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Effects of Mirror Therapy in Patients with Chronic Somatoform Pain Disorders on Psychometric Parameters and Heart Rate Variability

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Table of Contents

List of figures

List of tables

Acronyms

ANS ..... Autonomous nervous systems

BMI ..... Body mass index

CAN ..... Central autonomic network

CNS ..... Central nervous system

COMT ..... Catechol-O-Methyltransferase

CRPS ..... Complex regional pain syndrome

CTQ ..... Childhood Trauma Questionnaire

DASS ..... Depression, Anxiety and Stress Scale

DSF ..... German Pain Questionnaire

DSM ..... Diagnostic and Statistical Manual of Mental Disorders

HF ..... High-frequency

HRV ..... Heart rate variability

IASP ..... International Association for the Study of Pain

IBI ..... Inter-beat-interval

ICD ..... International Classification of Diseases

IPQ-R ..... Revised Illness Perception Questionnaire

IQOLA ..... International Quality of Life Assessment Project

IQR ..... Interquartile range

LF ..... Low-frequency

MFHW ..... Marburg Questionnaire on Habitual Health Findings

NRS ..... Numerical rating scale

PHQ-D ..... Patient Health Questionnaire - German Edition

PNS ..... Parasympathetic nervous system

PRIME MD ..... Primary Care Evaluation of Mental Disorders

PSQ-20 ..... Perceived Stress Questionnaire

RMSSD ..... Root mean square of successive differences

RSA ..... Respiratory sinus arrhythmia

SDNN ..... Standard deviation of the IBIs of normal heartbeats

SF-36 ..... 36-Item Short-Form Health Survey

SF-MPQ ..... short form McGill Pain Questionnaire

SNS ..... Sympathetic nervous system

ULF ..... Ultra-low frequency

VAS ..... Visual analogue scale

1 Introduction

1.1 Chronic pain

“The pain of the mind is worse than the pain of the body.”
Publilius Syrus, Latin writer 85 – 43 BC

“Pain makes us feel alive. Without it, we might as well be dead.”
Friedrich Nietzsche, German philosopher 1844 - 1900

“Pain is inevitable, suffering is optional.”
Haruki Murakami, Japanese Writer 1949 - today

The list of quotes about pain and suffering could go on endlessly. No matter the decade, no matter the profession – philosophers, writers, artists – humans always have dealt with pain and tried to express themselves in this regard in text, music and art. Pain seems to be essential to the human existence. However, the question of how much pain is too much or when does pain exceed a “normal” amount is not easy to answer. Medicine is the scientific discipline that attempts to define the boundaries between normal and pathological human states, including the aspects of suffering and pain. So first, one must define: what is pain. According to the International Association for the Study of Pain (IASP) the definition of pain was until recently “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or describe in terms of such damage” (Raja et al., 2020). In 2020 the definition was updated, and the now valid definition of pain is the following:

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

This updated definition was also accompanied by changed notes regarding different aspects of pain and its definition. According to the authors, pain is a highly individual and personal experience where various factors, i.e. biological, psychological and social, play a crucial role. They also stress that pain and nociception, i.e. the underlying physiological processes of the sensory nervous system, cannot be equated, and that pain is more than the pure activation of these sensory neurons. Additionally, they also state, that the concept of pain is learned over the lifetime of an individual and that patients should be respected when reporting of pain experiences. Lastly, the authors point out, that pain normally has an adaptive functional role but often still leads to impairment of social and psychological wellbeing (Raja et al., 2020).

In general, acute pain stems from harmful or noxious stimuli that are recognized by nociceptors in the respective tissue. Dependent on stimulus (e.g. mechanical or thermal), different nociceptors are involved which then forward the signal via nervous fibers (e.g. myelinated Aδ fibers and unmyelinated C-fibers resulting in “sharp” and “dull” pain respectively) to the dorsal horns in the spinal cord. From there ascending pathways project to various cortical and subcortical structures, including but not limited to the somatosensory cortex, the periaqueductal gray, the amygdala and thalamus. In these areas, the nociceptive information is integrated and ultimately gives rise to the sensation of pain (Rosenbaum et al., 2022; Yam et al., 2018, see Chapter 1.3.2 HRV and Pain). Acute pain and the organism’s reaction to it generally serves a purpose that is avoiding actual or potential tissue damage and injury. When looking at chronic pain, this shift from pain with its adaptive and useful role to a more maladaptive and burdening role is essential. But when does this useful and adaptive aspect of pain become pathological? When pain persists for more than three months, it is per definition chronic pain (Nicholas et al., 2019). Several alterations in the peripheral and central nervous system (CNS) occur concomitantly. Sensitization to (noxious) stimuli can occur on each level of the nervous system. Through repeated exposure to noxious stimuli the behavior of nociceptors can be altered in a way that they become more sensitive to these stimuli which leads to

decreased threshold and increased activity, a process called peripheral sensitization. A similar process can also occur in the CNS and is then called central sensitization. Here, repeated exposure to these stimuli leads to increased excitability of neurons in the spinal cord also resulting in elevated sensitivity to noxious or even non-noxious stimuli (Grace et al., 2021; Yam et al., 2018). Various other mechanisms may also play a crucial role in the facilitation of sensitization to painful stimuli. Descending inhibitory pathways that normally modulate and attenuate pain sensations may be diminished which then promotes the amplification of pain (Kwon et al., 2014). Overall, these central alterations are then reflected in alterations of brain morphology and connectivity. For example, regions in the brain responsible for inhibiting or augmenting pain are found to be having decreased activity and increased connectivity, respectively (Napadow et al., 2010; Seminowicz & Davis, 2007).

Chronic pain places a significant burden on individuals, the health care system, and society as a whole, with prevalence of chronic pain reaching up to 40-50 percent in the general population (Dahlhamer et al., 2018; Fayaz et al., 2016). Major efforts were undergone in the scientific community to further elucidate the mechanism behind chronic pain as well as the classification of pain types and disorders (Nicholas et al., 2019; The Lancet, 2021). Until recently, chronic pain was divided into nociceptive pain and neuropathic pain. Nociceptive pain hereby describes the most common form involving the pathways and physiology as described in this paragraph. Neuropathic pain on the other hand results from lesions or dysfunction of the somatosensory nervous system, e.g. through nerve (root) compression, inflammatory, metabolic, vascular or infectious processes (e.g. Cohen et al., 2021; Kosek et al., 2016). Common conditions of neuropathic pain for example are diabetic neuropathy and radiculopathies (Cohen & Mao, 2014). This dichotomy of chronic pain has just recently been extended to a third category of nociplastic pain with the following definition: “Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” (Fitzcharles et al., 2021; Kosek et al., 2016). The term was introduced as an

overarching terminology for all chronic pain conditions which do not fit into the established categories of nociceptive or neuropathic pain. All these conditions, however, may share underlying pathophysiological mechanisms and include accompanying non-pain and more psychological symptoms such as fatigue or depression. This new category of chronic pain is also reflected in the changes of the upcoming International Classification of Diseases (ICD) 11th Revision which now included several chronic primary pain conditions, such as chronic widespread pain (fibromyalgia), complex regional pain syndrome (CRPS), chronic primary visceral pain (e.g. irritable bowel syndrome) and chronic primary musculoskeletal pain (e.g. chronic primary low back pain). The diagnoses and therapy of these nociplastic pain disorders possess several challenges as symptoms are heavily subjective, hard to objectify and biomarkers by default absent. There is, however, a category of disorders where pain also plays a crucial role, but the non-pain symptoms may even be more essential and the somatic basis of complaints be debatable or at least secondary. Whether these disorders are distinct from nociplastic disorders or may actually be the same entity is an ongoing debate and cannot be answered conclusively at present (Cohen et al., 2022; Hausteiner-Wiehle & Henningsen, 2022)

1.2 Somatoform pain disorders

1.2.1 Diagnostic criteria

In general, somatoform disorders subsume a class of mental disorders whose main features are bodily or physical symptoms. These appear to be suggestive of a somatic disorder but lack sufficient evidence of a somatic involvement or organic pathology. There may be the clinical impression that psychological factors and psychosocial stressors play an important role in symptom formation (Kapfhammer, 2001). In ICD-10-GM (Dilling et al., 2011), chronic somatoform pain disorders are generally found in chapter V of mental and behavioral disorders, specifically in block F40-48, where neurotic, stress-related and somatoform disorders are coded. Somatoform disorders are then listed in the

subsection of F45.- where the persistent pain disorder (F45.4-) is found. While the English version of the ICD-10 offers only one disorder in this subsection, namely persistent somatoform pain disorder (F45.4), the German revision of the ICD-10 allows for the diagnosis of two disorders: persistent somatoform pain disorder (F45.40) and chronic pain disorder with somatic and psychological factors (F45.41). Diagnostic criteria in general for somatoform disorders (excluding F45.41) are: the repeated presentation of physical symptoms, persistent demands for medical examinations despite repeated negative results and medical assurances that the complaints are not physically justifiable, a temporal correlation to stressful life events (or difficulties and conflicts), frequent attention seeking behavior and that physical findings that may be present do not explain the extent of the complaints. For the diagnosis of F45.40, the following has to also be present: persistent, severe and distressing pain that cannot be explained fully by a physiological process or disorder; the pain occurs in association with emotional or psychosocial problems sufficient to allow the conclusion that they are the main causative influence; an increase in medical or personal support and attention. Exclusion criteria for this disorder are a psychogenic origin of pain during a depressive disorder or schizophrenia.

For the diagnosis of F45.41 the following diagnostic criteria apply: pain in one or more anatomical regions for a duration of more than six months with the origin of pain being a physiological process or physical disorder; psychological factors play an important role (regarding severity, exacerbation or maintenance of pain) but are not the causative role of pain; pain itself causes suffering and impairment in social, occupational or other areas of functioning in a clinically significant way. Here, exclusion criteria are other pain disorders associated with affective, anxiety, somatization or psychotic disorders. These two disorders therefore share some major overlap regarding their diagnostic criteria, especially concerning the importance of psychological factors in the maintenance of pain. The biggest difference between these disorders is probably that the symptoms cannot be explained by physical processes (F45.40) and that the origin of pain can indeed be a physical disorder (F45.41).

However, these diagnostic criteria are subject to constant change. In the upcoming ICD-11 these categories are undergoing major revisions and the new diagnosis of bodily distress disorder will subsume most of the somatoform disorder diagnoses of the ICD-10 (Gureje & Reed, 2016). The current classification has been criticized due to insufficient diagnostic criteria and its predictive validity (Löwe et al., 2008). As can be seen in the differences in the diagnoses of F45.40 and F45.41 respectively, one major criterion is the explicability of symptoms due to physiological processes, reflecting the ongoing debate in the psychosomatic research field between medically explainable versus unexplainable symptoms (Henningsen, Zipfel, et al., 2018). Due to the wish for more positive diagnostic criteria of somatoform disorders (Voigt et al., 2010) a restructuring of the respective classifications ensued (Rief & Isaac, 2014). The resulting new diagnosis of bodily distress disorder there drops the necessity of symptoms being “medically unexplained” and tries to cover not only somatoform disorders but functional somatic symptoms as well (Gureje & Reed, 2016; Henningsen, Zipfel, et al., 2018). Regarding functional somatic symptoms, different medical specialties have coined different diagnostic labels, e.g. irritable bowel syndrome in gastroenterology, non-cardiac chest pain in cardiology and myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia in neurology/infectiology and rheumatology, respectively (Petersen et al., 2020). While these disorders share some diagnostic and symptomatic overlap, which is especially the case for fibromyalgia and somatoform pain disorders (Eich et al., 2012, 2017), these disorders cannot be equated. However, this new diagnosis of bodily distress disorder will cover most of the somatoform disorders, including somatoform pain disorder and functional somatic syndromes. This overarching diagnosis has been shown to reliably capture the included disorders on a diagnostical level (Fink & Schröder, 2010). This concept of bodily distress and its diagnosis, which places its emphasis on the symptomatic burden, has recently been put to test and could be confirmed in a sample of the general population, also resulting in four subclusters which reflect the included “old” diagnoses, e.g. gastrointestinal or musculoskeletal focus of symptoms for irritable bowel syndrome and somatoform pain disorder, respectively (Petersen et al., 2020).

1.2.2 Epidemiological aspects

The prevalence of somatoform pain complaints is relatively high in the general population with back pain (30 %) being mentioned most often (Hessel et al., 2005). The prevalence of somatoform disorders varies relatively widely depending on which population is assessed by which method (Lahmann et al., 2010). Studies have shown that prevalences for somatoform disorders in a primary care setting are as high as 30 % (Mergl et al., 2007), with point prevalences and lifetime prevalences of chronic somatoform pain disorders being at 8.1% and 9.2 %, respectively (Haller et al., 2015). Meyer et al. (2000) reported lifetime prevalences of somatoform disorders in the general population of Germany of 12.9 %. On a wider scale, Wittchen et al. (2011) assessed prevalences of mental disorders in Europe and reported a prevalence of 6.3 % for somatoform disorders, representing the third most common illness, after anxiety disorders (14 %) and major depression (6.9%). Often, somatoform disorders are accompanied by further mental disorders, most commonly anxiety-related disorders and depressive disorders. In the study of Hanel et al. (2009) comorbidities of mental disorders were measured in a primary healthcare setting: of all patients with a somatoform disorder, 16 % had an additional diagnosis of depressive disorders, 19 % with a comorbidity of anxiety disorders and 12 % had both depressive and anxiety disorders as comorbidities. Women seem to be slightly more affected by somatoform disorders than men and some findings indicate, that the prevalences decline in the population of patients over 65 years (Dehoust et al., 2017; Hilderink et al., 2013; Meyer et al., 2000).

1.2.3 Etiology

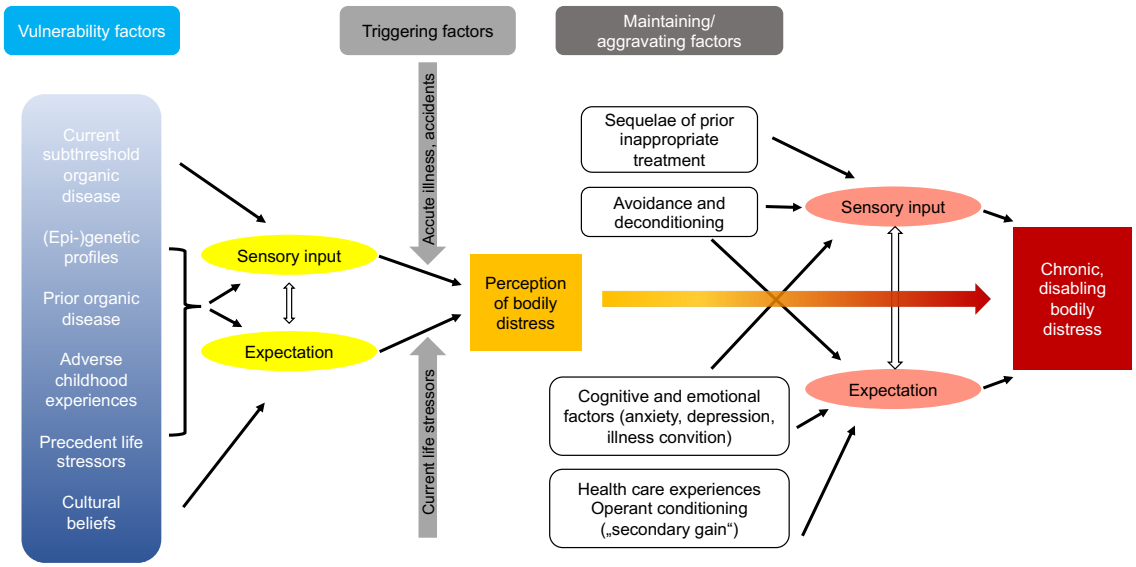
According to Noll-Hussong & Gündel (2012) and the S3-Guidelines for nonspecific, functional and somatoform bodily complaints (AWMF, 2012) “there are currently a number of conclusive etiopathogenetic models [...], none of which can be considered proven. All these models assume complex interactions of various psychosocial, biological, iatrogenic/medical systemic and sociocultural

factors (multifactorial genesis), which play a role in the disposition, triggering and chronification of non-specific, functional and somatoform bodily complaints. The directionality and specificity of these risk factors and their delimitation as etiological and prognostic factors have not been conclusively clarified." Similarly, the updated S3-Guideline for functional bodily complaints (which replaced the above-mentioned Guidelines of 2012 and therefore reflects the changes regarding terminology and classification of the ICD-11) states that the etiology of functional bodily complaints or bodily distress may be ultimately unresolved. In general, a multifactorial pathogenesis is assumed, where biological (including genetic and epigenetic), psychological and sociological factors are involved (AWMF, 2018; Papadimitriou, 2017). Such an etiological model (Henningsen, Zipfel, et al., 2018) includes and differentiates the following factors:

- Vulnerability factors: these factors precede the manifestation of symptoms and complaints and increase the probability of their occurrence, i.e. increase vulnerability but by no means can predict them.
- Triggering factors: they immediately precede the manifestation of the symptoms and complaints in time and are probably also causally associated with them but without being a necessary condition.
- Maintaining/aggravating factors: these prevent the symptoms and complaints from disappearing again or being ignored or overcome, which thus often cause their persistence, their chronification and, more importantly, their disease value in the first place.

However, these factors may not always be clearly separable from one another, e.g. a predisposing factor may also be a perpetuating factor and vice versa. A schematic depiction of the model of Henningsen, Zipfel, et al. (2018) can be seen in Figure 1.

Figure 1. Schematic depiction of the model of etiology of bodily distress



This model is adapted from Henningsen, Zipfel, et al. (2018)

Henningsen, Zipfel, et al. (2018) state that previous etiological models of these disorders, which mostly focus on bottom-up processes (like peripheral nociception being then amplified by other factors, e.g. central sensitization or psychological factors like anxiety) are not able to explain all phenomena that are present in these patients, like disturbed interoceptive capabilities and its effect on the disorder and being a therapeutic target as well. In their current model of bodily distress, the CNS is viewed as a predictive coding machine, which continuously predicts and constructs its environment including bodily and interoceptive states. Bodily distress disorders are here seen as a malfunctioning of perception, especially interoception. Bottom-up processes, like peripheral nociceptive signals, also play a role, but mainly when there is a mismatch between prediction and actual sensation. This mismatch is then seen as the basis of these disorders and leads in a second step to the symptoms of organic illnesses (Henningsen, Gündel, et al., 2018; Van den Bergh et al., 2017). As can be seen in Figure 1, various factors may then influence the sensory input (resulting in altered bottom-up processes) or expectation (e.g. malfunctioning top-down predictions of bodily perception). Henningsen, Zipfel, et al. (2018) also emphasize that in this model, maintaining and aggravating factors may be more important than vulnerability or

triggering factors (e.g. life stressors, serious illness, viral infections) because the disorder is chronic in nature.

But what are these specific factors, that play a crucial role in the development and maintenance of symptoms of somatoform pain or bodily distress in general? Genetic and epigenetic factors for example may represent a substantial vulnerability factor for the development of these disorders (Kato et al., 2010; McEwen, 2017). Candidate genes (Holliday & McBeth, 2011) being hereby involved are for example: the Catechol-O-Methyltransferase (COMT), that is involved in the metabolism of catecholamines, like dopamine and epinephrine; the ß2 Adrenergic Receptor (ADRB2), which is involved in norepinephric functioning; the μ-Opioid Receptor (OPRM1), which modulates exo- and endogenous opiate responsiveness; genes that modulate pathways in the serotonergic system (e.g. HTR2A and SLC6A4) and the hypothalamic-pituitary-adrenal axis that is crucial for the adaptability of the body to stress and its response to it (e.g. SERPINA6, POMC or MC2R).

Relevant psychosocial factors are adverse childhood experiences, personality factors and attachment patterns of patients. Research shows that the experience of traumatic events, e.g. during childhood, are markedly associated with an increased risk of the development of functional somatic syndromes. Traumatic events lead to a roughly threefold increase in risk for chronic pain disorders (Afari et al., 2014). These traumatic experiences in affected patients are also reflected in measurable alterations in functional neuroimaging studies, where, when comparing abused to non-abused patients, increased activation in the left lateral and medial superior frontal gyrus as well as reduced activation in the left hippocampus was found (Noll-Hussong et al., 2010). Besides traumatic experiences, deviant attachment patterns may also play an important role regarding the vulnerability for somatoform complaints and bodily distress. Insecure attachment is generally associated with an increased risk regarding (psychosomatic) disease, supposedly by elevated susceptibility to stress, alterations in affect regulation and help-seeking behavior (Maunder & Hunter, 2001). More specifically, an insecure attachment style seems to be positively correlated with the occurrence of somatoform pain disorders and is associated

with increased somatization in children and adults (Maunder et al., 2017; Nacak et al., 2017). Various other psychosocial and cultural factors, e.g. female sex, unemployment, low socio-economic status, low intelligence, and culturally learned symptom attribution, are also significant contributing factors (Claussen et al., 1993; Kingma et al., 2011; Kirmayer & Sartorius, 2007; Kroenke & Spitzer, 1998).

1.2.4 Treatment options

There are several treatment options available for patients with somatoform pain disorders or bodily distress disorders respectively. Based on the S3-Guideline for functional bodily complaints (AWMF, 2018, see above) Roenneberg et al. (2019) recommend a stepped-care approach based on the severity of the disorder: Starting with initial primary care, which focuses on restraint, careful questioning and examination and empathy and calming in the interaction with the patient. This is then followed by extended primary care that includes well-considered diagnostics, clarification of the disease value and diagnostic assignment as well as the development and establishment of an explanatory model for coping with the disorder, managing expectations and working on symptom reduction and improvement of self-care and self-efficacy. The final step in this approach is a multimodal treatment which can include psychotherapy, pharmacotherapy, inpatient or day-care treatment, rehabilitation as well as evaluation and prevention. Regarding specific treatments, psychotherapy, especially cognitive behavioral therapy but psychodynamic therapies as well, have been found to be effective (Henningsen, Zipfel, et al., 2018; Koelen et al., 2014; van Dessel et al., 2014). Additionally, body- or mindfulness-based interventions which are incorporated in a multimodal treatment are also included in the recent guidelines (Roenneberg et al., 2019). Depending on the specific disorder, pharmacotherapy is also a viable option, which includes treatment via nonsteroidal anti-inflammatory drugs (e.g. for chronic widespread pain) or tricyclic antidepressants such as amitriptylin (for an overview see Roenneberg et al., 2019). The S1-

Guidelines for chronic pain hereby emphasize to not use opioids when treating functional pain (AWMF, 2013).

1.3 Heart rate variability

Heart rate and the interval between successive heartbeats are subject to various influences and result in corresponding variability. This heart rate variability (HRV) does not only concern the interval between heartbeats but also the fluctuation of heart rates itself (Task Force, 1996). These fluctuations stem from various different physiological systems and their complex interactions. Here the autonomous nervous systems (ANS) with its sympathetic (SNS) and parasympathetic (PNS) branch play a crucial role (Shaffer et al., 2014). Therefore, the measurement of HRV allows for a non-invasive evaluation of the cardiovascular system, autonomous functioning and the individuals' capability of adapting and responding to internal and external demands (Berntson et al., 1997; Heiss et al., 2021). Various parameters can be derived from HRV measurements that correspond to different physiological mechanisms and processes.

1.3.1 HRV metrics

Generally, these parameters or metrics can be divided into time-domain and frequency-domain indices (Shaffer & Ginsberg, 2017). One of the most commonly used time-domain metrics which is primarily used to investigate vagally-mediated changes in HRV is the root mean square of successive differences (RMSSD) of successive inter-beat-intervals (IBIs). RMSSD is conventionally recorded over five minutes and reflects the beat-to-beat variability of the heart rate, which is mainly mediated by the vagus nerve. Another metric is the standard deviation of IBIs of "normal" heartbeats (SDNN), i.e. heartbeats where false or abnormal heartbeats are removed. The SDNN is often referred to as the "gold standard" of assessing cardiovascular risk, predicting both morbidity and mortality (e. g. Shaffer & Ginsberg, 2017).

Recording of HRV also yields several frequency-domain indices which can be linked to different physiological phenomena. Through mathematical methods, e. g. fast Fourier transformation or autoregressive modeling, it is possible to decompose the assessed HRV into different frequency bands. For five-minute recordings of HRV, the ultra-low frequency band (ULF, ≤ 0.003 Hz) and the very-low frequency band (VLF, 0.0033 – 0.04 Hz) can be neglected as the duration of the recording does not allow for a sensible collection of these slow frequency rhythms. The two most important frequency-domain metrics of short-term HRV are the low-frequency (LF, 0.04 – 0.15 Hz) and high-frequency band (HF, 0.15 – 0.40 Hz). The LF band was first thought to reflect sympathetic power, but, as studies have shown, is probably mainly influenced by baroreceptor activity and is arguably primarily produced by the PNS or baroreflex activity alone (Heathers, 2014; Reyes del Paso et al., 2013; Shaffer & Ginsberg, 2017). The baroreflex describes the adaptability of the cardiovascular system to changes in blood pressure, which are captured by baroreceptors (located in the heart, carotid sinuses or vena cavae) and then result in an appropriate counterregulation via the ANS (Shaffer et al., 2014). During slow breathing, the LF band may be heavily influenced by these respiration-related vagally-mediated efferences (T. E. Brown et al., 1993; Shaffer & Ginsberg, 2017).

The HF band is thought to mainly reflect PNS activity. Due to the fact that it also corresponds to respiratory activity, i.e. the respiratory sinus arrhythmia (RSA), it is also called the “respiratory band” (Grossman & Taylor, 2007). The RSA describes the phenomenon that during inspiration and expiration heart rate increases and decreases respectively, which is mediated by vagal cardiac outflow (Eckberg, 1983). The LF and HF band can be used to form the corresponding quotient, the LF/HF ratio. When the LF band was thought to reflect SNS activity, this quotient was interpreted as an indicator of autonomic balance, i.e. high values indicating increased SNS and/or decreased PNS activity and low values indicating increased PNS activity and/or decreased SNS activity. However, as described, as the LF band cannot be used as a clear indicator of SNS activity, the interpretation of the LF/HF ratio also changes and should therefore be interpreted with caution (Shaffer et al., 2014).

1.3.2 HRV and pain

Initially, HRV was primarily a predictor of (cardiac) mortality (e.g. Jarczok et al., 2022; Task Force, 1996) but as research progressed, it became apparent that the different parameters were also related to other physiological and psychological phenomena beyond the vagal and parasympathetic components (e.g. Berntson et al., 1997; Shaffer et al., 2014). Several studies in the last years could clearly demonstrate a relationship between pain and HRV, i.e. changes or abnormalities in HRV due to (experimentally) induced pain and altered HRV in various pain disorders (Forte et al., 2022; Ying-Chih et al., 2020). As HRV does, among other things, reflect autonomic functioning and adapting to pain also requires the activation and regulation of autonomic processes, the relationship between HRV and pain is therefore logical. Thus, the link between (adapting to) pain and autonomic control does not only make sense on a theoretical but also a neuronal and structural level (Benarroch, 2006; Forte et al., 2022). Researchers have proposed a central autonomic network (CAN) that is involved in integrating pain sensation and the modulation of an adaptive response via the ANS. Structurally, this network consists a.o. of the insular and anterior cingulate cortex, several areas of the hypothalamus, the central nucleus of the amygdala and the periaqueductal gray. The CAN receives nociceptive and visceral input and then generates an autonomic response via the SNS and PNS. The CAN is not only involved in circuits of pain modulation but is theoretically part of a general neurovisceral integration model describing a regulatory system through which the organism responds and adapts to a variety of stimuli and stressors (Benarroch, 2006; Thayer & Lane, 2000).

Looking specifically at the links between HRV and pain, the meta-analysis of Tracy et al. (2016) suggests that patients with chronic pain conditions show decreased PNS activity as indicated by specific reduction of HRV in the HF band. Bandeira et al. (2021) were able to demonstrate that patients with chronic low back pain show, when compared to healthy controls, increased SNS activity as indicated by an increase in the LF band. The meta-analysis of Ying-Chih et al. (2020) looked at a wide variety of somatic symptom disorders and functional

somatic syndromes and their association with HRV abnormalities. Overall, they found decreased HRV in a variety of metrics, namely SDNN, HF and RMSSD. These findings bolster the results from the meta-analysis of Koenig et al. (2016) who also report reduced RMSSD and HF HRV in patients with chronic pain conditions. Overall, this research suggests that PNS or vagal activity may be reduced in patients with a variety of chronic pain disorders, a finding also presents in psychosomatic inpatient samples (Zimmermann-Viehoff et al., 2016). Similarly, alterations of HRV could also be found in experimentally-induced pain. In their systematic review, Forte et al. (2022) conclude that HRV allows for a measurement of induced pain and the respective autonomous reaction, i.e. generally increased SNS and decreased PNS activity. Based on the included studies, they also infer that elevated parasympathetic HRV allows for a better handling of painful stimuli or pain conditions.

1.4 Mirror therapy

Mirror therapy is a non-pharmacological movement-oriented intervention, initially utilized for the treatment of phantom limb pain (Ramachandran et al., 1995). The therapy involves a mirror, which is mostly placed in the midsagittal plane to allow for a mirroring of the lateral upper and lower extremities. Target of the treatment is originally pain sensations that occur in amputated limbs, i.e. phantom limb pain. However, research then applied the concept of mirror therapy to still present but painful limbs. In these cases, during therapy these affected limbs are then moved out of the field of view (e.g. hiding in a box or moving behind the body) of the participant. The non-affected limb is then placed in front of the mirror so that it appears in the mirror as being in place of the affected limb. Various exercises are then performed with the non-affected limb while watching the mirror-image, creating the illusion as if the affected limb is performing the movement. Mirror therapy can be used on its own or as part of a graded motor imagery regimen, where mirror therapy is the last stage of intervention protocol which includes among other things motor imagery, i.e. only imagining the execution of limb movements (Bowering et al., 2013). The initial findings of Ramachandran et al.

(1995) could not only be replicated in patients with phantom limb pain (Chan et al., 2007; Foell et al., 2014) but also be extended to various other conditions characterized by chronic pain: Patients suffering from hemiparesis after stroke (Altschuler et al., 1999; Michielsen et al., 2011; Thieme et al., 2018), patients suffering from CRPS1 (Moseley, 2006; Pervane Vural et al., 2016) and shoulder pain (Louw et al., 2017).

The exact therapeutic mechanism of action could still not be completely elucidated. However, several components which probably play a crucial role have been identified. For example, mirror therapy may (partially) undo the maladaptive cortical reorganization which is found in patients with chronic pain (e.g. after stroke or lesion) by integration of perception and action, i.e. being able to observe (in the mirror) that the movement of limbs is possible without the sensation of pain or impairment. Visual input hereby may “override” the tactile input of the impaired limb (Moseley et al., 2008). Mirror therapy may also increase cortical excitability, possibly involving the system of mirror neurons, as is the case by observing motor movements for example in graded motor imagery (Funase et al., 2007), which then may lead to improvements in functional rehabilitation. Crucially, performance of mirror therapy can also lead to the facilitation and recruitment of motor pathways of the impaired limb. Similarly, somatosensory areas are also bilaterally involved on a neurophysiological level, i.e. not only in the hemisphere of the affected but also the non-affected limb (Deconinck et al., 2015). Regarding pain, Wittkopf & Johnson (2017) also summarize, that mirror therapy may be effective through the restoration of congruence of faulty sensory and motor output leading to an improvement in pain symptoms or motor functioning. Additionally, mirror therapy possibly provides a way of modifying or normalizing a distorted body scheme and “unlearning the learned pain” (Moseley et al., 2012; Ramachandran & Altschuler, 2009). Moseley et al. (2008) propose that the visual and tactile aspect of mirror therapy, i.e. observing the mirror limb moving and touching objects pain-free, may also facilitate neuronal descending inhibitory mechanisms, resulting in relief and reduction of pain. However, they also emphasize that more robust clinical and experimental studies are needed overall

to further demonstrate the evidence for the efficacy of mirror therapy and enlighten its therapeutic mechanism of action.

1.5 Research questions

Overall, the following can be stated: patients suffering from chronic somatoform pain disorders carry a high burden of disease that leads to severe impairments in their daily lives. While there are a variety of treatment options available that are routinely applied in the form of a multimodal treatment approach, there is still room for improvement of existing therapies or even development of new therapeutic approaches. In the case of mirror therapy, which has been adapted from its initial target of phantom limb pain to multiple new conditions, such as CRPS, it seems plausible, to try to expand the application of mirror therapy once more.

Thus, the following study tries to close this gap and is investigating the application of mirror therapy to patients with chronic somatoform pain disorders. As this study is the first of its kind, its main goal was to produce preliminary evidence for the potential efficacy of mirror therapy in this patient group. While chronic somatoform pain disorders are clearly distinct from the disorders previously investigated in combination with mirror therapy, e.g. stroke or CRPS patients, parts of the underlying rationale regarding its therapeutic mechanism of action could still apply: For example, while patients with chronic somatoform pain disorders are not suffering from phantom limb pain, their pain conditions could also improve and benefit from the restoration of sensory input and motor output congruence and modifying behavioral and learned dysfunction regarding utilization of impaired and painful limbs. Mirror therapy may also allow for a disruption of dysfunctional expectations of body movement and activity or the partial reversal of phenomena like central sensitization, through the facilitation of descending inhibitory neuronal pathways.

Additionally, the goal of this study is not only to evaluate the efficacy and feasibility of mirror therapy in patients with chronic somatoform pain disorders regarding the reduction of pain. This study is also evaluating the possibly altered

autonomous functioning. Via the measurement of HRV, this study tries to measure and evaluate these abnormalities in this patient sample and wants to investigate if and to what extent these HRV deviations are malleable through mirror therapy.

2 Materials and Methods

2.1 Ethical statement

The study (no. 500/2018B02) was conducted with all practices being in accordance with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of the Eberhard Karls University Tübingen. The participants of the study all gave their written and informed consent and took part voluntarily, receiving no monetary compensation for their participation in the study.

2.2 Subjects

Overall, fifteen patients could be recruited for partaking in the study. All patients were diagnosed with either persistent somatoform pain disorder (F45.40, ICD-10-GM) or chronic pain disorder with somatic and psychological factors (F45.41, ICD-10-GM) and continued their individual multi-modal treatment throughout the study. The patients were recruited from 2019 to 2021 through the Outpatient Clinic for Psychosomatic Medicine at the University Hospital Tübingen, Department of Psychosomatic Medicine and Psychotherapy. Before enrolling in the study, patients were checked for exclusion and inclusion criteria, which are listed in Table 1. Patients taking the mentioned medication were excluded due to the effect of the medication on the functioning of the autonomous nervous system. Analysis of the recorded HRV data would have not been sufficient in the case of respective medication intake.

Table 1. Inclusion and exclusion criteria for partaking in the study.

Inclusion criteria
Age between 18 and 65

Persistent somatoform pain disorder or chronic pain disorder with somatic and psychological factors (ICD-10-GM F45.40, F45.41)
Laterality of pain (Pain dominance in left or right side of body or higher pain intensity on one side of the body)

Exclusion criteria	
Recent oncological disease	Intake of amitryptilin > 50 mg
Recent psychotic disease	Intake of α-blockers
Pregnancy/breastfeeding period	Intake of β-blockers
Substance abuse	Participation in drug trials <3 months prior

2.3 Procedure

All measurements took place at the autonomous function laboratory of the Department of Psychosomatic Medicine and Psychotherapy of the University Hospital of Tübingen. Baseline characteristics, psychometric parameters and HRV were assessed before mirror therapy was performed (T0). In this measurement session, patients were first instructed and informed about the study and its design and then gave their informed consent. After that, patients answered the questionnaires. This was then followed by the measurement of HRV. Subsequently, pain thresholds were also measured, but these were used as part of a separate investigation and analysis.

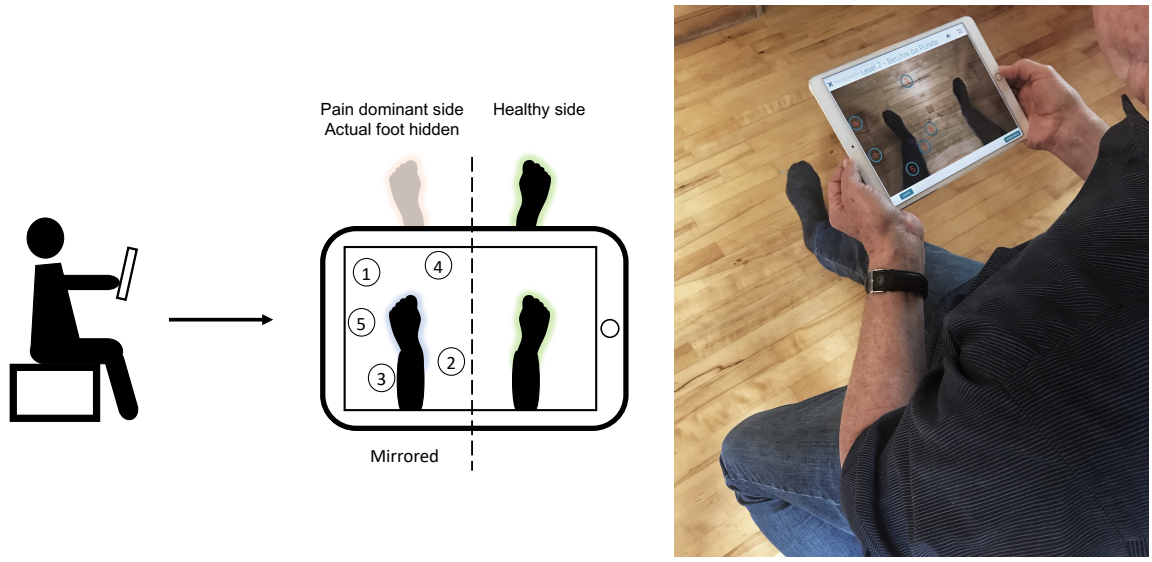
After T0, patients then received four weeks of guided mirror therapy incorporating a tablet. Mirror therapy was performed at home for a duration of approximately 15 minutes per day. After completing the four-week therapy program, patients were assessed a second time (T1). In this second measurement session, patients also answered the questionnaires first and then HRV measurement followed. The psychometric parameters, e.g. psychological and social functioning, pain and symptom severity, were assessed digitally via the tablet.

2.4 Mirror therapy

On T0 the concept of mirror therapy and its implementation in the study were introduced to the subjects and then explained by qualified study staff. The utilized mirror therapy program consisted of separate exercises for the upper and lower limb of the body side, where pain was dominant or pain intensity was higher. For all exercises, the tablet and the included application Routine Reha (Routine Health GmbH, Germany) were used as a guidance and instructional tool, where subjects had access to videos of the respective exercises. This application has been developed for the teletreatment and monitoring of patients with phantom limb pain (Rothgangel et al., 2018). In this study, only the functionality of mirror therapy has been utilized. Exercises were mostly comprised of fine-motor tasks where the respective limb had to be moved deliberately and precisely, e.g. limbs had to be rotated carefully (counter)clockwise, number points or certain figures had to be traced in the correct order while seeing the limb only in the mirror. Exercises for the lower limbs used the tablet including its onboard camera system as a digital mirror to reflect and mirror the movement of the patients (Figure 2). A separate table mirror was used for the exercises targeted at the upper limb. Here, the tablet was utilized just as an instructional device. All subjects were instructed to perform the exercises for the upper and lower limb at home for fifteen minutes per day for a total duration of four weeks. The fifteen minutes had to be evenly split between the three exercises for the upper and lower limbs, respectively, and were ordered to be in increasing difficulty.

Figure 2. Schematic depiction of mirror therapy (A) and its implementation on the tablet (B).

A B



2.5 Psychometric parameters

The assessment of the psychometric data was based on validated and established questionnaires consisting of the German Pain Questionnaire (DSF), the 36-Item Short-Form Health Survey (SF-36), the short form McGill Pain Questionnaire (SF-MPQ), the Patient Health Questionnaire (PHQ-D), the Perceived Stress Questionnaire (PSQ-20), the Childhood Trauma Questionnaire (CTQ) and the Revised Illness Perception Questionnaire (IPQ-R). The DSF, the SF-36 and the SF-MPQ were measured on T0 and T1 and used to evaluate the changes induced by mirror therapy on respective psychometric parameters. The PHQ-D, the PSQ-20, the CTQ and the IPQ-R were assessed only at T0 for a detailed psychometric characterization of the investigated patient sample. Additionally, those questionnaires were used to identify possible predictors regarding the therapeutic efficacy of mirror therapy.

2.5.1 DSF

The DSF (Petzke et al., 2022) is a standardized questionnaire of the German Pain Association routinely utilized in practical settings and used for prescreening of newly registered patients with pain, as information basis for extended medical and psychological anamnesis, as data basis for later follow-up examinations and for internal and external quality assurance (KEDOQ-Schmerz, Casser et al., 2012). The questionnaire allows for a detailed assessment of pain symptoms, including pain localization, current pain intensity, average and highest pain intensity, overall pain duration and progression as well as pain-related disability (Nagel et al., 2002). The questionnaire additionally allows for the evaluation of general wellbeing via the Marburg Questionnaire on Habitual Health Findings (MFHW, Basler et al., 2003) and includes a screening tool for depressive, anxiety and stress symptoms, namely the German adaptation (Nilges & Essau, 2021) of the Depression, Anxiety and Stress Scale (DASS, Lovibond & Lovibond, 1995). Parameters of interest for the comparison of T0 and T1 values were the score of *pain intensity* (scores ranging from 0 to 100), the *disability* score (ranging from 0 to 6), *wellbeing* (as measured with the MFHW with scores ranging from 0 to 35) and the three scales for *depression*, *anxiety*, and *stress* of the DASS (all scores ranging from 0 to 21).

2.5.2 SF-36

The SF-36 was developed and constructed by the RAND Corporation for the Medical Outcomes Study to be able to survey the health status of participants (Ware & Sherbourne, 1993). It allows for the assessment of health-related quality of life across all medical illnesses and diagnoses and was developed with research, clinical practice and population survey applications in mind. The questionnaire has been translated into several languages by the International Quality of Life Assessment Project (IQOLA), including a German version utilized in this study (Bullinger et al., 1995). The SF-36 contains the following eight subscales which can be grouped to two superordinate themes:

Physical health

- *Physical functioning*:
  Ability to perform all types of physical activities, e.g. bathing or dressing without being impaired due to health problems
- *Role limitations due to physical problems*:
  Problems and impairments with daily activities or work as the result of physical health
- *Bodily pain*:
  Frequency of pain and discomfort and its limiting influence on normal activities
- *General health perceptions*:
  Believes about current personal health and expectations about its development in the future

Psychological health

- *Vitality*:
  Rating of subjective state, whether feeling worn out and tired or full of energy
- *Social functioning*:
  Ability to perform social activities without frequent interference due to emotional or physical problems
- *Role limitations due to emotional problems*:
  Problems and impairments with daily activities or work as the result of emotional problems
- *General mental health*:
  Assessment of the psychological state, i.e. if feelings of depression and nervousness or peacefulness and calmness prevail

The answers of the subjects are transformed into scores for each subscale, ranging from 0 to 100, and indicate higher functioning with higher scores, i.e. low scores imply poor functioning or greater impairment, respectively. All eight scales were used to compare the values of T0 and T1.

2.5.3 SF-MPQ

The SF-MPQ (Melzack, 1987) is a widely used questionnaire for the assessment of pain intensity and quality, and is based on the McGill Pain Questionnaire (Melzack, 1975). The short-form of the questionnaire uses fifteen adjectives describing sensoric as well as affective aspects of pain and measures the corresponding severity. In this study, a German version was used (Tal, 2008), which is based on the translation and adaptation by Radvila et al. (1987). The included visual analogue scale (VAS) of the questionnaire was replaced by a numerical rating scale (NRS) due to technical reasons of the digital format in which the questionnaire was applied. The SF-MPQ eventually provides the following scales which are used for statistical comparison of T0 and T1 values: a *sensory pain* scale ranging from 0 to 33, an *affective pain* scale ranging from 0 to 12, a *NRS* ranging from 0 to 10 and a *total score* ranging from 0 to 60.

2.5.4 PHQ-D

The PHQ-D (Löwe et al., 2002) is a routinely utilized questionnaire and can be used for the screening and diagnosing of the most common mental disorders. It is the German adaption of the Patient Health Questionnaire (PHQ, Spitzer et al., 1999), a further development of the Primary Care Evaluation of Mental Disorders (PRIME MD, Spitzer et al., 1995), which was developed as a screening tool for mental disorders in primary care medicine. The PHQ-D enables categorial diagnostic or screening of mental disorders and syndromes based on the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-4) such as depressive disorders (i.e. major depressive syndrome, other depressive syndromes), anxiety disorders (i.e. panic syndrome, other anxiety syndromes), somatoform syndrome, alcohol syndrome and eating disorders (suspected bulimia nervosa, suspected binge eating disorder). It also includes questions regarding critical live events, psychosocial functioning and life stressors.

In addition to the categorial diagnostic or evaluation of the subjects' answers, a continuous evaluation is also possible: for the areas of *depression*,

somatic symptoms and *stress*, scale sum values can also be calculated. These are more sensitive (Löwe et al., 2004) and can be understood as degrees of severity (Löwe et al., 2002). The values of the scale of *depression* range from 0 to 27, values below five can be interpreted as the absence of a depressive disorder, values of five to ten correspond to mild or subthreshold depressive disorders and values above ten indicate the presence of a major depressive disorder of moderate (values 10 to 14), pronounced (values 15 to 19) or severe (values 20 to 27) extent. Values for the scale of *somatic symptoms* range between 0 and 30 and those of *stress* between 0 and 20. For utilization in the statistical analysis these scales were preferred over the categorial diagnostic because of their favorable psychometric properties regarding sensitivity and level of measurement (Löwe et al., 2004).

2.5.5 PSQ-20

In this study, the PSQ-20 (Fliege et al., 2001, 2005) was used to capture the subjective stress and burden perception and impact of life stressors in the last four weeks. It is the German adaptation of the Perceived Stress Questionnaire (Levenstein et al., 1993). As the original questionnaire consisted of thirty questions, the here used PSQ-20 uses twenty questions and allows for the assessment of four thematic domains through the following scales: *worries*, *tension*, *joy*, *demands* and one *overall score.* After evaluation of the subjects' answers all scales result in values between 0 and 100 with the scales of *worries*, *tension*, *demands* and *overall score* being interpreted negatively, i.e. higher scores reflecting higher amounts of worries, tensions, demands and impairment respectively. The scale *joy* can be interpreted positively, i.e. higher scores indicate a higher amount of joy and positive emotions.

2.5.6 CTQ

The CTQ is a reliable and internationally established questionnaire for the assessment of traumatic childhood experiences (Bernstein et al., 2003). In this

study, the German translation of the CTQ was utilized, which has repeatedly been methodologically verified (e.g. Klinitzke et al., 2012; Wingenfeld et al., 2010). The original version of the CTQ consisted of 70 items in a five-point Likert scale response format, which has been condensed into the 28-item short form most commonly used today. Here, the short form was also used, which allows for the assessment of the following five factors of abuse and neglect: *emotional abuse*, *physical abuse, sexual abuse*, *emotional neglect* and *physical neglect*. Values of all scales range from 5 to 25. The resulting scale values can be interpreted as depicted in Table 2 (Häuser et al., 2011).

Table 2. Interpretation and severity classification of the CTQ

Scale	Severity			
	None to minimal	Slight to moderate	Moderate to severe	Severe to extreme
Emotional abuse	5 – 8	9 - 12	13 – 15	16 – 25
Physical abuse	5 – 7	8 – 9	10 – 12	13 – 25
Sexual abuse	5	6 – 7	8 – 12	13 – 25
Emotional neglect	5 – 9	10 – 14	15 – 17	18 – 25
Physical neglect	5 – 7	8 – 9	10 – 12	13 – 25

2.5.7 IPQ-R

With the IPQ-R, a questionnaire for the quantitative and comprehensive assessment of the patients' perception of illness was also used (Moss-Morris et al., 2002). It is theoretically based on Leventhal's self-regulatory model and its five components of illness representation, namely identity, consequences, timeline, control and causality (e.g. Leventhal et al., 2016). In this study, the German adaptation of the IPQ-R was used (Glattacker et al., 2009). The questionnaire consists of two parts, the first one measuring the scale *identity* by querying various symptoms in a yes/no response format (with the scale ranging

from values of 0 to 28). In the second part, the main scales of the IPQ-R are measured: *timeline chronic*, *timeline cyclical, consequences*, *personal control*, *treatment control*, *illness coherence* and *emotional representations*. All scales of the second part of the questionnaire are based on items with a five-point Likert scale as response format. The answers are then summed up to get the final value of the respective scale with values ranging from 5 to 25.

Regarding the interpretation of the scales, the following applies: *identity* measures the number of symptoms reported and attributed to the illness of the subject; *timeline chronic* assesses the chronicity of the illness, i.e. higher scores represent a more chronic and less acute course of the illness; *timeline cyclical* measures the degree to which the illness is experienced in a cyclical manner; *consequences* represents the negative consequences of the illness; *personal control* and *treatment control* measures the positive beliefs of the subjects about the controllability of the illness in the personal domain and regarding treatment options respectively; *coherence* assesses the extent to which the subjects have developed a personal understanding of their illness and *emotional representations* measures the amount of negative emotions which are linked to their illness. Overall, the scales of *identity*, *timeline chronic*, *timeline cyclical*, *consequences* and *emotional representations* can be interpreted as negative scales and the scales of *personal control*, *treatment control* and *illness coherence* as positive scales, i.e. higher values indicate less desirable and more desirable conditions, respectively.

2.6 Heart rate variability

HRV was recorded with eMotion Faros 180° (Mega Electronics Ltd., Finland) after subjects filled out the psychometric questionnaires. HRV was recorded during a time period of five minutes where subjects were verbally instructed by the study staff to relax and not talk, similar to the procedure described in Mazurak et al. (2016). Data were recorded with a sampling rate of 1000 Hz and saved on the device to perform an offline analysis. Analysis of HRV data was performed with Kubios HRV Premium 3.3.1 (Kubios Ltd., Finland) using its built-in algorithm for

artifact correction, which has been shown to reliably correct for artifacts with high sensitivity and specificity (Lipponen & Tarvainen, 2019). The following parameters were computed and of interest for the subsequent statistical analysis: the standard deviation of IBIs of normal (i.e. excluding abnormal or false beats) heartbeats (SDNN) and the root mean square of successive differences of successive IBIs (RMSSD) as the primary time-domain indices measuring the overall short-term HRV and the LF band (0.04 – 0.15Hz) and the HF band (0.15 – 0.40 Hz) as frequency domain indices of HRV. The LF and HF bands of HRV were analyzed as absolute power values and as normalized units with each frequency band reflecting influences of SNS and PNS on HRV via modulation of baroreceptor activity and parasympathetic activation, respectively (Shaffer & Ginsberg, 2017; Task Force, 1996).

2.7 Statistical analysis

The statistical analysis was conducted using SPSS Version 27.0.1.0 (IBM Corp., 2020) and R Version 4.1.3 (R Core Team, 2022) including the packages ggplot2 (Wickham, 2016) and car (Fox & Weisberg, 2019) utilizing the interface of RStudio Version 2022.2.0.443 (RStudio Team, 2022). Normality of the data was tested utilizing Kolmogorov-Smirnov-Lilliefors-Test. When a normal distribution of the data could be assumed, paired t-tests were used for comparison of data before (T0) and after (T1) the therapy regimen. In case of non-normality, Wilcoxon signed-rank tests were utilized. For comparing questionnaire data of the study sample with normative data of corresponding questionnaires, the Welch modified two-sample t-test was utilized. Regarding HRV analysis, data of one participant had to be removed as the respective values of the absolute power in the LF band were outliers, i.e. were more than three interquartile-ranges above the upper quartile. Exploratory data analysis was performed using stepwise regression models utilizing a stepwise selection method (with the built-in step()-function of R). This stepwise selection method combines the forward and backward selection modes and is therefore also called bidirectional elimination. At each step variables that contain significant information (according to the

Akaike information criterion (AIC) of respective variables) are added to the model, while variables that no longer meet this prerequisite are removed. This approach was used to identify variables that predict the efficacy of the therapeutic intervention. In the regression models, the reduction of pain intensity as measured by the DSF (∆T0-T1) was set as dependent variable and the baseline sample characteristics, i.e. age, sex, comorbidities and Body mass index (BMI) as well as the scales of the utilized questionnaires at T0 were entered as possible predictors for each stepwise regression model respectively. The alpha level of significance was set to $p < 0.05$ for all statistical analysis.

3 Results

3.1 Baseline measurements

3.1.1 Sample characteristics

Overall, fifteen (n=15) patients participated in the study, with a median age of 39 years (Interquartile range IQR: 28 – 55). Nine of the fifteen patients were female (60 %) and had a median BMI of 28.5 kg/m^2 (IQR: 26.00 – 29.25). Concerning their primary chronic somatoform pain disorder, four patients (26.67 %) had a diagnosis of persistent somatoform pain disorder (ICD-10-GM: F45.40) and the other eleven patients (73.33 %) had a diagnosis of chronic pain disorder with somatic and psychological factors (ICD-10-GM: F45.41). Regarding diagnosed comorbidities, nine patients (60 %) had also a diagnosis of a depressive disorder and four patients (26.7 %) had an additional anxiety disorder. While checking the inclusion and exclusion criteria, the medication was also recorded and yielded the following results: five patients (33.3 %) reported intake of antidepressant medication, one patient (6.7 %) reported taking antipsychotic medication, four (26.7 %) and five (33.3 %) reported to take anticonvulsant medication and opioids, respectively. For a better overview, baseline sample characteristics are also shown in Table 3.

Table 3. Baseline sample characteristics of n=15 participants.

Parameter	**Value: n (%), median [IQR: Q1-Q3]**
Female	9 (60.00)
Age (years)	39 [28-55]
BMI (kg/m^2)	28.5 [26.00-29.25]
Overweight (BMI > 25)	9 (60.00)
Obesity (BMI > 30)	3 (20.00)
Children (yes)	9 (60.00)
Marriage (yes)	9 (60.00)

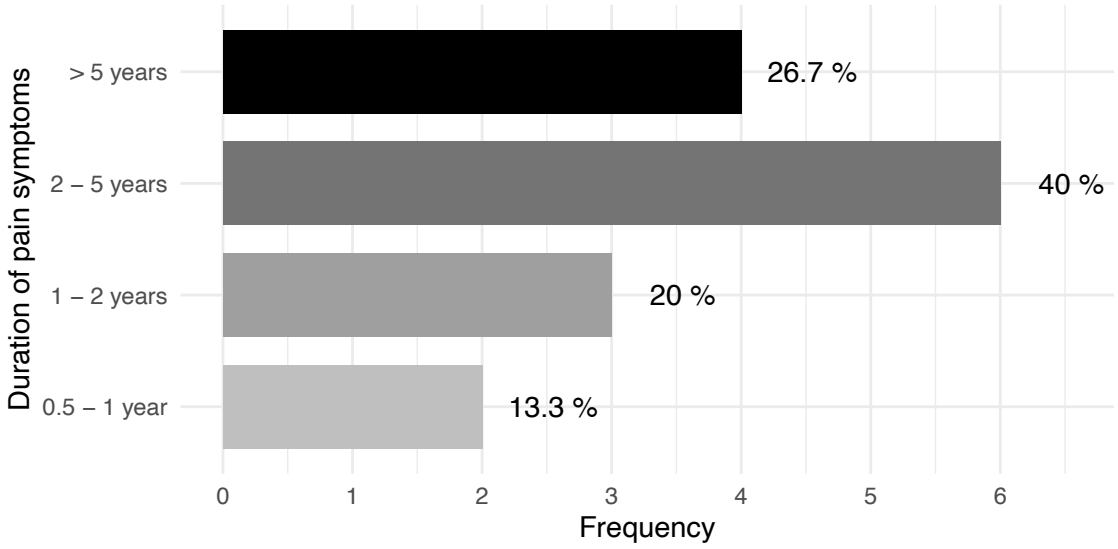
Smoking (yes)	4 (26.67)
Somatoform pain disorder diagnosis (ICD-10-GM)	
F45.40	4 (26.67)
F45.41	11 (73.33)
Diagnosed Comorbidities	
Depressive Disorder	9 (60)
Anxiety Disorder	4 (26.67)
Medication at baseline	
Antidepressant	5 (33.33)
Antipsychotics	1 (6.67)
Anticonvulsant drugs	4 (26.67)
Opioids	5 (33.33)

3.1.2 Psychometric parameters

3.1.2.1 DSF

Regarding the duration of pain symptoms, most patients reported having their pain symptoms for two to five years (40 % of patients). Figure 3 shows detailed distribution of patients answers regarding pain symptoms duration.

Figure 3. Duration of pain symptoms in patients



Pain profile, i.e. the temporal course of the pain experienced and the extent to which the pain was experienced more in the form of constant pain or pain attacks, is shown in Figure 4. The majority of patients described their pain as continuous, with severe fluctuations of pain levels (40 % of patients). Having pain attacks while being pain-free in between was only reported by one patient (6.7 %).

Patients were also asked where their main pain complaints were localized (e.g. lower or upper extremities, back pain etc.), this is shown in Figure 5. Pain was predominantly experienced in the back area (40 % of patients), followed closely by pain in the upper extremities (33.3 % of patients).

Figure 4. Pain profile of patients.

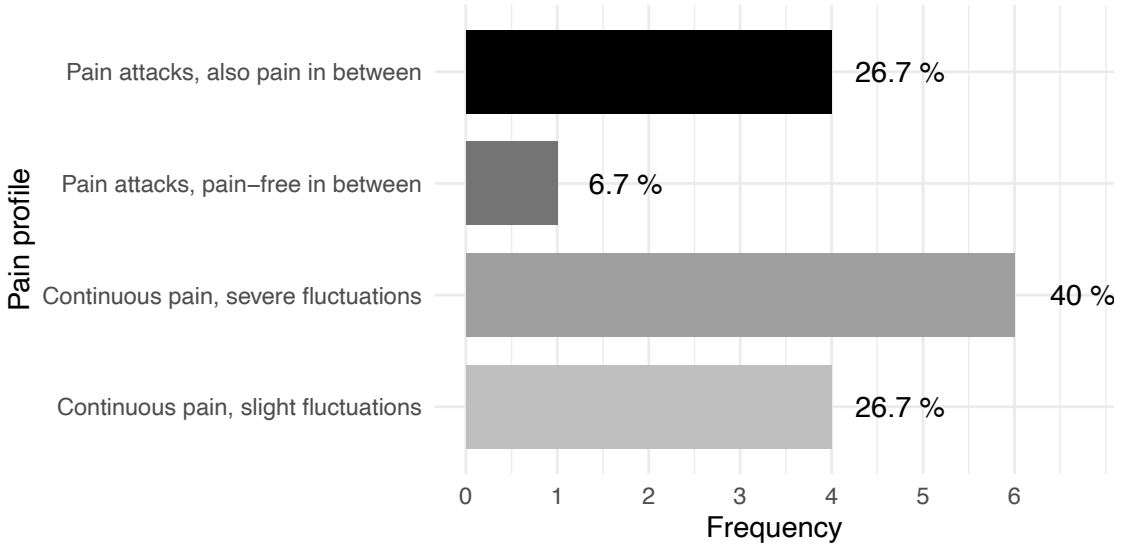
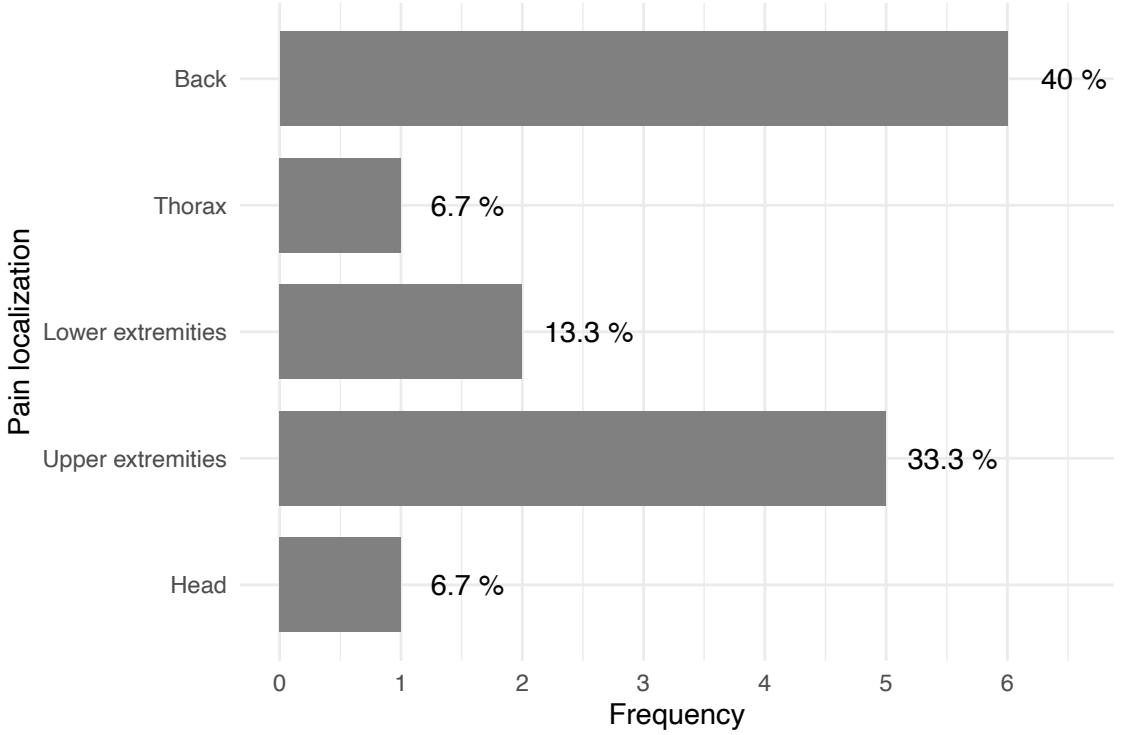
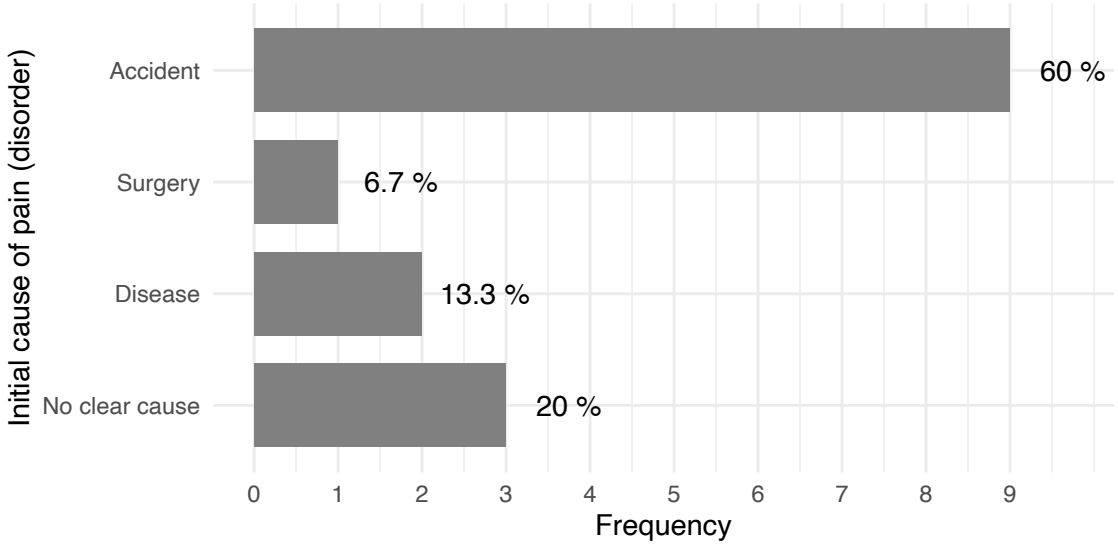


Figure 5. Pain localization of patients



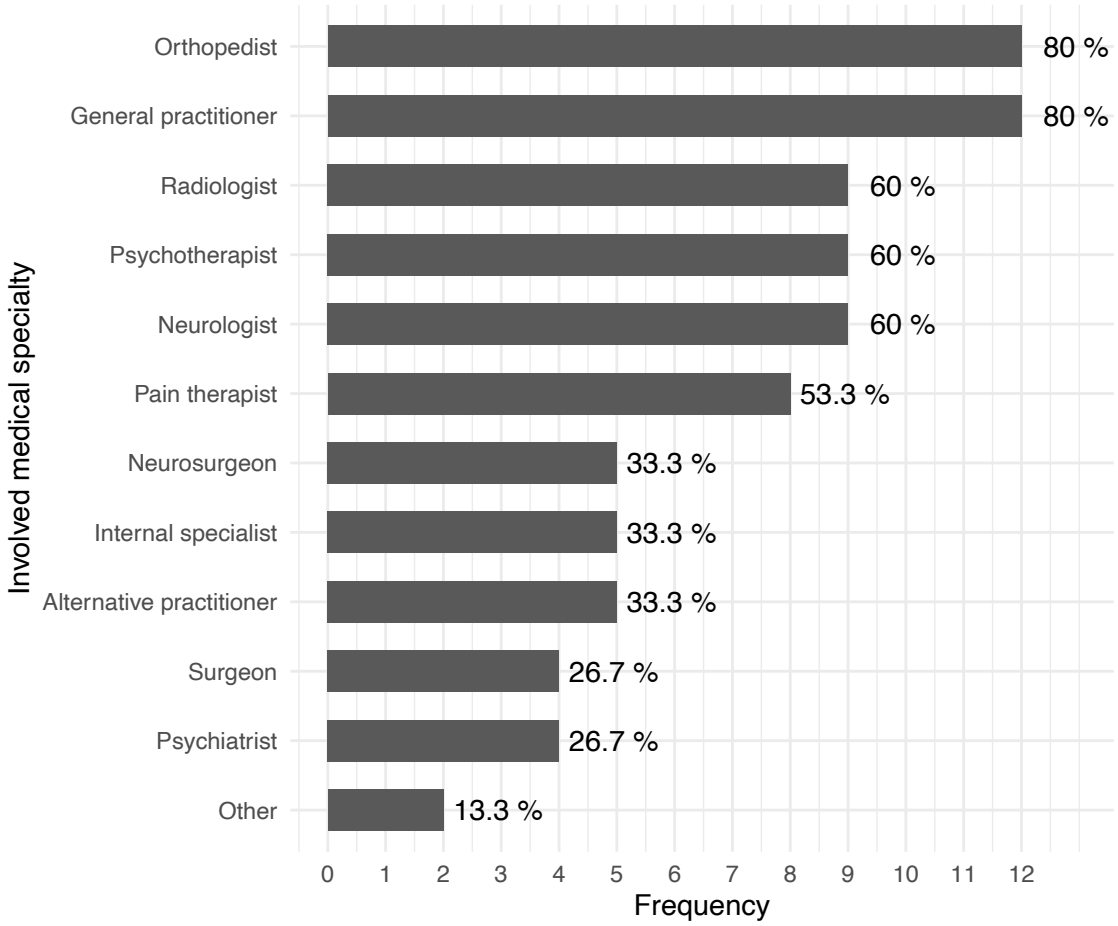
Patients were also asked what they personally thought was the original cause of their pain or pain disorder. Figure 6 shows the distribution of answers, indicating that most patients see an accident as the origin of their pain disorder (60 % of patients).

Figure 6. Initial cause of pain (disorder)



At last, patients were also asked about their history of treatments and involved medical specialties, where multiple answers were allowed. On average, each patient received treatment from $M = 5.67$ ($SD = 2.69$) medical specialties. General practitioners and orthopedists were most frequently mentioned (each n = 12) and psychotherapists, radiologists and neurologists were also mentioned commonly (each n = 9). The detailed composition of the medical specialties involved is listed in Figure 7.

Figure 7. History of treatment with involved medical specialties



Multiple answers were allowed.

As measured by the DSF, patients reported an average pain intensity of *M* = 74.67 (*SD* = 11.67) with pain symptoms persisting on average for two to five years. According to interpretation guidelines of the DSF-manual, the characteristic pain intensity of patients can be regarded as high (Petzke et al., 2022). When compared to reference data of patients in an outpatient-setting (*M* = 65.40, *SD* = 15.70) of the DSF-manual (Petzke et al., 2022), patients in this study show elevated levels of pain intensity ($t(19.21) = 2.84$, $p = .010$).

The measured level of disability of patients caused by the pain disorder was *M* = 4.40 (*SD* = 1.76). Because no reference data are available for this measure but a maximum value of six applies to this scale, the patients' experienced disability may be considered severe.

Patients' wellbeing, as measured by the MFHW, in this study (*M* = 12.27, *SD* = 8.84) seems to be on a comparable level as patients in an outpatient setting (*M* = 9.30, *SD* = 7.20, *t*(15.83) = 1.26, *p* = .225, data from the DSF-Manual Petzke et al., 2022).

Regarding the scales of the DASS, data of patients of the study was compared to data of healthy individuals and patients with pain disorders (Petzke et al., 2022). Comparison of the *depression* scale indicates, that patients in this study (*M* = 15.07, *SD* = 6.75) show higher scores than healthy individuals (*M* = 4.10, *SD* = 3.00, *t*(14.20) = 6.27, *p* < .001) and patients with pain disorders (*M* = 6.70, *SD* = 6.00, *t*(15.12) = 4.71, *p* < .001).

The analysis of the anxiety scale provides a similar result: patients in this study (*M* = 13.07, *SD* = 6.03) show elevated levels of anxiety compared to healthy individuals (*M* = 2.50, *SD* = 1.00, t(14.03) = 6.79, *p* < .001) and patients with pain disorders (*M* = 4.50, *SD* = 4.00, *t*(14.62) = 5.45, *p* < .001). For the scale of *stress*, patients in this study (*M* = 15.60, *SD* = 5.55) seem to be more severely affected than healthy individuals (*M* = 5.90, *SD* = 5.00, *t*(14.84) = 6.67, *p* < .001) as well as patients with pain disorders (*M* = 7.60, *SD* = 7.00, *t*(16.30) = 5.37, *p* < .001). With the results of these comparisons and the following cut-off scores for the scales of depression (> 10), anxiety (> 6) and stress (> 10), the patients in this study appear to be severely affected in all three domains, indicating the presence of significant distress.

3.1.2.2 SF-36

In order to obtain an estimate of the patients' degree of impairment with regard to the scales of the SF-36, the patient data collected were compared with the normalization data from the German general population (Ellert & Kurth, 2013) and the data from patients with long-term health problems (Bowling et al., 1999). Table 4 and 5 display SF-36 data from the study sample, compared in each case with the corresponding data sets.

Table 4. Comparison of SF-36 scales with normative data from the general population in Germany

Scale	**Sample data**	**General population**	**Test value**	***p* value**
	M (SD)	*M* (SD)		
Physical functioning	48.00 (22.18)	86.60 (26.84)	$t(14.08) = 6.73$	**< .001**
Role limitations (physical)	18.33 (32.00)	82.10 (33.51)	$t(14.06) = 7.71$	**< .001**
Bodily pain	32.53 (15.37)	74.80 (33.76)	$t(14.26) = 10.60$	**< .001**
General health perceptions	43.67 (11.87)	69.30 (26.88)	$t(14.28) = 8.32$	**< .001**
Vitality	34.33 (15.91)	61.60 (24.67)	$t(14.13) = 6.62$	**< .001**
Social functioning	44.20 (18.81)	86.10 (29.28)	$t(14.13) = 8.61$	**< .001**
Role limitations (emotional)	44.44 (48.25)	86.00 (29.03)	$t(14.02) = 3.34$	**.005**
General mental health	55.20 (21.87)	72.90 (22.41)	$t(14.06) = 3.13$	**.007**

Normative data used for comparison of scales is used from Ellert & Kurth (2013).

Comparing study sample data with the normative data of the general population in Germany (Ellert & Kurth, 2013), the patients in this study show significantly lower scores in all scales of the SF-36 questionnaire (all *p*s < .05).

Table 5. Comparison of SF-36 scales with normative data of a population with long-term health problems in Great Britain

Scale	**Sample data**	**Long-term health problems**	**Test value**	***p* value**
	M (*SD*)	*M* (*SD*)		
Physical functioning	48.00 (22.18)	52.30 (28.90)	*t*(15.63) = 0.73	.476
Role limitations (physical)	18.33 (32.00)	44.10 (42.50)	*t*(15.72) = 3.03	**.008**
Bodily pain	32.53 (15.37)	56.00 (30.2)	*t*(17.85) = 5.56	**< .001**
General health perceptions	43.67 (11.87)	44.80 (23.5)	*t*(17.94) = 0.35	.733
Vitality	34.33 (15.91)	44.10 (23.90)	*t*(16.20) = 2.29	**.036**
Social functioning	44.20 (18.81)	65.30 (30.50)	*t*(16.59) = 4.16	**< .001**
Role limitations (emotional)	44.44 (48.25)	71.60 (41.70)	*t*(14.72) = 2.15	**.048**
General mental health	55.20 (21.87)	67.50 (22.10)	*t*(14.98) = 2.14	**.049**

Normative data used for comparison of scales is used from Bowling et al. (1999).

The comparison with the normative data of a population with long-term health problems (Bowling et al., 1999) shows a more differentiated result: patients in the study showed lower scores on the scales of *Role limitations (physical)*, *Bodily pain*, *Vitality*, *Social functioning*, *Role limitations (emotional)* and *General mental health* (all *p*s < .05). The scale values of *Physical functioning* and *General health perceptions* did not differ from the population with long-term health problems.

3.1.2.3 SF-MPQ

In the absence of normative data or interpretive guidelines for the SF-MPQ (Hawker et al., 2011), the scale values are reported in simple form: *Sensory pain* (*M* = 14.20, *SD* = 5.81), *Affective pain* (*M* = 3.00, *SD* = 3.00), *NRS* (*M* = 6.27, *SD* = 2.02), *Total score* (*M* = 26.53, *SD* = 9.17). With regard to the maximum achievable scores of the respective scales (i.e. maximum score for sensory and affective pain being 33 and 12 respectively), the results suggest that patients in the study are more severely affected by sensory aspects of pain.

3.1.2.4 PHQ-D

Categorial evaluation of the PHQ-D indicated that of fifteen patients (n = 15), two had no signs of a depressive disorder (n = 2), six met the criteria for a mild depressive disorder (n = 6), two met the criteria for a moderate depressive disorder (n = 2), another two met criteria for a pronounced depressive disorder (n = 2) and three met the criteria for a severe depressive disorder (n = 3). Regarding the categorial evaluation of anxiety-related disorders, four patients (n = 4) met the criteria for panic syndrome and three patients (n = 3) met the criteria for other anxiety syndromes. In three patients (n = 3) the criteria for a suspected binge eating disorder were met.

The results for the continuous scales of the PHQ-D are as follows: the *depression* scale had a mean of *M* = 12.27 (*SD* = 6.93), the *somatic symptoms* scale a mean of *M* = 15.47 (*SD* = 8.32) and the *stress* scale a mean of *M* = 8.93 (*SD* = 6.71). According to the interpretative guidelines of the PHQ-D manual (Löwe et al., 2002) the score of the depression scale can be regarded as a major depressive disorder of moderate extent being present. Comparing the scores of patients of the study with validation data of the PHQ-D (Gräfe et al., 2004), the sample in this study had similar scores to these of a sample of patients with a diagnosed depression (*M* = 11.70, *SD* = 5.00, *t*(15.64) = 0.31, *p* = .761) and higher scores, when compared to the sample of patients without a diagnosis of depression (*M* = 5.90, *SD* = 4.20, *t*(14.40) = 3.54, *p* = .003). Regarding somatic

symptoms, the PHQ-D manual offers no clear interpretative guidelines. However, when comparing study sample data with the validation data (Gräfe et al., 2004), the patients show elevated somatic symptoms compared both to psychosomatic patients (M = 9.70, SD = 5.50, t(15.09) = 2.64, p = .019) as well as medical patients (M = 5.90, SD = 4.20, t(14.30) = 4.43, p < .001). For the stress scale, unfortunately, there are no validation data or interpretative guidelines available. When the study sample data is compared to a population of patients in primary care (Klapow et al., 2002), the patients in this study are affected more by psychosocial stressors than the patients in primary care (M = 4.70, SD = 3.50, t(14.05) = 2.44, p = .029).

3.1.2.5 PSQ-20

To obtain a good estimate of patient impairment in the study regarding the scales of the PSQ-20 (i.e *worries, tension, joy, demands* and the *overall score*), the study sample data were compared with reference data from healthy individuals and a sample of psychosomatic outpatients (Fliege et al., 2005). These comparisons are shown in Table 6 and 7.

Table 6. Comparison of PSQ-20 scales with reference data of healthy adults

Scale	**Sample data**	**Healthy adults**	**Test value**	***p* value**
	M (SD)	*M* (SD)		
Worries	42.20 (31.11)	26.00 (20.00)	t(14.52) = 2.00	.065
Tension	56.44 (22.15)	34.00 (21.00)	t(15.15) = 3.85	**.002**
Joy	45.82 (12.57)	62.00 (21.00)	t(17.72) = -4.70	**< .001**
Demands	43.53 (22.65)	36.00 (21.00)	t(15.10) = 1.26	.226
Overall score	49.62 (20.81)	33.00 (17.00)	t(14.85) = 3.05	**.008**

Reference data for comparison of scales is used from Fliege et al. (2005). Data was transformed from a 0-1 format to the 0-100 format used in this study.

The comparison indicates that patients in this study are having higher scores on the *tension* scale, reduced *joy* and an increased *overall score* when compared to healthy adults (all *p*s < .05). Regarding the *worries* and *demands* scale, impairment is presumably on a level comparable to healthy adults (all *p*s > .05).

Table 7. Comparison of PSQ-20 scales with reference data of psychosomatic outpatients

Scale	**Sample data**	**Psychosomatic out-patients**	**Test value**	***p* value**
	M (SD)	*M* (SD)		
Worries	42.20 (31.11)	60.00 (27.00)	*t*(14.52) = -2.19	**.045**
Tension	56.44 (22.15)	66.00 (23.00)	*t*(14.82) = -1.65	.120
Joy	45.82 (12.57)	37.00 (21.00)	*t*(16.17) = 2.62	**.018**
Demands	43.53 (22.65)	47.00 (25.00)	*t*(14.93) = -0.58	.568
Overall score	49.62 (20.81)	59.00 (19.00)	*t*(14.63) = -1.73	.105

Reference data for comparison of scales is used from Fliege et al. (2005). Data was transformed from a 0-1 format to the 0-100 format used in this study.

When comparing the study sample data with reference data of psychosomatic outpatients, the patients in this study show similar impairment in the scales of *tension*, *demands* and the *overall score* (all *p*s > .05). Patients in this study seem to have lesser *worries* but greater *joy* when compared to psychosomatic outpatients (all *p*s < .05).

Overall, it can be said that the patients in this sample are comparable with psychosomatic patients in an outpatient setting in terms of overall subjective stress and are significantly more affected than healthy adults.

3.1.2.6 CTQ

Evaluation of the scales of the CTQ yielded the following results: emotional abuse (*M* = 8.20, *SD* = 4.48), physical abuse (*M* = 5.73, *SD* = 1.79), sexual abuse (*M* =

5.00, *SD* = 0.65), emotional neglect (M = 10.87, SD = 5.97) and physical neglect (M = 6.67, *SD* = 2.38). According to the interpretation guidelines and severity classification (Häuser et al., 2011) the study sample as a whole can be regarded as having experienced non to minimal emotional, physical and sexual abuse and physical neglect but moderate to severe emotional neglect. On an individual level, Table 8 displays the number of patients being classified in the respective categories.

Table 8. Number of patients and their CTQ classifications

Scale	Severity			
	None to minimal	Slight to moderate	Moderate to severe	Severe to extreme
Emotional abuse	9	5	0	1
Physical abuse	13	1	1	0
Sexual abuse	14	1	0	0
Emotional neglect	7	5	1	2
Physical neglect	11	2	1	1

3.1.2.7 IPQR

There are no official interpretative guidelines or reference values for the IPQ-R available. Therefore, the study sample data was compared with data from patients with chronic somatic diseases in rehabilitation clinics, which was collected during the psychometric evaluation of the German version of the IPQ-R (Glattacker et al., 2009). This comparison is displayed in Table 9.

Table 9. Comparison of IPQ-R scales with data of patients with a chronic somatic illness

Scale	**Sample data**	**Chronic somatic illness**	**Test value**	***p* value**
	M (SD)	*M* (SD)		
Timeline chronic	14.00 (1.20)	19.81 (3.61)	*t*(53.79) = -9.03	**< .001**
Timeline cyclical	11.87 (2.03)	13.72 (2.76)	*t*(33.59) = -2.74	**.010**
Consequences	15.20 (2.62)	17.93 (4.20)	*t*(40.25) = -2.90	**.006**
Personal control	10.08 (4.11)	13.11 (2.74)	*t*(18.87) = -2.64	**.016**
Treatment control	11.80 (2.51)	*N/A*	*N/A*	*N/A*
Illness coherence	16.40 (2.80)	16.62 (4.48)	*t*(40.17) = -0.29	.828
Emotional representations	16.53 (3.62)	15.08 (5.07)	*t*(35.00) = 1.18	.244

Data used for comparison of scales is from Glattacker et al. (2009). Data for the scale of *treatment control* was not available.

These results suggest that the patients in this study, when compared to patients with a chronic somatic illness, have the perception of a more acute than chronic, and less cyclical illness (all *p*s < .05). Patients in this study seem to believe that their illness has fewer negative consequences than patients with a chronic somatic illness (*p* = .006). However, in terms of the perceived personal control that they have over their illness, the results suggest that patients in this study have less control (*p* = .016). The level of coherence, i.e. the personal understanding of the illness, and the amount of negative emotions associated with it, seems to be at a comparable level as in patients with a chronic somatic illness (all *p*s > .05).

3.1.3 HRV

The evaluation of baseline HRV data is shown in Table 10. Study sample data was compared to normative data gathered by Nunan et al. (2010). This systematic review was comprised of 44 studies of short-term HRV data and included a total of n = 21.438 normally healthy participants. Regarding time-domain measurements of HRV, the statistical comparison with this normative data suggests that patients in this study had a lower IBI, i.e. higher heart rate, had a reduced SDNN and also reduced RMSSD (all ps < .05). Analyzing frequency-domain measurements of HRV, compared to the data of healthy individuals, the patients in this study had increased HRV in the LF band when normalized, and reduced HRV in the HF band for absolute as well as normalized values (all ps < .05). Absolute values of HRV in the LF band showed no statistically significant differences when compared to healthy controls. Although being numerically higher, the lack of statistical differences is probably due to high variability in the study sample. The total power of HRV could not be compared, as the systematic review of Nunan et al. (2010) did not include normative data for this HRV metric. The LF/HF ratio of patients in this study did also not significantly differ from the sample of healthy individuals.

Overall, this analysis suggests that the patients in this study differ on a variety of HRV metrics, with dysfunction in both time-domain measurements, i.e. SDNN and RMSSD, as well as both frequency-domain measurements, i.e. HRV in the low- and high-frequency band.

Table 10. HRV study sample data compared to a sample of healthy adults

Parameter	**Sample data**	**Healthy adults**	**Test value**	***p* value**
	M (SD)	*M* (SD)		
Mean RR (ms)	804.14 (149.62)	926.00 (90.00)	*t*(15.55) = -3.07	**.007**
SDNN (ms)	32.65 (12.83)	50.00 (16.00)	*t*(21.13) = -4.72	**< .001**
RMSSD (ms)	23.94 (10.71)	42.00 (15.00)	*t*(23.17) = -5.74	**< .001**
LF absolute (ms)	659.64 (473.93)	519.00 (219.00)	*t*(15.62) = -1.12	.280
LF normalized (nu)	72.18 (12.05)	52.00 (10.00)	*t*(17.02) = 6.17	**< .001**
HF absolute (ms)	230.07 (155.95)	657.00 (777.00)	*t*(105.51) = -4.88	**< .001**
HF normalized (nu)	27.78 (12.04)	40.00 (10.00)	*t*(17.02) = -3.74	**.002**
Total power (ms)	1091.65 (774.84)	*N/A*	*N/A*	*N/A*
LF/HF ratio	3.19 (1.63)	2.80 (2.60)	*t*(26.19) = 0.79	**.**438

Data used for the comparison of scales was taken from the systematic review by Nunan et al. (2010) with data for *total power* being not available. There was also no explicit data available regarding sample sizes, but with a total of n = 21.438 participants included in the systematic review, a very conservative estimate (n = 100) was entered for the statistical analysis in the comparison of scales. HF = high-frequency; LF = low-frequency; RMSSD = root mean square of successive differences; RR = Interbeat interval; SDNN = Standard deviation of normal-to-normal intervals

3.2 Comparison of T0 and T1

3.2.1 Psychometric parameters

3.2.1.1 DSF

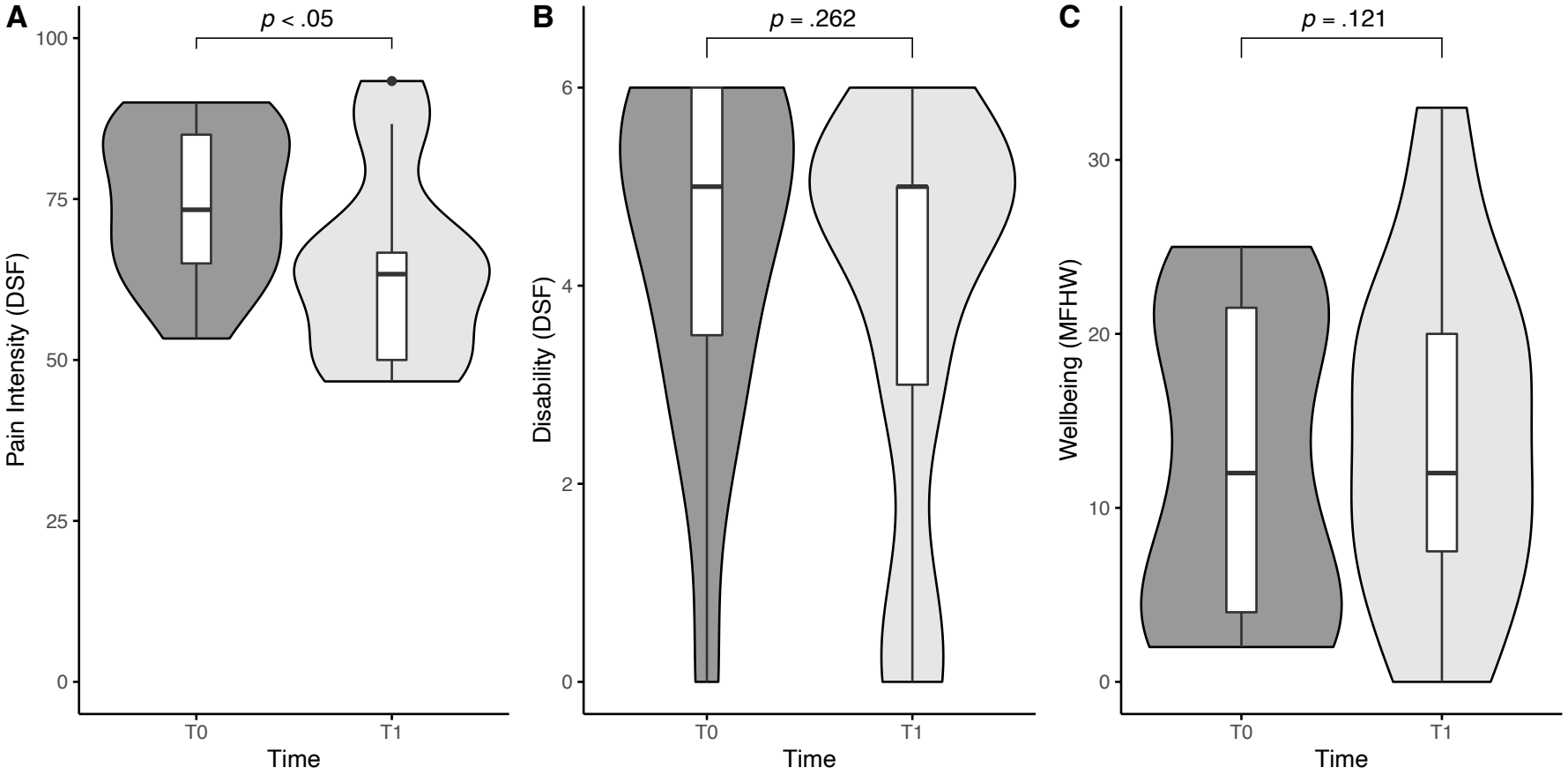
The analysis of the DSF data for the time points of T0 and T1 indicated a statistically significant reduction in pain intensity (p = .004, Table 11 and Figure 8A). The improvements on the disability scale (Figure 8B) and wellbeing (Figure 8C) did not reach statistical significance (p > .05, Table 11). All other parameters of the DASS failed to reach statistical significance as well (p > .05, Table 11).

Table 11. Comparison of the scales of DSF for T0 and T1

Scale	**T0: *M* (*SD*)**	**T1: *M* (*SD*)**	**Test value**	***p* value**
Pain intensity	74.67 (11.67)	64.44 (14.67)	z = -2.88	**.004**
Disability	4.40 (1.77)	3.87 (2.03)	z = -1.12	.262
Wellbeing (MFHW)	12.27 (8.84)	14.27 (9.53)	$t(14)$ = -1.65	.121
Depression (DASS)	15.07 (6.75)	15.00 (5.92)	t(14) = 0.07	.948
Anxiety (DASS)	13.07 (6.03)	12.67 (5.62)	z = -0.45	.654
Stress (DASS)	15.60 (5.55)	14.80 (5.72)	$t(14)$ = 0.94	.364

DASS = Depression, Anxiety and Stress Scale; MFHW = Marburg Questionnaire on Habitual Health Findings

Figure 8. Violin plots with nested box plots of DSF parameters at T0 (dark grey) and T1 (light grey)



(A) Pain intensity measured with the DSF was significantly reduced after mirror therapy (z = -2.88, p = .004) (B) Disability as measured with the DSF was not significantly reduced (z = -1.12, p = .262) (C) Wellbeing measured with the MFHW of DSF was not significantly improved ($t(14)$ = -1.65, p = 0.121); DSF = German pain questionnaire; MFHW = Marburg Questionnaire on Habitual Health Finding

3.2.1.2 SF-36

The evaluation of the data of the SF-36 scales can be found in Table 12. No significant differences were found when comparing values before (T0) and after (T1) mirror therapy (all *p*s > .05). The numerical increase in the scale of bodily pain could be interpreted as a marginally significant pain reduction (T0: *M* = 32.53, *SD* = 15.37; T1: *M* = 43.53, *SD* = 24.56; *t*(14) = -1.92, *p* = .076).

Table 12. Comparison of the scales of the SF-36 for T0 and T1

Scale	**T0: *M* (*SD*)**	**T1: *M* (*SD*)**	**Test value**	***p* value**
Physical functioning	48.00 (22.18)	49.33 (26.38)	z = -0.63	.527
Role limitations (physical)	18.33 (32.00)	26.67 (30.57)	z = -1.10	.273
Bodily pain	32.53 (15.37)	43.53 (24.56)	*t*(14) = -1.92	.076
General health perceptions	43.67 (11.87)	44.33 (14.38)	*t*(14) = -0.23	.825
Vitality	34.33 (15.91)	33.00 (19.80)	*t*(14) = 0.37	.719
Social functioning	44.20 (18.81)	40.07 (28.09)	*t*(14) = 0.54	.600
Role limitations (emotional)	44.44 (48.25)	46.64 (43.29)	*z* = -0.37	.715
General mental health	55.20 (21.87)	55.73 (23.40)	*t*(14) = -0.13	.902

Scale values range from 0 to 100, and indicate higher functioning with higher scores, i.e. low scores imply poor functioning or greater impairment respectively.

3.2.1.3 SF-MPQ

The analysis of data of the subjects for the SF-MPQ did not show significant differences, when comparing values before and after mirror therapy. Test statistics and corresponding data can be found in Table 13.

Table 13. Comparison of the scales of the SF-MPQ for T0 and T1

Scale	**T0: *M* (*SD*)**	**T1: *M* (*SD*)**	**test value**	***p* value**
NRS	6.27 (2.02)	5.47 (2.00)	$t(14) = 1.45$	.171
Sensory pain	14.20 (5.81)	13.67 (6.28)	$t(14) = 0.65$	.524
Affective pain	3.00 (3.00)	2.60 (2.82)	$z = -0.32$	.748
Total score	26.53 (9.17)	24.53 (9.75)	$t(14) = 1.51$	.153

The NRS ranges from 0 to 10, sensory pain values range from 0 to 33; affective pain values range from 0 to 12 and the total score ranges from 0 to 60.

3.2.2 HRV

All statistical comparisons of HRV of measurement points T0 and T1 are shown in Table 14. Absolute power in the LF band of HRV was significantly reduced after the completion of mirror therapy ($p = .025$, Table 14 and Figure 9A). This effect however did not remain when normalized values of the LF band HRV were analyzed ($p = .868$, Table 14 and Figure 9B). All other comparisons failed to reach statistical significance (all *p*s > .05, Figure 10A and 10B).

Table 14. Comparison of HRV metrics before (T0) and after (T1) completion of mirror therapy

Parameter	**T0**	**T1**	**Test value**	***p* value**
	M (SD)	*M* (SD)		
Mean RR (ms)	804.14 (149.62)	743.59 (138.23)	$t(13) = 1.83$	.091

SDNN (ms)	32.65 (12.83)	28.57 (10.09)	$t(13) = 1.09$	.297
RMSSD (ms)	23.94 (10.71)	20.57 (11.64)	$t(13) = 0.86$	.406
LF absolute (ms^2)	659.64 (473.93)	372.46 (239.18)	$t(13) = 2.54$	**.025**
LF normalized (nu)	72.18 (12.05)	71.35 (17.31)	$t(13) = 0.18$	.863
HF absolute (ms^2)	230.07 (155.95)	213.93 (202.75)	$z = -0.72$	.470
HF normalized (nu)	27.78 (12.04)	28.57 (17.20)	$t(13) = -0.17$	.868
Total power (ms^2)	1091.65 (774.84)	791.01 (462.32)	$t(13) = 1.45$	.172
LF/HF ratio	3.19 (1.63)	4.35 (5.19)	$z = -1.04$	.300

Figure 9. Violin plots with nested box plots of low-frequency HRV at T0 (dark grey) and T1 (light grey) in absolute power (A) and normalized units (B)

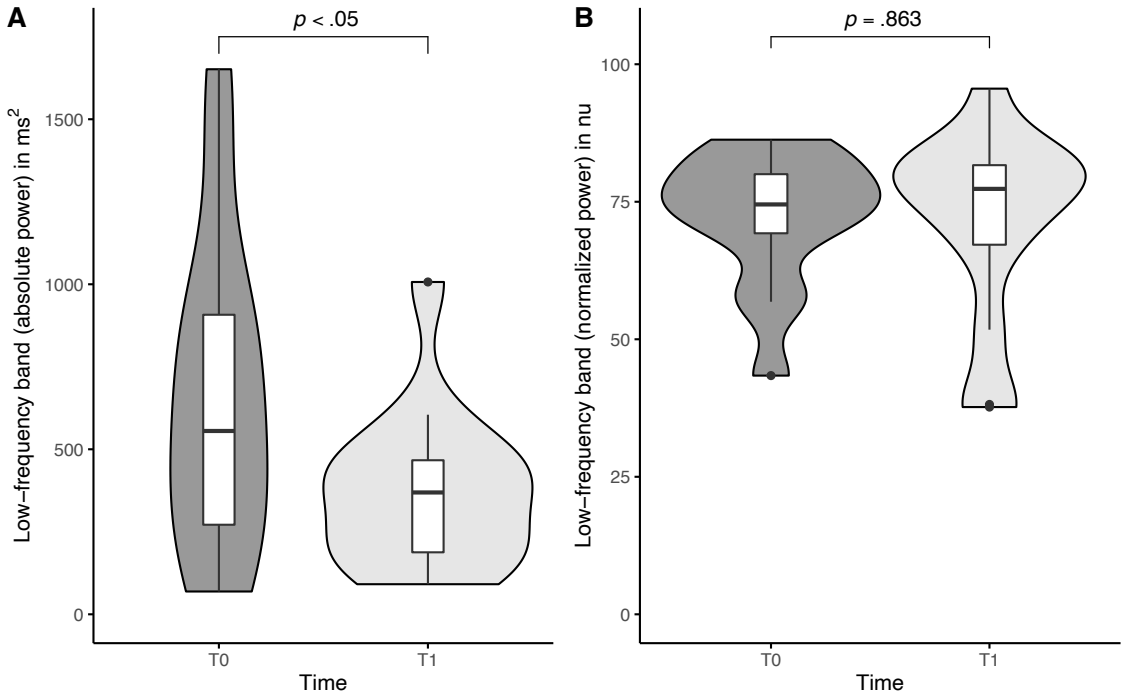
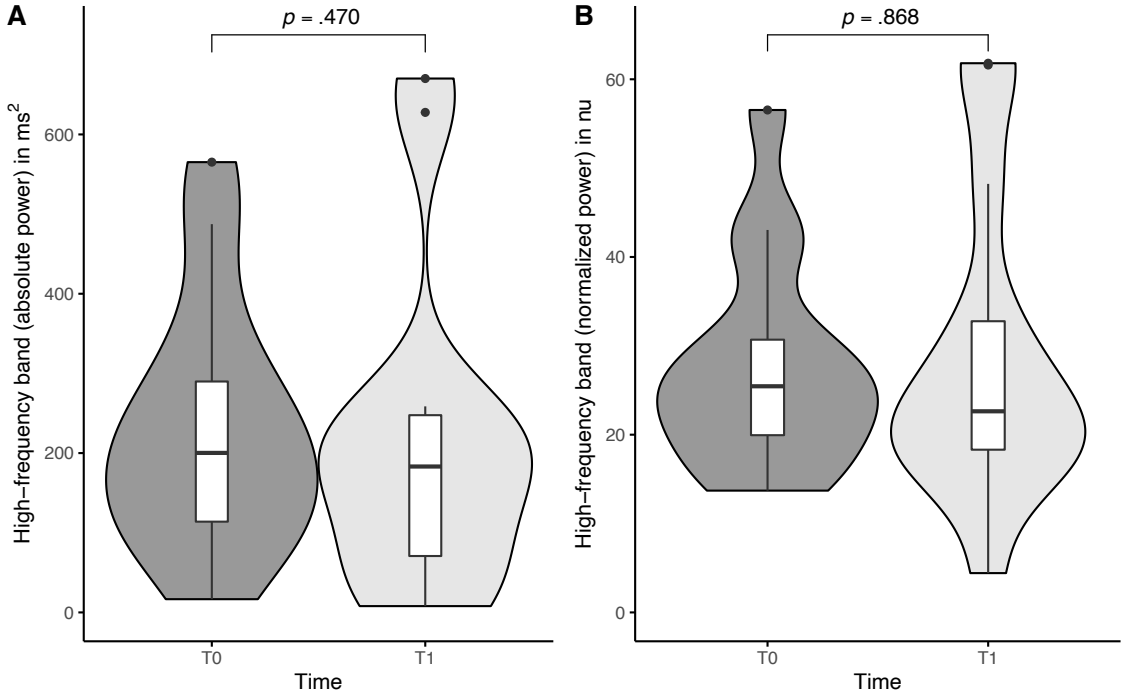


Figure 10. Violin plots with nested box plots of high-frequency HRV at T0 (dark grey) and T1 (light grey) in absolute power (A) and normalized units (B)



3.2.3 Exploratory data analysis

Each stepwise regression model was calculated with the reduction of *pain intensity* of the DSF between measurement (∆T0-T1) as dependent variable and baseline characteristics and scale values of the used questionnaires at T0 as possible predictors respectively.

3.2.3.1 Baseline characteristics and DSF

With all possible predictors being the baseline characteristics (i.e. age, sex, BMI, comorbidity depressive disorder, comorbidity anxiety disorder) and the scales of the DSF at T0 (i.e. disability, wellbeing and the depression, anxiety and stress scale of the DASS), the stepwise regression model approach showed a linear regression model ($F(3,11) = 8.638$, $p = .003$, $R^2 = .702$) with the following predictors: *comorbidity depressive disorder* ($\beta = 16.65$, SE = 4.53, $t(11) = 3.674$, $p = .004$), *disability* ($\beta = -2.61$, SE = 1.05, $t(11) = -2.476$, $p = .031$) and *depression*

(β = -0.92, SE = 0.34, $t(11)$ = -2.710, p = .020). This indicates that patients who had a depressive disorder as comorbidity, had greater reduction in pain intensity than patients without this comorbid disorder. Additionally, higher levels of disability and depressive symptoms at T0 seem to reduce the improvement in pain intensity through mirror therapy.

3.2.3.2 Other questionnaires

For each remaining questionnaire assessed at T0, i.e. SF-36, SF-MPQ, PSQ-20, CTQ and IPQR, a separate stepwise regression model was calculated and all scales of respective questionnaires were entered as possible predictors. The stepwise regression model approach, however, yielded no significant linear regression and significant predictors regarding the improvement of pain intensity through mirror therapy (all *p*s > .05).

4 Discussion

This study tried to evaluate the effects of a mirror therapy regimen in patients with chronic somatoform pain disorders on psychometric parameters and HRV. A total of fifteen patients were consecutively recruited through the Outpatient Clinic for Psychosomatic Medicine at the University Hospital Tübingen. Patients were assessed regarding pain characteristics and psychometric variables on two measurement sessions and underwent a four-week mirror therapy regimen in between. Additionally, HRV was assessed before and after the completion of the mirror therapy. This study is the first of its kind, evaluating mirror therapy and its capability to decrease pain symptoms and modulate associated physiological parameters, i.e. HRV, in this patient group with chronic somatoform pain disorders.

The key findings of this pilot study are first that mirror therapy is able to significantly reduce levels of pain intensity in one of several metrics measuring pain symptoms and second, that completion of the mirror therapy regime leads to a significant decrease of HRV in the LF band, an effect only seen in absolute power values but not normalized values of LF HRV. Third, regarding pain intensity reduction, patients with an additional comorbid depressive disorder might especially profit from performing mirror therapy.

4.1 Baseline measurements

4.1.1 Psychometric parameters

The study aimed to investigate this new form of therapy in patients with chronic somatoform pain disorders, as these patients have been shown to suffer from high disease burden despite extensive and often only partially successful treatments (Cohen et al., 2021; Rask et al., 2015; Wittchen et al., 2011). Analysis of baseline measurements of the patient sample clearly showed that patients were heavily afflicted by their disorder. Two-thirds of patients reported having their pain symptoms for at least two to five years with most of them experiencing

continuous pain symptoms with severe fluctuations in intensity. Pain of patients was predominantly located in the back area and the upper extremities. Here, our results are pretty much in line with these of Hessel et al. (2005), which also found, back and joint pain as well as pain in legs and/or arms to be most prevalent. Regarding the subjective causality of their disorder, the majority of patients named an accident as initial cause of their pain disorder. The severe burden of disease of these patients is also reflected in the number of medical specialties involved in their treatment. On average, each patient received treatment from more than five medical practitioners with general practitioners, orthopedists, psychotherapists, radiologists and neurologists being the most frequented medical specialties. Interestingly enough, pain therapists were only the sixth most frequently mentioned specialty.

Regarding pain intensity as measured by the DSF, patients in this study were more affected than a comparable reference group of patients in an outpatient setting (Petzke et al., 2022). On the other hand, wellbeing of patients in this study was impaired to about the same extent as the sample of patients in an outpatient setting (Petzke et al., 2022). For the depression, anxiety and stress symptoms measured by the DASS of the DSF, a similar picture emerges: patients in this study showed scores well above cut-off of respective scales and were severely affected, showing even higher symptom burden than the sample of patients with pain disorders by Petzke et al. (2022).

As expected, on all scales of the SF-36, patients in this study were more impaired than people of the general population (Ellert & Kurth, 2013). However, on six out of eight scales, patients in this study were even more afflicted than a population of patients with long-term health problems (Bowling et al., 1999). Patients were therefore especially impaired concerning their daily and social activities and work because of physical as well as emotional problems. As one would expect, pain symptoms and their influence on normal activities were also more pronounced, compared to the population of patients with long-term health problems. However, patients in this study showed also elevated restrictions regarding their overall mental health and feelings of being worn out and tired. Our results are thus in line with the findings of Elliott et al. (2003), who demonstrated

that chronic pain patients show low scores on the SF-36. This was even more the case in patients with an additional diagnosis of major depressive disorder. As nine out of the fifteen patients in the current study had also a comorbid depression, our results underline and confirm the particularly pronounced impairment these patients are facing.

The results of the PHQ-D present a similar picture: patients in this study show depressive symptoms comparable to the sample of patients with diagnosed depression (Gräfe et al., 2004) and especially pronounced somatic symptoms, being in this regard more impaired than psychosomatic patients of the reference sample (Gräfe et al., 2004). The same applies to stress symptoms where patients in this study also showed elevated levels compared to patients in primary care (Klapow et al., 2002).

Evaluation of the PSQ-20 further supports these findings of elevated stress levels in these patients. These results indicate that patients in this study were overall suffering more from subjective stress than healthy adults (Fliege et al., 2005) with a focus on increased tension, e.g. feeling exhausted and being unable to relax. In this regard, patients in this study were on the same level as the sample of psychosomatic outpatients (Fliege et al., 2005). Psychological distress is thought to play a major role in the pathogenesis of chronic pain disorders (Diatchenko et al., 2006) and, as our results demonstrate, this relationship may be bidirectional, i.e. pain disorders also lead to increased distress in return.

It is also an ongoing debate if and to what extent previously experienced abuse is associated with or leads to the development of pain disorders later in life (Tietjen, 2010). Some studies found an association between self-reported experienced sexual abuse (J. Brown et al., 2005) and self-reported childhood abuse (including sexual abuse, physical abuse and neglect, Raphael et al., 2001). Patients in the present study on the other hand showed no to minimal abuse or neglect, except for emotional neglect, where overall moderate levels of neglect were found.

Patients' beliefs about their illness has been found to be associated with treatment outcome in patients with chronic pain, especially for the dimensions of perceived consequences of the disability, chronicity of symptoms and the

perceived control of the disability (Foster et al., 2008; Galli et al., 2010). As the patients in this study showed comparable scores as the sample of patients with chronic somatic illness (Glattacker et al., 2009), the partially missing response to treatment in this study may be in part attributed to these dysfunctional beliefs about their disorder.

4.1.2 HRV

At the baseline measurement session, patients in this study showed a multitude of abnormal HRV parameters, e.g. reduced time-domain variability as measured by SDNN and RMSSD, as well as frequency-domain parameters deviating from the norm. Here, when compared to healthy adults, HRV in the LF band was increased and HRV in the HF band decreased. These findings are in line with the meta-analysis of Ying-Chih et al. (2020), who reported decreased SDNN, RMSSD and HF HRV in patients with somatic symptom disorders or functional somatic syndromes. Bandeira et al. (2021) reported similar findings in their systematic review and described elevated levels of LF HRV and decreased levels of HF HRV in patients with chronic low back pain. The same finding was reported by Pollatos et al. (2011) in patients with somatoform disorders. However, not all studies show these distinct alterations of HRV in patients with chronic pain or somatoform disorders. For example, Huang et al. (2017) did not find differences in SDNN or HF HRV in patients with somatic symptom disorder compared to healthy adults. On the contrary, they reported decreased LF HRV in these patients. Similarly, Van Den Houte et al. (2018) found no differences in RMSSD between patients with functional somatic syndromes and healthy controls. These in part heterogenous findings might be explained by the variability in the patient collectives studied. In general, our findings match the robust meta-analyses and reviews (Bandeira et al., 2021; Ying-Chih et al., 2020) and underpin the assumption of abnormal HRV in patients with somatoform pain disorders.

Overall, the results of baseline measurements indicate that the sample of patients in this study is indeed heavily affected by their disorder. Not only do they exhibit substantial burden of pain symptoms, including receiving extensive

treatment options, but are also suffering from pronounced impairment in a variety of other areas of mental or psychological health, including depressive, anxiety and stress-related symptoms as well as quality of life and respective daily functioning. Furthermore, this is also reflected in distinct abnormalities in objective physiological parameters, i.e. various HRV metrics, indicating impaired autonomic function and (para)sympathetic imbalances.

4.2 Comparison of T0 and T1

4.2.1 Psychometric parameters

Regarding the DSF, our analysis showed a reduction in pain intensity through the four-week mirror therapy regimen. This finding is in line with several studies, that demonstrated the efficacy of mirror therapy regarding pain symptoms in various disorders, e.g. phantom limb pain (Foell et al., 2014; Ramachandran et al., 1995), hemiparesis after stroke (Altschuler et al., 1999), motor impairment and pain after stroke (Thieme et al., 2018) and CRPS (Cacchio et al., 2009; Pervane Vural et al., 2016). However, pain symptoms measured by other questionnaires than the DSF, i.e. the SF-MPQ or the SF-36, were not improved by mirror therapy. Wittkopf & Johnson (2017) state in their review on mirror therapy that efficacy and effect sizes of the intervention are quite heterogenous and that the therapy itself and its application seem to vary between studies. Furthermore, not all studies investigating the efficacy of mirror therapy report positive results, with the studies of Brodie et al. (2007) and Michielsen et al. (2011) finding no effect on pain reduction in patients with phantom limb pain and after stroke, respectively. The fact that only the pain assessment by the DSF showed a reduction may also be explained by the fact that this questionnaire allows for a very thorough and detailed evaluation of pain symptoms. In contrast to other questionnaires, the DSF includes questions regarding current pain intensity as well as the highest pain intensity in the last four weeks and the average pain intensity. The SF-36 scale for pain consists only of one item for pain assessment, and the SF-MPQ measures overall pain characteristics with a focus on sensoric and affective

qualities of pain symptoms. Consequent post-hoc statistical analysis of the DSF questions regarding pain intensity suggests that changes in questions addressing the average pain intensity but not highest or current pain intensity were largely responsible for the significant reduction in pain intensity. Nonetheless, an established pain questionnaire like the SF-MPQ, which is routinely used to assess the responsiveness to pain treatments (Hawker et al., 2011), should also reflect changes in pain through mirror therapy if they ought to be robust and clinically significant.

The results of the exploratory data analysis are suggesting that patients with a depressive disorder as a comorbidity might benefit in particular from mirror therapy. However, results also indicate that patients with lower scores of depressive symptoms and disability might improve more regarding pain intensity. This finding may seem contradictory at first sight but could be explained by a differential effect of disability and depressive symptoms on the overall efficacy of mirror therapy. Patients with the additional diagnosis of depression might benefit especially from mirror therapy due to unspecific and unintended effects of the therapy regimen. As physical activity has been shown to be effective in treating depressive symptoms (e.g. Kandola et al., 2019) and mirror therapy involves the regular execution of physical activity in the form of fine-motor exercises, it would be conceivable that this may be a potential mechanism of action. This effect may then be counterbalanced by the severity of depressive symptoms and disability: when symptoms are too aggravated the efficacy of the intervention is diminished reflecting a possible inverted U-shaped relationship between depressive symptoms severity and its effect to modulate the efficacy of mirror therapy. A similar effect was found by Schröder et al. (2015) where less severely ill patients with somatoform disorders showed a greater benefit of cognitive behavioral therapy than most severely ill patients.

All other psychometric parameters measured at baseline and after completion of mirror therapy were also not malleable by the intervention. Possible explanations for this result may be the general limitations of this study regarding sample size and treatment duration (see further below). Alternatively, mirror therapy could be also very specific regarding its impact. Mirror therapy may

primarily target pain symptoms in patients with somatoform pain disorders. Additionally, effects that go beyond this may only occur if pain symptoms are reduced even further or if the treatment is intensified even more.

4.2.2 HRV

Besides these effects, we also found that mirror therapy can influence HRV. Absolute power in the LF band of HRV was reduced after the therapy. Previous research has demonstrated that patients with functional somatic syndromes or somatic symptom disorder display altered HRV (e.g. Ying-Chih et al., 2020) and that HRV is tightly associated with the perception of pain and its intensity (Koenig et al., 2014), more precisely that the induction of pain leads to increases of heart rate variability in the LF band (Chouchoul et al., 2011; Terkelsen et al., 2005). Our findings of reduced pain intensity and reduced HRV in the LF band are therefore consistent with the possible assumption of a direct relationship between these two variables, i.e. higher levels of pain may be reflected in increased HRV in the LF band. Furthermore, as already mentioned, patients in our study showed abnormal HRV in the LF band when compared to healthy adults. The decrease in LF HRV could therefore be interpreted as a step toward renormalization towards the healthy range of HRV (Heiss et al., 2021).

However, the results should be treated with caution. On the one hand, the literature regarding HRV and its association with chronic pain or somatoform disorders is quite heterogenous (Tracy et al., 2016; Ying-Chih et al., 2020). Several studies did not find differences regarding HRV (including the HF band) and some even show contradictory findings, for example with decreased LF HRV (Huang et al., 2017). Also, not all studies investigating novel therapeutic approaches for pain conditions find improvements in HRV (e.g. Galaasen Bakken et al., 2021). On the other hand, our finding of a reduction of LF HRV did vanish when normalized power of the LF HRV was analyzed. Methodologically, normalized units show some advantages over absolute power values and are therefore preferred, as results may be more reliable and robust (Heathers, 2014). The argument in favor of using absolute power values is that the use of

normalized units may lead to the underestimation of changes in HRV (Task Force, 1996; Xhyheri et al., 2012).

A key metric of HRV regarding somatoform and pain disorders is HF HRV which was also not altered by mirror therapy. HF HRV is able to predict therapy outcomes in pain-predominant somatoform disorders (Angelovski et al., 2016) and chronic pain patients (Mathersul et al., 2021) and is often found to be decreased in patients with somatic symptom disorder or functional somatic syndromes (Ying-Chih et al., 2020) reflecting the (para)sympathetic dysbalanced in patients with chronic pain (e.g. Gatchel et al., 2007; Kalezic et al., 2007; Tracy et al., 2016). Subsequent studies should therefore focus on this HRV metric in particular.

4.3 General limitations and future directions

The study conducted here is the first of its kind to examine the efficacy of mirror therapy as a new intervention method for patients with chronic somatoform pain disorders. Yet, there are several limitations and open questions regarding the results and their interpretations of this study.

We only found improvements in one metric assessing pain symptoms of these patients. It would be desirable if the therapy under study could bring about improvements not only regarding pain but also in other areas, such as limitations in daily life due to diminished social functioning or role limitations. Additionally, the current study did not involve a control group. Therefore, it remains unclear if the found effects can be clearly attributed to the intervention of mirror therapy. It may also be plausible, that patients would have shown improved pain symptoms due to variations in their symptoms or phenomena like regression to the mean. The inclusion of control groups or implementation of a crossover-design might be beneficial to further validate the results. It also remains unclear if the described improvements regarding pain symptoms are due to specific effects of mirror therapy or if they are due to unspecific effects. For example, these effects could be the regular implementation of physical activity, the fact that patients actively engaged with their bodies, and effects of mindfulness, which could occur during

mirror therapy. These mechanisms and interventions have shown to be effective in the treatment of chronic pain conditions (Geneen et al., 2017; Majeed et al., 2018) and could also be responsible for the effects found in this study. Thus, future studies investigating mirror therapy could also incorporate such active control groups to further elucidate the therapeutic mechanisms on which the efficacy of mirror therapy relies. Additionally, future studies could try to evaluate the efficacy of mirror therapy, when incorporated into a larger intervention like graded motor imagery to possibly create greater therapeutic effects. Following studies could also include imaging methods, like functional magnetic resonance imaging to allow for a measurement of the neuronal correlates possibly altered by the intervention. This could further elucidate the mechanism behind mirror therapy in patients with chronic somatoform pain disorders and would bolster the rationale behind the application of mirror therapy in these patient populations.

Another limitation of this study relates to the sample size. Our study consisted of a rather small sample size, which diminishes the significance of the findings especially regarding their robustness. Follow-up measurement may also be included in future studies to allow for an evaluation of long-term effects and the durability of improvements. However, as the current study was designed as a pilot study to also evaluate the principal applicability and feasibility of mirror therapy in these patients, these points of criticism may therefore be somewhat less severe. Nonetheless, studies investigating mirror therapy for these patients with a randomized controlled study design including larger sample sizes and the utilization of (active) control groups are mandatory to corroborate the preliminary results of this study.

In summary, the results of the present study provide first evidence for the efficacy of mirror therapy in patients with chronic somatoform pain disorders. As mirror therapy is low in side effects, is, compared to other interventions, relatively cost efficient and can therefore be made widely accessible, it appears as a promising therapeutic addition to be used within the existing multimodal pain therapy framework currently available for patients with chronic somatoform pain disorders.

5 Summary

Patients with chronic somatoform pain disorders often report impaired quality of life and high symptom burden, often responding inadequately to available treatment options. Mirror therapy has been shown to be effective in treating phantom limb pain following limb amputation and has been used successfully for other disorders, such as complex regional pain syndrome (CRPS). This pilot study examined the efficacy of mirror therapy in patients with chronic somatoform pain disorder, specifically whether and to what extent it can reduce symptom severity and modulate associated autonomic dysregulation. Fifteen patients (n = 15) diagnosed with a chronic somatoform pain disorder (F45.40, F45.41) were enrolled in the study and received four weeks of tablet-based mirror therapy including exercises for the upper and lower limb. Symptom severity was assessed with established questionnaires. In addition, heart rate variability (HRV) was recorded. After mirror therapy, there was a significant reduction in pain intensity (z = -2.878, p = .004). In addition, a reduction in absolute power in the low-frequency band of HRV ($t(13)$ = 2.536, p = .025) was also found. The present pilot study was the first to examine the effect of mirror therapy in individuals with chronic somatoform pain disorders. The results suggest that this intervention may reduce pain intensity and influence associated dysfunctional HRV. Because this is a pilot study, these results and their explanatory power are limited by several factors, such as a small sample size and lack of a control group. Nevertheless, these promising results should be validated in further studies to pave the way for this new additional therapeutic option for these patients.

6 Zusammenfassung

Patienten mit chronischen somatoformen Schmerzstörungen berichten oft über eine eingeschränkte Lebensqualität und eine hohe Symptombelastung, wobei sie teilweise nur unzureichend auf die verfügbaren Behandlungsoptionen ansprechen. Die Spiegeltherapie hat sich bei der Behandlung von Phantomschmerzen nach einer Gliedmaßenamputation als wirksam erwiesen und wurde auch erfolgreich bei anderen Störungsbildern, wie z.B. dem komplexen regionalen Schmerzsyndrom (CRPS), eingesetzt. In dieser Pilotstudie wurde die Wirksamkeit der Spiegeltherapie bei Patient:innen mit chronischen somatoformen Schmerzstörungen untersucht, vor allem ob und inwieweit eine Verringerung der Symptomschwere sowie eine Veränderung der damit einhergehenden autonomen Dysregulationen möglich ist. Fünfzehn Patient:innen (n = 15), bei denen eine chronische somatoforme Schmerzstörung (F45.40, F45.41) diagnostiziert wurde, wurden in die Studie eingeschlossen und erhielten vier Wochen lang eine Tablet-basierte Spiegeltherapie mit Übungen für die oberen und unteren Gliedmaßen. Der Schweregrad der Symptome wurde mit etablierten Fragebögen erfasst. Zusätzlich wurde die Herzfrequenzvariabilität (HRV) erfasst. Nach der Spiegeltherapie zeigte sich eine signifikante Reduktion der Schmerzintensität (z = -2,878, p = .004). Darüber hinaus wurde eine Verringerung der absoluten Power im niederfrequenten Band der HRV ($t(13)$ = 2,536, p = .025) festgestellt. In der vorliegenden Pilotstudie wurde zum ersten Mal die Wirkung der Spiegeltherapie bei Personen mit chronischen somatoformen Schmerzstörungen untersucht. Die Ergebnisse legen nahe, dass diese Intervention die Schmerzintensität verringern und die damit assoziierten dysfunktionale HRV beeinflussen kann. Da es sich um eine Pilotstudie handelt, sind diese Ergebnisse und ihre Aussagekraft durch mehrere Faktoren eingeschränkt sind, z. B. durch eine geringe Stichprobengröße und fehlende Kontrollgruppe. Dennoch sollten diese vielversprechenden Ergebnisse in weiteren Studien validiert werden, um den Weg für eine neue weitere Therapieoption für diese Patient:innen zu bereiten.

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8 Declaration of own contribution

Die Arbeit wurde in der Abteilung für Psychosomatischen Medizin und Psychotherapie der Medizinischen Klinik Tübingen unter Leitung von Prof. Dr. Stephan Zipfel durchgeführt.

Die Konzeption der Studie erfolgte in Zusammenarbeit mit Prof. Dr. Andreas Stengel (Leitender Oberarzt und stellvertretender ärztlicher Direktor der Abteilung) und den ärztlichen Kollegen der Abteilung.

Die Einweisung in die Methode und Geräte der Herzratenvariabilitätsmessung erfolge hierbei durch Herrn Dr. Nazar Mazurak. Bei der Anpassung und Verwaltung der digitalen Fragebögen half Frau Dr. Anna-Maria Jurjut. Bei der Einführung in das klinikinterne Verwaltungssystem der Patientendaten unterstützte Frau Dr. Caroline Rometsch.

Die Erhebung der Daten wurde durch mich (in Zusammenarbeit mit Doktorandin Larissa Hetterich) durchgeführt. Dabei waren Frau Hetterich und ich gleichermaßen an der Rekrutierung der Patienten sowie der Datenerhebung beteiligt. Während Frau Hetterich sich vorrangig um die Erhebung der Schmerzschwellen kümmerte, habe ich die Messung der Herzratenvariabilität vorgenommen. In besonderen Fällen wurden einzelne Messungen auch von einer Person allein durchgeführt. Die Verwaltung und Analyse der Daten der Schmerzschwellen wurde stets von Frau Hetterich vorgenommen, die der Herzratenvariabilität ausschließlich von mir.

Die statistische Auswertung erfolgte eigenständig durch mich. Ich versichere, das Manuskript, die Abbildungen und Tabellen selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Tübingen, den 24.05.2023

9 Publications

Die Ergebnisse der Studie wurden in folgender Publikation veröffentlicht:

Ruf, S.P.*, Hetterich, L.*, Mazurak, N., Rometsch, C., Jurjut, A-M., Ott, S., Herrmann-Werner, A., Zipfel, S., Stengel, A. (2023). Mirror Therapy in Patients with Somatoform Pain Disorders – A Pilot Study. *Behavioral Sciences, 13*(5), 432. doi: 10.3390/bs13050432

Zusätzlich wurden die Ergebnisse auf folgenden Kongressen vorgestellt:

Ruf, S.P.*, Hetterich, L.*, Mazurak, N., Ott, S., Jurjut, A.-M., Rometsch, C., Hermann-Werner, A., Zipfel, S., & Stengel, A. (2022). A pilot study of mirror therapy on patients with chronic somatoform pain disorders and its effect on psychometric and physiological parameters. (Vortrag von Prof. Zipfel auf dem Kongress der European Association of Psychosomatic Medicine 2022).

Hetterich, L.*, Ruf, S.P.*, Mazurak, N., Ott, S., Jurjut, A.-M., Rometsch, C., Zipfel, S., Herrmann-Werner, A., & Stengel, A. (2021). Effekte der Spiegeltherapie auf psychometrische und autonome Parameter bei Patienten mit chronischen somatoformen Schmerzstörungen - Eine Pilotstudie. (ePoster Deutscher Kongress für Psychosomatische Medizin und Psychotherapie 2021)

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