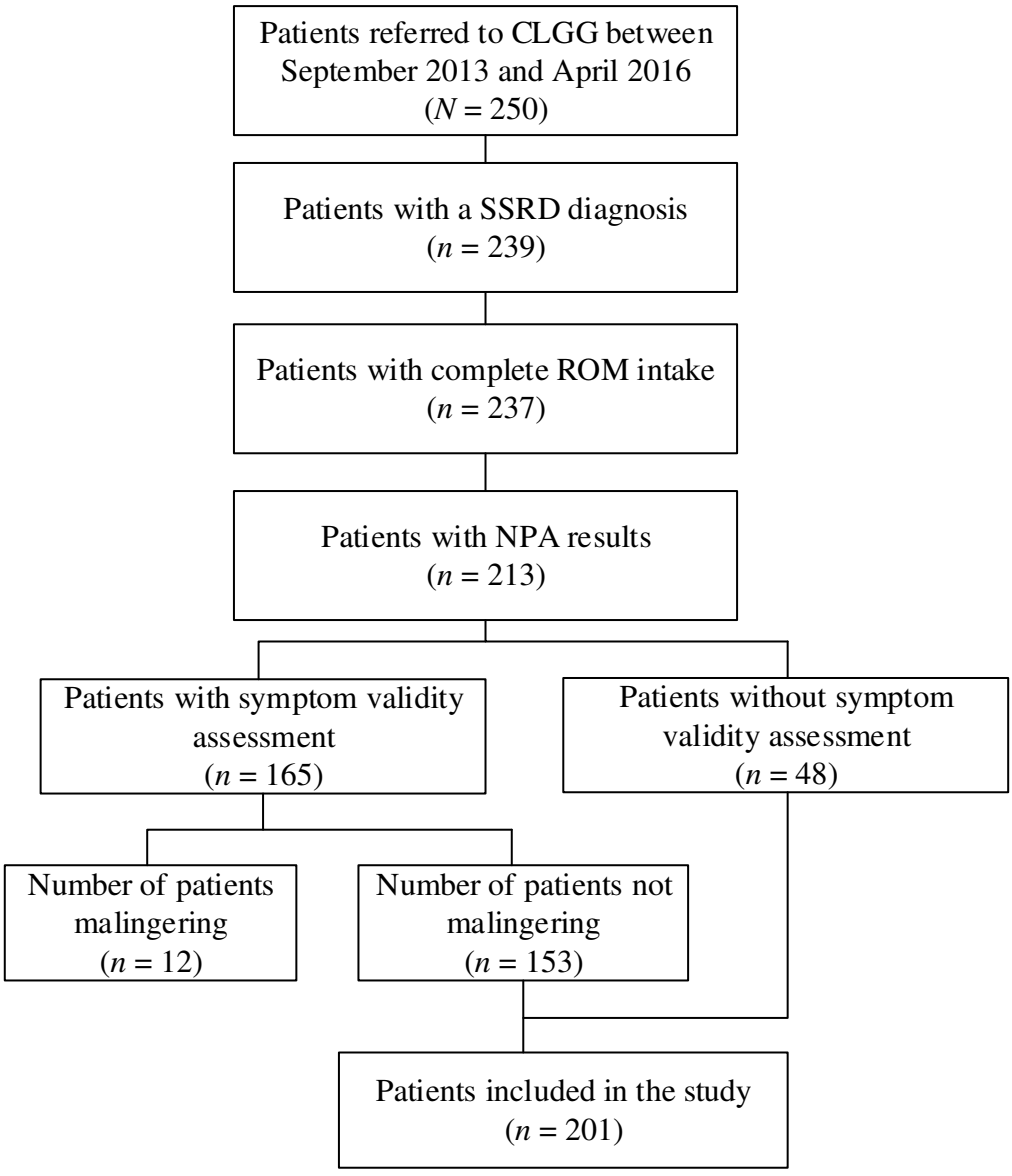


Figure 1. Flowchart of patients included in this study.
Abbreviations: CLGG: Dutch abbreviations: Clinical Centre of Excellence for Body, Mind, and Health, SSRD: somatic symptom and related disorders, ROM: routine outcome monitoring, NPA: neuropsychological assessment.

The Commission of Scientific Research of GGz Breburg (CWO 2014-16) approved the study. In the intake letter, patients of CLGG were asked for informed consent to participate in scientific research. Patients who decided not to participate did not suffer consequences for treatment options. We excluded patients from this study who did not agree to the use of their data for research purposes.

Variables

Somatic symptom and related disorder. SSRD classification was established as follows. The psychiatrists at CLGG diagnosed SSRD DSM-5 classifications based on a checklist administered after psychiatric examination. Trained psychologists used the MINI to interview the patients. Discrepancies between interview and initial symptom-check diagnoses were settled by consensus.

Demographic variables. During intake, we obtained demographic variables such as age, sex and education. Educational level was classified using the method described by Verhage (1964) and further divided in low level of education (Verhage 1-4), average level of education (Verhage 5), and high level of education (Verhage 6-7). Level of education was dichotomized into low level of education (Verhage 1-5) and high level of education (Verhage 6-7). We used the Dutch version of the National Adult Reading Test (Schmand, Lindeboom, & van Harskamp, 1992) to assess verbal premorbid intelligence.

Neuropsychological assessment. We administered a standardized comprehensive NPA covering a broad range of neurocognitive domains. NPAs were administered under supervision of a mental health psychologist by bachelor's-level clinicians and extensively trained (neuro)psychologists. Table 1 displays the neurocognitive tests that were used for assessing the neurocognitive domains. More specifically, we used the d2 test (Brickenkamp, 2002) to measure sustained attention. The d2 test is considered a valid test (Bates & Lemay, 2004). We measured divided attention using the Trail Making Test (TMT; Reitan, 1992) B-version. The TMT-B score is a measure for divided attention (Lezak, Howieson, Bigler, & Tranel, 2012). The subtest Digit Span from the Wechsler Adult Intelligence Scale (WAIS)-IV was used to assess working memory (Wechsler, 2014). We used the delayed test score of the Dutch translation of the Rey Auditory Verbal Test (RAVLT; Saan & Deelman, 1986) to measure verbal memory. We used the delayed recall score of the Rey Osterrieth Complex Figure Test (ROCFT; Osterrieth, 1944) to assess visual memory (Lezak et al., 2012). We assessed information processing speed using the subtest Coding from the WAIS-IV (Wechsler, 2014). Furthermore, we used three tests to assess several domains of executive functioning. We used the Zoo map and the Rule Shift Cards of the Behavioural Assessment

of the Dysexecutive Syndrome (BADS) to assess planning and mental flexibility (Wilson, Alderman, Burgess, Emslie, & Evans, 1996), respectively. We used the 'N' and 'A' test to assess phonological verbal fluency (Deelman, Koning-Haanstra, & Liebrand, 1981).

Table 1
Neurocognitive domains and tests used in the NPA.

Neurocognitive domain	Neuropsychological test
Sustained attention	d2 (Brickenkamp, 2002)
Divided attention	TMT B (Reitan, 1992)
Working memory	Digit Span WAIS-IV (Wechsler, 2014)
Verbal memory	Dutch RAVLT (Saan & Deelman, 1986)
Visual memory	ROCFT (Osterrieth, 1944)
Information processing speed	Coding WAIS-IV (Wechsler, 2014)
Planning (executive function)	Zoo Map BADS (Wilson et al., 1996)
Mental flexibility (executive function)	Rule Shift Cards BADS (Wilson et al., 1996)
Verbal fluency	Fluency 'N' and 'A' 1 minute (Deelman et al., 1981)

Abbreviations: TMT: Trail Making Test, WAIS-IV: Wechsler Adult Intelligence Scale – fourth edition, RAVLT: Rey Auditory Verbal Learning Test, ROCFT: Rey Osterrieth Complex Figure Test, BADS: Behavioural Assessment of the Dysexecutive Syndrome.

To explore neurocognitive dysfunctioning in SSRD patients with respect to the general population, we compared the scores on the neuropsychological tests to the tests' most recent general-population norms, taking into account sex, age, and education. For the TMT-B and the RAVLT, we used the norms provided by Schmand, Houx, and de Koning (2012). For the other neuropsychological tests, we used the norms provided in the test manuals. More specifically, we defined three levels of neurocognitive dysfunction. They were (1) "no neurocognitive dysfunctioning", which includes scores larger than or equal to the score at the 20th percentile in the general Dutch population; (2) "deficit", which includes scores in between 2.4th percentile (inclusive) and the 20th percentile of the score distribution in the general Dutch population; and (3) "disorder": scores below the 2.4th percentile of the score distribution in the general Dutch population (Lezak et al., 2012). This means that for the comparison with the general population, as a benchmark we used the percentages for no neurocognitive problems, deficit, and disorder, equal to 80%, 17.6%, and 2.4%, respectively.

Before administering the NPA, we explored malingering using the Test of Memory Malingering (TOMM; Tombaugh, 1996). If the TOMM raised suspicion of malingering (TOMM $\leq$ 45 on trial 1 and/or trial 2) (Denning, 2012; O'Bryant et al., 2008), the importance of motivation was stressed and discussed with the patient. After a break, the Amsterdam Short-Term Memory Test (Dutch abbreviation: AKTG; Schmand & Lindeboom, 2005) was

used to further assess malingering. If patients also scored positive on the AKTG (AKTG < 85; i.e., possible malingering), the NPA was discontinued and patients were excluded from this study.

A symptom validity task was completed by 165 patients to rule out bias related to malingering. Twelve patients displayed signs of malingering and did not complete the neuropsychological assessment. Demographic characteristics (age, sex, and educational level) and baseline symptom severity (Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder questionnaire (GAD-7)) did not significantly differ between patients who were suspected of malingering and patients who were not suspected of malingering.

Depression and anxiety. The self-report scale PHQ-9 (Kroenke et al., 2001) was used to measure depression. The PHQ-9 has good psychometric properties (Kocalevent, Hinz, & Brähler, 2013; Kroenke et al., 2001), with coefficient alpha equal to .89 and sensitivity and specificity both equal to 88%. A cut-off at least equal to 10 is advised for identifying moderate levels of depression (Kroenke & Spitzer, 2002).

We used the GAD-7 (Spitzer et al., 2006) to measure anxiety. The GAD-7 is a 7-item self-report questionnaire that measures symptoms of anxiety the patient experienced during the two weeks prior to testing. The GAD-7 has good psychometric properties (Löwe et al., 2008; Spitzer et al., 2006), with coefficient alpha equal to .92, and sensitivity and specificity equal to 89% and 82%, respectively. A cut-off of 10 or higher is advised for identifying moderate levels of anxiety (Spitzer et al., 2006). A recent report advised to use the PHQ-9 and GAD-7 as measures for assessing two of the most common psychological conditions in patients with somatic symptoms (Kroenke et al., 2016).

Statistical methods

We explored the prevalence of neurocognitive dysfunctioning of SSRD patients using the percentages of patients with deficits or disorder in the neurocognitive domains. Differences between the general population and the SSRD patients were tested using a chi-square statistic. Analyses showed that the scores on the subtests of the BADS were not normally distributed (i.e., only 23.0% of the patients scored below 4 on the Rule Shift Cards). The variables for divided attention, verbal memory, phonological fluency, planning, and mental flexibility were not normally distributed and were therefore log-transformed.

We explored the association of comorbid depression and comorbid anxiety with neurocognitive functioning separately. Associations between continuous depression and anxiety scores with neurocognitive performance were examined using correlations and multiple regression analyses. In particular, we first obtained the correlations between

neurocognitive dysfunctioning with the PHQ-9 and GAD-7 scores. Second, we used regression analyses to study the relationships between neurocognitive functioning and depression, and neurocognitive functioning and anxiety, while controlling for age, sex, and education level (i.e., high or low educational level) using regression analyses, for assessing the relationship between the PHQ-9 and GAD-7 scores with neurocognitive domains. For these analyses, we used the log-transformed variables that were not normally distributed (i.e., divided attention, verbal memory, phonological verbal fluency, planning, and mental flexibility).

We also used a categorical operationalization of depression and anxiety, categorizing patients into two clinical groups. The SSRD+D group was defined as SSRD patients having a PHQ-9 score ≥ 10, and the SSRD-D group as SSRD patients having a PHQ-9 score < 10. The SSRD+A group was defined as SSRD patients having a GAD-7 ≥ 10, and the SSRD-A group as SSRD patients having a GAD-7 < 10. Hence, the SSRD+D and SSRD+A groups show at least moderate levels of depression and moderate levels of anxiety, respectively. Differences with regard to demographic characteristics and questionnaire scores, between SSRD+D and SSRD-D, and between SSRD+A and SSRD-A, were examined using independent samples *t*-tests (for continuous variables) and Chi-square tests (for categorical variables). We conducted a sensitivity analysis for demographic and baseline characteristics to compare patients who were suspected of malingering versus patients who were not.

We compared neurocognitive profile of SSRD patients with a comorbid depression and without comorbid depression, and also with and without comorbid anxiety. Mean differences were tested for significance using MANCOVA, where we controlled for gender, education and age. For these analyses, the raw test scores were used. For these analyses, we used the non-transformed variables, because MANCOVA is robust to non-normality (Tabachnick & Fidell, 2007). Subsequently, differences between neurocognitive domains of patients with SSRD+D and SSRD-D and between patients with SSRD+A and SSRD-A were considered separately. These analyses were also adjusted for age, sex, and education level. Differences between SSRD+D and SSRD-D and SSRD+A and SSRD-A with respect to percentages of absence of neurocognitive impairments, deficits, and disorders were explored by means of Chi-square tests and Fisher's exact tests in case any of the cells had a frequency less than five. We used the Statistical Package for the Social Sciences version 22.0 (IBM Corp., 2011) for all analyses.

Results

Participants

Table 2 gives an overview of the demographic characteristics of the total sample and the sample stratified for depression and stratified for anxiety. Two hundred and one patients were included in the analyses (see Figure 1 for the flowchart). Age ranged from 18 to 79 years. The mean age was 43, and the standard deviation (*SD*) was 13 years. Sixty-two percent of the sample was female. Comorbid depression (i.e., PHQ-9 ≥ 10) was observed for 75.1% of the patients. The mean of the PHQ-9 total score was 14.3 ($SD = 6.0$). Comorbid anxiety (i.e., GAD-7 ≥ 10) was found for 65.7% of the patients. The mean score on the GAD-7 was 11.6 ($SD = 5.5$). Depression and anxiety scores were significantly correlated ($r = .72, p < .001$). One hundred and twenty patients (60.7%) suffered from at least moderate levels of both depression and anxiety, whereas 19.9% did not meet the criterion for either moderate depression or moderate anxiety.

Demographic characteristics of patients suffering from at least moderate depression did not significantly differ from patients without depression. Patients suffering from anxiety were on average significantly younger than patients not suffering from anxiety ($t(199) = 2.36$, $p = .02, d = -0.36$). Furthermore, we assessed the premorbid IQ of 185 patients and found a mean IQ of 102 (range 72 — 127). Seven patients had an IQ below 80 and ten patients had an IQ ranging from 80 to 87. Patients with an IQ below 80 were on average older ($Mean(M) = 55.3, SD = 16.4$) than patients with an IQ higher than 80 ($M = 42.0, SD = 16.6$); the difference was significant at the 5% level, $t(183) = 2.71, p = .007, d = -0.80$. No significant differences were found regarding gender, and the mean scores on the PHQ-9 and GAD-7. Patients having an IQ less than 80 were included in the analyses, because we considered these patients members of the target population, and the neurocognitive tests used are suited for patients having low IQ. Patients whose IQ was not assessed and thus unknown, were included.

Table 2

Descriptive statistics of the total sample of somatic symptom and related disorders (SSRD) and stratified for comorbid depression and anxiety

		Depression				Anxiety			
	Total (N = 201)	No depression (n = 50)	Depression (n = 151)			No anxiety (n = 69)	Anxiety (n = 132)		
Variable	*M (SD)/ n (%)*	*M (SD)/ n (%)*	*M (SD)/ n (%)*	*p*	*ES*	*M (SD)/ n (%)*	*M (SD)/ n (%)*	*p*	*ES*
Age (years)	42.6 (12.8)	45.2 (14.0)	41.7 (12.3)	.092	.27[1]	45.59 (13.5)	41.0 (12.2)	.019	-.36[1]
Male	76 (37.8)	17 (34.0)	59 (39.1)	.614	.05[2]	22 (31.9)	54 (40.9)	.224	.21[2]
Education level				.582	.07[3]			.326	.11[3]
Low	54 (26.9)	16 (32.0)	38 (25.2)			20 (29.0)	34 (25.8)		
Average	87 (43.3)	19 (38.0)	68 (45.0)			25 (36.2)	62 (47.0)		
High	60 (29.9)	15 (30.0)	45 (29.8)			24 (34.8)	36 (27.3)		
PHQ-9	14.3 (6.0)	6.7 (2.1)	16.8 (4.6)	<.00	2.45	9.2 (4.0)	17.0 (5.0)	<.001	1.67[1]
GAD-7	11.6 (5.5)	6.2 (3.6)	13.4 (4.8)	<.00	1.59	5.4 (2.5)	14.9 (3.4)	<.001	3.04[1]

Abbreviations: ES: Effect size, PHQ-9: Patient Health Questionnaire, GAD-7: Generalized Anxiety Disorder questionnaire. For depression; a cut-off of 10 or higher on the PHQ-9 was used, and for anxiety; a cut-off of 10 on the GAD-7 was used.

[1] Cohen's d

[2] Chi-square tests

[3] Cramer's V

Note: Education level is divided as follows: Low (Verhage 1-4), Average (Verhage 5), and High (Verhage 6-7). Means (M) and standard deviations (SD) are presented for the continuous variables and the number (n) and percentage of patients (%) is presented for the categorical variables.

Objective one: neurocognitive dysfunctioning of SSRD patients compared to normative data

Table 3 (column 2) describes neurocognitive functioning of SSRD patients. For each of the cognitive domains, the distribution in the SSRD population differed significantly from the general population (Chi-square test). Both deficits and clinically impaired neurocognitive disorders were prevalent among SSRD patients, particularly regarding sustained attention, divided attention, information processing speed, working memory, verbal memory, visual memory, and phonological verbal fluency, for which the percentages of deficit and disorder were substantially larger than in the general population. Specifically, 67 (37.2%) patients had a deficit and 13 (7.2%) had a disorder with respect to sustained attention. With regard to divided attention, 32 (19.0%) patients had a deficit and 16 (9.5%) had a disorder. Sixty-seven (34.7%) patients suffered from a deficit and 23 (11.9%) from a disorder with respect to information processing speed. Sixty-seven (34.0%) patients had a deficit and 20 (10.2%) suffered from a disorder with respect to working memory. With regard to verbal memory, 57 (29.2%) patients had a deficit and 25 (12.8%) had a disorder. Forty-five (22.2%) suffered from a deficit and 37 (19.6%) from a disorder with respect to visual memory. Sixty-nine (36.1%) suffered from a deficit with respect to phonological verbal fluency. However, for the domains planning and mental flexibility, SSRD patients showed better performance than the general population. In particular, 180 patients (94.2%) did not have cognitive problems, twelve patients (6.3%) had a deficit, and two patients (1.0%) had a disorder with respect to planning. With regard to mental flexibility, six patients (3.1%) had a deficit and five patients (2.6%) had a disorder.

Table 3

Neurocognitive functioning of the study sample (N = 201) of somatic symptom and related disorders and stratified for comorbid depression and for comorbid anxiety

		Depression			Anxiety		
	Total sample	No depression	Depression		No anxiety	Anxiety	
Neurocognitive domain	*N* (%)	*n* (%)	*n* (%)	*p*	*n* (%)	*n* (%)	*p*
Sustained attention (valid *N* = 180)				.326[2]			.587[2]
No neurocognitive problems	100 (55.6)	30 (65.2)	70 (52.2)		37 (59.7)	63 (53.4)	
Deficit	67 (37.2)	14 (30.4)	53 (39.6)		20 (32.3)	47 (39.8)	
Disorder	13 (7.2)	2 (4.3)	11 (8.2)		5 (8.1)	8 (6.8)	
Divided attention (valid *N* = 168)				.027[1]			.050[1]
No neurocognitive problems	120 (71.4)	36 (87.8)	84 (66.1)		47 (77.1)	73 (68.2)	
Deficit	32 (19.0)	3 (7.3)	29 (22.8)		6 (9.8)	26 (24.3)	
Disorder	16 (9.5)	2 (4.9)	14 (11.0)		8 (13.1)	8 (7.5)	
Information processing speed (valid *N* = 193)				.013[1]			.419[1]
No neurocognitive problems	103 (53.4)	33 (68.8)	70 (48.3)		40 (59.7)	63 (50.0)	
Deficit	67 (34.7)	14 (29.2)	53 (36.6)		21 (31.3)	46 (36.5)	
Disorder	23 (11.9)	1 (2.1)	22 (15.2)		6 (9.0)	17 (13.5)	
Working memory (valid *N* = 197)				.009[1]			.054[1]
No neurocognitive problems	110 (55.8)	34 (69.4)	76 (51.4)		46 (66.7)	64 (50.0)	
Deficit	67 (34.0)	8 (16.3)	59 (39.9)		16 (23.2)	51 (39.8)	
Disorder	20 (10.2)	7 (14.3)	13 (8.8)		7 (10.1)	13 (10.2)	
Verbal memory (valid *N* = 195)				.471[1]			.124[1]
No neurocognitive problems	113 (57.9)	32 (65.3)	81 (55.5)		46 (67.7)	67 (52.8)	
Deficit	57 (29.2)	12 (24.5)	45 (30.8)		16 (23.5)	41 (32.3)	
Disorder	25 (12.8)	5 (10.2)	20 (13.7)		6 (8.8)	19 (15.0)	

Table 3, continued.

Visual memory (valid *N* = 189)				.594[1]		.547[1]
No neurocognitive problems	110 (58.2)	29 (60.4)	81 (57.4)		39 (60.0)	71 (57.3)
Deficit	42 (22.2)	12 (25.0)	30 (21.3)		16 (24.6)	26 (21.0)
Disorder	37 (19.6)	7 (14.6)	30 (21.3)		10 (15.4)	27 (21.8)
Planning (valid *N* = 191)				.348[2]		.599[2]
No neurocognitive problems	177 (92.7)	44 (89.8)	133 (93.7)		62 (92.5)	115 (92.7)
Deficit	12 (6.3)	5 (10.2)	7 (4.9)		5 (7.5)	7 (5.7)
Disorder	2 (1.0)	0 (0.0)	2 (1.4)		0 (0.0)	2 (1.6)
Mental flexibility (valid *N* = 191)				.640[2]		.193[2]
No neurocognitive problems	180 (94.2)	47 (97.9)	133 (93.0)		66 (98.5)	114 (91.9)
Deficit	6 (3.1)	1 (2.1)	5 (3.5)		1 (1.5)	5 (4.0)
Disorder	5 (2.6)	0 (0.0)	5 (3.5)		0 (0.0)	5 (4.0)
Phonological verbal fluency (valid *N* = 191)				.037[1]		.050[1]
No neurocognitive problems	122 (63.9)	36 (76.6)	86 (59.7)		49 (73.1)	73 (58.9)
Deficit	69 (36.1)	11 (23.4)	58 (40.3)		18 (26.9)	51 (41.1)
Disorder	--	--	--		--	--

Note: Not all 201 patients completed every test; sample size varied between *n* = 168 and *n* = 197. The p-values are given for the Chi-square test and Fisher‘s exact test. As a benchmark we used percentages of no neurocognitive problems, deficit, and disorder are 80%, 17.6%, and 2.4% respectively.

[1] Differences between patients with and without comorbid depression/anxiety were tested using Chi-square tests.[2] Fisher’s exact tests were used in the analysis of contingency tables because of violation of the minimum expected cell frequency.

Objective two: association of comorbid depression and comorbid anxiety with neurocognitive dysfunctioning

Table 4 shows the zero-order correlations between depression and anxiety scores and neurocognitive measures as well as the regression coefficients adjusted for sex, age, and education. The total score of the PHQ-9 significantly correlated with information processing speed ($r = -.17, p = .030$) and phonological verbal fluency ($r = -.17, p = .025$), suggesting that a higher depression score was associated with impaired neurocognitive performance within these domains. However, correlations were small. The total score of the GAD-7 did not significantly correlate with any neurocognitive measure.

When adjusting for sex, age, and education, the total score of the PHQ-9 was significantly associated with sustained attention ($\beta = -.13, p = .044$), information processing speed ($\beta = -.20, p = .002$), working memory ($\beta = -.17, p = .016$), verbal memory ($\beta = -.14, p = .037$), and phonological verbal fluency ($\beta = -.15, p = .036$), suggesting that a higher depression score was associated with an impaired neurocognitive performance within these domains. The total score of the GAD-7 was significantly associated with lower information processing speed ($\beta = -.16, p = .018$) and visual memory ($\beta = -.14, p = .044$), indicating that a higher score of anxiety was associated with impaired neurocognitive performance within these domains.

Table 4
Zero-order correlations and the regression coefficients (adjusted for age, sex, and education) between neurocognitive functioning, depression, and anxiety

Neurocognitive domain	Depression		Anxiety	
	r	*beta*	*r*	*beta*
Sustained attention	-.07	**-.13**	.03	-.10
Divided attention[a]	.03	.05	.02	.09
Information processing speed	**-.17**	**-.20**	-.06	**-.16**
Working memory	-.15	**-.17**	-.04	-.11
Verbal memory[a]	-.11	**-.14**	-.08	-.13
Visual memory	-.09	-.12	-.05	**-.14**
Phonological verbal fluency[a]	**-.17**	**-.15**	-.05	-.07
Planning[a]	-.02	-.07	.08	-.05
Mental flexibility[a]	.01	.16	-.10	.05

[a] logarithmic transformed values were used in the analysis because test scores were not normally distributed.
Note: Higher scores on neuropsychological tests indicate better performance, except for divided attention. Correlations and regression coefficients were obtained using list wise deletion. Significant correlations and regression coefficients are printed in bold.

Relationship between neurocognitive dysfunctioning and anxiety and depression within SSRD patients

MANCOVA suggested that comorbid depression in SSRD patients was associated with neurocognitive dysfunctioning ($F(9,157) = 2.047, p = .038, \eta^2 = .105$) whereas anxiety in SSRD was not associated with neurocognitive dysfunctioning ($F(9,157) = 0.836, p = .584, \eta^2 = .046$).

Table 3 (columns 3 — 8) displays for each neurocognitive domain the percentages of patients suffering from a disorder or a deficit, for depressed and non-depressed patients. Significant mean differences between depressed and non-depressed patients suffering from SSRD with respect to neurocognitive functioning were found for the domains divided attention, information processing speed, working memory, and phonological verbal fluency. For these domains, the percentages of deficit and disorder were larger for depressed SSRD patients than for non-depressed patients. In particular, for divided attention, 22.8% of the depressed SSRD patients showed deficits and 11.0% showed disorders, whereas in the non-depressed SSRD patients the percentages of deficits and disorders were 7.3% and 4.9%, respectively. For information processing speed, percentages of deficit and disorders were 36.6% and 15.2% for depressed SSRD patients, and 29.2% and 2.1% for non-depressed SSRD patients. Working memory was also significantly more impaired among SSRD patients. For depressed patients, percentages for deficit and disorder were 39.9% and 8.8%, respectively. For non-depressed patients, percentages of deficit and disorders were 16.3% and 14.3%, respectively. For phonological verbal fluency, the percentage of deficits for depressed SSRD patients equals 40.3% whereas the percentage of deficits is 23.4% for non-depressed SSRD patients.

Consistent with the MANCOVA based on the continuous GAD-7 anxiety scores, no significant differences with regard to percentages of neurocognitive dysfunctioning were found between SSRD+A and SSRD-A groups amongst all neurocognitive domains. Because 66.7% of the patients suffered from both comorbid depression and anxiety, we also described neurocognitive functioning stratified for patient with comorbid depression only, with comorbid anxiety only, and with both comorbid depression and anxiety. Table 5 (columns 2 — 5) describe the percentages of patients with a neurocognitive disorder, a neurocognitive deficit and without a neurocognitive disorder for each neurocognitive domain stratified for comorbid depression and anxiety, comorbid depression only, and comorbid anxiety only. Compared to the benchmark (Dutch general population), percentages of deficits and disorders were higher in the domains sustained attention, divided attention, information processing

speed, working memory, verbal and visual memory for SSRD patients with comorbid depression and anxiety and for SSRD patients with comorbid depression. Percentages of deficits were higher in the domain of phonological verbal fluency for SSRD patients with comorbid depression and anxiety and comorbid depression. Percentages of deficits and disorders were higher in the domains of information processing, working memory, verbal and visual memory for SSRD patients with comorbid anxiety. Higher percentages of deficits were found in the domains of sustained and divided attention for SSRD patients with comorbid anxiety. Patients without comorbid depression and anxiety had higher percentages of deficits and disorder in the domains sustained attention, working memory verbal and visual memory, higher percentages of deficits in the domain of information processing speed, planning, and phonological verbal fluency and higher percentages of disorders in the domain of divided attention.

Table 5

Neurocognitive functioning of the study sample (N = 201) of somatic symptom and related disorders and stratified for comorbid depression and anxiety, comorbid depression, comorbid anxiety, and no comorbid depression or anxiety

	Depression and anxiety (*n* = 122)	Depression only (*n* = 29)	Anxiety only (*n* = 10)	No depression and anxiety (*n* = 40)
Neurocognitive domain	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Sustained attention (valid *N* = 180)				
No neurocognitive problems	56 (51.4)	14 (56.0)	7 (77.8)	23 (62.2)
Deficit	45 (41.3)	8 (32.0)	2 (22.2)	12 (32.4)
Disorder	8 (7.3)	3 (12.0)	0 (0.0)	2 (5.4)
Missing	13	4	1	3
Divided attention (valid *N* = 168)				
No neurocognitive problems	67 (67.0)	17 (63.0)	6 (85.7)	30 (88.2)
Deficit	25 (25.0)	4 (14.8)	1 (14.3)	2 (5.9)
Disorder	8 (8.0)	6 (22.2)	0 (0.0)	2 (5.9)
Missing	22	2	3	6
Information processing speed (valid *N* = 193)				
No neurocognitive problems	56 (47.9)	14 (50.0)	7 (77.8)	26 (66.7)
Deficit	45 (38.5)	8 (28.6)	1 (11.1)	13 (33.3)
Disorder	16 (13.7)	6 (21.4)	1 (11.1)	0 (0.0)
Missing	5	1	1	1
Working memory (valid *N* = 197)				
No neurocognitive problems	58 (48.7)	18 (62.1)	6 (66.7)	28 (70.0)
Deficit	50 (42.0)	9 (31.0)	1 (11.1)	7 (17.5)
Disorder	11 (9.2)	2 (6.9)	2 (22.2)	5 (12.5)
Missing	3	0	1	0

Table 5, continued.

Verbal memory (valid *N* = 195)				
No neurocognitive problems	61 (51.7)	20 (71.4)	6 (66.7)	26 (65.0)
Deficit	40 (33.9)	5 (17.9)	1 (11.1)	11 (27.5)
Disorder	17 (14.4)	3 (10.7)	2 (22.2)	3 (7.5)
Missing	4	1	1	0
Visual memory (valid *N* = 189)				
No neurocognitive problems	66 (57.4)	15 (57.7)	5 (55.6)	24 (61.5)
Deficit	23 (20.0)	7 (26.9)	3 (33.3)	9 (23.1)
Disorder	26 (22.6)	4 (15.4)	1 (11.1)	6 (15.4)
Missing	7	3	1	1
Planning (valid *N* = 191)				
No neurocognitive problems	106 (92.2)	27 (100.0)	9 (100.0)	35 (87.5)
Deficit	7 (6.1)	0 (0.0)	0 (0.0)	5 (12.5)
Disorder	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	7	2	1	0
Mental flexibility (valid *N* = 191)				
No neurocognitive problems	180 (94.2)	28 (100.0)	9 (100.0)	38 (97.4)
Deficit	6 (3.1)	0 (0.0)	0 (0.0)	1 (2.6)
Disorder	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	7	1	1	1
Phonological verbal fluency (valid *N* = 191)				
No neurocognitive problems	67 (57.8)	19 (67.9)	6 (75.0)	30 (76.9)
Deficit	49 (42.2)	9 (32.1)	2 (25.0)	9 (23.1)
Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	6	1	2	1

Note: Patients were assigned to the group with comorbid depression and anxiety if both scores of the PHQ-9 and GAD-7 were higher than the cut-off score. As a benchmark we used percentages of no neurocognitive problems, deficit, and disorder are 80%, 17.6%, and 2.4% respectively.

Discussion

Regarding our first objective, the present results suggest substantial impairments of information processing speed, sustained attention, divided attention, working memory, verbal memory, visual memory, and phonological verbal fluency in SSRD patients. Within the domain of executive functioning (planning and mental flexibility), a relatively small percentage of impairments were found. Compared to the benchmark, scores in some neurocognitive domains are better than compared to the norms (i.e., expected percentages of disorders and deficits in the general population). Regarding our second objective, a higher level of comorbid depression in SSRD patients intensifies neurocognitive dysfunctioning, in particular divided attention, information processing speed, and working memory. Contrary to our hypothesis, comorbid anxiety in SSRD was not significantly associated with neurocognitive dysfunctioning.

Previous studies that focused on neurocognitive dysfunctioning of patients with somatoform disorder reported impaired executive functioning (Al-Adawi et al., 2010; Brown et al., 2014; Demir et al., 2013). However, we found relatively low levels of impairment within the domain of executive functioning and documented more deficits in sustained attention, information processing speed, and working memory. This finding may be related to the fact that, unlike in somatoform disorders, SSRD can occur in patients with known chronic medical conditions, and chronic medical conditions are related to influence executive functioning (i.e., diabetes) (Mõttus, Luciano, Starr, & Deary, 2013) which may have had an influence on our results. This warrants further research amongst patients suffering from SSRD.

In addition, executive functioning also includes a system of interconnected behaviors and thus consists of more components than planning and mental flexibility (Fuster, 1997; Stuss & Benson, 1986). Therefore, the absence of neurocognitive dysfunctioning within planning or mental flexibility does not necessarily indicate an absence of problems in the whole spectrum of executive functioning. In fact, we found substantial percentages of impairment in phonological verbal fluency, which is also part of executive functioning (Fisk & Sharp, 2004). Because of these inconsistent results, conclusions about executive functioning of patients suffering from SSRD requires further investigation. Nevertheless, this study provides a detailed description of neurocognitive dysfunctioning of SSRD patients in addition to a previous study that already reported the presence of neurocognitive dysfunctioning in general (Inamura et al., 2015).

Regarding our second objective, our results suggested that depressed SSRD patients experience more neurocognitive dysfunction than non-depressed SSRD patients. Previous studies suggested that patients suffering from severe depressive symptoms are more likely to experience memory difficulties than patients suffering from minimal to moderate depressive symptoms (Lee et al., 2012; Wang et al., 2006). Our sample consisted of moderately depressed SSRD patients (mean PHQ-9 score in total sample equal to 14.3) which may explain why we did not find enhanced memory problems in SSRD+D patients. In contrast to attentional and executive dysfunctioning, memory problems are not a trait-marker for a major depressive disorder, because memory deficits do not persist after remission of depressive symptoms (Lee et al., 2012; Rock et al., 2014). Therefore, memory problems associated with SSRD might be more dependent on the severity of depressive symptoms (state-marker) and thus only present themselves in patients with severe depression. To explore whether or not memory problems are state dependent in SSRD patients, examination of differences in memory functioning between patients with minimal to moderate depression (PHQ-9 < 15) and moderately severe to severe depression (PHQ-9 ≥ 15) (Kroenke et al., 2002) is warranted.

Our results did not support our hypothesis that anxiety affects neurocognitive dysfunctioning of SSRD patients. However, previous studies reported impaired executive functioning, memory, attention, and learning for patients suffering from an anxiety disorder (Castaneda et al., 2008; de Geus et al., 2007; Harkin & Kessler, 2011; Polak et al., 2012; Tempesta et al., 2012; Tempesta et al., 2013), but none of these studies focused on the influence of comorbid anxiety on neurocognitive dysfunctioning of SSRD patients. The present results suggest that depression, rather than anxiety intensifies neurocognitive dysfunctioning on several domains in SSRD patients. However, to explore the role of severe anxiety on neurocognitive dysfunctioning of SSRD patients, examination of patients with severe anxiety (GAD-7 > 15) (Löwe et al., 2008) is warranted.

To our knowledge, this is the first study that investigated associations of neurocognitive dysfunctioning with depression and anxiety in SSRD patients. In addition, this study excluded patients suspected of malingering, which prevents results biased by invalid conclusions regarding neurocognitive dysfunctioning of SSRD patients. Even though our exclusion criteria included an IQ estimated above 80, seven patients were included with an IQ below 80 and 10 patients had an IQ within the range of 80 to 87 (corresponding to 2.4% - 20.0%). This may have influenced the results, so results should be interpreted with caution. Sensitivity analysis showed that patients with an IQ below 80 were significantly older but did

not differ with respect to other demographic characteristic and mean PHQ-9 and GAD-7 scores. We therefore decided to include the patients with an IQ below 80 in the further analyses of this study.

Several methodological limitations may apply to the present study. Because the sample consisted of consecutive patients of a Clinical Centre of Excellence for patients suffering from SSRD, which takes national referrals as last resort for such patients, our results might not automatically apply to patients suffering from SSRD of less severe symptomatology.

Second, the symptom validity task was not administered to all patients, because of the limited availability of the symptom validity tests (i.e., TOMM and AKTG). In the case of two or more simultaneous intakes, some patients could not be tested with a symptom validity task. As a consequence, some patients who might have scored positive on malingering were included in this study. However, because only 12 of the 165 patients were suspected of malingering, we estimate the number of patients suspected of malingering who were not tested to be relatively small and their impact on the results to be minor.

Other factors might have influenced neurocognitive dysfunctioning and were not taken into account, such as medication use and other comorbidities (e.g., attention deficit-hyperactivity disorder) (Alderson, Kasper, Hudec, & Patros, 2013; Mowinckel, Pedersen, Eilertsen, & Biele, 2015). It is also possible that the joint presence of depression and anxiety had disproportionate adverse effects on neurocognitive dysfunctioning of SSRD patients and we therefore described neurocognitive dysfunctioning of patients with comorbid depression and anxiety. However, these results should be interpreted cautiously, because our sample included few patients with comorbid anxiety only which prevents us from drawing solid conclusions whether the presence of comorbid depression and anxiety intensifies neurocognitive dysfunctioning compared to comorbid depression only or comorbid anxiety only in SSRD patients. To conclude, a relationship between severity of SSRD and severity of depressive symptoms related to neurocognitive functioning may be present. Future studies may explore whether severity of depression and severity of SSRD independently influence neurocognitive functioning of SSRD patients.

Cognitive behavioral therapy (CBT) is the most frequently used therapy for treating psychological disorder in SSRD patients (Kroenke, 2007) but the effectivity of this treatment may be negatively influenced by neurocognitive dysfunctioning. For example, patients may forget to do homework or homework assignments may be too demanding. A recent case description of a patient with conversion disorder describes the negative effect of severe neurocognitive impairment within information processing speed on CBT. CBT had to be

paused and the patient was offered cognitive rehabilitation treatment (CRT). After CRT, neurocognitive functioning improved and CBT was successfully continued (De Vroege, Khasho, Foruz, & Van der Feltz-Cornelis, 2017). Although this case report is the first to report successful influence on CBT via CRT in a patient with conversion disorder, this finding suggests that patients with severe impairment in information processing speed are less likely to be able to engage in CBT.

We conclude that neurocognitive dysfunction is present in the majority of SSRD patients and that these impairments occur across different neurocognitive domains. Depression intensifies neurocognitive dysfunction, mainly within the domains of sustained attention, information processing speed, working memory, verbal memory, and phonological verbal fluency. However, future studies with larger samples are needed to document the potential synergy between depression and anxiety and their influence on neurocognitive functioning of patients suffering from SSRD. The presence of profound neurocognitive impairment in patients suffering from SSRD implies that exploring neurocognitive dysfunctioning, using a NPA within SSRD patients, is warranted. Furthermore, future randomized controlled studies need to explore the effectivity of neurocognitive treatments with a repeated NPA to evaluate the improvement of neurocognitive functioning of patients suffering from SSRD.

Part two
Treatment outcomes in relation to clinical characteristics

Chapter 5

Alexithymia and treatment outcome of patients suffering from somatic symptom and related disorders. A clinical prospective study

This chapter is based on:

De Vroege, L., Emons, W.H.M., Sijtsma, K., & Van der Feltz-Cornelis, C.M. (under review). Alexithymia and treatment outcome of patients suffering from somatic symptom and related disorders. A clinical prospective study.

Abstract

Alexithymia may moderate the effectiveness of psychotherapy and may predict impaired general functioning in patients suffering from somatic symptom and related disorders (SSRD). The objectives of this study were twofold. First, we examined the level of alexithymia of patients with SSRD compared to the general population. Second, we explored whether alexithymia is associated with treatment outcome and explore if presence of chronic medical condition affects the association of alexithymia with treatment outcomes. A clinical prospective study was done. In total 234 consecutive patients suffering from SSRD from the Centre of Excellence for Body, Mind, and Health, Tilburg were included. Alexithymia scores at intake were compared with the general Dutch population. Treatment outcomes included changes in levels of depression, anxiety, physical symptoms, and general functioning between intake and completion of the treatment. Hierarchical logistic regression analyses were used to explore the association of alexithymia with treatment outcomes, and the influence of chronic medical condition on this association. Compared to the general population, alexithymia scores regarding verbalizing, identifying, fantasizing, and scores on the cognitive dimension of alexithymia were elevated in patients suffering from SSRD. Our results suggested that alexithymia affects treatment outcome, but the effects were considered clinically irrelevant. Future studies should focus on other interpersonal characteristics that extend Criterion B of SSRD. Studies focusing on such characteristics and comparing patients suffering from SSRD with patients with other mental disorders are needed to further explore what kind of interpersonal characteristics specifically influence treatment outcome for patients suffering from SSRD.

Alexithymia and treatment outcome of patients suffering from somatic symptom and related disorders. A clinical prospective study

Nemiah and Sifneos (1970) introduced the concept of alexithymia to describe an emotional deficiency in patients with classic psychosomatic disorders such as asthma and hypertension. Patients were unaware of their feelings or were incapable to verbalize them, and they were unable to fantasize about their inner thoughts, feelings, and attitudes. Although the concept originated from psychoanalytical research, in time it also incorporated other perspectives such as those originating from cognitive behavioral and from stress research. In the 1990s, alexithymia was described as a combination of the following features: (a) difficulty identifying and describing feelings, (b) difficulty distinguishing feelings and bodily sensations caused by emotional arousal, (c) constricted imaginal processes, and (d) a cognitive style characterized by a preoccupation with the details of external events (Cox, Kuch, Parker, Schulman, & Evans, 1994). Alexithymia is comparable to a personality trait that involves a deficiency in emotional literacy, affective and cognitive functioning. These characteristics are related to stress and adaptation and have repercussions for psychotherapeutic treatment possibilities.

Although alexithemic patients were found to be equally willing to participate in psychotherapy (Leweke, Bausch, Leichsenring, Walter, & Stingl, 2009), alexithymia has been described as interfering with psychotherapy (Bach & Bach, 1995; Leweke et al., 2009; Ogrodniczuk et al., 2011). In particular, recent studies found that specifically focusing on alexithymia during treatment improved treatment outcomes in terms of symptom reduction and general functioning (Beck, Breuss, Kumnig, & Schüßler, 2013; Cameron, Ogrodniczuk, & Hadjipavlou, 2014; Gay, Hanin, & Luminet, 2008; Ogrodniczuk, Sochting, Piper, & Joyce, 2012; Tulipani et al., 2010). However, as far as we know, studies exploring the association between alexithymia and treatment outcome at symptom level in patients suffering from somatic symptom and related disorder (SSRD) are lacking.

Because alexithymia was found to be related to impoverished general functioning in somatoform disorders (Bach & Bach, 1995; Burba et al., 2006; Cohen, Auld, & Brooker, 1994; Cox et al., 1994; Duddu, Isaac, & Chaturvedi, 2003; Kooijman, 1998; Kosturek, Gregory, Sousou, & Trief, 1998; Moreno-Jiménez, Blanco, Rodríguez-Muñoz, & Hernández, 2007; Taylor, Parker, Bagby, & Acklin, 1992; Verissimo, Mota-Cardoso, & Taylor, 1998; Von Rimscha et al., 2013; Wolf et al., 2015), following the classification of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR (American Psychiatric Association (APA), 2000) and other precursors of SSRD, as described in DSM-5 (APA, 2013), general

functioning also may be a relevant outcome of treatment. However, as far as we know, so far studies exploring this aspect of treatment outcome in patients suffering from SSRD have not been done. This study explores whether alexithymia has a moderating effect in treating depressive, anxiety, physical symptoms, and general functioning in SSRD patients.

Objectives and hypotheses

The first objective of this study was to estimate the level of alexithymia of patients suffering from SSRD and compare this level to known general population scores. The second objective was to examine the influence of alexithymia on treatment outcomes with regard to depression, anxiety, physical symptoms, and general functioning in patients suffering from SSRD. We predict a negative association between alexithymia and treatment outcome with respect to depression, anxiety, physical symptoms, and general functioning. The third objective was to examine the influence of chronic medical conditions on the association between alexithymia and treatment outcome. We hypothesized that having chronic medical conditions is associated with lower treatment response than when chronic medical conditions are absent.

Method

Study design

The study uses data from a longitudinal observational design in a clinical setting. The sample existed of patients suffering from SSRD who were treated at the Clinical Centre of Excellence for Body, Mind and Health (Dutch abbreviation: CLGG), a department of GGz Breburg, Tilburg, the Netherlands. We assessed alexithymia at intake, and outcome measures including depression, anxiety, physical symptoms, and general functioning were assessed at intake before treatment and at discharge. All patients who were referred to CLGG between August 2013 and April 2016 were included.

The standard intake procedure at the CLGG consists of questionnaire assessment during intake (referred to as baseline measurement), case history, physical assessment, psychiatric evaluation, psycho-diagnostic assessment, and neuropsychological assessment. The Bermond-Vorst Alexithymia Questionnaire (BVAQ) was self-administered during the psycho-diagnostic assessment at intake. Level of education was determined using Verhage coding (Verhage, 1964), which includes seven levels ranging from low (levels 1 through 4), medium (level 5) to high (levels 6-7). Throughout treatment, patient's progress is evaluated using computerized Routine Outcome Monitoring (ROM) during treatment at CLGG (Van der Feltz-Cornelis et al., 2014). We used ROM data for this study. Patients were informed at intake about the scientific research conducted at CLGG. Patients who did not give their

consent to use their data for this study were excluded from the dataset. Data were coded. The Commission of Scientific Research of GGz Breburg approved of this study (file number: CWO 2014-09).

Setting and participants

Inclusion/exclusion criteria were evaluated for all patients that were referred to CLGG. Inclusion criteria were (1) completion of the intake, and (2) an age equal or above 18 years. Patients were excluded if they (1) were engaged in personal or professional injury procedures, (2) were not able to come to CLGG, (3) did not complete questionnaires from the ROM during intake and during treatment, (4) had an IQ below 80, and (5) if the primary care focus was not related to physical symptoms. Other exclusion criteria were (6) presence of psychosis or psychotic features that hampered treatment, (7) an active suicide risk (threatening), and (8) substance dependency.

Treatment at CLGG consisted of cognitive behavioral therapy (CBT) or other psychological interventions in combination with pharmacotherapy. This type of treatment is suggested by the multidisciplinary guideline for medically unexplained symptoms and somatic disorders (Van der Feltz-Cornelis et al., 2010; Van der Feltz-Cornelis et al., 2012) which are provided in a Shared Decision Making model (Van der Feltz-Cornelis et al., 2014). We assessed alexithymia, depression, anxiety, physical symptoms, and general functioning before and after treatment by means of questionnaires. Figure 1 shows a flow chart of the study. Two hundred and thirty-five patients filled out the BVAQ at intake. One patient, who gave no consent, was excluded from the study. Of the remaining 234 patients, 145 (62.0%) completed treatment. Of the patients who completed treatment, 142 patients (97.9%) filled out the Physical Symptom Checklist (PSC), 142 (97.9%) filled out the Generalized Anxiety Disorder questionnaire (GAD-7), 144 (99.3%) filled out the Patient Health Questionnaire (PHQ-9) for assessing depression, and 126 (86.9%) filled out the 36-item Short Form Health Survey (SF-36), both at intake and at discharge.

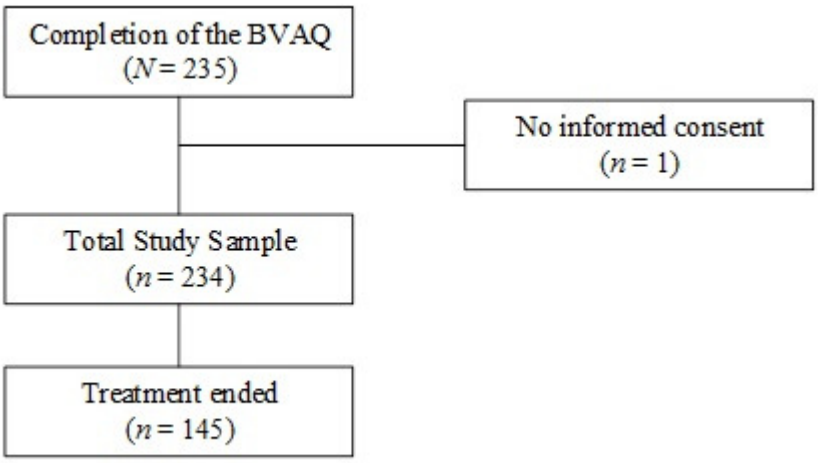


Figure 1. Flowchart of patients included in the study. Sample sizes are given for patients who completed treatment and questionnaire assessment.
Abbreviation: BVAQ: Bermond-Vorst Alexithymia Questionnaire.

Instruments

Bermond-Vorst Alexithymia Questionnaire (BVAQ). Alexithymia was assessed using the BVAQ (Vorst & Bermond, 2001). The BVAQ was preferred, because this questionnaire incorporates a cognitive dimension and an affective dimension of alexithymia. The BVAQ provides valid and reliable measures of cognitive and affective dimensions of alexithymia (Bermond et al., 2007; Deborde et al., 2007; Müller, Bühner, & Ellgring, 2004; Vorst & Bermond, 2001; Zech, Luminet, Rimé, & Wagner, 1999).

Responses to the items were scored on a five-point Likert scale. Higher scores indicate higher levels of alexithymia. The BVAQ consists of five subscales containing eight items each. The subscales are identifying, verbalizing, analyzing, fantasizing, and emotionalizing, each in accordance with the five-factor model of alexithymia (Vorst & Bermond, 2001). The five subscales constitute two alexithymia dimensions, which are a cognitive dimension and an affective dimension. Scores on the cognitive dimension were obtained by adding the scores of the subscales identifying, analyzing and verbalizing (scores ranged from 24 through 120). Scores on the affective dimension were obtained by adding the scores of the subscales emotionalizing and fantasizing (scores ranged from 16 through 80). Score reliability of the BVAQ was assessed for our SSRD study sample by means of coefficient alpha (Cronbach, 1951). Coefficient alpha for the cognitive dimension equaled .90 and for the affective dimension alpha equaled .68.

The Patient Health Questionnaire (PHQ-9). Depression was assessed using the PHQ-9 (Kroenke et al., 2001). The PHQ-9 is a reliable 9-item self-report questionnaire, with higher

scores indicating higher levels of depressive symptoms (Kroenke et al., 2001). Item scores ranged from 0 (not at all) to 3 (nearly every day), and total scores ranged from 0 to 27 (Kroenke et al., 2001). Cutoff points of 5, 10, 15, and 20 represent mild, moderate, moderately severe and sever levels of depression (Kroenke et al., 2010).

Generalized Anxiety Disorder questionnaire (GAD-7). Anxiety was assessed using the GAD-7. The GAD-7 is a reliable 7-item self-report questionnaire that measures symptoms of anxiety during the last two weeks (Spitzer et al., 2006). GAD-7 scores range from 0 to 21, where cutoff scores of 5, 10, and 15 represent mild, moderate and severe levels of anxiety (Kroenke et al., 2010).

Physical Symptom Checklist (PSC). Physical symptoms were measured using the PSC (Van Hemert, 2003) is a 51-item questionnaire. The total scores on the PSC range from 0 to 51 and represent the number of physical symptoms that were regularly or often present in the last week (Van Hemert (2003). De Waal and Van Hemert (2013) provided normative data.

36-Item Short Form Health Survey (SF-36). To assess general functioning, the SF-36 (Ware, Keller, & Kosinski, 1994) was used. Studies have confirmed the SF-36's validity and reliability (Aaronson et al., 1998; Garratt, Ruta, Abdalla, & Russell, 1994; McHorney, Ware Jr, & Raczek, 1993). The SF-36 is a self-report questionnaire that contains 36 items, which are distributed across eight scales. Using the developers' scoring algorithm (Ware, Kosinski, & Keller, 2001), the eight subscales were converted into two summary measures: a physical component summary measure (PCS) and a mental component summary measure (MCS). Scores range from 0 to 100, where higher scores on the PCS and MCs indicate better general functioning. Normative data are available in Maglinte, Hays, and Kaplan (2012).

Treatment outcome variables

Raw change. For each outcome, a change score variable was created by subtracting the score after treatment from the scores at intake. This way, change scores were calculated representing treatment outcomes with respect to depression, anxiety, physical symptoms, and general functioning (PCS and MCS).

Reliable change. For each patient, we computed the RCIs (Jacobson & Truax, 1991) for each questionnaire. RCIs enabled us to assess at an individual level whether reliable change was present. A dichotomous reliable change variable was created, reflecting reliable change at a 90% confidence level; that is, scores equal to 0 reflected no reliable change (i.e., $-1.645 < RCI < 1.645$) and scores equal to 1 reflected reliable change (i.e., $RCI < -1.645$ or $RCI > 1.645$).

Clinical change. To study the association between alexithymia and clinical change, we defined a categorical variable called clinical remission. A patient shows clinical remission if his/her score at intake exceeds a clinical cutoff and after treatment is located in the normal range after treatment. The following clinical cutoffs were used to define remission. For both the PHQ-9 and GAD-7, we used a score of 5, which identifies at least mild levels of depression or anxiety. For the PSC, we also used 5 as the cutoff. This cutoff coincides with the 75th percentile of PSC scores in normative data from general practitioner's offices (De Waal & Van Hemert, 2013). This means that remission is observed if after the treatment the patient's PSC score is no longer among the highest 25% in the general population. To define remission on the PCS and MCS of the SF-36, the mean scores in the general population were used (Maglinte et al., 2012). In particular, the cutoffs for remission were 50 for the PCS and 54 for the MCS after treatment. Furthermore, to speak of clinical remission, patients must also have shown a reliable change. This results in a clinical change variable having three levels: 0 = no reliable change (i.e., $|RCI| < 1.645$), 1 = reliable change but no remission, and 2 = remission.

Statistical methods

Objective 1: Alexithymia in SSRD patients. Level of alexithymia was described by means of normed scores. These normed scores were obtained using normative data from the general population (described in chapter 3 of this PhD dissertation). We used one-sample *t*-tests to test whether mean differences in the normed scores between patients suffering from SSRD and the general population were significant.

Objective 2: Examine the association between alexithymia and treatment outcomes in SSRD patients. First, we studied mean differences between the raw scores at intake and at discharge for the PHQ-9, GAD-7, PSC, and PCS and MCS of the SF-36, using the paired-sample *t*-tests. For each outcome measure, effect-size measure Cohen's *d* was obtained following Rosner (2015). Effect sizes equal to $d = 0.2$ are considered small, $d = 0.5$ medium, and $d \geq 0.8$ large (Cohen, 1988).

Second, we used linear regression analysis to explore the association of alexithymia with depression, anxiety, physical symptoms, and general functioning. The change score variables for the PHQ-9, the GAD-7, the PSC, the PCS of the SF-36, or the MCS of the SF-36 were used as dependent variables. Age, gender, education level, the affective and cognitive dimensions of alexithymia, chronic medical condition, and the two interaction terms of the dimension of alexithymia with chronic medical condition were used as independent variables.

Third, we used logistic regression to explore the association of alexithymia with the RCI for depression, anxiety, physical symptoms, and general functioning. The dichotomous RCI variables for the PHQ-9, the GAD-7, the PSC, the PCS of the SF-36, or the MCS of the SF-36 were used as dependent variables. Age, gender, education level, the cognitive and affective dimensions, chronic medical condition, and the interactions between the dimensions of alexithymia and chronic medical condition were used as independent variables. Fourth, we used multinomial logistic regression to explore the association of alexithymia with clinical change for depression, anxiety, physical symptoms, and general functioning.

For each outcome variable, the regression analyses were done as follows. First, we fitted the full model that included as predictors the background variables, the first-order effects of the cognitive and affective alexithymia dimensions, and chronic medical conditions, and the interaction effects between the alexithymia dimensions and medical conditions. To study the interaction effects, we used centered variables to avoid potential problems with multicollinearity (Cohen & Cohen, 2013). Second, in case some of the interaction effects were non-significant, we refitted the model without the non-significant interaction effects.

We used Nagelkerke's *R*-square to gauge effect size. Formally, the pseudo *R*-square does not represent proportions of explained variance, but we interpreted the pseudo *R*-square as the proportion of the variation the model explained (Nagelkerke, 1992). We used the guidelines of Cohen (1992) to interpret Nagelkerke's pseudo *R*-square (i.e., *R*-square = .02 was considered small, *R*-square = .13 was considered medium, *R*-square $\geq$ .26 was considered large). All analyses were done by means of the Statistical Package for the Social Sciences version 22 (IBM Corp., 2011).

Results

Sample characteristics

Table 1 (upper panel) describes the socio-demographic characteristics of the SSRD patient sample. The SSRD sample consisted of 234 patients (59.0% females). The sample had a mean (*M*) age of 42.8 (standard deviation (*SD*) = 12.56; range: 1 to 79). Seven patients had missing values on the BVAQ items. One of these patients had six missing item scores and was excluded from further analyses. The only missing item score for the remaining six patients was imputed using two-way imputation (Bernaards & Sijtsma, 2000; Van Ginkel, Van der Ark, Sijtsma, & Vermunt, 2007).

Objective 1: Alexithymia in SSRD patients. Table 1 (lower panel) shows the means for the raw scores (Column 2) and normed scores (Column 5) on the BVAQ. Significant mean differences with respect to the general population were found for the subscales verbalizing ($t(233) = 4.239, p < .001$), fantasizing ($t(233) = 3.770, p < .001$), identifying ($t(233) = 7.759, p < .001$), emotionalizing ($t(233) = -8.106, p < .001$). A significant mean differences was found for the cognitive dimension ($t(233) = 4.944, p < .001$). For the subscales of the cognitive dimension, we found elevated levels of identifying (*M* = 0.69; range -1.97 to 4.26) and verbalizing (*M* = 0.39; range -2.87 to 3.08) compared to the general population. For the subscales of the affective dimension in the BVAQ, we found lowered levels of emotionalizing (*M* = -0.55; range -2.96 to 2.48), but higher mean values for fantasizing (*M* = 0.27; range -2.51 to 2.42).

Objective 2: Examine the association between alexithymia and treatment outcomes in SSRD patients. Table 2 shows the mean scores before and after treatment for the PSC, GAD-7, PHQ-9, and the MCS and PCS of the SF-36. Results suggested substantive mean changes in the treatment outcomes. PSC means before and after treatment differed significantly ($t(141) = 4.207, p < .001, d = 1.82$), the mean scores on the PHQ-9 also differed significantly before and after treatment ($t(143) = 4.837, p < .001, d = 1.43$), and also the mean scores on the GAD-7 differed significantly before and after treatment ($t(141) = 5.090, p < .001, d = 1.21$). Mean MCS and PCS scores for the SF-36 did not differ significantly before and after treatment.

Table 1
Socio-demographic characteristics and descriptive statistics for the BVAQ in the SSRD sample at intake (N=234)

Characteristic	*M* (*SD*)	Min / Max	*n* (%)	Normed scores[1] (min / max)
		Background variables		
Gender				
Men			96 (41.0)	
Women			138 (59.0)	
Age	42.78 (12.56)	19/79		
Educational level*				
Low (1-4)			56 (24.9)	
Medium (5)			103 (45.8)	
High (6-7)			66 (29.2)	
(Missing Value)			(9)	
Marital status				
Married/Living together			150 (71.4)	
Divorced			11 (5.2)	
Widow(er)			1 (0.5)	
Single			48 (22.9)	
(Missing value)			(24)	
PSC	16.57 (8.08)	0/38		
GAD-7	11.51 (5.47)	0/21		
PHQ-9	14.21 (6.07)	0/27		
SF-36 (n = 225)[2]				
PCS	40.48 (5.44)	27.49/57.43		
MCS	44.01 (5.16)	21.30/55.55		
Comorbidity at intake				
Comorbid anxiety			2 (0.9)	
Comorbid depression			25 (11.4)	
Comorbid depression and anxiety			193 (87.7)	
		BVAQ scores		
Cognitive dim.	67.12 (17.64)	32 / 106		0.43 (-2.38 / 3.25)
Identifying	22.10 (7.02)	8 / 40		0.69 (-1.97 / 4.26)
Analyzing	19.61 (6.02)	8 / 34		-0.04 (-2.52 / 2.97)
Verbalizing	25.41 (8.29)	8 / 40		0.39 (-2.87 / 3.08)
Affective dim.	45.48 (8.88)	19 / 66		-0.10 (-2.79 / 2.45)
Fantasizing	26.74 (6.92)	8 / 40		0.27 (-2.51 / 2.42)
Emotionalizing	18.74 (5.16)	8 / 32		-0.55 (-2.96 / 2.48)

Abbreviations: SSRD: Somatic Symptom and Related Disorders, PSC: Physical Symptom Checklist, GAD-7: Generalized Anxiety Disorder questionnaire, PHQ-9: Patient Health Questionnaire, SF-36: 36-item Short Form Health Survey, MCS: Mental Component Summary, PCS: Physical Component Summary, BVAQ: Bermond-Vorst Alexithymia Questionnaire.
Note: [1] Normed scores were based on normative data from chapter 3 in this PhD dissertation

Table 2
Mean scores on the PHQ-9, GAD-7, PSC, and SF-36 of the SSRD sample at intake and after treatment

Outcome measure	*n*	Measurement occasion			
		At intake		After treatment	
		M	SD	M	SD
PSC	142	16.26	7.68	13.54	9.22
GAD-7	142	11.18	5.41	9.09	6.17
PHQ-9	144	13.94	6.12	11.50	7.36
SF-36	126				
PCS		41.10	5.44	40.42	5.48
MCS		43.47	5.73	43.03	5.82

Abbreviations: M: Mean, SD: Standard Deviation, PHQ-9: Patient Health Questionaire-9, GAD-7: General Anxiety Disorder questionnaire, PSC: Physical Symptom Checklist, SF-36: 36-item Short Form Health Survey, MCS: Mental Component Summary, PCS: Physical Component Summary.
Note: n = the number of patients who completed the treatment and who filled out the questionnaire both at intake and after treatment.

Alexithymia had significant effect on treatment outcome regarding anxiety (see Table 3). More specifically, cognitive dimension and medical condition showed a significant interaction effect. Simple effects analysis suggested a negative effect for patients without a chronic medical condition ($B = -0.08, p = .022$), and a positive but non-significant effect for patients with a chronic medical condition ($B = 0.04, p = .329$). The cognitive and affective dimension did not significantly predict change on depression, physical symptoms scores and general health functioning.

Table 3
Linear regression of raw change scores for the GAD-7 on the BVAQ dimensions and covariates

Predictors	Change scores for the GAD-7		
	B	95% CI	*p*
Cognitive dimension	-0.08	[-0.15, -0.01]	.021
Affective dimension	0.01	[-0.13, 0.12]	.911
Chron med cond	0.76	[-0.97, 2.49]	.386
Int cogn_med	0.12	[0.02, 0.22]	.022
Int aff_med	-0.15	[-0.35, 0.05]	.140

Abbreviations: GAD-7: Generalized Anxiety Disorder questionnaire, 95% CI: 95% confidence interval for B, Chron med cond: chronic medical condition, Int cogn_med: interaction between cognitive dimension of alexithymia and chronic medical condition, Int aff_med: interaction between the affective dimension and chronic medical condition.

Table 4 shows the results of logistic regression analyses. The interaction between the cognitive dimension and medical chronic condition had a significant effect on reliable change with regard to depression (Odds Ratio $(OR) = .95, p = .015$). The squared semi-partial correlation for this interaction was 0.06, which means that 6% of the total variability in treatment outcome for depression is uniquely associated with the interaction of cognitive dimension and medical chronic condition. Results suggest that the association between the cognitive dimension and treatment outcome on depression is slightly weaker for patients with chronic medical condition than patients without a chronic medical condition. However, simple effects analysis for depression showed no significant simple effects. The cognitive dimension had a significant main negative effect on treatment outcome with respect to anxiety. The squared semi-partial correlation for this dimension was 0.05, which means that 5% of the total variability in treatment outcome for anxiety is uniquely associated with the cognitive dimension. A significant interaction effect between cognitive dimension and chronic condition was also found for the PSC ($OR = .95, p = .033$). The squared semi-partial correlation for this interaction was 0.05, which means that 5% of the total variability in treatment outcome for physical symptoms is uniquely associated with this interaction. Simple effects analysis for PSC showed a significant negative effect for patients with a chronic condition ($p = 0.028$), but the effect was not significant in the subgroup of patients without a chronic condition. The affective dimension had a significant positive effect on treatment outcome with respect to general mental health functioning. Removing the affective dimension would decrease the *R*-square to .15, rendering the effect substantial.

Table 5 shows the results for predicting reliable and clinical change. Regarding depression, the interaction between the cognitive dimension and chronic medical condition is

significantly associated with clinical change and no remission versus no clinical change and no remission ($OR = .94, p = .021$). The interaction between the affective dimension and chronic medical condition is significantly associated with clinical change and no remission versus no clinical change and no remission ($OR = 1.12, p = .048$). With regard to general functioning (MCS of the SF-36), the affective dimension was significantly associated with clinical change and no remission versus no clinical change and no remission ($OR = 1.24, p = .003$). Results for clinical change and remission versus no clinical change and no remission could not be computed, because none of the patients showed remission on the MCS. No significant associations were found for anxiety and for the PCS of the SF-36.

To conclude, our results suggest some effects of alexithymia on clinical change with respect to depression, physical symptoms, and general functioning. However, the estimated ORs of around 1.00, suggest that these effects are very small and negligible.

Table 4

Logistic regression analyses predicting reliable change regarding depression, physical symptoms, and general functioning

Predictors	Depression (PHQ-9)			Anxiety (GAD-7)			Physical symptoms (PSC)			General functioning (MSC of the SF-36)		
	OR	95% CI	R^{2a}	*OR*	95% CI	R^{2a}	*OR*	95% CI	R^{2a}	*OR*	95% CI	R^{2a}
			.10			.08			.14			.43
Cogn dim	1.03	[1.00, 1.06]		**1.02**	[1.00, 1.05]		1.01	[0.98, 1.04]		1.00	[0.96, 1.04]	
Aff dim	1.03	[0.98, 1.09]		0.98	[0.94, 1.03]		0.99	[0.94, 1.05]		**1.25**	[1.09, 1.44]	
Chron med cond	1.06	[0.50, 2.26]		0.93	[0.45, 1.92]		1.38	[0.63, 2.98]		0.42	[0.08, 2.28]	
Int cogn	**0.95**	[0.91, 0.99]		---	---		**0.95**	[0.91, 1.00]		---	---	
Int aff	1.01	[0.92, 1.10]		---	---		1.10	[1.00, 1.21]		---	---	

Abbreviations: PHQ-9: Patient Health Questionnaire, GAD-7: Generalized Anxiety Disorder questionnaire, PSC: Physical Symptom Checklist, MCS: Mental Component Summary, SF-36: 36-item Short Form Health Survey, OR: Odds Ratio, 95% CI: 95% confidence interval, Chron med cond: chronic medical condition, Int cognmed: interaction term of the cognitive dimension of alexithymia and chronic medical condition, Int aff: interaction term of the affective dimension and chronic medical condition.

Note: --- : results for chronic medical condition, and for the interaction terms of the alexithymia dimension and chronic medical condition (Model 3 and 4, respectively) yielded no significant results. [a]Nagelkerke's pseudo R-square. All coefficients in bold are significant at the 5% significance level.

Table 5

Multinomial logistic regression analyses predicting clinical change regarding depression, physical symptoms, and general functioning.

Predictors	Depression (PHQ-9)			Physical symptoms (PSC)			General functioning (MCS of the SF-36)		
	OR	95% CI	*p*	*OR*	95% CI	*p*	*OR*	95% CI	*p*
Clinical change/No remission versus No clinical change/No remission									
Affective dimension	1.02	[0.95, 1.09]	.561	1.00	[0.94, 1.06]	.880	1.24	[1.08, 1.42]	.003
Cognitive dimension	1.03	[1.00, 1.07]	.091	1.01	[0.98, 1.04]	.572	0.90	[0.95, 1.04]	.630
Chron med cond	0.86	[0.33, 2.22]	.751	1.25	[0.53, 2.94]	.618	0.39	[0.07, 2.12]	.276
Int aff_med	1.00	[0.89, 1.11]	.944	1.12	[1.00, 1.24]	.048	---	---	---
Int cogn_med	0.94	[0.89, 0.99]	.021	0.95	[0.91, 1.00]	.054	---	---	---
Clinical change/Remission versus No clinical change/No remission									
Affective dimension	1.03	[0.95, 1.12]	.424	1.01	[0.90, 1.15]	.822	---	---	---
Cognitive dimension	1.02	[0.98, 1.07]	.301	1.00	[0.94, 1.07]	.977	---	---	---
Chron med cond	1.46	[0.52, 4.12]	.613	1.19	[0.22, 6.40]	.836	---	---	---
Int aff_med	0.97	[0.91, 1.02]	.230	1.03	[0.86, 1.25]	.732	---	---	---
Int cogn_med	1.03	[0.91, 1.16]	.643	0.95	[0.87, 1.05]	.319	---	---	---

Abbreviations: PHQ-9: Patient Health Questionnaire, PSC: Physical Symptom Checklist, MCS: Mental Component Summary, SF-36: 36-item Short Form Health Survey, OR: Odds Ratio, 95% CI: 95% confidence interval, Chron med cond: chronic medical condition, Int cogn_med: interaction term of the cognitive dimension of alexithymia and chronic medical condition, Int aff_med: interaction term of the affective dimension and chronic medical condition.

Note: --- : results not reported because interaction effect was not significant, or effect could not be estimated because no patients showed remission on the MCS.

Discussion

Alexithymia levels in patients suffering from SSRD were compared to normative data from the general population. A remarkable result was the low mean score on emotionalizing for SSRD patients compared to the general population, while elevated scores were found for other BVAQ subscales. This result raises doubts about the theoretical conceptualization of alexithymia as entertained by the BVAQ. The BVAQ differs from other instruments (e.g., the Toronto Alexithymia Scale developed by Bagby, Parker, & Taylor, 1994) in that it includes a subscale for emotionalizing. However, no consensus exists whether emotionalizing should be conceived as a distinctive factor of alexithymia. Our results support the view that emotionalizing may be better conceived as a personality characteristic independent from alexithymia. Our results suggest that SSRD patients can be characterized as having elevated levels of identifying, verbalizing, and fantasizing, and a strong tendency to become emotionally aroused by emotional events. However, we found no evidence that alexithymia affects treatment outcome regarding depression, anxiety, physical symptoms, and general functioning. Chronical medical condition had a significant main effect on treatment outcome.

SSRD patients in this study received standard cognitive and behavioral therapy, focusing on reducing physical complaints. However, treatment options for somatoform disorders include affective mentalizing as prominent factor because affective mentalization is involved in the onset and prolongation of physical symptomatology and the interpersonal problems that co-occur with these physical symptoms (Luyten et al., 2012; Tominaga et al., 2014). The link between emotional states and bodily distress and how to restore this link could be improved by enhancing ones capacity of emotional awareness. A recent study suggested that women with fibromyalgia might benefit from an emotional disclosure or expression intervention (Geenen, Van Ooijen-van der Linden, Lumley, Bijlsma, & Van Middendorp, 2012). Our results suggested that SSRD patients have difficulties with identification and verbalization of emotions. Therefore, treatment of SSRD patients should focus on improving identification and verbalization of emotions which was also suggested by a previous study (Cameron et al., 2014).

The DSM-5 introduced the Somatic Symptom Disorder (SSD) category, which is defined by three criteria (A, B, and C) (APA, 2013). Criterion A refers to the presence of symptoms, and criterion C to chronicity. Criterion B includes the presence of abnormal, maladaptive, excessive, and disproportionate thoughts, feelings, and/or behavior related to somatic symptoms (APA, 2013). Two or more of these psychological symptoms have to be present to satisfy criterion B. If alexithymia, or any of its subcomponents, is a key

psychological feature in SSD patients, alexithymia might be indicative of criterion B. Alexithymia is an interesting concept and it is hypothesized that alexithymic individuals are prone to ruminating thoughts and make use of vicious cycles. These cause more frequently occurring thoughts about the somatic symptoms, and ultimately increase the sense of that specific somatic symptom and intensify somatic symptomatology. The alexithymia concept has potential for evaluating whether patients satisfy criterion B but further research on the diagnostic value of alexithymia and its effect on emotion regulation is needed.

Previous studies also found a relationship between alexithymia and interpersonal dysfunction, aggression, and personality disorders (Fossati et al., 2009; Nicolò et al., 2011). This association is not yet explored amongst patients suffering from SSRD. Personality characteristics such as interpersonal dysfunction, aggressive behavior or coping strategies may also increase insights in the personal characteristics of patients suffering from SSRD and might offer treatment options. Studies focusing on these kinds of personality characteristics are warranted in order to establish such new therapies. Future studies should also include other patient groups (e.g., depressed patients), to explore differences in emotion regulation between patients having SSRD and other patients. This way, researchers are able to explore whether or not impoverished emotional regulation is a specific feature of SSRD or a common feature of patients suffering from other mental disorders.

The sample was a convenience sample, including patients who were referred to the CLGG by their general practitioner or their medical specialist. Although this is a clinical centre for patients with Somatic Symptom Disorder, most patients lived near the institute. Patients suffered from psychological comorbidities in addition to their physical symptoms. Treatment consisted of a combination of cognitive behavioral therapy and/or medication, and physical therapy. This treatment follows the multidisciplinary guidelines for medically unexplained symptoms and somatic disorders, which are generally accepted in the field. Because no random sampling from the target population, which includes all Dutch adults suffering from SSRD according to the DSM-5, was possible, we had to use this convenience sample. The use of convenience samples raises concerns about the representativeness and generalizability of the results (Singleton, Straits, & Straits, 1993). However, although the composition of patient populations may differ across regions, it is unlikely that the underlying mechanisms of treatment outcome differ across institutions. Therefore, we expect that the trends found in this study are generalizable to the SSRD population, but caution should be exercised when interpreting the size of the effects, in particular the prevalence rates.

Future studies should include large samples and compare treatment outcome of patients that finished either pharmacotherapy or CBT. The use of a large sample from the general population as a reference group accounts as a major strength. Furthermore, our sample was too small to explore the relationship between alexithymia with treatment outcome for different SSRD categories (e.g., somatic symptom disorder and illness anxiety disorder). Our sample thus consists of a heterogeneous sample of patients with several SSRD diagnoses. Future studies on the relationship between alexithymia and treatment outcome should differentiate between SSRD categories.

Chapter 6

Type D personality and treatment outcome in somatic symptom and related disorders: an observational longitudinal cohort study

Abstract

We evaluated the association of Type D personality with treatment outcome in patients suffering from somatic symptom and related disorders (SSRD) in this longitudinal observational cohort study. Type D personality, physical symptoms, anxiety, and depression were assessed in consecutive outpatients of a Clinical Centre of Excellence for SSRD. Paired-sample *t*-tests and hierarchical logistic regression analyses were conducted to explore treatment outcome in patients suffering from SSRD and the association with Type D personality. The prevalence of Type D personality in SSRD patients was 63%. Compared to patients without a Type D personality, patients with a Type D personality experienced significantly higher levels of depression and anxiety at baseline. One hundred and eighty-seven patients completed treatment. Presence of Type D personality decreased the probability of symptom remission. More specifically, presence of Type D personality decreased probability of remission of anxiety and depression. Higher levels of negative affectivity (NA) decreased probability of treatment remission. More specifically, higher levels of NA decreased the probability of remission of physical symptoms, anxiety, and depression. Social inhibition was not associated with treatment outcome. The prevalence of Type D personality in SSRD exceeds prevalence estimates in previous studies in other patient groups. Subjects with Type D personality and higher levels of NA were less likely to show treatment remission. Therefore, our results suggest taking Type D personality and level of NA into account for treatment of patients suffering from SSRD.

Type D personality and treatment outcome in somatic symptom and related disorders: an observational longitudinal cohort study

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) includes Somatic Symptom and Related Disorders (SSRD) (American Psychiatric Association (APA), 2013), which replaces Somatoform Disorders of the DSM-IV-TR (APA, 2000). The common feature of the SSRD classification is the prominence of somatic symptoms associated with significant distress and impairment, irrespective of the question whether the somatic symptoms co-occur with a diagnosed physical condition (APA, 2013). SSRD has a broader scope than the former somatoform disorders, which were exclusively linked to the concept of somatization (Van der Feltz-Cornelis & Van Balkom, 2010).

The experience of somatic symptoms has been associated with harm avoidance and negative affectivity (Russo, Katon, Sullivan, Clark, & Buchwald, 1994). Compared to non-somatizing patients, patients with somatization more often show self-defeating, depressive, and passive-aggressive behavior and on average have higher levels of neuroticism, lower levels of agreeableness and lower levels of extraversion (Noyes et al., 2001).

The personality characteristic of Type D personality might be relevant when focusing on personality characteristics in SSRD. Type D personality is a personality construct that combines two traits, which are negative affectivity (NA) and social inhibition (SI; Denollet, 2005). NA refers to the tendency to experience negative emotions across time and situations (Watson & Pennebaker, 1989) and SI refers to the tendency to inhibit the expression of emotions and behaviors in social interactions to avoid disapproval (Asendorpf, 1993). Individuals with high levels of both NA and SI are referred to as individuals with a Type D (i.e., distressed) personality (Denollet, 2005). Prevalence of Type D personality ranged from 21% to 33% in general populations (Denollet, 2005; Michal, Wiltink, Grande, Beutel, & Brähler, 2011), 28 to 53% in the cardiac population (Denollet, 2005), 36% in patients suffering from tinnitus (Bartels et al., 2010), 43% in patients suffering from chronic pain (Barnett, Ledoux, Garcini, & Baker, 2009) and 57% in patients suffering from fibromyalgia (Van Middendorp et al., 2016). The prevalence of Type D personality in patients suffering from SSRD is unknown.

Numerous studies in cardiac populations have shown increasing evidence that, compared to patients without Type D personality, Type D personality is associated with a wide range of emotional distress states, such as anxiety and depression (Michal et al., 2011; Schiffer, Denollet, Widdershoven, Hendriks, & Smith, 2007), poor health status, an increase in medical, social, and private help consumption (Michal et al., 2011), poor self-management

(Schiffer et al., 2007), impaired quality of life, myocardial infarcts, and higher mortality rates (Denollet, Vaes, & Brutsaert, 2000). One study found that after a cardiac rehabilitation program, Type D personality was associated with higher levels of anxious and depressive mood (Sogaro et al., 2015). A systematic review in other than cardiac patient populations, showed that Type D personality was associated with higher perception of negative emotions such as depression and anxiety, poor treatment adherence, and an increased number or severity of reported health symptoms in chronic pain and traumatic brain injury (Mols & Denollet, 2010). Other studies showed that Type D personality was associated with lower adherence to treatment in patients with sleep-disordered breathing (Dieltjens et al., 2013; Ekici et al., 2013). Considering these results, patients suffering from SSRD and having a Type D personality might benefit less from treatment than patients suffering from SSRD and without Type D personality. However, as far as we know, the association of Type D personality with treatment outcome in SSRD patients has not been investigated.

Rationale and objectives

The objectives of this study were: (1) to assess the prevalence of Type D personality in patients suffering from SSRD; and (2) to determine the association between Type D personality and physical and psychological treatment outcomes in patients suffering from SSRD. Because we conceive Type D personality as an emotion-regulation problem, typical of patients suffering from SSRD, we hypothesized a higher prevalence of Type D personality in patients suffering from SSRD than in other patient groups. To participate successfully in cognitive behavioral therapy, patients have to be able to talk about their feelings and to express themselves. Patients with Type D personality usually have trouble talking about themselves. Therefore, the second aim of this study was to determine the association between Type D personality and treatment outcome. We hypothesize that patients having a Type D personality benefit less from treatment than patients not having a Type D personality.

Method

Study design

This longitudinal cohort study existed of consecutive outpatients suffering from SSRD, presenting themselves and receiving treatment between September 2013 and April 2016 at the Clinical Centre of Excellence for Body, Mind and Health (CLGG) of GGz Breburg, a Specialty Mental Health Institution in Tilburg, the Netherlands.

CLGG uses computerized Routine Outcome Monitoring (ROM) to evaluate progress of treatment. ROM consists of a set of questionnaires that give an indication of the severity and frequency of the symptom(s) (Van der Feltz-Cornelis et al., 2014). Patients were informed at

intake about use of treatment outcome data for scientific research purposes on an anonymous basis. If the patient refused to give her consent, this was recorded in the administration system and the patient was excluded from the study. Data of all patients who participated in the study were anonymized to ensure privacy. For this study, we used a selection of the ROM questionnaires assessed at baseline and at the end of treatment. Patients could decide to withdraw from the study at any time without any consequences for their treatment. The scientific committee of GGZ Breburg approved of this study (file number: CWO 2014-11).

Setting and participants

All patients at CLGG, older than 18 years, and who were willing to participate in research were included in the study. Patients were excluded from CLGG and this study, if they (a) suffered from a psychosis or psychotic features that hampered effective treatment; (b) experienced substance abuse or dependency (alcohol/drugs); (c) had an active (threatening) suicide risk; (d) had a personality disorder hampering effective treatment; (e) were unwilling to complete the ROM measures; (f) were engaged in professional- or personal injury procedures; or (g) were unable to come to Tilburg. After intake, treatment options at CLGG existed of a combination of cognitive behavioral therapy and/or medication treatment often also in combination with physical therapy, as suggested by the multidisciplinary guideline for medically unexplained symptoms and somatic disorders (Van der Feltz-Cornelis et al., 2012; Van der Feltz-Cornelis, Swinkels, Blankenstein, Hoedeman, & Keuter, 2011). These treatment options were offered to the patients in a Shared Decision Making model (Van der Feltz-Cornelis et al., 2014).

Figure 1 shows a flow chart of the study. Two hundred and twenty-eight patients completed the Type D scale (DS14) at baseline. Sixteen (7.0%) of these patients were not diagnosed having SSRD and were excluded from the analyses. Of the remaining 212 patients, 187 patients (88.2%) completed treatment. Of the patients who completed treatment, 125 patients (66.9%) completed the PSC, 124 patients (66.3%) completed the GAD-7, and 126 patients (67.4%) completed the PHQ-9.

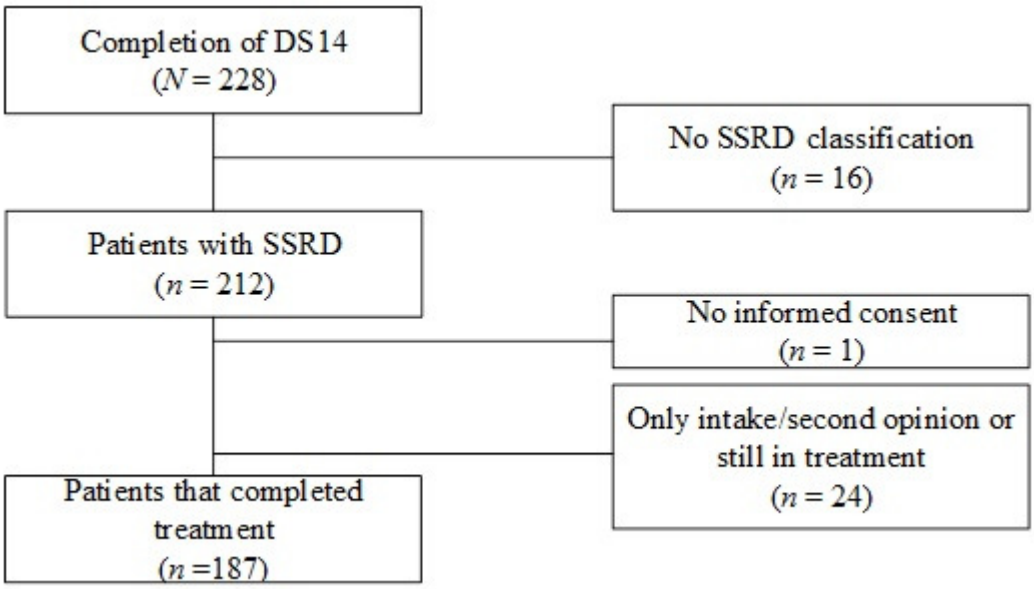


Figure 1. Flowchart of patients included in the study. Sample size is given for patients completing treatment and questionnaire assessment.
Abbreviations: DS14: Type D Scale, SSRD: Somatic Symptom and Related Disorders.

Instruments

Patient characteristics. Sociodemographic variables included age, education level, and gender. Educational level was classified following Verhage (1964). For this study, we dichotomized educational level to prevent categories having only few observations due to the relatively small sample of patients that completed treatment. Educational level was categorized as follows: the four lowest classifications were classified as 'low' and the three highest classifications were classified as 'high'. DSM-5 SSRD diagnoses were established by two psychiatrists after a psychiatric interview.

Type D personality. Type D personality was measured at intake by means of the DS14 (Denollet, 2005). This self-report questionnaire consists of two 7-item subscales, one scale that assessing NA and the other assesses SI. Items were scored on a 5-point Likert scale ranging from 0 (false) to 4 (true). Total scores on each of the two subscales can range from 0 to 28, with higher scores indicating higher levels of NA and/or SI. The DS14 has good psychometric properties (Denollet, 2005). Following convention, individuals who scored at least 10 on each of the subscales are classified as having a Type D personality (Denollet, 2005).

This means that the Type D personality is conceived as a dichotomous typology. The typology may be useful from a clinical perspective, where dichotomous treatment decisions have to be made. However, the scientific foundations of this dichotomous topology have been

challenged (Ferguson et al., 2009) and it has been argued that it is more appropriate to use the underlying continuous NA and SI scales and their interaction to study Type D personality. Therefore, we also explored to what extent NA, SI, and their interaction predicts treatment outcomes.

Physical symptoms. The *Lichamelijke Klachtenvragenlijst* (The Physical Symptom Checklist, PSC; Van Hemert, 2003) is a 51-item self-report questionnaire that measures physical symptoms during the previous week. Scores ranged from 0 (does not burden me) to 3 (often burden me). We followed the guidelines of Van Hemert (2003), in which the item scores were converted to dichotomous scores, where 0 and 1 were transformed to 0, and 2 and 3 were transformed to 1. Total scores ranged from 0 to 51. A higher score on the PSC indicates that more symptoms were present in the previous week (Van Hemert, 2003). The PSC is a valid questionnaire to assess physical symptoms (De Waal et al., 2009).

Anxiety. To assess anxiety symptoms, the Generalized Anxiety Disorder questionnaire (GAD-7) was used. The GAD-7 is a 7-item self-report questionnaire that measures symptoms of anxiety during the previous two weeks. For each item, scores ranged from 0 (not at all) to 3 (nearly every day) (Spitzer et al., 2006). Total scores ranged from 0 to 21, with higher scores indicating higher levels of anxiety symptoms. The GAD-7 is a reliable questionnaire (Löwe et al., 2008; Spitzer et al., 2006).

Depression. To assess depression, the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) was used. The PHQ-9 is a 9-item self-report questionnaire. For each item, scores ranged from 0 (not at all) to 3 (nearly every day). Total scores ranged from 0 to 27, with higher scores indicating higher levels of depressive symptoms (Kroenke et al., 2001). The PHQ-9 has been shown to be a reliable questionnaire (Kroenke et al., 2001).

Treatment outcome: Remission

Symptom remission was observed if the patient's score moved from the clinical range into the healthy range. For each of the outcome measures (i.e., PSC, GAD-7, and PHQ-9), remission on a single outcome was defined as follows. For the PSC, the average score for patients visiting the general practitioners office equaled 6 for women and 4 for men (De Waal & Van Hemert, 2013). We defined positive treatment remission as a score of at least 5 at intake and below 5 at the end of treatment. In addition, scores smaller than 5 on the GAD-7 and PHQ-9 represent absence of symptoms to mild symptoms of depression and anxiety (Kroenke et al., 2010). Symptom remission for anxiety and depression was defined as having a score of 5 or higher at intake and a score below 5 at the end of treatment.

Statistical methods

Prevalence. Descriptive statistics were obtained to describe patient characteristics and prevalence of Type D personality. To test whether the Type D personality group and the non-Type D personality group differed on baseline characteristics, independent *t*-tests and Chi-square tests were executed. Cohen's *d* was used to gauge the effect size. Effect sizes of at least $d = 0.2$ are considered small, at least $d = 0.5$ medium, and at least $d = 0.8$ large (Cohen, 1988). For the PSC, the GAD-7, and the PHQ-9, we also studied mean differences between raw scores before and after treatment. Paired-sample *t*-tests were conducted to test if patients who completed treatment, on average showed significant lower physical, anxiety, and depressive symptoms at the end of treatment. Unpaired t-tests were performed to test mean differences between the Type D and non-Type D groups. Using the McNemar test, we tested whether a significant proportion of patients showed symptom remission.

Association with treatment outcome. To study the hypothesized relationship between Type D personality and the dichotomous outcome variables, we used hierarchical logistic regression analyses. For each outcome variable, the following three nested models were applied: Model 1 only included the background variables age, gender, and education level. This model served as the baseline model. Model 2 extended Model 1 by including NA and SI (i.e., main effects only). Model 3 extended Model 2 by including the interaction term between NA and SI, denoted NA×SI. In a separate analysis, we also estimated logistic regression models with background variables (Model 1) and the dichotomous Type D variable (Model 2) as predictors to evaluate the associations of Type D personality with treatment outcome.

Likelihood-ratio tests were used to test whether model fit improved when adding predictors. Nagelkerke's pseudo *R*-square was used to gauge the effect sizes. Following Nagelkerke (1992), we interpret the pseudo *R*-square as the proportion of the variation the model explained, but we are aware that, formally, pseudo *R*-squares do not represent the proportions of explained variance. For all models, we used Cohen (1988) guidelines for *R*-square to interpret Nagelkerke's pseudo *R*-square (i.e., *R*-square = .02 was considered small, *R*-square = .13 was considered medium, and *R*-square $\geq$ .26 was considered large). All analyses were performed by means of the Statistical Package for the Social Sciences version 22 (IBM Corp., 2011).

Results

Sample characteristics

Table 1 shows background characteristics. The mean age of all SSRD patients (N = 212) was 42.51 years (SD = 12.43), 38.67% were male and 26.89% had a low education level. The mean total score on the DS14 was 31.70 (SD = 12.15), the mean score on NA was 17.94 (SD = 6.59), and the mean score on SI was 13.76 (SD = 7.51). Mean scores on the PSC, the GAD-7, and PHQ-9 were 16.89 (SD = 8.00), 11.78 (SD = 5.45), and 14.34 (SD = 6.10), respectively. The mean age of SSRD patients who completed treatment (n = 187) was 42.34 (SD = 12.36), 72 (38.50%) were male, and 49 (26.20%) had a low education level. Mean total score on the DS14 equaled 31.87 (SD = 12.34), the mean score on NA equaled 17.90 (SD = 6.71), and the mean score on SI equaled 13.98 (SD = 7.49). Mean scores on the PSC, the GAD-7, and PHQ-9 equaled 16.84 (SD = 7.99), 11.80 (SD = 5.42), and 14.24 (SD = 6.13), respectively. Furthermore, of the patients who completed treatment, 15 (8.0%) were diagnosed having a conversion disorder, eleven patients (5.9%) having an illness anxiety disorder, and 161 (86.1%) having a somatic symptom disorder. Most patients (85%) had at least mild symptoms on all three domains.

Objective one: Assess the prevalence of Type D personality

Table 2 shows the baseline characteristics for the SSRD patients in the total sample and for patients who completed treatment. Prevalence of Type D personality in the total sample was 61.79% (n = 131). Type D patients did not differ significantly from non-Type D patients with respect to age, gender, and educational level. Compared to the non-Type D patients at intake, patients with a Type D personality experienced significantly higher levels of depression and anxiety.

With regard to the patients who completed treatment, the prevalence of Type D personality was 62.57% (n = 117). No significant differences were found regarding demographic variables between patients with and without a Type D personality who finished treatment. Compared to the non-Type D patients, at intake patients having a Type D personality, finishing treatment, experienced significantly higher levels of depression and anxiety.

Table 1
Sociodemographic variables, predictors and outcome variables measured at intake of the total sample of SSRD patients and of the SSRD patients who completed treatment

Characteristics	Total sample SSRD patients (N = 212)	SSRD patients who completed treatment (n = 187)
	M (*SD*) / *n (%)*	*M* (*SD*) / *n (%)*
Gender (male)	82 (38.67)	72 (38.50)
Age in years	42.51 (12.43)	42.34 (12.36)
Education level (low)	57 (26.89)	49 (26.20)
DS14 total score	31.70 (12.15)	31.87 (12.34)
Negative affectivity	17.94 (6.59)	17.90 (6.71)
Social inhibition	13.76 (7.51)	13.98 (7.49)
PSC	16.89 (8.00)	16.84 (7.99)
GAD-7	11.78 (5.45)	11.80 (5.42)
PHQ-9	14.34 (6.10)	14.24 (6.13)
Comorbidity at intake		
No mild symptoms	2 (0.9)	2 (1.1)
Mild physical symptoms	4 (1.9)	3 (1.6)
Mild anxiety	2 (0.9)	2 (1.1)
Mild depression	1 (0.5)	1 (0.5)
Mild depression and anxiety	8 (3.8)	8 (4.3)
Mild depression and physical symptoms	0 (0.0)	0 (0.0)
Mild physical symptoms and depression	14 (6.6)	12 (6.4)
Mild physical symptoms and anxiety	0 (0.0)	0 (0.0)
Mild physical symptoms, depression and anxiety	181 (85.4)	159 (85.0)

Abbreviations: M: mean, SD: standard deviation, DS14: Type D Scale 14, PSC: Physical Symptom Checklist, GAD-7: Generalized Anxiety Disorder questionnaire, PHQ-9: Patient Health Questionnaire.
Note: comorbidities were calculated using the cutoffs.

Table 2

Sociodemographic variables, predictors and outcome variables of the total sample of patients with and without Type D personality and of patients with and without Type D personality who completed treatment

Sociodemographic variables	Total sample (n = 212)			Patients who completed treatment (n = 187)		
	Type D (n = 131)	Non-Type D (n = 81)		Type D (n = 117)	Non-Type D (n = 70)	
	M (*SD*) / *n* (%)	*M* (*SD*) / *n* (%)	*p*	*M* (*SD*) / *n* (%)	*M* (*SD*) / *n* (%)	*p*
Gender (male)	56 (42.75)	26 (32.10)	.122[a]	50 (42.74)	22 (31.43)	.124[a]
Age in years	41.26 (11.53)	44.54 (13.58)	.061[b]	41.15 (11.37)	44.31 (13.70)	.091[b]
Education level (low)	36 (27.48)	21 (25.93)	.804[a]	30 (25.64)	19 (27.14)	.821[a]
DS14 total	38.94 (8.24)	19.99 (7.39)	<.001[b]	39.19 (8.21)	19.65 (7.42)	<.001[b]
Negative affectivity	20.73 (4.77)	13.44 (6.65)	<.001[b]	20.89 (4.74)	12.89 (6.56)	<.001[b]
Social inhibition	18.21 (5.46)	6.56 (3.93)	<.001[b]	18.30 (5.50)	6.76 (3.97)	<.001[b]
PSC	17.67 (8.13)	15.63 (7.65)	.071[b]	17.58 (7.88)	15.60 (8.05)	.101[b]
GAD-7	13.00 (4.79)	9.83 (5.89)	<.001[b]	12.97 (4.76)	9.84 (5.90)	<.001[b]
PHQ-9	15.75 (5.67)	12.05 (6.11)	<.001[b]	15.69 (5.71)	11.80 (6.08)	<.001[b]

Abbreviations: M: mean, SD: standard deviation, DS14: Type D Scale 14, PSC: Physical Symptom Checklist, GAD-7: Generalized Anxiety Disorder questionnaire, PHQ-9: Patient Health Questionnaire.

Note: PSC, GAD-7, and PHQ-9 are displayed as mean scores at intake. Significance probabilities were computed for scores between patients with and without Type D personality for the total sample (p-levels in column 4) and for the patients who completed treatment (p-levels in column 7).

[a] Pearson Chi-Square test

[b] Students t-test

Objective two: Determine the association between Type D personality and treatment outcome

Mean changes from intake. The 187 patients who completed treatment showed a significant change of the mean scores on the PSC at intake (*M* = 16.77, *SD* = 7.80) and after treatment (*M* = 13.43, *SD* = 9.66), $t\ (122) = \ 4.786, p\ <\ .001$. A significant mean change was found between the mean scores on the GAD-7 at intake (*M* = 11.73, *SD* = 5.24) and after treatment (*M* = 9.02, *SD* = 6.40), $t\ (122) = \ 5.969, p\ <\ .001$. A significant mean change was found between the PHQ-9 at intake (*M* = 14.30, *SD* = 6.10) and after treatment (*M* = 11.26, *SD* = 7.45), $t\ (124) = \ 5.758, p\ <\ .001$.

Table 3 shows the frequencies and percentages of patients who scored above the cutoff used to define remission, before and after treatment. Approximately 93.5% of the patients showed mild levels of physical symptoms, and at least 90% of the patients were at least mildly depressed or mildly anxious at intake. 13.8% of the patients showed remission for physical symptoms, 21.1% showed remission for anxiety symptoms, and 20.0% showed remission for depression. All percentages differed significantly from 0 (McNemar test).

Table 3
Frequencies (percentages) of patients who score above the clinical cutoff at intake and after treatment, and show remission

Questionnaire	*n*	Percentage above cutoff		Percentage remission	McNemar Test[a]
		At intake	After treatment		
		n (%)	*n* (%)	%	*p*
PSC	123	115 (93.5)	98 (79.7)	13.8	<.001
GAD-7	123	111 (90.2)	85 (69.1)	21.1	<.001
PHQ-9	125	120 (96.0)	95 (76.0)	20.0	<.001

Abbreviations: PSC: Physical Symptom Checklist, GAD-7: Generalized Anxiety Disorder questionnaire, PHQ-9: Patient Health Questionnaire. Cutoff scores were 5 for each scale.
[a] McNemar test tests whether the percentage of remission is significantly larger than 0.

Predicting treatment outcome. Table 4 shows the results of the logistic regression analyses for predicting remission from NA, SI, and NA×SI. NA had a significant effect on remission of physical symptoms ($OR\ =\ .85, p\ =\ .002$; change in Nagelkerke's pseudo R^2 equaled 16.4%; $\chi^2(2) = 12.372, p\ =\ .002$). Results for remission of anxiety and depression followed the same trend; NA had a significant effect on remission of anxiety ($OR\ =\ .85, p = .001$; change in Nagelkerke's pseudo R^2 equaled 17.3%; $\chi^2(2) = 14.029, p\ =\ .001$), and NA had a significant effect on remission of depression ($OR\ =\ .91, p = .028$; change in

Nagelkerke's pseudo R^2 equaled 15.4%; $\chi^2(2) = 12.783, p = .002$). These results suggest that if levels of NA are elevated, the probability of remission of physical symptoms, anxiety, and depression decreases. Interaction NA×SI was not associated with remission of physical symptoms, anxiety, or depression.

Table 5 shows the results of the logistic regression analyses for predicting remission from the dichotomous operationalization of Type D personality. Type D personality had a significant effect on remission on anxiety ($OR = .29, p = .009$; change in Nagelkerke's pseudo R^2 equaled 8.8%; $\chi^2(1) = 6.931, p = .008$) and had a significant effect on remission of depression ($OR = .21, p = .001$; change in Nagelkerke's pseudo R^2 equaled 12.9%; $\chi^2(1) = 10.665, p = .001$). These results suggest that presence of Type D personality decreases the probability of remission of anxiety and depression but not remission of physical symptoms.

Table 4

Logistic regression predicting remission from Type D personality dimensions

	Outcome variables								
	Physical symptoms (PSC)			Anxiety (GAD-7)			Depression (PHQ-9)		
Models	*OR*	95% CI	ΔR^{2c}	*OR*	95% CI	ΔR^{2c}	*OR*	95% CI	ΔR^{2c}
Baseline model [a]			.076			.009			.035
Model 2[b]			.164*			.173*			.154*
SI	1.03	[0.94, 1.13]		1.01	[0.94, 1.08]		0.94	[0.87, 1.02]	
NA	0.85*	[0.77, 0.94]		0.85*	[0.77, 0.94]		0.91*	[0.84, 0.99]	
Model 3 [b]			.062			.024			.003
SI	1.45	[1.00, 2.10]		1.22	[0.92, 1.62]		1.00	[0.79, 1.26]	
NA	1.07	[0.83, 1.38]		0.97	[0.79, 1.18]		0.94	[0.81, 1.10]	
NA x SI	0.98	[0.96, 1.00]		0.99	[0.98, 1.00]		1.00	[0.99, 1.01]	

Abbreviations: PSC: Physical Symptom Checklist, GAD-7: Generalized Anxiety Disorder questionnaire, PHQ-9: Patient Health Questionnaire, OR: Odds Ratio, 95% CI: 95% Confidence Interval, SI: Social Inhibition, NA: Negative Affectivity, NA x SI: interaction term of NA and SI.

Notes: A Baseline model only included background variables. [b] Included background variables education level, gender, and age. [C] Nagelkerke's Pseudo R-square. All coefficients marked by an * are significant at the 5% significance level.

Table 5

Logistic regression predicting remission from Type D personality

	Outcome variables								
	Physical symptoms (PSC)			Anxiety (GAD-7)			Depression (PHQ-9)		
Models	*OR*	95% CI	ΔR^{2c}	*OR*	95% CI	ΔR^{2c}	*OR*	95% CI	ΔR^{2c}
Baseline model [a]			.076			.009			.035
Model 2[b]			.044			.088*			.129*
Type D	0.38	[0.13, 1.10]		0.29*	[0.12, 0.73]		0.21*	[0.08, 0.55]	

Abbreviations: PSC: Physical Symptom Checklist, GAD-7: Generalized Anxiety Disorder questionnaire, PHQ-9: Patient Health Questionnaire, OR: Odds Ratio, 95% CI: 95% Confidence Interval.

Notes: A Baseline model only included background variables. [b] Included background variables education level, gender, and age. [C]Nagelkerke's Pseudo R-square. All coefficients marked by an * are significant at the 5% significance level.

Discussion

The high prevalence of Type D personality among SSRD patients found in our study suggests an association of Type D personality with somatization. This result is consistent with several theories about the development of somatoform disorders due to disturbances in the regulation of affect and emotions (Waller & Scheidt, 2006). An impoverished capacity of maintaining negative affect can lead to rumination, which can lead an impaired processing of emotions and to physiological hyperactivity (Brosschot, Gerin, & Thayer, 2006; Cameron & Jago, 2008), such as increased cardiovascular, immunological, endocrinological, and neurovisceral activity.

We analyzed the association of Type D personality with treatment outcome using the conventional dichotomous typology of Type D versus non-Type D and also using the continuous dimensions of NA, SI and the interaction the two components, that is NA x SI. The dichotomous operationalization of Type D personality was strongly associated with treatment outcome. The analyses using the NA and SI subscales showed a non-significant interaction effect of NA x SI. More importantly, we only found a main effect of NA on treatment outcome, but not of SI. These results suggest that even though SSRD patients tend to have high levels of NA and SI, only NA predicts treatment outcome rather than Type D personality. To gauge the effect of NA, we also ran an analysis with a dichotomized NA variable and we found an *R*-square value that was even higher (8.6% for depression, 8.8% for anxiety, and 10.2% for physical symptoms) than when using the categorical Type D variable. These results have important implications for future research with respect to Type D personality as predictor of adverse health outcomes, because they show that the categorical Type D variable may erroneously suggest a significant effect of SI.

The effect of NA on health outcomes is consistent with other studies (Williams, O'Connor, Grubb, & O'Carroll, 2012). For example, NA was associated with worse mental and physical health in patients for fibromyalgia (Van Middendorp et al., 2016). A possible explanation for the predictive power of NA is its substantial overlap with distress and neuroticism (Coyne et al., 2011; De Fruyt & Denollet, 2002). Therapy focusses on emotion regulation and suppression of distress, more than on increasing patients' tendency to express emotions in social interactions. One can argue that a focus on the experience of negative emotions during the therapeutic process can be beneficial. Our results also show that the interaction of NA and SI was not associated with poorer treatment outcome, which is also in line with another study that reported that the interaction of NA and SI was not associated with disability and quality of life (Williams, O'Connor, Grubb, & O'Carroll, 2012).

Strengths and limitations of the study were the following. The strength of this study is that it explores the association of Type D personality and treatment outcome using the NA, SI and the interaction NA and SI. The first limitation of the study is that it is observational, which prevents us from drawing causal conclusions about causality. The second limitation is that the subjects were recruited in a specialty outpatient mental health centre where the top 5% (regarding complexity) of the patients with SSRD are treated. A large number of patients in our sample suffered from psychological comorbidities in addition to their physical symptoms. The use of the resulting convenience sample limits the generalizability of the results (Singleton, Straits, & Straits, 1993). However, we expect that the results of this study are generalizable to patients suffering from SSRD with comorbidity, because the underlying mechanisms are unlikely to differ across institutions. Nevertheless, the size of the effects should be interpreted with caution. A third limitation is the self-reporting of Type D personality, and physical, anxiety and depressive symptoms at intake. Patients may over-report chronic physical illness, because they want to receive treatment, or they may underreport psychological characteristics, because they consider their symptoms not psychological.

Interventions that address emotional expression have been successful in reducing distress in fibromyalgia (Geenen et al., 2012; Gillis, Lumley, Mosley-Williams, Leisen, & Roehrs, 2006) and other clinical populations (Frisina, Borod, & Lepore, 2004).One promising intervention called mindfulness-based stress reduction already has been shown to reduce levels of NA in cardiac patients (Nyklíček, Van Beugen, & Denollet, 2013). Future studies should explore whether mindfulness-based training of SSRD patients having Type D personality results in better treatment outcome than the regular treatment of SSRD in which emotion regulation is not specifically addressed. Another topic is whether mindfulness training reduces psychological distress and improves quality of life.

Epilogue

Retrospect

We addressed the following questions in this dissertation: 1) Do the Patient Health Questionnaire-15 (PHQ-15), the somatization subscale of the four-Dimensional Symptom Questionnaire (4DSQ), and the Bermond-Vorst Alexithymia Questionnaire (BVAQ) have sufficient psychometric quality to screen for somatoform disorders and clinical characteristics in patients suffering from somatic symptom and related disorders (SSRD)? 2) Which kind of neurocognitive impairment is present in patients suffering from SSRD, and does comorbid anxiety or depression intensify these impairments? 3) Do clinical characteristics such as alexithymia and Type D personality affect treatment outcome in patients suffering from SSRD?

The PHQ-15 and the somatization subscale of the 4DSQ have moderate sensitivity and efficiency. The literature is inconclusive (Terluin, Smits, Brouwers, & De Vet, 2016; Van Ravesteijn, Lucassen, & Speckens, 2008), and based on our findings we conclude that both subscales can be used tentatively as screener but the sole use of one of these questionnaires for assessing clinical characteristics of SSRD is insufficient. It is clear that neither questionnaire covers the complex symptomatology of SSRD (Van Eck van der Sluijs et al., 2017). Hence, the diagnostic process requires diagnostic information beyond what is provided by these questionnaires.

The BVAQ is a Dutch questionnaire for assessing alexithymia. Chapter 3 contributes to the body of evidence with regard to validity of the BVAQ, and provides normative data obtained in a large sample from the general population. Our findings suggest that the BVAQ is a valid measure for assessing alexithymia. The BVAQ claims measuring the construct of alexithymia, distinguishing a cognitive and an affective dimension, and at a finer-grained level five first-order factors, each loading on one dimension. However, we found that the subscale analyzing loaded on both dimensions. Our results suggest the use of the five first-order factor rather than the two dimensions but further research is necessary to replicate these findings. Maes et al. (2015) advise a multi-modal approach, in which alexithymia is measured both by using a structured interview and a self-report questionnaire.

The results in chapter 4 suggest that patients suffering from SSRD have substantial neurocognitive impairments within the domains of divided attention, sustained attention, information processing speed, (working) memory, and phonological fluency. Additionally, neurocognitive functioning was worse in patients suffering from SSRD and comorbid depression. Different from other studies amongst patients with somatoform disorders (e.g., Al-Adawi et al., 2010; Brown et al., 2014; Demir et al., 2013; Grace et al., 1999; Luerding et

al., 2008; Niemi et al., 2002), we explored a broader range of neurocognitive domains and found more impairment within the domains of neurocognitive functioning than reported in previous studies. Based upon these results, we advise to assess a broad range of neurocognitive domains during neuropsychological assessment (NPA) in patients suffering from SSRD. This ensures that during treatment, clinicians do not only focus on the physical domain but also on possibly neurocognitive impairment (Carson, Hallet, & Stone, 2016), but that a broad perspective can also serve as starting point for therapy. Cognitive rehabilitation treatment (CRT) (Ponds, Van Heugten, Fasotti, & Wekking, 2010) may offer such an approach and a pilot in SSRD patients showed already promising results (De Vroege et al., 2017).

In chapters 5 and 6, we explored the effect of alexithymia and Type D personality on treatment outcome. Alexithymia was unrelated to treatment outcome, which suggests that the assessment of alexithymia in patients suffering from SSRD is irrelevant to clinical treatment. The presence of Type D personality decreased the probability of remission of anxiety and depression in patients suffering from SSRD. Results for the subscales showed that higher levels of negative affectivity decreased the probability of remission of physical symptoms, anxiety, and depression, but higher levels of social inhibition did not, and also the interaction effect was not significant. The question whether Type D personality or higher levels of negative affectivity on its own explain negative treatment outcome remains. Future studies should therefore use the continuous subscales of the Type D personality scale to evaluate the effect of Type D personality and its constituent dimensions on treatment outcome, and not limit themselves to the sole use of the dichotomous topology (Ferguson et al., 2009). We recommend the diagnostic application of Type D personality in clinical care for SSRD, because our results suggested that Type D personality is related to treatment outcome.

Limitations

The samples used in the research reported in chapters 1 and 2 are small, which limits the precision of the results. The reasons of being sick-listed and duration of sick-leave were unknown. The results of chapter 3 showed that alexithymia was associated with age and because significant differences were found between responders and non-responders regarding age, caution should be exercised when generalizing the results. In chapter 4, we were unable to use a gold standard for assessing alexithymia, because none exists. A symptom validity test was not administered to all of the patients, because of the limited availability of the symptom validity tests in the clinic. We made use of a patient sample of all patients from one specialty outpatient mental health centre where the top 5% (regarding complexity) of the patients with

SSRD are treated. Hence, the sample used is a sample of convenience and this limits the representativeness and generalizability (Singleton, Straits, & Straits, 1993) of the prevalence rates and reported effect sizes. However, we do consider the trends described in this PhD dissertation generalizable to the top 5% complex SSRD patients (Van Eck van der Sluijs et al., 2017). Hence, we expect that significant associations found in this study can be generalized to the SSRD population, but future research is needed to have more precise measures of the strength of the relationship. Finally, the use of self-report questionnaires for assessing alexithymia and type D personality but also for assessing general functioning, anxiety, depression, and physical symptoms is a limitation, because this may have led to over-reporting or underreporting of symptoms.

Strengths

We used a clinical interview as a gold standard in chapters 1 and 2, which enabled us to provide the reader with estimates of diagnostic accuracy of screening questionnaires (i.e., sensitivity and specificity rates). We estimated confidence intervals for diagnostic accuracy, which allowed us to estimate the degree of precision of the results, and provided information about the generalizability of the results to the population. In chapter 3, we removed respondents having aberrant response patterns and for whom the validity of the assessments was doubtful. By doing so, we improved the quality of the data. This study addressed the validity of the BVAQ in a general population, using patients suffering from SSRD, and the study provided population-based norm data. In chapter 6, we focused on type D personality and its constituent dimensions of negative affectivity and social inhibition, and their interaction on treatment outcome. The use of symptom validity tests in chapter 4 limited the chance of erroneous conclusions regarding neurocognitive functioning. Furthermore, we explored neurocognitive functioning of patients suffering from SSRD amongst a broad range of neurocognitive domains that allowed us to describe neurocognitive functioning across a broader range of domains than previous studies. Investigating the additional effect of comorbid anxiety and depression accounts as a strength since depression and anxiety often co-occur with SSRD and are known to influence neurocognitive functioning.

We explored the use of questionnaires and clinical characteristics in different settings, using different designs. Two validation studies for screening instruments were performed in the occupational health setting. Alexithymia and its assessment by means of the BVAQ was studied in the general population using a cross-sectional data. Alexithymia and Type D personality were studied in a longitudinal design using a clinical cohort of patients suffering from SSRD. We explored neurocognitive characteristics in patients suffering from SSRD using cross sectional data from a clinical cohort study.

Clinical implications and directions for future research

Clinical implications

The results of this dissertation are relevant for the treatment of patients suffering from SSRD. The results warrant a systematic evaluation of clinical characteristics and neurocognitive symptoms in patients suffering from SSRD. Incorporating the assessment of type D personality, and neurocognitive functioning in the diagnostic process, are warranted, because treatment options can be based on these characteristics. This approach allows the clinician to communicate with the patient and improve self-understanding of the patient.

Directions for future research

Future studies should continue to explore the clinical characteristics of patients suffering from SSRD. The role of type D personality and negativity affectivity in SSRD is worthwhile studying, because they were associated with treatment outcome. Future studies should address the effectivity of therapies focusing on patients having Type D personality who suffer from SSRD, because such therapies look promising (Constantinou et al., 2015; Weidner et al., 2016). In case of neurocognitive impairments, CRT has potential to be an effective treatment prior to CBT or in addition to CBT according to a recent case report that described effective treatment of neurocognitive impairment using Time Pressure Management (Fasotti, Kovacs, Eling, & Brouwer, 2000) as CRT in a patient with conversion disorder (De Vroege et al., 2017). Randomized controlled trials are necessary to establish the effectiveness of CRT with current treatment options. Future studies describing neurocognitive functioning in patients suffering from SSRD should also include other patients groups, preferably from different settings, to improve generalizability of the results. Factors such as comorbid disorders (e.g., attention deficit disorder) and medication use should also be taken into account. Furthermore, symptom validity should be assessed systematically (Dandachi-Fitzgerald, 2017), because otherwise erroneous conclusions may be drawn resulting in inappropriate treatment selection (Roor, Dandachi-FitzGerald, & Ponds, 2016).

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Summary

The first part of this PhD dissertation was titled 'Diagnostic assessment and clinical characteristics' and explored the usability of two questionnaires to assess somatoform disorder in the occupational health care setting. We also explored alexithymia and neurocognitive functioning in patients suffering from somatic symptom and related disorders (SSRD). The results in chapter 1 suggested that the Patient Health Questionnaire-15 (PHQ-15) has moderate specificity but lacks sensitivity using the cut point of 10. The results of chapter 2 suggested that the somatization subscale of the 4-Dimensional Symptom Questionnaire (4DSQ) had moderate specificity and sensitivity using the cut point of 9. Nevertheless, we concluded that both questionnaires can be used tentatively for screening but the diagnostic process for assessing clinical characteristics of patients suffering from SSRD requires more that solely the use of these questionnaires.

These results indicated that apart from physical symptomatology, other characteristics might be present in patients suffering from somatoform disorder that are not part of the current questionnaires for somatoform disorder. This might have led to limited sensitivity and specificity of the questionnaires. This assumption led to the initiation of the following studies in this PhD dissertation in which other characteristics of patients suffering from SSRD (SSRD; which replaced the classification somatoform disorder) were investigated.

One of these characteristics was alexithymia. We used the Bermond-Vorst Alexithymia Questionnaire (BVAQ) for assessing alexithymia in patients suffering from SSRD. A disadvantage of using this questionnaire relates to its psychometric qualities: the BVAQ was only validated in small samples of (psychology) students. Therefore, we conducted a validation study of which the results are reported in chapter 3. We administered the BVAQ among the Dutch general population ($N = 974$) using the Longitudinal Internet Studies for the Social Sciences panel, and among patients suffering from SSRD ($N = 234$). First, we validated the BVAQ by exploring the factor structure of the questionnaire that was suggested by the developers. The first-order five factor model and the second-order two-factor model were replicated. The second-order model showed that the analyzing ability loaded on both the affective and cognitive factor. Additional analyses showed that the first-order test scores were more reliable than the second-order test scores. Construct validity was acceptable, which was supported by the finding that scores of patients suffering from SSRD were significantly higher than the scores of the general population. More specifically, scores on the subscales identifying, verbalizing, and on the cognitive dimension were significantly higher in patients suffering from SSRD. We also provided representative norm scores in this study, so that the BVAQ may be used in the clinic.

Patients suffering from SSRD often report cognitive problems during intake. We investigated these problems in chapter 4. We studied neurocognitive functioning in patients suffering from SSRD (N = 201), and the impact of comorbid depression and anxiety on neurocognitive functioning. Based on these results, we concluded that compared to norm scores (Dutch general population), patients suffering from SSRD showed impaired neurocognitive functioning within the domains of sustained attention, divided attention, information processing speed, working memory, verbal memory, visual memory, and phonological verbal fluency. Furthermore, neurocognitive dysfunctioning was associated with comorbid depression but not with comorbid anxiety. Neurocognitive impairments may explain treatment dropout and suggests the need of novel interventions that target neurocognitive dysfunctioning.

In the second part, titled 'Treatment outcome in relation to clinical characteristics', we continued investigating the effect of alexithymia on treatment outcome (chapter 5). We conducted a study to explore the association between alexithymia and treatment outcomes measures for depression, anxiety, physical symptomatology, and general functioning in patients suffering from SSRD (N = 234). Additionally, we investigated the role of chronic medical condition in this relationship. Our results suggested interaction effects of alexithymia and chronic medical condition and an effect of the affective dimension of alexithymia, but the estimated odds ratios were approximately 1.00, suggesting that the effect can be considered small and marginal.

Chapter 6 discusses a study on the association between Type D personality and treatment outcome in patients suffering from SSRD (N = 212). The prevalence of type D personality in patients suffering from SSRD was 63%. Patients with Type D personality experienced higher levels of depression and anxiety at intake. Our results suggested that elevated levels of negative affectivity decreased the probability of remission of physical symptoms, anxiety, and depression. Presence of Type D personality decreased the probability of remission of anxiety and depression. Our results thus suggest that presence of Type D personality and, more specifically, high levels of negative affectivity were negatively associated with treatment outcome in patients suffering from SSRD. Type D personality may be a relevant patient characteristic worthwhile exploring at intake and taking into account during treatment.

Based upon the results, several recommendations can be made. The PHQ-15 and the somatization subscale of the 4DSQ can be used tentatively as screener but the diagnostic process requires information beyond what is provided by these questionnaires. The BVAQ is

a valid measure for assessing alexithymia and we recommend using the five first-order factors of the BVAQ rather than the two dimensions. Patients suffering from SSRD showed substantial neurocognitive impairment within several neurocognitive domains and comorbid depression was associated with worse neurocognitive functioning. Impairment of neurocognitive functioning may serve as a starting point for therapy. Regarding other clinical characteristics in SSRD, alexithymia was unrelated to treatment outcome, which suggests that it is irrelevant to clinical treatment. Type D personality decreased the probability of positive treatment outcome. More specifically, higher levels of negative affectivity were negatively associated with treatment outcome. Therefore, the assessment of Type D personality is recommended during the diagnostic process of patients suffering from SSRD.

Samenvatting

Het eerste gedeelte van dit proefschrift is getiteld 'Diagnostic assessment and clinical characteristics' waarin de bruikbaarheid onderzocht werd van twee vragenlijsten om somatoforme stoornissen in de arbeids-setting in kaart te brengen. In dit hoofdstuk hebben we ook gekeken naar alexithymie en het neurocognitief functioneren van patiënten met somatische-symptoomstoornis (SSS). De resultaten in hoofdstuk 1 laten zien dat de Patient Health Questionnaire-15 (PHQ-15) over redelijke specificiteit beschikt maar de sensitiviteit is ontoereikend wanneer er een afkapwaarde van 10 wordt gebruikt. De resultaten van hoofdstuk 2 suggereren dat de somatisatieschaal van de 4-Dimensional Symptom Questionnaire (4DSQ) over redelijke specificiteit en sensitiviteit beschikt. Wij concluderen dat beide vragenlijsten onder voorbehoud gebruikt kunnen worden voor screening maar dat het in kaart brengen van klinische eigenschappen van patiënten met een SSS meer dan enkel deze twee vragenlijsten dient te behelzen.

Deze resultaten laten ook zien dat los van de fysieke symptomatologie, ook andere eigenschappen aanwezig zijn bij patiënten met een somatoforme stoornis en dat deze niet deel uitmaken van de huidige vragenlijsten voor somatoforme stoornissen. Dit kan verklarend zijn voor de teleurstellende waarden met betrekking tot sensitiviteit en specificiteit van de onderzochte vragenlijsten. Deze assumptie leidde tot het uitvoeren van de volgende studies naar andere eigenschappen van patiënten met SSS (de classificatie die 'somatoforme stoornissen' verving), welke zijn opgenomen in dit proefschrift.

Eén van deze karakteristieken is alexithymie. In dit proefschrift hebben we gebruik gemaakt van de Bermond-Vorst Alexithymia Questionnaire (BVAQ) om alexithymie te meten bij patiënten met SSS. Een nadeel van het gebruik van deze vragenlijst heeft betrekking op de psychometrische kwaliteiten van de vragenlijst: de BVAQ is met name gevalideerd onder kleine samples bestaande uit (psychologie) studenten. Hierom is er eerst een validatie-studie uitgevoerd naar de BVAQ waarvan de resultaten gerapporteerd staan in hoofdstuk 3. We hebben de BVAQ afgenomen in de Nederlandse algemene populatie (N = 974) met behulp van de Longitudinal Internet Studies for the Social Sciences panel en onder patiënten met SSS (N = 234). Allereerst hebben we gekeken naar de factorstructuur van de BVAQ en deze vergeleken met hoe de ontwikkelaars van de BVAQ deze structuur hadden voorgesteld. Het eerste-orde vijf factoren model en het tweede-orde twee factoren model werd gerepliceerd. Het tweede-orde model liet echter zien dat de factor analyseren zowel op de cognitieve als op de affectieve factor laadde. Aanvullende analyses lieten zien dat de eerste-orde test scores betrouwbaarder waren dan de tweede-orde test scores. De constructvaliditeit van de BVAQ was acceptabel, wat werd bevestigd door significant hogere

scores van patiënten met SSS ten opzichte van de scores verkregen bij de Nederlandse algemene populatie. Scores op de subschalen identificeren, verbalizeren en op de cognitieve factor waren significant hoger in patiënten met SSS. We hebben in deze studie ook representatieve normgegevens gerapporteerd zodat de BVAQ in de kliniek gebruikt kan worden.

Patiënten met SSS rapporteren tijdens de intake vaak neurocognitieve klachten. Deze klachten hebben we in hoofdstuk 4 nader onderzocht. We onderzochten neurocognitief functioneren bij patiënten met SSS (N = 201) en keken naar de invloed van comorbide depressie en angst op het neurocognitief functioneren. Gebaseerd op onze bevindingen kunnen we concluderen dat, vergeleken met normgegevens (Nederlandse algemene populatie), patiënten met SSS een slechter neurocognitief functioneren laten zien binnen de domeinen volgehouden aandacht, verdeelde aandacht, informatieverwerkingssnelheid, werkgeheugen, verbaal geheugen, visueel geheugen en fonologische woordvloeiendheid. Neurocognitief functioneren was verder geassocieerd met comorbide depressie maar niet met comorbide angst. Een verminderd neurocognitief functioneren kan het vroegtijdig stoppen van de behandeling verklaren en biedt de mogelijkheid voor een vernieuwende interventie die gericht is op neurocognitief functioneren.

Het tweede gedeelte van dit proefschrift is getiteld ‘Treatment outcome in relation to clinical characteristics’ waarin we gekeken hebben naar het mogelijke effect van alexithymie op de behandeluitkomst (hoofdstuk 5). We hebben een studie uitgevoerd om de associatie tussen alexithymie en behandeluitkomst te onderzoeken waarin we gekeken hebben naar de mate van depressie, angst, lichamelijke symptomatologie en algemeen functioneren bij patiënten met SSS (N = 234). Tevens hebben we gekeken naar de rol van chronische medische aandoening in deze associatie. Onze resultaten suggereerden interactie-effecten van alexithymie en chronische medische aandoening en een effect van de affectieve factor van alexithymie maar de odds ratios lagen rond de 1.00 waardoor het effect van alexithymie klein en marginaal beschouwd mag worden.

In hoofdstuk 6 bespreken we de associatie tussen Type D persoonlijkheid en behandeluitkomst van patiënten met SSS (N = 212). De prevalentie van Type D persoonlijkheid in patiënten met SSS was 63%. Patiënten met een Type D persoonlijkheid hadden hogere levels van depressie en angst tijdens de intake. Onze resultaten suggereerden dat verhoogde levels van negatieve affectiviteit de waarschijnlijkheid van remissie van lichamelijke klachten, angst en depressie verlaagde. Aanwezigheid van Type D persoonlijkheid verlaagde de waarschijnlijkheid op remissie van angst en depressie. Deze

resultaten suggereren dat de aanwezigheid van Type D persoonlijkheid en, specifieker, hogere levels van negatieve affectiviteit negatief geassocieerd zijn met behandeluitkomst in patiënten met SSS. Dit maakt Type D persoonlijkheid een relevant eigenschap voor patiënten met SSS en het is waardevol om Type D tijdens de intake te onderzoeken en er rekening mee te houden gedurende de behandeling.

Gebaseerd op de resultaten van dit proefschrift kunnen enkele aanbevelingen gedaan worden. De PHQ-15 en de somatisatieschaal van de 4DSQ kunnen als screener gebruikt worden maar het diagnostische proces kan niet enkel bestaan uit de informatie die deze vragenlijsten geven. De BVAQ is een valide vragenlijst voor het in kaart brengen van alexithymie en wij adviseren het gebruik van de eerste-orde vijf factoren van de BVAQ in plaats van de tweede-orde twee factoren. Patiënten met SSS lieten forse neurocognitieve problemen zien binnen diverse cognitieve domeinen en verminderd neurocognitief functioneren was geassocieerd met comorbide depressie. Verminderd neurocognitief functioneren kan gebruikt worden binnen de behandeling. Met betrekking tot andere klinische eigenschappen van patiënten met SSS bleek alexithymie niet gerelateerd met behandeluitkomst wat suggereert dat alexithymie irrelevant is tijdens de behandeling. Type D persoonlijkheid verlaagde de waarschijnlijkheid op positieve behandeluitkomst. Met name hogere levels van negatieve affectiviteit waren negatief geassocieerd met behandeluitkomst. Daarom is het bepalen van Type D persoonlijkheid tijdens het diagnostische proces bij patiënten met SSS relevant.

Dankwoord

Een proefschrift zonder dankwoord is een incompleet proefschrift. Daarom ook hier een dankwoord waarin ik mij richt tot iedereen die bijgedragen heeft aan dit proefschrift. Tenminste, dat is het streven. Mocht ik onverhoopt iemand vergeten zijn te noemen, mijn excuses daarvoor.

Allereerst wil ik alle patiënten die ik de afgelopen jaren bij het Topklinisch Centrum voor Lichaam, Geest en Gezondheid (CLGG) heb gezien voor (neuro)psychologisch onderzoek en behandeling van harte bedanken. Zonder hen zou dit proefschrift niet hebben kunnen bestaan. Dank voor hun inzet tijdens de onderzoeken waar collega psychologen en ik hen aan onderwierpen.

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maakte van het commentaar van de reviewers. Terwijl je daarmee bezig was stopte je ineens middenin een zin, wees naar het raam en riep 'kijk, kijk, kijk, een eekhoorn!' Je was net van werkplek veranderd en begon vervolgens te vertellen dat de verhuizing qua flora en fauna een grote vooruitgang was. Na dit zijpad bewandeld te hebben ging je onverstoorbaar weer door met commentaar geven op de comments van de reviewers. Heel erg bedankt voor jouw steun en feedback van de afgelopen jaren!

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De (neuro)psychologische onderzoeken en behandelingen konden niet uitgevoerd worden zonder de steun van het secretariaat van CLGG. De invoering van een psychodiagnostische module in de reguliere zorg van het centrum bracht de nodige 'hobbels' met zich mee, met name plan-technisch. Ik wil dan ook Anita, Tineke en later ook Lisanne ontzettend bedanken voor het inplannen van alle afspraken en voor hun flexibiliteit. Ook wil ik Lisette bedanken voor haar rol als management ondersteuner/AOIC-er, waarin ook zij zorg heeft gedragen voor het opzetten van deze diagnostiekprocedure.

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Op deze plek wil ik ook Irene nog van harte bedanken voor het ontwerpen van de cover. Helemaal top gedaan!

Mijn paranimfen.
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List of publications

This thesis:

de Vroege, L., Hoedeman, R., Sijtsma, K., & van der Feltz-Cornelis, C.M. (2012). Validation of the PHQ-15 for somatoform disorder in the occupational health care setting. *Journal of Occupational Rehabilitation, 22,* 51-58.

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de Vroege, L., Emons, W.H.M., Sijtsma, K., & van der Feltz-Cornelis, C.M. (under review). Psychometric properties of the Bermond-Vorst Alextihymia Questionnaire (BVAQ) in the general population and a clinical population.

de Vroege, L., Emons, W.H.M., Sijtsma, K., & van der Feltz-Cornelis, C.M. (under review). Alexithymia and treatment outcome of patients suffering from Somatic Symptom and Related Disorder. A clinical prospective study.

Other publications:

van Meerkerk-Aanen, P., **de Vroege, L.**, Khasho, D., Foruz, A., van Asseldonk, J.T.H., & van der Feltz-Cornelis, C.M. (2017). La Belle Indifférence revisited: A case report on progressive supranuclear palsy misdiagnosed as conversion disorder. *Neuropsychiatric Disease and Treatment*, *13,* 2057-2067.

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Curriculum Vitae

Lars de Vroege werd geboren op 17 juli 1987 te Delft. In 2006 behaalde hij zijn VWO-diploma aan Het Baarnsch Lyceum in Baarn en ging hij Biomedische Wetenschappen studeren aan de Universiteit van Amsterdam. Na een half jaar stapte hij over op de studie Psychobiologie en studeerde in 2009 af. In dat jaar begon hij te werken als junior wetenschappelijk medewerker bij het Trimbos-instituut onder leiding van prof. dr. Christina van der Feltz-Cornelis. Na een half jaar rondgereisd te hebben door Zuidoost-Azië begon hij aan de researchmaster Cognitive Neuropsychology aan de William James Graduate School (Vrije Universiteit (VU), Amsterdam). In het eerste jaar van deze opleiding heeft het enthousiasme van prof. dr. Erik Scherder hem ertoe gedreven om daarnaast ook de master Klinische Neuropsychologie (VU, Amsterdam) te volgen. Zijn masteropleidingen heeft hij afgesloten middels een klinische stage op het Universitair Medisch Centrum Utrecht, afdeling Neurochirurgie/Neuropsychologie. In 2013 behaalde hij zijn doctoraaldiploma's en sindsdien combineert hij klinisch werk met wetenschappelijk onderzoek. Hij was als neuropsycholoog verbonden aan het Topklinisch Centrum Lichaam, Geest en Gezondheid, GGz Breburg te Tilburg en als science practioner aan de academische werkplaats Geestdrift, Tranzo, Tilburg University. Onder supervisie van promotores prof. dr. Christina van der Feltz-Cornelis en prof. dr. Klaas Sijtsma en copromotor dr. Wilco Emons heeft hij promotieonderzoek verricht waarvan de resultaten in dit proefschrift staan. In januari 2018 is hij gestart met de opleiding tot gezondheidszorgpsycholoog bij GGz Breburg.