Is Functional Neurological Symptom Disorder (FNSD) a (somatic) stress disorder with altered emotion processing? An approach to an answer via different methods, disorders and over time.

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Contents

Abstract

Functional neurological symptoms (FNS) are neurological symptoms without sufficient medical/neurological explanation. They are common and severe but still little understood. Different factors are discussed to contribute to the origination and maintenance of FNSD: Traumatic experiences are frequently linked with FNSD, which is why the disorder is oftentimes perceived as a stress-related disorder. Alterations in emotion processing are consistently reported for patients with FNSD and targeted in treatment approaches. However, little is known on the variability of such alterations and possibly underlying alterations in neural networks. Somatic sensation is supposed to be altered in FNSD but objective measures in the assessement of such alterations are missing. The objective of the present thesis was to clarify the role of FNSD as a stress-related disorder and to evaluate somatic sensation (via a new method), emotion regulation and their variability (across time and therapy).

Study 1: Patients with FNSD frequently report traumatic experiences and show symptoms similar to those of patients with posttraumatic stress disorder (PTSD). Study 1 evaluated the classification of FNSD as a trauma-related disorder by comparing dissociative symptoms, symptoms of posttraumatic stress, lifetime traumata, and affect regulation between patients diagnosed with dissociative disorder (characterized by negative functional neurological symptoms), patients diagnosed with PTSD and healthy comparison participants. FNSD patients with co-occuring PTSD differed from PTSD patients in the amount of reported psychoform dissociation. FNSD patients with co-occuring PTSD reported more emotional maltreatment than those without co-occuring PTSD. Results challenge the conceptualization of FNSD as trauma-related disorder but advocate the consideration of traumatic experiences as an intensifying factor in the generation and maintenance of the disorder.

Study 2: The meaning of eventually altered somatic sensation in FNSD seems still unclear, which may be related to the challenging assessment of the concept. Study 2 aimed to contribute to the understanding of alterations in body sensation in patients with FNSD by comparing somatic sensation (defined by perception and discomfort threshold on transcutaneous electric nerve stimulation (TENS)) between patients with FNSD, major depressive disorder (MDD), posttraumatic stress disorder (PTSD) and healthy comparison subjects (HC). Somatic Sensation was measured at baseline as well as before and after an interview on traumatic life experiences, to examine the impact of acute stress. Results revealed similar somatic sensation at baseline across groups. FNSD patients showed higher thresholds for somatic perception post-interview compared to pre-interview. Somatic sensation could not be confirmed as specific feature in FNSD. Results encourage the application of TENS in further studies on somatic sensation in FNSD.

Study 3: Altered emotion processing has been established as a prominent feature in FNSD and is targeted in many treatment approaches. Study 3 investigated cortical correlates (experimentally induced emotion regulation task under EEG - monitoring) and behavioural correlates (questionnaires on alexithymia and emotion regulation strategies) of emotion processing as well as symptom intensity and it‘s variation in context of a standard treatment program in patients with FNSD. While patients reported an increase in use of cognitive reappraisal strategies of emotion across the assessed time interval, cortical correlates of emotion processing did not change, nor did symptom intensity. Results encourage the consideration of emotion processing in treatment of FNSD and further prolonged studies to determine the contribution of treatment-related changes of emotion regulation on FNS.

Zusammenfassung

Funktionelle neurologische Symptome (FNS) sind neurologische Symptome, die nur unzureichend medizinisch erklärbar sind. Sie sind häufig und schwerwiegend aber noch nicht ausreichend verstanden. Es werden verschiedene Faktoren diskutiert, die zur Entstehung und Aufrechterhaltung von FNSD beitragen könnten: Traumatische Erfahrungen werden häufig mit FNSD in Verbindung gebracht, was dazu führt, dass die Störung oft als Stressfolgestörung verstanden wird. Eine veränderte Emotionsverarbeitung wird übereinstimmend für FNSD berichtet und in vielen Behandlungsansätzen adressiert. Bisher ist allerdings nur wenig über die Variabilität dieser veränderten Emotionsverarbeitung und mögliche zugrundeliegende Veränderungen in neuronalen Netzwerken bekannt. Patienten mit FNSD scheinen eine veränderte Körpersensitivität zu haben, es fehlen jedoch Instrumente um diese möglichst objektiv zu messen. Das Ziel der vorliegenden Dissertation war die Evaluation einer möglichen Einordnung von FNSD als Stressfolgestörung und die Untersuchung von Körpersensitivität und Emotionsverarbeitung und deren Variabilität.

Studie 1: Patienten mit der Diagnose FNSD (Störung mit funktionellen neurologischen Symptomen) berichten häufig von traumatische Erfahrungen und zeigen Symptome ähnlich denen einer Posttraumatischen Belastungsstörung. Studie 1 untersuchte eine mögliche Einordnung von FNSD als Traumafolgestörung und verglich dazu dissoziative Symptomatik, Symptome von posttraumatischem Stress, traumatische Erfahrungen über die Lebenszeit sowie Affekt-Regulation zwischen Patienten mit der Diagnose FNSD (gekennzeichnet durch negative funktionelle neurologische Symptome), Patienten mit einer PTSD Diagnose und gesunden Vergleichspersonen. FNSD Patienten mit einer komorbiden PTSD Diagnose berichteten mehr psychoformen Dissoziationssymptome als PTSD Patienten. Sie berichteten mehr emotionale Vernachlässigung als Pa-

tienten mit FNSD ohne komorbide PTSD Diagnose. Die Einordnung von FNSD als Traumafolgestörung scheint vor dem Hintergund der gezeigten Ergebnisse zweifelhaft. Traumatische Erfahrungen sollten als intensivierender Faktor in der Entstehung und Aufrechterhaltung von FNSD berücksichtigt werden.

Studie 2: Die Bedeutung eventuell veränderter somatischen Wahrnehmung in der Entstehung von FNSD ist noch unklar, was womöglich mit der schwierigen Operationalisierbarkeit des Konzeptes der somatischen Wahrnehmung zusammenhängt. Studie 2 verglich die somatische Wahrnehmung (definiert durch die Wahrnehmungsschwelle für mittels transkutaner elektrischer Nervenstimulation (TENS) dargebotener Reize und die Schwelle, ab der diese Reize als unangenehm empfunden werden) zwischen Patienten mit der Diagnose einer FNSD, einer Depression oder einer PTSD und gesunden Vergleichspersonen. Dabei wurde die somatische Wahrnehmung zu einem Referenzzeitpunkt gemessen, sowie vor und nach einem Interview über traumatische Lebenserfahrungen. Dies diente der Untersuchung eines möglichen Einflusses von akutem Stress auf die somatische Wahrnehmung. Die Ergebnisse zeigten eine ähnliche somatische Wahrnehmung zum Referenzzeitpunkt zwischen den Gruppen. Patienten mit FNSD hatten höhere Wahrnehmungsschwellen nach dem Interview im Vergleich zu vor dem Interview. Somatische Wahrnehmung konnte nicht als spezifisches Merkmal von FNSD bestätigt werden. Die Ergebnisse bestärken jedoch die Nutzung von TENS in weiteren Studien zu somatischer Wahrnehmung in FNSD.

Studie 3: Veränderte Emotionsverarbeitung konnte als bedeutendes Merkmal von FNSD etabliert werden und wird in vielen Behandlungsansätzen adressiert. Studie 3 untersuchte Korrelate veränderter Emotionsverarbeitung auf kortikaler Ebene (Emotionsregulations - Aufgabe unter Ableitung eines EEGs) und Verhaltensebene (Fragebögen zu Alexithymie und Emotionsverarbeitungsstrategien), sowie die Symptomschwere und

deren Variabilität im Verlauf einer Standardbehandlung bei FNSD Patienten. Patienten zeigten einen Anstieg in der Nutzung kognitiver Neubewertungsstrategien von Emotion über den untersuchten Zeitraum. Kortikale Korrelate der Emotionsverarbeitung sowie die Symptomschwere blieben unverändert. Die Ergebnisse unterstützen die Berücksichtigung von Emotionsverarbeitung in der Behandlung von FNSD. Weitere Studien mit längeren Untersuchungszeiträumen sollten den Beitrag von (Therapie-induzierten) Veränderungen in der Emotionsverarbeitung auf FNSD untersuchen.

Abbreviations

ANOVA Analysis of Variance

CIMH Central Institute for Mental Health

DASH Disabilities of the Arm, Shoulder and Hand

DD Dissociative Disorder

DD$^-$ Dissociative disorder without co-occuring PTSD

DD$^+$ Dissociative disorder with co-occuring PTSD

DES Dissociative Experience Scale

DICS Dynamic Imaging of Coherent Sources

DSM Diagnostic and Statistical Manual of Mental Disorders

EEG Electroencephalogram

ERP Event-related Potentials

ERQ Emotion Regulation Questionnaire

FMDRS Functional Movement Disorder Rating Scale

FNS(D) Functional Neurological Symptom (Disorder)

GSI Global Severity Index

HADS Hospital Anxiety and Depression

HC Healthy Comparison Subject

IAPS International Affective Picture System

ICD International Statistical Classification of Diseases and Related Health Problems

IRB Institutional Review Board

LPP	Late Positive Potential
NW	Neutral Watch
PNES	Psychogenic Non-epileptic Seizures
PDS	Posttraumatic Stress Disorder Scale
PDS_Event	Sum of lifetime traumatic events
PDS_Sym	Load of posttraumatic stress symptoms
PTSD	Posttraumatic Stress Disorder
ROI	Region of Interest
SDQ	Somatoform Dissociation Questionnaire
SCL-90R	Symptom Checklist-90-Revised
TAS-26	Toronto Alexithymia Scale-26
TENS	Transcutaneous Electric Nerve Stimulation
TOI	Time of Interest
UW	Unpleasant Watch
UR	Unpleasant Regulate
WSAS	Work and Social Adjustment Scale

List of Figures

List of Tables

1 General Introduction

1.1 Definition and Epidemiology of Functional Neurological Symptom Disorder (FNSD)

The diagnosis of Functional Neurological Symptom Disorder characterizes patients suffering from impairments in voluntary motor or sensory function that cannot be sufficiently explained by a neurological or medical cause (DSM-5). Functional neurological symptoms (FNS) can be subdivided into 1) positive symptoms, referring to the existence of abnormal sensory or motor functioning and 2) negative symptoms, referring to the absence of normal sensory or motor functioning. Impairments in motor function comprise symptoms like paralysis, general weakness/slowness and Parkinsonism (negative symptoms) or tremor, myoclonus (referred to as non-epileptic seizures) and tics (positive symptoms). FNS affecting the sensory system can manifest in alterations in somatic sensation, gait, vision or audition.

With an incidence of 4-12 per 100 000 per year and a prevalence of 50 per 100 000, (Carson & Lehn, 2016) FNSD is among the most common diagnoses in neurology practice (Fobian & Elliott, 2018) and patients report high rates of physical and psychological comorbidity (Gelauff & Stone, 2016). The actual number of patients with FNSD could be even higher considering the fact, that the disorder seems to be under-documented (Leaver, Yi, Evans, Bullock, & Dearlove, 2016), probably because of the fear to overlook the "real" underlying neurological cause und thus to misdiagnose. This insecurity, regarding the diagnosis of FNSD, has been reported in various studies, showing that neurologists find it more difficult to help patients with symptoms unexplained by organic disease (Carson, Stone, Warlow, & Sharpe, 2004) and have low confidence in their ability to successfully treat the disorder (Shneker & Elliott, 2008). It leads to long

delays (up to 7 years in case of nonepliептic seizures (Reuber, 2009)) and unnecessary and costly diagnostic procedures before patients are diagnosed correctly, which is accompanied with poor prognosis of the disorder (Espay, Aybek, & Carson, 2018; Gelauff & Stone, 2016; Gupta & Lang, 2009). Thus 50-90% of patients report ongoing or worsening of symptoms (Feinstein, Stergiopoulos, Fine, & Lang, 2001; Thomas, Vuong, & Jankovic, 2006).

Patients with FNSD show severe suffering (Carson et al., 2000) and severity of disability is comparable to that of parkinson, with high impact on function and daily life (Anderson et al., 2007; Carson et al., 2011). Interest in FNSD has increased over the last years and literature was able to show, that the fear of misdiagnosis is without cause, since only 0.4 – 4 % of patients diagnosed with FNSD received a different diagnosis at follow up (Stone, Carson, Duncan, et al., 2009; Stone et al., 2005). However, FNSD still seems a "crisis for neurology" (Hallett, 2006).

Summing up, FNSD is frequent, severe but still little understood and thus further research (some of which is described in the following chapters) is mandatory.

1.2 Nomenclature

The nomenclature of FNSD has changed constantly, thus it is helpful to look at these changes and the underlying conceptual ambiguities when trying to understand the idea of FNSD. Historically referred to as hysteria (Crommelinck, 2014a), Freud and Breuer introduced the term "conversion" to describe neurological symptoms without underlying organic/neurologic disease (Breuer & Freud, 1985): Psychic conditions are supposed to be converted into bodily symptoms, if they cannot be tolerated otherwise. While still being a popular term, that is also used in ICD-10 when referring to FNS, it has been criticised for its assumption of a psychological stressor as a prerequisite for the disorder,

as this can be confirmed for only about 1/3 of the patients (Roelofs & Spinhoven, 2007). "Psychogenic" is yet another term describing FNS. While being the most popular under clinicians (Edwards, Stone, & Lang, 2014; Espay et al., 2009), it seems to be less accepted by patients and their relatives, due to the general negative connotation of the term "psychic" (Ding & Kanaan, 2017; Morgan, Dvorchik, Williams, Jarrar, & Buchhalter, 2013). "Medically unexplained", "non-organic", "non-neurological" are examples for "labelling-by-exclusion" (Ding & Kanaan, 2017) and imply a diagnostic uncertainty, that must be hardly satisfying for patients. Stigmatization with all its negative consequences is a problem in the field of FNSD (Rommelfanger et al., 2017) and various of the terms described above are interpreted as equivalent to "putting it on" or "imagining symptoms" (Edwards et al., 2014), which might explain why patients report feeling angry or "dumped" after medical consultation (Reuber, 2009). FNS may also be understood as somatoform dissociative symptoms, focusing on dissociation as the underlying process of the disorder (R. Brown, Cardena, Nijenhuis, Sar, & van der Hart, 2007).

DSM-5 introduced the term "functional neurological symptom disorder", assigning the disorder to the category of "somatic symptom and related disorders". This has the advantage of being more neutral but still entails a mechanism (change in function but not structure) accepted by patients (Stone et al., 2003, 2002), which seems to have strong impact on treatment outcome (Carton, Thompson, & Duncan, 2003). The term "functional neurological disorder" also integrates psychological and neurological approaches to this disorder (Demartini, D'Agostino, & Gambini, 2016; Susman, 2018). Thus, no clear mechanism of FNSD could be identified so far, instead different predisposing and sustentative factors have been suggested via different terms (see below).

1.3 Trauma and accute stress in FNSD

Traumatic experience have constantly been associated with FNSD (Ludwig et al., 2018) and used to be a diagnostic criterion of the disorder in DSMIV. Studies report high rates of sexual (Roelofs, Keijsers, Hoogduin, Nä, & Moene, 2002; Sack, Lahmann, Jaeger, & Henningsen, 2007; Sar, Akyüz, Kundakci, Kizilitan, & Dogan, 2004) and emotional abuse or neglect (Ozcetin et al., 2009; Sar, Islam, & Ozturk, 2009; Steffen, Fiess, Schmidt, & Rockstroh, 2015; Steffen-Klatt, Fiess, Beckh, Schmidt, & Rockstroh, 2018). The connection between traumatic events and FNSD can be interpreted in different ways. As already suggested by Freud and Breuer (view above) it might be that unbearable psychic conditions/events turn or "convert" into physical symptoms. One might also explain the connection between trauma and FNSD against the background of the well-established model of the defense cascade: a traumatic/life-threatening event provokes a cascade of fear responses, beginning with a fight/flight reaction that is reflected in excessive physiological arousal. In the further course of the cascade when the threat persits but fight/flight is no longer possible, the physiological arousal turns into a "shutdown" response that is characterized by somatoform dissociation leading to fright and faint. This process is accompanied by a disruption in the integration of sensational, cognitive and emotional parts of the event into memory (Schauer & Elbert, 2010). If somatoform dissociative symptoms persist beyond the presence of a life-threatening stimulus, they can be interpreted as the symptoms described by patients with FNSD.

However, the growing body of research in the field changed the picture and meaning about the importance of trauma in the generation of FNSD – mirrored in DSM-5, where traumatic experiences are now "only" listed as specification criterion, acknowledging the fact, that they are reported in only approximately 1/3 of the patients (Aybek, 2015; Crommelinck, 2014a; Kaplan et al., 2013; Ludwig et al., 2018; Roelofs & Pasman, 2016).

Only few studies so far evaluated the effect of acute stress on the generation of functional neurological symptoms, but those that exist demonstrate, that not only life-threatening stimuli but also mild levels of stress can lead to somatoform dissociative symptoms and FNS (Bob, Selesova, Raboch, & Kukla, 2013). Furthermore, stress seems to differently affect patients with FNSD compared to HC. A recent study by Apazoglou, Mazzola, Wegrzyk, Frasca Polara, and Aybek (2017) confirms a dissociation between perceived stress and biological markers during a social stress test in patients with FNSD, compared to HC. In patients with FNSD, subjectively perceived stress did not correlate with objective measures (amylase). Abnormal postural behaviour was reported in patients with FNSD during exposure to social stress (Zito, Apazoglou, Paraschiv-Ionescu, Aminian, & Aybek, 2018).

As illustrated in the literature introduced above, the role of traumatic experiences and stress in the generation of FNSD remains ambiguous. They may serve as risk factors, but cannot be assumed as solely mechanism. It remains further questionable, why similar traumatic experiences lead to the development of different symptoms/disorders. Summing up, the following questions arise: Are FNSD merely a sub-type of posttraumatic stress disorder? How does acute stress affect patients with FNSD?

1.4 Somatic sensation in FNSD

Altered sensory functioning is a diagnostic criterium of FNSD and can take different appearences. Altered somatic sensation, as an example for alterations in sensory functioning, is reported in FNSD. Patients show impaired capacities in discriminating tactile stimuli (Tinazzi et al., 2014) and heartbeats (Ricciardi et al., 2016). Furthermore, Fiess, Rockstroh, Schmidt, and Steffen (2015) reported altered somatic sensation in reaction to emotionally adversive stimuli in patients with FNSD in comparison to healthy sub-

jects, using transcutaneous electric nerve stimulation (TENS). After viewing negative pictures of the International Affective Picture System (IAPS), the threshold of electric current percieved as uncomfortable was higher in patients than in HC. However, it remains unclear, whether patients with FNSD have alterations in somatic sensation in terms of a trait or whether they probably misinterpret or mispercept "normal" body sensations. The latter is supported by studies, that show poor interoceptive awarness in patients with FNSD compared to HC (Ricciardi, Demartini, Crucianelli, Edwards, & Fotopoulou, 2014; Ricciardi et al., 2016; Sojka, Bareš, Kašpárek, & Světlák, 2018) or mismatch between subjectively reported and objectively measured tremor-times in patients with non-epileptic seizures (Parees et al., 2012). Edwards, Adams, Brown, Parees, and Friston (2012) introduced a convincing model, to explain misperception in FNSD: Perception develops by constantly comparing and adjusting external stimuli and internal expectations rearding those stimuli. Patients with FNSD may have abnormal prior internal expectations about upcoming external stimuli, thus biasing the acutal perception in direction of the expectation (forward prediction). Trait-like alterations in stress processing and somatic sensation can also be derived from studies, reporting higher diurnal cortisol levels in FNSD patients compared to HC (Apazoglou, Mazzola, Wegrzyk, Frasca Polara, & Aybek, 2017; Bakvis, Spinhoven, Zitman, & Roelofs, 2011) and increased mean heart rate (Kozlowska et al., 2015). Contrary findings of equivalent cortisol-levels in patients compared to HC are, however, reported as well (Maurer et al., 2016). Altered somatic sensation is an important feature of FNSD, but also reported in other trauma-related disorders, such as posttraumatic stress disorder (PTSD) and major depression disorder (Gupta, 2013; Kusevic et al., 2013; Tylee & Gandhi, 2005).

Summing up, the following open questions arise: Is altered somatic sensation a specific feature of FNSD (in the sense of an endophenotype of the disorder)? Do patients with FNSD have different somatic reactions to stress than HC?

1.5 Affective Processing in FNSD

Altered emotion processing is discussed as another contributing factor/characteristic feature of FNSD (see above and review by Pick et al.; (Pick, Goldstein, Perez, & Nicholson, 2018)). Research consistently reported alterations in emotion processing on different levels in patients with FNSD. On a behavioural level, patients with FNSD have been shown to have a rather suppressive emotion regulation styles than HC (Steffen et al., 2015) and elevated levels of alexithymia (Demartini et al., 2016; Gulpek, Kelemence Kaplan, Kesebir, & Bora, 2014), describing difficulties in the identification and expression of emotions (Gündel, 2000). Faster reaction times to sad faces are reported and may hint towards abnormal enhanced vigilance for threat stimuli in patients with FNSD (Kozlowska, Brown, Palmer, & Williams, 2013), an assumption that needs to be further debated, as P. Bakvis et al. (2009) did not find group reaction-time differences related to emotional content of stimuli in a stroop task (compared to HC)

Brain data report altered amygdala activity in patients with FNSD in reaction to fearful stimuli (Aybek, 2015; Voon et al., 2010). In contrast to HC, patients with FNSD did not habituate to fearful stimuli over time, which indicates abnormal emotion regulation. Altered amygdala activity in patients with FNSD was also reported recently in reaction to aversive stimuli (Espay, Maloney, et al., 2018) and further studies report the involvement of sensorimotor areas during the processing of affective pictures in patients with FNSD, (Fiess, Rockstroh, Schmidt, & Steffen, 2015; Fiess, Rockstroh, Schmidt, Wienbruch, & Steffen, 2016). Taken together, these results allow for conclusion of altered

emotion-processing networks in patients with FNSD.

Furthermore, Psychophysiological data showed reduced activity of the vagal nerve in patients with FNSD compared to HC (Bakvis et al., 2009), which has been associated with impaired emotion regulation and elevated emotional reactivity (Beauchaine, 2015). Just like alterations in somatic sensation reported above, alexithymia and altered emotion regulation are also present in trauma-related disorders like PTSD (Frewen, Dozois, Neufeld, & Lanius, 2008; Kusevic et al., 2013; Sondergaard & Theorell, 2004) and MDD (Honkalampi, Hintikka, Laukkanen, & Viinamäki, 2001).

Summing up, the following open questions arise: Do impairments in emotion processing play a specific role in patients with FNSD? Can they be modified (across time and therapy)? Do changes in emotion processing vary with changes in symptom severity?

1.6 FNSD, stability over time and therapeutic approaches

Little is known about the development of FNS over time. So far, studies report persistence or worsening of symptoms across 12-month follow-up in about 50-75% of patients (Feinstein et al., 2001). A study by J Stone, Sharpe, Rothwell, and Warlow (2003) accompanied patients across a period of 12 years and showed a persistence in symptoms in 83% of the patients. To date, there are no established clinical factors, indicating which treatment program is best suited for which patient and over which time period (Espay, Aybek, & Carson, 2018). Treatment approaches can be subdivided into psychological, physical, and pharmacological treatment. New treatment approaches also span transcranial magnetic stimulation or transcutaneous electrical stimulation (Espay, Aybek, & Carson, 2018). Within psychological treatment approaches, cognitive behavioural therapy as well as interdisciplinary psychodynamic interpersonal therapy (a variant of psychodynamic therapy, focusing on interpersonal processes), show the most promising

results so far (Goldstein et al., 2010; Hubschmid et al., 2015; LaFrance et al., 2014). One therapeutical focus lies on emotion regulation in conflict situations (Howlett & Reuber, 2009; Kleinstauber, Gottschalk, Berking, Rau, & Rief, 2016). Physical treatment has been shown to be successful in some patients when incorporating psychotherapeutic elements (Czarnecki et al., 2012; Nielsen et al., 2017; Nielsen, Stone, & Edwards, 2013).

1.7 Research questions of the present thesis

Based on the above cited literature that illustrates the interplay of trauma (stress), emotion regulation and somatic sensation in the generation of FNSD, the following model will be tested in the present thesis. This model was also the basis for the DFG-funded project (STE-2263/2-1) under diection of Dr. Astrid Steffen-Klatt and Prof. Dr. Brigitte Rockstroh, part of which the here reported studies were.

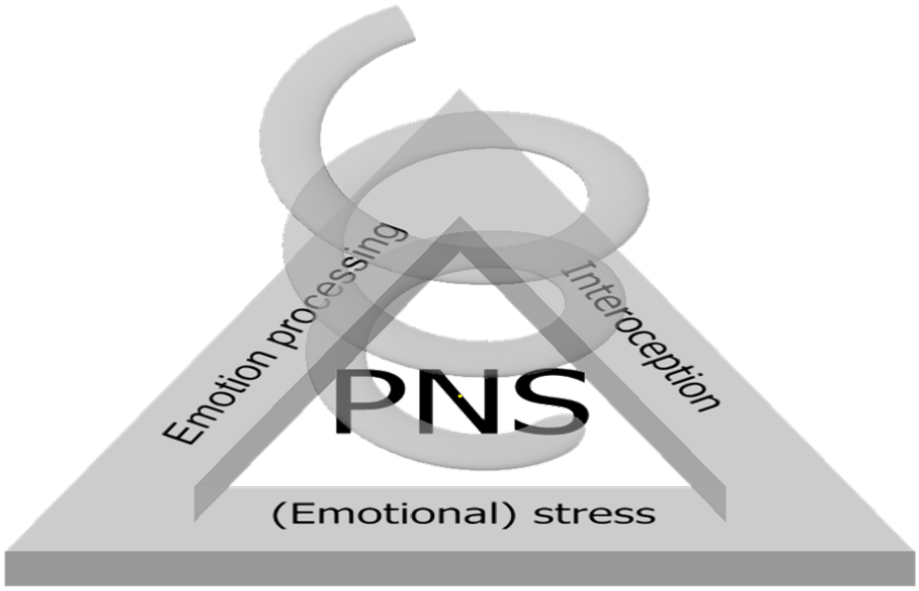

Figure 1: Hypothetical model on the interplay of (emotional) stress, emotion processing and interoception (somatic sensation) in the generation and maintenance of FNSD.

The present thesis aims to contribute to the understanding of FNS by specifically addressing the following questions:

1) Focusing on (emotional) stress: Are FNSD a sub-type of posttraumatic stress disorder? How does acute, biographically relevant stress affect patients with FNSD? (Study 1 and 2)

2) Focusing on emotion processing: Is emotion processing altered specifically (i.e. increased alexithymia, decreased use of cognitive reappraisal for emotion regulation) and dependent on symptom severity when FNS are present? Can these alterations be modified (across time and therapy)? (Study 1 and 3)

3) Focusing on somatic sensation: Is somatic sensation increased or decreased when FNS are present? Is this alteration specific in the sense of an endophenotype of the FNSD? Do patients with FNSD have different somatic reactions to stress than HC? (Study 2)

2 Somatoform dissociation and posttraumatic stress syndrome – two sides of the same medal? A comparison of symptom profiles, trauma history and altered affect regulation between patients with functional neurological symptoms and patients with PTSD

2.1 Abstract

Background: History of traumatic experience is common in dissociative disorder (DD), and similarity of symptoms and characteristics between DD and posttraumatic stress disorder (PTSD) encouraged to consider DD as traumarelated disorder. However, conceptualization of DD as a trauma-related syndrome would critically affect diagnosis and treatment strategies. The present study addressed overlap and disparity of DD and PTSD by directly comparing correspondence of symptoms, adverse/traumatic experience, and altered affect regulation between patients diagnosed with dissociative disorder (characterized by negative functional neurological symptoms) and patients diagnosed with PTSD.

Methods: Somatoform and psychoform dissociation, symptoms of posttraumatic stress, general childhood adversities and lifetime traumata, and alexithymia as index of altered affect regulation were screened with standardized questionnaires and semi-structured interviews in 60 patients with DD (ICD-codes F44.4, F44.6, F44.7), 39 patients with PTSD (ICD-code F43.1), and 40 healthy comparison participants (HC).

Results: DD and PTSD patients scored higher than HC on somatoform and psychoform dissociative symptom scales and alexithymia, and reported more childhood adversities and higher trauma load. PTSD patients reported higher symptom severity and more traumata than DD patients. Those 20 DD patients who met criteria of cooccuring PTSD did not differ from PTSD patients in the amount of reported symptoms of somatoform dissociation, physical and emotional childhood adversities and lifetime traumata, while emotional neglect/abuse in childhood distinguished DD patients with and without co-occuring PTSD (DD patients with co-occuring PTSD reporting more emotional maltreatment).

Conclusion: The pattern of distinctive somatoform and psychoform dissociative symptom severity, type of childhood and lifetime traumata, and amount of alexithymia suggests that DD and PTSD are distinctive syndromes and, therefore, challenges the conceptualization of DD as trauma-related disorder. Together with the detected close correspondence of symptom and experience profiles in DD patients with co-occuring PTSD and PTSD patients, these findings suggest that adverse/traumatic experience may intensify dissociative symptoms, but are not a necessary condition in the generation of functional neurological symptoms. Still, diagnosis and treatment of DD need to consider this impact of traumata and post-traumatic stress symptoms.

2.2 Background

Dissociative disorders (DD), characterized amongst others by loss of sensations and control of bodily movements, are often related to traumatic experience like sexual abuse (Sack et al., 2007; Sar et al., 2004), and emotional neglect or abuse (Ozcetin et al., 2009; Sar et al., 2009). Hence, it has been discussed whether DD can be conceived of as trauma-related syndrome (Fiszman, Alves-Leon, Nunes, D'Andrea, & Figueira,

2004; Nijenhuis, Spinhoven, Dyck, Hart, & Vanderlinden, 1998; van der Hart, Nijenhuis, Steele, & Brown, 2004) Posttraumatic stress disorder (PTSD), as a prominent representative of trauma-related disorders, is defined as response to life-threatening events (e.g. war, rape, torture or natural disaster) with symptoms like intrusions, hyperarousal and avoidance. Severe trauma, particularly sexual and here predominantly childhood sexual trauma, has been proposed as important source of somatoform and psychoform dissociation, potentially crucial in the development of DD (Draijer, 1999; Macfie, Cicchetti, & Toth, 2001; Putnam, Helmers, & Horowitz, 1995; Roelofs et al., 2002). Yet, somatoform dissociative symptoms have been reported in PTSD patients as well (Schalinski, Elbert, & Schauer, 2011), despite emphasis on psychoform dissociative symptoms (Armour, Contractor, Palmieri, & Elhai, 2014; Carlson, Dalenberg, & McDade-Montez, 2012; van der Hart, Nijenhuis, & Steele, 2005). Nijenhuis introduced the concept of somatoform dissociation, referring to dissociative symptoms, that phenomenologically involve the body and comprise reduction up to complete loss of sensory perception and/or loss of motor control (negative somatoform dissociation) as well as involuntary perception of sensory (e.g. prickling), motor (e.g. tremor) and/or pain symptoms (positive somatoform dissociation) (Ellert & Nijenhuis, 2009; Nijenhuis, 1996). On the contrary, psychoform dissociation describes a form of dissociation, that phenomenologically involves the mind (Ellert & Nijenhuis, 2009) and pertains to disrupted mental processes such as consciousness, memory, identity and emotion, manifest in symptoms of depersonalization, derealisation, dissociative amnesia and/or out-of-body experience (Carlson et al., 2012). Often only those phenomena that Nijenhuis and other authors describe as "psychoform dissociation/dissociative symptoms" are subsumed under the label of "dissociation" or "dissociative symptoms" (Carlson et al., 2012). Beyond similarity of dissociative symptoms in PTSD and DD, the impact of dissociation in PTSD is mainly

attributed to trauma severity, as peri-traumatic (mainly psychoform) dissociation and physiological components like fainting (see shut-down dissociation below) may foster later PTSD development and diagnosis (Carlson et al., 2012). Concerning somatoform dissociative symptoms in PTSD and DD, the concept of the defense cascade can explain the relation: Existential threat first prompts excessive physiological arousal (to prepare the organisms for fight/ flight responses), which upon lack of escape options turns into a "shutdown" response. Fainting and immobility as manifestations of vagal dominance represent typical symptoms of such "shutdown" (Nijenhuis, van der Hart, & Steele, 2010; Schalinski et al., 2011; Schalinski, Schauer, & Elbert, 2015; Schauer & Elbert, 2010) and can be described as somatoform dissociation, leading e.g. to functional neurological symptoms (Aybek, 2015; Roelofs & Pasman, 2016). Alexithymia, the deficient ability to perceive and verbally express emotions (Gündel, 2000), signifies another correspondence between DD and PTSD. As representative of altered affect regulation alexithymia has been shown in DD patients (Demartini et al., 2014; Gulpek et al., 2014; Kaplan et al., 2013), as well as in PTSD patients (Frewen, Pain, Dozois, & Lanius, 2006). Frewen and colleagues reported positive correlations between alexithymia, PTSD symptom severity, dissociative symptom severity, and childhood abuse and neglect in PTSD patients, while Sondergaard and Theorell (Sondergaard & Theorell, 2004) determined evolving alexithymia as predictor of selfrated PTSD (but not depressive) symptoms in refugees. A recent study by Terock and colleagues reported alexithymia as predictor of adult psychoform dissociative symptoms independent of the effects of PTSD and childhood trauma (Terock et al., 2016). Furthermore, alexithymia was found to predict suicidal attempt in veterans diagnosed with PTSD (Kusevic et al., 2013).

In the present study, symptom profiles, trauma histories and alexithymia were compared between the two diagnostic categories DD and PTSD with the hypotheses that (1) a common "trauma-related" syndrome becomes manifest in similar somatoform and psychoform dissociative symptoms and similar trauma histories across the diagnostic groups; (2) the relation of trauma history to symptom expression indicates a common meaning of trauma in the generation of DD and PTSD; (3) correspondence of alexithymia between the two diagnostic groups and its relation to dissociative symptom expression indicates the important role of affect regulation in the development of DD and PTSD. In the present sample, patients with ICD-10 diagnoses of DD were characterized by dissociative motor disorder, i.e. "loss of ability to move the whole or part of a limb or limbs" (ICD-10, p. 127), dissociative anaesthesia and sensory loss, referring to impaired tactile, auditory or sensory perception, or mixed dissociative disorder integrating both.[1] Patients with ICD-10 diagnosis of PTSD represented trauma-related disorders. Matching symptom profiles, trauma history, and alexithymia in the two diagnostic groups should indicate the correspondence of syndromes, thus clarifying the conception of DD as trauma-related disorder (thereby informing the meaning of trauma in the generation of DD and supporting attuned diagnostics and treatment strategies).

2.3 Methods

Participants

Sixty patients[2] with ICD-10 diagnoses of dissociative disorder (DD; ICD-10 codes F44.4, F44.6, F44.7), 39 patients with an ICD-10 diagnosis of posttraumatic stress disorder (PTSD; ICD-10 code F43.1), and 40 healthy comparison participants (HC) participated in the study. DD patients were recruited at the local neurological rehabilitation centre (Kliniken Schmieder Konstanz and Gailingen). Following neurological routine, inclusion

criteria were at least one core negative somatoform dissociative symptom. Exclusion criteria were central nervous lesions and positive somatoform dissociative symptoms (e.g. seizures). Similar subtypes of dissociative disorders, characterized by negative somatoform dissociative symptoms were selected in order to assure homogeneity of the study sample. Diagnoses were given by at least two experienced psychiatrics and neurologists. Patients diagnosed with PTSD were recruited at the Department of Psychosomatic Medicine and Psychotherapy of the Central Institute for Mental Health (CIMH, Mannheim). Diagnoses were based on DSM-IV criteria (Structured clinical interview for DSM-IV and International Personality Disorder Examination (First, Williams, Karg, & Spitzer, 2015; Loranger, 1997)). Comorbid conditions are summarized in Table 5. HC were recruited from the local community by flyer and oral advertisement and selected to be comparable to the patient samples with respect to age and gender distribution. HC were screened for DSM-axis I and II diagnoses using the German version of the MINI international Neuropsychiatric Interview (Ackenheil, Stotz, Dietz-Bauer, & Vossen, 1999). Volunteers who reported any kind of current or past neurological or mental disorders or the use of psychoactive medication were not included in the sample. Table 1 summarizes demographic information of the three groups. While groups did not differ in gender and age distribution, HC had a higher educational level than patients with DD and PTSD.

Table 1: Sociodemographic information of study samples

	DD patients	**PTSD patients**	**HC**	**Comparison across groups**
N	60	39	40	
Gender (f/m)	45/15	33/6	34/6	$\chi^2 = 2.09$, $p = .35$
Age (M ± SD)	42.6 ± 12.31	41.3 ± 9.32	40.6 ± 11.9	$H(2) = 0.9$, $p = .64$
Years schooling (M ± SD)	10.8 ± 2.27	10.7 ± 1.59	11.8 ± 1.49	$H(2) = 11.69$, $p = .003$

Note. DD = dissociative disorder; PTSD = posttraumatic stress disorder;
HC = healthy comparison participants; f = female; m = male

Design and procedure

The study design was approved by the ethics committee of the University of Konstanz, the board of the neurological rehabilitation centre Kliniken Schmieder and the board of Mannheim medical faculty of Heidelberg University. Prior to data assessment, participants were informed about the study purpose and the procedures and signed written informed consent. Thereafter, childhood adversities and lifetime traumata were assessed using standardized semi-structured interviews administered by trained project members. Each interview lasted about 1.5 h. In addition, dissociation, PTSD symptoms and alexithymia were screened with questionnaires, which participants filled in on their own (project members being available for questions). Data assessment was accomplished at the institution of recruitment and lasted altogether about 2-3 h per participant. HC and PTSD patients at the CIMH received a bonus of 20 Euro for participation, while DD patients filled in the questionnaires/interview set as part of their treatment.

Material

Somatoform *dissociative symptoms* were measured with the Somatoform Dissociation Questionnaire (SDQ-20 (Nijenhuis, 1996); German version by (Mueller-Pfeiffer et al., 2010), see appendix for details).[3] Psychoform dissociation was assessed with the Dissociative Experience Scale (DES (Bernstein & Putnam, 1986); German version by (Freyberger et al., 1998)).[4] Both scales, SDQ-20 and DES, show good internal consistency and reliability (SDQ-20, $\alpha = .914$, $r_{tt} = .89$, (Mueller-Pfeiffer et al., 2010), DES, $\alpha = .94$, $r_{tt} = .82$, (Bernstein & Putnam, 1986)). Severity of *PTSD symptoms* (hyperarousal, intrusions, avoidance) and number of *lifetime traumatic experience* were verified with the Posttraumatic Stress Diagnostic Scale (PDS (Foa, Cashman, Jaycox, & Perry, 1997))[5] which shows good internal consistency ($\alpha = .94$) and validity (Griesel, Wessa, & Flor, 2006). *Adverse experience in childhood and adolescence* were assessed using the Ger-

man version KERF ('Kindheitserfahrungen', (Isele et al., 2014)) of the Maltreatment and Abuse Chronology of Exposure (Teicher & Parigger, 2011).[6] As measure of altered affect regulation, alexithymia was assessed with the Toronto Alexithymia Scale (TAS-26 (Bagby, Taylor, & Parker, 1994); German version by (Kupfer, Brosig, & Brähler, 2000), internal consistency $\alpha = .84$).[7]

Data analysis

Measures of symptom severity, adverse/traumatic experience, and alexithymia were first compared between the three samples (DD, PTSD, HC). Per PDS, 20 of the 60 patients diagnosed with DD met criteria of cooccuring PTSD. Therefore, analyses were repeated for four subgroups: patients with DD and co-occuring PTSD (DD^+), patients with DD without co-occuring PTSD (DD^-), patients with PTSD, and HC. The four groups did not differ in gender (χ^2 (3, N = 139) = 4.01, $p = .26$) and age distribution (H(3) = .91, $p = .82$), while the significant difference in education between HC and the three patient groups remained. Since data within subgroups was not normally distributed, with positive skew in HC and negative skew in both patient groups and the assumption of homogeneity of variance was not met, we applied non-parametric testing of group differences using the Kruskall-Wallis test. Post-hoc subgroup differences were verified by Mann-Whitney tests Bonferroni-corrected for multiple comparisons with alpha corrected to .007. Effect sizes were calculated using the estimate "r" described by Rosenthal (1991) which is robust to unequal sample sizes (Rosenthal, 1991).

The impact of childhood adversities and traumata on somatoform symptom severity was examined by forced entry multiple regression analyses including overall childhood severity (KERF_Sum) or the number of lifetime traumata (PDS_Event) and PTSD symptom severity (PDS_Sym) as predictors of somatoform dissociative symptom severity (SDQ-20).

2.4 Results

Symptom severity across groups (HC vs. DD vs. PTSD)

PTSD patients scored higher on dissociative symptom scales and on the posttraumatic stress symptom scale than DD patients and HC (see Table 2 for mean scores and Table 3 for statistical group differences). The comparison of the four subgroups (DD^+ vs. DD^- vs. PTSD vs. HC; see Table 4) confirmed different somatoform dissociation and symptoms of posttraumatic stress between subgroups except for the comparison between DD^+ and PTSD patients (see Table 4). This indicates symptom correspondence between these two subgroups, although DD^+ expressed less psychoform dissociation than PTSD patients.

Adversity and trauma measures across groups (HC vs. DD vs PTSD)

PTSD patients reported more traumatic events across lifetime than the other groups (median see Tables 2 and 3). PTSD patients had also experienced more childhood adversities (KERF_Sum) than DD and HC. Differences between DD patients and PTSD patients were confirmed for physical, emotional and sexual maltreatment in childhood (see Table 3). Importantly, physical and emotional maltreatment, and lifetime traumata did not differ between DD^+ and PTSD patients, whereas PTSD patients reported more sexual abuse than DD^+. Emotional neglect/abuse in childhood distinguished DD^+ and DD^- (DD^+ reported more emotional maltreatment than DD^-; see Table 4). DD patients reported more overall exposure to childhood adversities than HC, however there was no significant difference between the subgroup of DD patients without co-occuring PTSD and HC. Except for physical maltreatment, childhood adversities did not differ between DD^- and HC.

Table 2: Median and range of symptom severity, adversity/trauma measures, and alexithymia scores

	HC n = 40 median (range)	**DD$^-$** n = 40 median (range)	**DD$^+$** n = 20 median (range)	**PTSD patients** n = 39 median (range)
Symptom severity				
SDQ-20	21 (20-26) n = 40	28.5 (20-54) n = 40	36.5 (29-56) n = 18	36 (20-91) n = 39
DES	6.49 (0-25.36) n = 40	12.14 (0-48.57) n = 40	19.64 (9.64-51.79) n = 20	38.57 (8.57-80.71) n = 39
PDS_Sym	0 (0-8) n = 40	4 (0-38) n = 40	30 (16-46) n = 20	36 (13-48) n = 39
Adversity/trauma measures				
KERF_Sum	35.08 (0-235.5) n = 40	90.17 (0-533.08) n = 38	219.67 (18.83-605) n = 17	369 (60-885.75) n = 39
KERF_Phy	7.33 (0-141.67) n = 40	40.33 (0-229.3) n = 38	33 (1.67-304) n = 17	141 (0-462) n = 39
KERF_Emo	25 (0-218) n = 40	52.5 (0-329) n = 38	141 (14.5-362) n = 17	239.5 (51-423.5) n = 39
KERF_Sex	0 (0-1.3) n = 40	0 (0-23.8) n = 38	0 (0-27.5) n = 17	7.5 (0-40) n = 39
PDS_Event	1.5 (0-5) n = 40	3 (0-7) n = 40	4 (2-7) n = 20	5 (2-8) n = 39
Alexithymia				
TAS-26	1.94 (1.33-3.05) n = 40	2.58 (1.39-3.44) n = 40	2.92 (1.83-4.33) n = 20	3.44 (1.66-4.55) n = 39

Note. HC healthy comparison participants; DD$^-$ patients diagnosed with dissociative disorder without co-occuring PTSD; DD$^+$ patients diagnosed with dissociative disorder with co-occuring PTSD; PTSD posttraumatic stress disorder; SDQ-20 severity of somatoform dissociative symptoms, verified by the Somatoform Dissociation Questionnaire; DES severity of psychoform dissociative symptoms, using the Dissociative Experience Scale; PDS_Sym load of posttraumatic symptoms; KERF_Sum overall exposure to childhood adversities; KERF_Phy physical maltreatment during childhood; KERF_Emo emotional neglect and maltreatment during childhood; KERF_Sex sexual violence during childhood; PDS_Event Sum of lifetime traumatic experiences assessed with the Posttraumatic Diagnostic Scale; TAS-26 Alexithymia, assessed with the Toronto Alexithymia Scale.

Table 3: Group comparisons (DD, HC, PTSD) – Inferential statistics of symptom severity, adversity/trauma measures, and alexithymia scores

	Comparison across groups	**DD patients vs. HC** n = 100	**PTSD patients vs. HC** n = 79	**DD patients vs. PTSD patients** n = 99
Symptom severity				
SDQ-20	H(2) = 70.62	U = 172.5	U = 62	U = 727
		z = -7.17	*z = -7.07*	*z = -2.98*
	p < .001	p < .001	p < .001	p = .021
		r = -0.72	r = -0.80	r = -0.30
DES	H(2) = 68.77	U = 585	U = 24.5	U = 348
		z = -4.33	*z = -7.41*	*z = -5.89*
	p < .001	p < .001	p < .001	p < .001
		r = -0.43	r = -0.83	r = -0.59
PDS_Sym	H(2) = 82.23	U = 402.5	U = 0	U = 322
		z = -5.80	*z = -7.8*	*z = -6.08*
	p < .001	p < .001	p < .001	p < .001
		r = -0.58	r = -0.88	r = -0.61
Adversity/trauma measures				
KERF_Sum	H(2) = 57.55	U = 610	U = 49	U = 364.5
		p = -3.70	*z = -7.05*	*z = -5.20*
	p < .001	p < .001	p < .001	p < .001
		r = -0.37	r = -0.79	r = -0.52
KERF_Phy	H(2) = 49.07	U = 647.5	U = 113.5	U = 460
		z = -3.43	*p = -6.55*	*z = -4.70*
	p < .001	p = .001	p < .001	p < .001
		r = -0.34	r = -0.73	r = -0.47
KERF_Emo	H(2) = 60.12	U = 606	U = 47.5	U = 377.5
		z = -3.72	*z = -7.19*	*z = -5.33*
	p < .001	p < .001	p < .001	p < .001
		r = -0.37	r = -0.80	r = -0.53
KERF_Sex	H(2) = 52.83	U = 943.5	U = 226	U = 472.5
		z = -2.22	*z = -6.29*	*z = -5.22*
	p < .001	n.s.	p < .001	p < .001
			r = -0.70	r = -0.52
PDS_Event	H(2) = 49.32	U = 536	U = 108.5	U = 708.5
		z = -4.73	*z = -6.66*	*z = -3.36*
	p < .001	p < .001	p < .001	p = .007
		r = -0.47	r = -0.74	r = -0.34
Alexithymia				
TAS-26	H(2) = 70.34	U = 387	U = 67.5	U = 408
		z = -5.72	*z = -6.99*	*z = -5.46*
	p < .001	p < .001	p < .001	p < .001
		r = -0.57	r = -0.78	r = -0.54

Note. HC healthy comparison participants; DD patients diagnosed with dissociative disorder; PTSD posttraumatic stress disorder; SDQ-20 severity of somatoform dissociative symptoms, verified by the Somatoform Dissociation Questionnaire; DES severity of psychoform dissociative symptoms, using the Dissociative Experience Scale; PDS_Sym load of posttraumatic symptoms; KERF_Sum overall exposure to childhood adversities; KERF_Phy physical maltreatment during childhood; KERF_Emo emotional neglect and maltreatment during childhood; KERF_Sex sexual violence during childhood; PDS_Event Sum of lifetime traumatic experiences assessed with the Posttraumatic Diagnostic Scale; TAS-26 Alexithymia, assessed with the Toronto Alexithymia Scale.

Relationship between trauma/maltreatment and symptom severity (overall and within subgroups)

The relationship between the sum of adverse childhood experience, posttraumatic symptom severity, and somatoform dissociative symptom severity is illustrated for the entire sample (HC, DD, PTSD) in figure 2 and for the two subsamples of DD patients (DD^+ and DD^-) in figure 3. Figure 4 shows the association between the number of lifetime traumatic events, posttraumatic symptom severity, and somatoform dissociation for the two subsamples of DD patients. Figures 3 and 4 suggest a relationship between PTSD symptoms and severity of somatoform dissociation in DD patients with low and with high number of adverse childhood experience and traumata. Multiple regression analysis confirmed that adverse childhood experience, number of lifetime traumatic events, and severity of PTSD symptoms did explain 30% of variance of somatoform dissociation in DD patients ($R2 = .30$, $F(3, 53) = 7.25$, $p < .001$). However, adverse childhood experience ($\beta = -.002$, $p = .99$) and number of lifetime traumatic events ($\beta = .27$, $p = .08$) did not explain variance in addition to severity of PTSD symptoms ($\beta = .38, p < .001$). This relationship was also observed in patients with PTSD: the three factors did account for 31% of variation in somatoform dissociation ($R2 = .31$, $F(3, 36) = 5.11$, $p < .01$). Again, adverse childhood experience ($\beta = .075$, $p = .63$) and number of liefetime traumatic events ($\beta = .055$, $p = .71$) did not explain variance in addition to severity of PTSD symptoms ($\beta = .52$, $p < .001$).

Alexithymia across groups (HC vs. DD vs. PTSD)

PTSD patients scored higher on the alexithymia scale (TAS-26) than DD patients, and both patient groups expressed more alexithymia than HC (see Table 2). Although alexithymia scores in the present DD sample were lower than expected from the literature, alexithymia was related to dissociative and posttraumatic stress symptom severity in

Table 4: Group comparisons (DD^+, DD^-, HC, PTSD) – Inferential statistics of symptom severity, adversity/trauma measures, and alexithymia scores

	Comparison across groups	**DD^+ vs. PTSD patients** n = 59	**DD^- vs. PTSD patients** n = 79	**DD^- vs. HC** n = 80	**DD^+ vs. DD^-** n = 60
Symptom severity					
SDQ	H(3) = 77.61	U = 332.5	U = 394.5	U = 172.5	U = 151.5
		z = -3.20	*z = -3.78*	*z = -6.08*	*z = -3.51*
	p < .001	*n.s.*	p < .001	p < .001	p < .001
			r = -0.41	r = -0.68	r = -0.45
DES	H(3) = 78.20	U = 197.5	U = 150.5	U = 528.5	U = 168.5
		z = -3.08	*z = -6.17*	*z = -2.61*	*z = -3.63*
	p < .001	p = .014	p < .001	*n.s.*	p < .001
		r = -0.40	r = -0.61		r = -0.47
PDS_Sym	H(3) = 102.77	U = 267.5	U = 54.5	U = 402.5	U = 37
		z = -1.96	*z = -7.13*	*, z = -4.09*	*z = -5.72*
	p < .001	*n.s.*	p < .001	p < .001	p < .001
			r = -0.8	r = -0.46	r = -0.74
Adversity/trauma measures					
KERF_Sum	H(3) = 61.63	U = 169	U = 195.5	U = 510	U = 203
		z = -2.71	*z = -5.38*	*z = -2.5*	*z = -2.19*
	p < .001	p = .049	p < .001	n.s.	n.s.
		r = -0.35	r = -0.61		
KERF_Phy	H(3) = 49.98	U = 183	U = 277	U = 481.5	U = 271
		z = -2.65	*z = -4.73*	*z = -2.8*	*z = -0.95*
	p < .001	*n.s.*	p < .001	p = 0.03	*n.s.*
			r = -0.53	r = -0.31	
KERF_Emo	H(3) = 66.10	U = 194.5	U = 183	U = 512.5	U = 169.5
		z = -2.44	*z = -5.69*	*z = -2.47*	*z = -2.80*
	p < .001	*n.s.*	p < .001	*n.s.*	p = .035
			r = -0.63		r = -0.36
Mace_Sex	H(3) = 53.50	U = 173	U = 299.5	U = 676.5	U = 287.5
		z = -2.94	*z = 4.99*	*z = -1.81*	*z = -1.00*
	p < .001	p = .021	p < .001	*n.s.*	*n.s.*
		r = -0.38	r = -0.56		
PDS_Event	H(3) = 52.07	U = 301.5	U = 407	U = 424.5	U = 291.5
		z = -1.45	*z = -3.72*	*z = 3.67*	*z = -1.73*
	p < .001	*n.s.*	p < .001	p < .001	*n.s.*
			r = -0.42	r = -0.41	
Alexithymia					
TAS-26	H(3) = 74.97	U = 211, z = -2.87	U = 197, z = -5.72	U = 325.0, z = 4.58	U = 226, z = -2.73
	p < .001	p = .028	p < .001	p < .001	p = 0.042
		r = -0.37	r = -0.64	r = -0.51	r = -0.35

Note. HC healthy comparison participants; DD^- patients diagnosed with dissociative disorder without co-occuring PTSD; DD^+ patients diagnosed with dissociative disorder with co-occuring PTSD; PTSD posttraumatic stress disorder; SDQ-20 severity of somatoform dissociative symptoms, verified by the Somatoform Dissociation Questionnaire; DES severity of psychoform dissociative symptoms, using the Dissociative Experience Scale; PDS_Sym load of posttraumatic symptoms; KERF_Sum overall exposure to childhood adversities; KERF_Phy physical maltreatment during childhood; KERF_Emo emotional neglect and maltreatment during childhood; KERF_Sex sexual violence during childhood; PDS_Event Sum of lifetime traumatic experiences assessed with the Posttraumatic Diagnostic Scale; TAS-26 Alexithymia, assessed with the Toronto Alexithymia Scale.

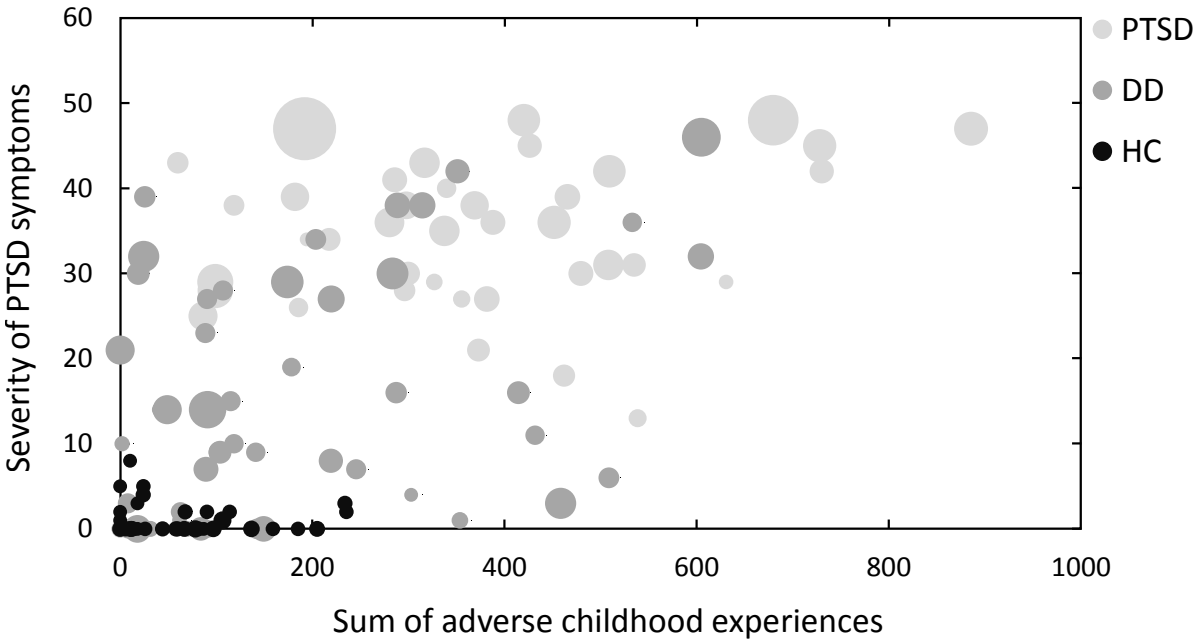

Figure 2: Relationship between the sum of adverse childhood experience (abscissa), severity of PTSD symptoms (ordinate), and somatoform dissociation (SDQ-20 scores), expressed by size of filled circles: larger filled circles correspond to higher SDQ-scores. Each circle represents a participant; subgroups are reflected by color-coding with *light grey circles* representing PTSD patients, *dark grey circles* DD patients, *black circles* HC

DD patients, in that more intense alexithymia varied with more intense somatoform dissociative ($r = .30$, $p = .02$), psychoform dissociative ($r = .40$, $p = .001$), and PTSD symptoms ($r = .31$, $p = .02$). For patients with PTSD, alexithymia was also positively related to somatoform dissociative symptoms ($r = .34$, $p = .03$).

2.5 Discussion

A history of traumatic experience and corresponding symptoms in affected patients have encouraged the association of dissociative and posttraumatic stress disorders. However, conceiving of both diagnoses as the same syndrome asks for conformity on all levels. The present comparison of characteristic symptoms, trauma and maltreatment history between patients diagnosed with DD or PTSD (per hypothesis 1) demonstrated group

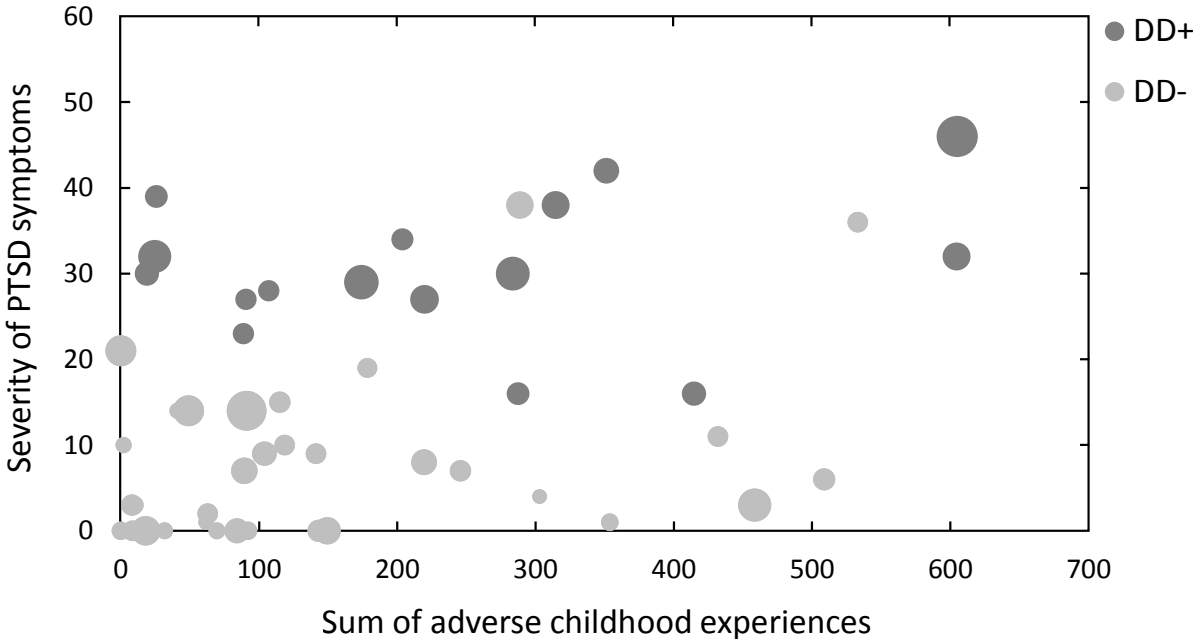

Figure 3: Relationship between the sum of adverse childhood experience (abscissa), severity of PTSD symptoms (ordinate), and somatoform dissociation (expressed by size of filled circles: larger filled circles correspond to higher SDQ-scores) illustrated separately for DD patients with (DD^+; *dark grey circles*) and DD patients without (DD^-; *light grey circles*) co-occuring PTSD diagnosis

differences in symptom prominence (e.g., psychoform vs. somatoform symptoms) and trauma profiles (e.g. emotional vs. sexual abuse) that challenge a global assignment of DD to the category of trauma-related disorders. Rather, the conformity of DD patients with co-occuring PTSD and PTSD patients on several measures (number of lifetime traumata, amount of physical and emotional abuse in childhood, PTSD symptom severity and severity of somatoform dissociation) suggests the portrayal of a "trauma-related DD syndrome". While accumulated traumatic experience may add to symptom severity, they are not critical for the generation of DD (compare also research by Stone and colleagues (Stone & Edwards, 2011)). Distinction of syndromes per symptom and trauma profile does not render the association between trauma and dissociation obsolete (hypothesis 2). Indeed, the variation of severity of posttraumatic stress symptoms and

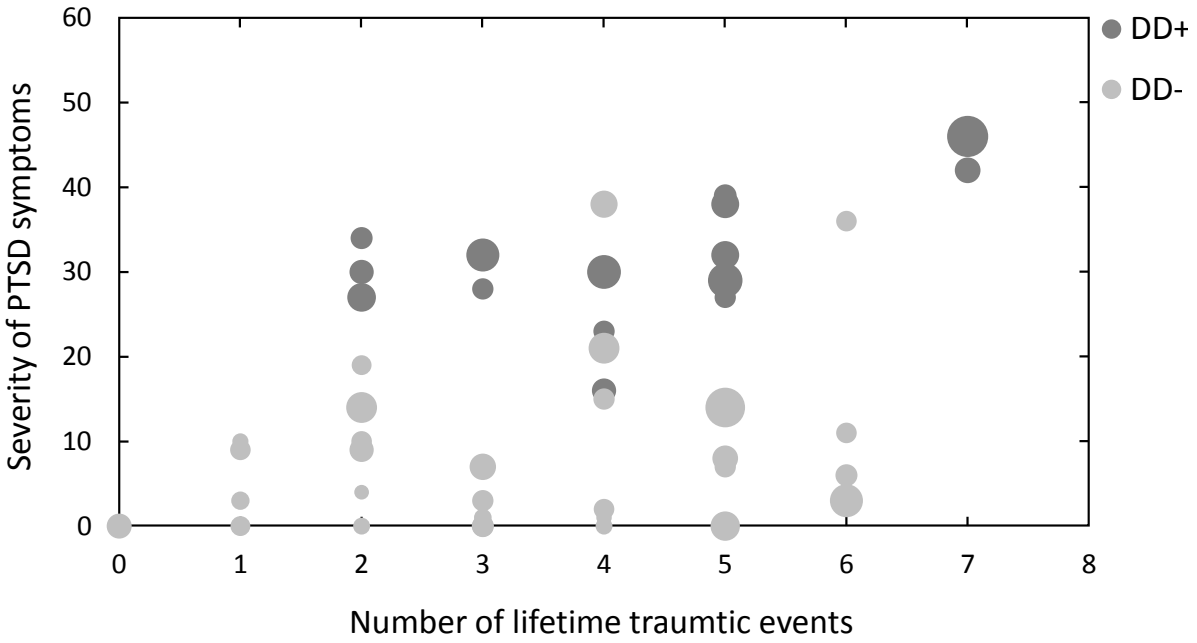

Figure 4: Relationship between the number of lifetime traumatic events (abscissa), severity of PTSD symptoms (ordinate), and somatoform dissociation (expressed by size of filled circles: larger filled circles correspond to higher SDQ-scores) separately for DD patients with (DD^+; *dark grey circles*) and DD patients without (DD^-; *light grey circles*) co-occuring PTSD diagnosis

dissociative symptoms with traumata and childhood maltreatment, illustrated in Figs. 1, 2 and 3, suggests an impact of coping with such experience on augmented somatoform dissociation and the development of DD. Moreover, chronic dissociative symptoms in DD and PTSD may be explained as a conditioned response upon repeated adverse experience (Nijenhuis et al., 2010; Schalinski et al., 2011, 2015; Schauer & Elbert, 2010). It is conceivable, that the individual post-traumatic learning and coping history shapes development and type of dissociative symptom (psychoform or somatoform) upon later confrontation with adverse and traumatic events (Schauer & Elbert, 2010). For instance a learning history of early coping with the emotional consequences of trauma and maltreatment with somatic symptoms and somatoform dissociation may favour the development of DD. Alexithymia as an expression of altered emotion processing was

expected to be increased in patient groups and related to symptom expression. The present diagnostic groups differed in alexithymia, in that DD patients had lower TAS scores than PTSD patients. This suggests that DD patients were able to perceive and express their emotions, although less efficiently than HC. In line with the hypothesis of modulation by learning history, and the literature (Steffen et al., 2015), the positive relation between alexithymia and somatoform symptom severity might reflect the learned attribution of feelings to somatic sensations. A further factor to explain the evolution of trauma-related and dissociation-related disorders (PTSD and DD in the present example) might be the dose: The coincidence of higher trauma load (childhood adversities and lifetime traumata) and higher symptom scores in PTSD patients and DD patients with comorbid PTSD may indicate a "dose effect", i.e., higher trauma load results in the more severe disorder as characterized by comorbidity and symptom severity (Neuner et al., 2004). Commonly, higher trauma load in patients with PTSD as well as in DD patients is described to be related to more sexual traumata. In contrast, in the present data this relation was replicated for the PTSD group only, while both DD groups report similar sexual traumata as HC. Interestingly, emotional adverse experience do differentiate between both DD groups, which may point towards emotional neglect/abuse as a distinguishing factor. Potential influences of comorbid conditions also have to be taken into account here: Depression is a frequent comorbid disorder in PTSD (Rytwinski, Scur, Feeny, & Youngstrom, 2013) and DD (Stone et al., 2012) also in the present groups (Table 5). Recent research found evidence for a depressive subtype of PTSD that is associated with greater dissociative experience (Contractor, Roley-Roberts, Lagdon, & Armour, 2017). Since 38.5% of the current sample of PTSD patients suffered from a comorbid depressive disorder or depressive episode, this may explain the high amount of dissociative symptoms. Frequency of comorbid depressive and anxiety dis-

orders (identified as further comorbid conditions across groups) did not significantly differ between the current patient groups, so that a major impact of this comorbidity on the between-group differences of interest seems unlikely. Current group-specific comorbidities, i.e. comorbid somatoform disorder in DD patients and comorbid borderline personality disorder in PTSD patients are comparable to results from previous studies (Frias & Palma, 2015; Meyer et al., 2016; Sar et al., 2004; Stone & Edwards, 2011) and indicate common contributions to dissociative symptoms. Dissociative disorders are characterized by somatoform dissociative symptoms independent of comorbid PTSD diagnosis – as reflected by the amount of comorbid somatoform disorder diagnoses, which was significantly higher in patients diagnosed with DD compared to patients diagnosed with PTSD.

Limitations of the present study have to be noted: (1) Different syndromes of PTSD and DD were concluded from different symptom profiles. However, as patient samples were recruited in different institutions, differences in treatment settings between the two patient groups are likely. It cannot be ruled out, that these differences may have influenced the results. (2) Many DD patients showed substantial signs of severe somatoform dissociative symptoms (like sitting in a wheelchair) parallel to low self-evaluation of somatoform dissociation (lower SDQ-20 scores than PTSD patients). This suggests, that the SDQ-20 may not properly mirror severity of functional neurological symptoms in DD patients. For each symptom the SDQ-20 evaluated the frequency of experience, while symptom duration was not assessed. Somatoform dissociative symptoms are long lasting or permanent in DD, while they may last for minutes or hours in PTSD. Thus, including symptom duration in the measurement of dissociative symptoms seems mandatory for the specification of DD syndrome and its distinction from PTSD. (3) Involving PTSD as an example of trauma-related syndrome in the present study does not justify the

generalization of the present results and conclusions. Further studies should consider other trauma-related syndromes, such as acute stress disorder, adjustment disorder etc. However, complex PTSD was chosen as an example for trauma-related disorders in the present study, since it is associated with high levels of dissociation – which is especially documented in manifold studies reporting psychoform dissociative symptoms in PTSD patients (Armour et al., 2014; Carlson et al., 2012; van der Hart et al., 2005) and multiple trauma experience in patients with conversion or other dissociative disorders (Draijer, 1999; Putnam et al., 1995; Roelofs & Pasman, 2016).

2.6 Conclusion

The present comparison of symptoms and trauma history between DD and PTSD revealed a clear distinction between the diagnostic groups, disconfirming hypothesis (1) of a common syndrome. Still, results indicate an important role of adverse/traumatic experiences and the experience of posttraumatic stress symptoms in the development of dissociative symptoms (per hypothesis 2). This specification matches the diagnostic descriptions in DSM-V, in that a relevant psychological stressor preceding the onset of functional neurological symptom disorder, earlier required as diagnostic criterion, is now labelled as a specification feature. Moreover, distinct sub-groups of DD patients with and without PTSD are also reflected in the specification of a dissociative subtype of PTSD in DSM-5. The results have important clinical implications: Adopting a context of linking dissociative and trauma-related disorders asks to consider a broad range of dissociative symptoms, not only psychoform derealization or depersonalization phenomena but also somatoform dissociative symptoms (Mullerova, Hansen, Contractor, Elhai, & Armour, 2016; Schalinski et al., 2011, 2015; Schauer & Elbert, 2010). Present results further direct attention to individual maltreatment and coping/learning history to be

considered in diagnostics and treatment: While the number of traumatic events may determine the severity of distress, the individual coping history with adversities and traumata may modulate, how symptoms develop and accentuate in patients diagnosed with DD, and potentially overlap with those of individuals diagnosed with PTSD. This advocates the careful assessment of trauma history and its consequences in diagnostics and treatment of DD.

2.7 Endnotes

[1]In DSM-V these subtypes of dissociative disorder are part of the diagnosis of conversion disorder or functional neurological symptom disorder (FNSD).

[2]The present sample partially overlaps with the one reported in (Steffen et al., 2015).

[3]The 20-item self-report instrument assesses the frequency of somatoform dissociation experienced in the preceding 1 months. It includes negative symptoms of dissociation like sensory losses and loss of motor control as well as positive symptoms of dissociation like alterations of vision, audition, taste and smell. Items are evaluated on a 5-point Likert Scale (from "This applies to me not at all" to "This applies to me extremely"), resulting in possible sum-scores between 20 and 100.

[4]The DES is a 28-item self-report measure covering the domains amnesia, absorption and derealisation/depersonalisation. The percentage of experienced symptoms across lifetime is evaluated on a continuum between 0% ("never") to 100% ("always"). Mean values are ranging from 0 to 100.

[5]The PDS-symptom scale comprises 17 items, severity of each symptom being scored on a scale from 0 to 3, resulting in sum-scores between 0 and 51.

[6]The KERF includes 70 items covering ten domains of experience (parental verbal abuse, parental non-verbal emotional abuse, parental physical abuse, emotional neglect, physi-

cal neglect, familial and non-familial sexual abuse, witnessed physical violence towards parents, witnessed violence towards siblings, peer emotional and peer physical violence), together with age of onset and duration of the respective experience up to age 18. The following analyses include all experience until individual onset of puberty, determined by first menarche/puberty vocal change. Convergent validity of the KERF was verified by correlation with the Childhood Trauma Questionnaire and good test-retest reliability was established ($r_{tt} = .91$ at 10 weeks [42]). For the present analyses sum-scores of subscales were collapsed to three broader categories: emotional abuse/neglect (KERF_Emo) with a range from 0 to 720 (including parental verbal abuse, parental non-verbal emotional abuse, emotional neglect, peer emotional violence), physical abuse/neglect (KERF_Phy) with a range from 0 to 900 (including parental physical abuse and neglect, witnessed physical violence towards parents, witnessed violence towards siblings, peer physical violence) and sexual violence (KERF_Sex) with a range from 0 to 180 (including familial and nonfamilial sexual abuse). In addition, the overall severity of exposure to childhood adversities until individual onset of puberty (KERF_Sum), ranging from 0 ("no childhood adversities at all") to 1800 ("maximal exposure to all types of childhood adversities") was calculated.

[7]The 26-item self-report questionnaire assesses alexithymia on three dimensions: "difficulty identifying feelings", "difficulty describing feelings" and "externally oriented thinking". Overall mean values, ranging from 1 to 5 are reported.

3 Body Sensations in Functional Neurological Symptom Disorder – typical or specific feature?

3.1 Abstract

Introduction: Altered somatic sensation is common in different mental disorders and linked to traumatic experiences, which in turn are associated with functional neurological symptom disorder (FNSD). Measuring somatic sensation in FNSD is challenging and often based on discrimination tasks and self-report measures. The present study examined as to what extent altered somatic sensation is a specific feature to FNSD, defining somatic sensation by perception and discomfort threshold on transcutaneous electric nerve stimulation (TENS).

Methods and materials: TENS was applied in a sample of $n = 28$ patients diagnosed with FNSD, n = 29 patients with major depressive disorder (MDD), $n = 22$ patients with posttraumatic stress disorder (PTSD) and $n = 31$ healthy comparison subjects (HC) at three time-points: at baseline as well as before and after an interview on traumatic life experiences. Somatic sensation at baseline was compared across groups and related to somatic symptom load, depressive symptoms, posttraumatic stress symptoms and to the amount of childhood adversities within the FNSD group. The impact of acute stress (induced by the interview) was assessed by comparing TENS values before and after the interview in patients with FNSD.

Results: At baseline measurement, (TENS) perception and discomfort threshold were similar across groups. Somatic sensation thresholds for perception and discomfort at baseline did neither vary with somatic- nor with depressive- or posttraumatic stress symptoms of FNSD patients. Adverse childhood experience did not affect somatic sen-

sation thresholds at baseline, but following an interview on these experience perception threshold was elevated in FNSD patients.

Discussion: Although altered somatic sensation could not be confirmed as specific feature in FNSD, the result of blunted somatic sensation following the interview on traumatic experiences points in the direction of an important role of acute stress on the generation of functional neurological symptoms and encourages the application of TENS in further studies on somatic sensation in FNSD.

3.2 Introduction

Patients diagnosed with functional neurological disorders (FNSD) present various somatic symptoms and impaired sensory function (DSM-5;(Association, 2013)), associated with significant distress and compromised functioning in everyday life (Carson et al., 2000; Fobian & Elliott, 2018). Whereas somatic symptoms are not specific for FNSD (or somatoform disorders) but also evident in major depressive disorder (MDD) and post-traumatic stress disorder (PTSD; (Gupta, 2013; Kusevic et al., 2013; Tylee & Gandhi, 2005)), impaired sensory function is listed as specific diagnostic criterion for FNSD in DSM-5. As to what extent these sensory and somatic symptoms indicate a specific, thus diagnostically relevant, feature in FNSD, is unclear. For instance, altered somatic sensation in patients with FNSD was deduced from diminished capacities to discriminate tactile stimuli (Tinazzi et al., 2014) and heartbeats (Ricciardi et al., 2016). However, measuring somatic sensation in FNSD seems challenging. Diagnostic measurements most often rely on self-report measures or discrimination tasks (tactile, heartbeat – see above). As an alternative, the assessment of cutaneous perception threshold by transcutaneous electric nerve stimuation (TENS) was probed as objective and symptom-independent measure. An exploratory study (Fiess et al., 2015) verified similar perception thresholds

in FNSD and healthy comparison participants under conditions of emotionally upsetting (versus neutral) visual stimulation, whereas discomfort threshold was lowered after the emotional challenge in FNSD but not in control participants. Building on these preliminary results, TENS was used to clarify altered somatic sensation as specific feature in FNSD in the present study.

Altered somatic sensation is not only common in many mental disorders, it is also associated with stress (Bob et al., 2013) and traumatic experience (Afari et al., 2014; Rabellino et al., 2018). Alterations in somatic sensation as consequence of traumatic experiences have been explained using the concept of the shutdown dissociation (Schalinski et al., 2015; Schauer & Elbert, 2010). Under the confrontation of life-threatening stimuli, (somatoform) dissociative responding seems to be adaptive for the organism at a certain stage. This somatoform dissociation leads to blunted somatic sensation, which, if chronified might lead to persisting functional neurological symptoms (FNS).

Several studies have derived a contribution of adverse experience to the generation of FNSD (Crommelinck, 2014b; Kaplan et al., 2013; Ludwig et al., 2018; Roelofs & Pasman, 2016; Sar et al., 2004; Steffen-Klatt et al., 2018). Thus, it is unclear, whether altered somatic sensation represents a general consequence of traumatic experience, or bears a specific role in FNSD. Moreover a temporal relationship with psychological stress is assumed as diagnostic criterion for FNSD in ICD-10 and a recent study showed dissociation between perceived stress and biological markers during social stress in patients with FNSD, compared to HC (Apazoglou et al., 2017). Unfortunately, it remains unclear, whether somatic sensation is blunted (following shutdown dissociation) or sensitized in patients with FNSD - probably depending on different types of measures, results so far vary dramatically: Poor, i.e. blunted, interoceptive awareness has been reported in patients with FNSD compared to HC (Ricciardi et al., 2014, 2016; Sojka et al., 2018).

Alterations in stress processing and somatic sensation can also be derived from studies, reporting higher diurnal cortisol levels in FNSD patients compared to HC (Apazoglou et al., 2017; Bakvis et al., 2011) and increased mean heart rate (Kozlowska et al., 2015), pointing into direction of sensitized somatic sensation. Contrary findings of equivalent cortisol-levels in patients compared to HC are however reported as well (Maurer et al., 2016). Furthermore, Fiess et al. (2015) reported lowered discomfort thresholds in FNSD patients in reaction to emotionally adverse stimuli, deducing sensitization of somatic sensation.

The present study examined characteristics of somatic sensation in FNSD, defining somatic sensation by perception and discomfort threshold on transcutaneous stimulation (Fiess et al., 2015). FNSD-characteristic somatic sensation was examined in patients diagnosed with FNSD, MDD, and PTSD and healthy comparison subjects (HC; (hypothesis 1), and by relating somatic sensation to symptoms: Hypothesis 2 proposed a specific relationship between somatic sensation at baseline and somatic symptom load (as measure of FNSD symptom severity) in FNSD patients, but no relationship with depressive or posttraumatic stress symptoms. Referring to reports of a specific impact of stress on somatic sensation in FNSD, hypothesis 3a tested the relationship between somatic sensation at baseline and the amount of experienced life events and childhood adversities, in that more stressfull experience lead to blunted somatic sensitivity, thus higher perception and discomfort thresholds (following shutdown dissociation). Hypothesis 3b evaluated the impact of acute, biographically relevant stress, induced by an emotionally challenging interview on adverse childhood experiences, on somatic sensation in FNSD patients, by comparing perception and discomfort thresholds before and after the interview. We expected that somatic sensitivity would be blunted after compared to before the interview, which should be accompanied by higher perception and

discomfort thresholds.

3.3 Materials and Method

Participants: The present study included four samples: $N = 28$ patients, diagnosed with FNSD (ICD-10 codes F44.4, F44.6, F44.7), recruited from local neurological rehabilitation centers (Kliniken Schmieder Konstanz and Gailingen). The present sample was identical to the one reported in (Kienle et al., 2018). The presence of at least one negative somatoform dissociative symptom e.g. reduction of sensory perception and/or motor control was required to get included in the study, whereas positive somatoform dissociative symptoms e.g. involuntary perception of sensory, motor or pain symptoms as well as central nervous lesions served as exclusion criteria. Data of one patient had to be excluded from data analysis because TENS electrodes could not be attached to the skin, leaving 27 data sets for analyses. $N = 29$ patients with MDD (ICD-10 codes F30-33), treated for recurrent severe episodes without psychotic features ($n = 12$), or recurrent depressive disorder ($n = 17$), were recruited at the local Center for Psychiatry Reichenau.

The PTSD sample comprised $n = 22$ patients (ICD-10 code F43.1) recruited from at the Department of Psychosomatic Medicine and Psychotherapy of the Central Institute for Mental Health (CIMH, Mannheim). (This sample was part of a sample of 39 patients reported in (Kienle et al., 2017)). Diagnoses were based on DSM-IV criteria (Structured clinical interview for DSM-IV and International Personality Disorder Examination (First et al., 2015; Loranger, 1997)). Two data sets had to be excluded from analyses, due to unrealistically high discomfort thresholds, whereas one patient could not distinguish perception and discomfort even at the lowest stimulation intensity, leaving data of $n = 20$ PTSD patients for analyses.

A sample of $n = 31$ healthy comparison participants (HC) was recruited from the local community using flyers and oral advertising, and screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) to exclude any psychiatric disorder. Patient groups differed in age ($F(3, 106) = 2.93$, $p = .037$), as MDD patients and HC (who did not differ) were older than FNSD and PTSD patients (who did not differ in age; subgroup comparisons showed a significant difference of age between MDD and PTSD only: $t(49) = -2.81$, $p = .007$). Moreover, patient groups differed in gender distribution (see Table 5), including more female than male FNSD and PTSD patients, whereas the MDD sample included more male than female patients ($\chi^2 = 11.63$, $p < .001$; two group comparisons MDD-PTSD: $\chi^2 = 8.45$, $p = .004$; FNSD-MDD, $\chi^2 = 5.22$, $p = .022$) . Groups did not differ in years of education.

Table 5: Sociodemographic information of study samples

	FNSD patients	**MDD patients**	**PTSD patients**	**HC**	**Comparison across groups**
N	28	29	22	31	
Gender (f/m)	20/8	12/17	18/4	23/8	$\chi^2 = 11.63$ $p = .009$
Age (M ± SD)	42 ± 13.04	46.8 ± 10.1	39.3 ± 8.45	49.2 ± 16.8	$F(3, 106) = 2.93$ $p = .037$
Years schooling (M ± SD)	12.6 ± 4.58	14.6 ± 3.3	13.4 ± 2.71	13.9 ± 2.1	n.s.

FNSD = functional neurological symptom disorder; MDD = major depressive disorder; PTSD = posttraumatic stress disorder; f = female; m = male

Design and Procedure: The study was approved by the ethics committee of the University of Konstanz and the boards of the Kliniken Schmieder and Mannheim medical faculty of Heidelberg University. Participants were informed about the study goals and procedures and signed written informed consent prior to assessment. Childhood adversities were assessed by trained project members using standardized semi-structured interviews (lasting about 1.5 h). Somatic and PTSD symptoms were screened with self-

report questionnaires. Data assessment lasted about 2-3 h per participant. While PTSD patients at the CIMH received a bonus of 20 Euro for participation, FNSD and MDD patients filled in the questionnaires/interview set as part of their treatment.

Material: Somatic sensation was measured by transcutaneous electrical nerve stimulation (TENS) (see Figure 5). The frequency of TENS was set to 100 Hz and pulse duration fixed at 150 µs. Two $5 \times 5 - \text{cm}$ self-adhesive electrodes were placed on the left forearm over the distal radial bone near the wrist joint, avoiding the coverage of big muscles as good as possible. Stimulus intensity was increased stepwise (1 mA) and perception threshold was defined as the stimulus intensity, at which participants indicated to perceive any sensation. By further stepwise increasing the intensity, a discomfort threshold was assessed, defined as the intensity experienced as uncomfortable. These thresholds were assessed three times (1) after written informed consent (baseline), (2) right before the start of the interview and (3) after the interview.

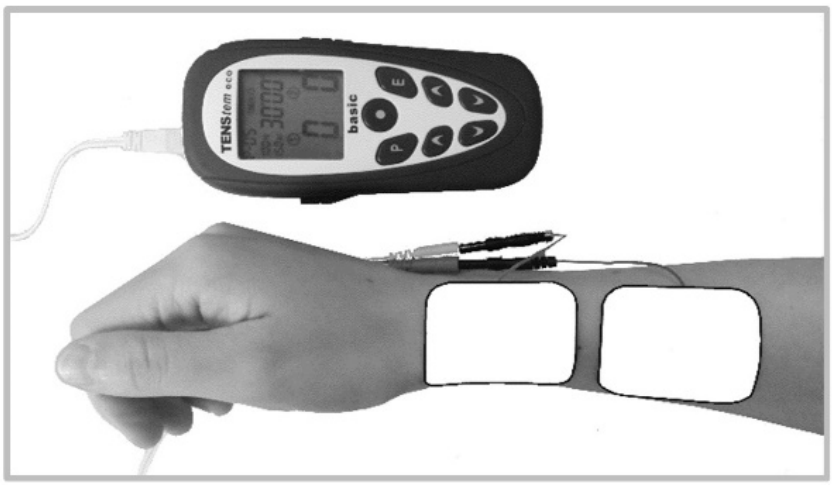

Figure 5: Display of the arrangement of electrodes on the participants' forearm to assess somatic sensation via transcutaneous electrical nerve stimulation (TENS). The self-adhesive electrodes were placed on the left forearm over the distal radial bone, near the wrist joint.

Symptom measures: Somatic symptoms were recorded using the Screening for Somatoform Disorders questionnaire ("Screening für somatoforme Störungen"; SOMS-2; (Rief & Hiller, 2008)). Participants respond to 68 items on medically unexplainable somatic symptoms, whether they experienced the respective symptom during the last two years ("yes") or not ("no"). Somatization, defined as somatic symptoms without organic desease, is represented by three indices: one representing DSM-IV diagnostic criteria (DSM-IV Index), one representing ICD-10 diagnostic criteria (ICD-Index) and one representing diagnostic criteria of somatoform autonomic functional disorder (SAD-Index; neglected in the presented data analyses as no patients with somatoform autonomic functional disorder were included). The retest-reliability of SOMS-2 (after 72 h) is between $r = .85$ and $r = .87$. For the present analyses the ICD-index was used. Depressive symptom severity was screened with the Beck Depression Inventory (BDI-2; (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)) a 21-item self-report instrument with good internal consistency ($\alpha = .86$) and validity (Beck et al., 1961).

Stress: Negative life events over the preceding twelve months were screened using the Life Events Questionnaire (LEQ; (Sarason, Johnson, & Siegel, 1978)), which shows test-retest reliability of $r_{tt} = 0.78$ to $r_{tt} = 0.83$ (Norbeck, 1984). Adverse and traumatic experiences during childhood and adolescence were assessed via the German version of the Maltreatment and Abuse chronology of exposure (MACE; (Teicher & Parigger, 2015): The KERF (Kindheitserfahrungen; (Isele et al., 2014)) includes 70 items covering ten domains of experience (parental verbal abuse, parental non-verbal emotional abuse, parental physical abuse, emotional neglect, physical neglect, familial and non-familial sexual abuse, witnessed physical violence towards parents, witnessed violence towards siblings, peer emotional and peer physical violence), together with age of onset and duration of the respective experience up to age 18. Testing hypothesis (3a) considered

the overall severity of exposure to childhood adversities between the ages of 4 to 18 years (KERF_Sum), which varies between 0 (no childhood adversities at all) to 1800 (maximum exposure to all different types of childhood adversities). Convergent validity of the KERF has been verified by correlation with the Childhood Trauma Questionnaire and good test-retest reliability was established ($rtt = .91$ at 10 weeks (Isele et al., 2014)). At the same time, the KERF-Interview was used to trigger a accute stress-responses in the group of FNSD patients.

Statistical Analyses: Adressing hypothesis 1 perception and discomfort threshold at baseline were compared between groups. Adressing hypothesis 2 perception and discomfort threshold at baseline was related to symptom measures (somatic symptoms, depression, posstraumatic stress symptoms) in FNSD patients. Hypothesis 3a related perception and discomfort threshold at baseline to overall stress load (determined in the interview), whereas hypothesis 3b compared the difference of intraindividual variations in perception and discomfort thresholds in the FNSD patients (between pre- and post- KERF-Interview). Since the assumption of normal distribution were not met, non-parametric Kruskall-Wallis tests were used for analyis. Post-hoc Mann-Whitney tests Bonferroni-corrected for multiple comparisons with alpha corrected to .008 were used to verify differences between groups. Adressing hypothesis 2 perception and discomfort threshold at baseline were related to symptom measures (SOMS ICD-Index) and depression in FNSD patients by Spearman correlation. Hypothesis 3a related perception and discomfort thresholds at baseline to negative Life Events during the last year and amount of childhood maltreatment by Spearman correlation.

3.4 Results

Somatic Sensation: At baseline measurement, (TENS) perception and discomfort threshold were similar across groups (Group $U < 1$; see Figure 6). Thus, hypothesis (1) was disconfirmed, in that FNSD were not characterized by generally altered somatic sensation as measured by TENS.

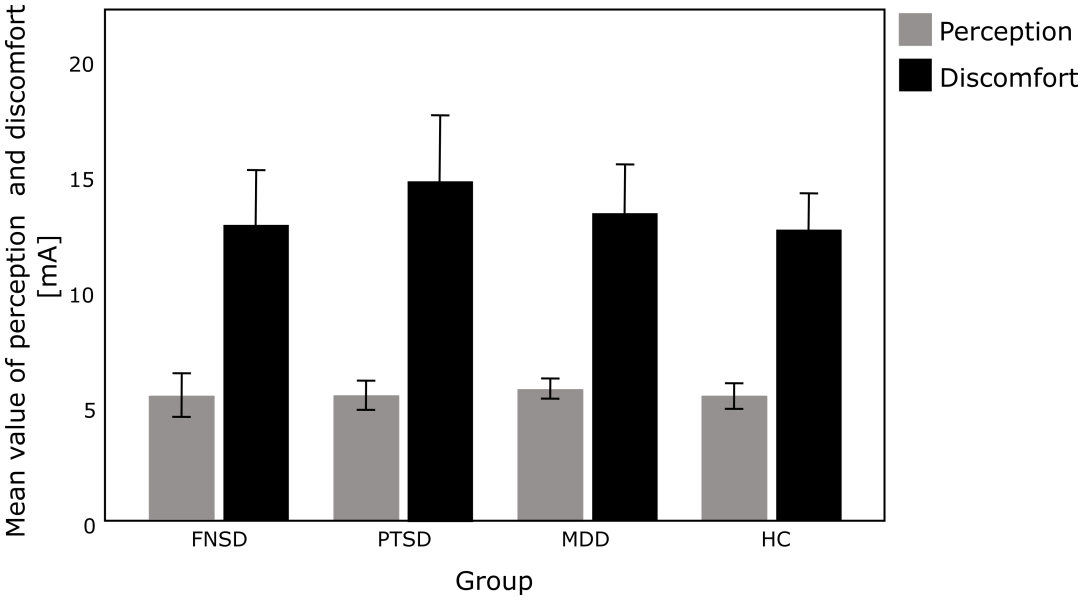

Figure 6: Mean values of Perception and Discomfort at baseline for healthy comparison subjects (HC) and patients with functional neurological symptom disorder (FNSD), posttraumatic stress disorder (PTSD) and major depressive disorder (MDD).

Somatic sensation related to symptom severity: As to be expected, FNSD patients report higher amount of somatic ($U = 82$, $p < .001$), depressive ($U = 86$, $p < .001$) and PTSD symptoms ($U = 159.5$, $p < .001$) than HC. Somatic sensation thresholds for perception and discomfort at baseline did neither vary with somatic symptoms (SOMS ICD-Index; $p = .81$, $rs = .05$ resp. $p = .49$, $r_s = .14$) nor with depressive symptoms (BDI; $p = .23$, $r_s = .23$ resp. $p = .96$, $r_s = .01$) or posttraumatic stress symptoms ($p = .78$, $r_s = .05$ resp. $p = .58$, $r_s = .11$) of FNSD patients. Thus, hypothesis 2 was not supported.

Stress-related somatic sensation: As to be expected, FNSD patients reported considerable more childhood maltreatment and a higher number of negative life events during the last year than HC: ($U = 175.5$, $p < .001$ resp. $U = 171.5$, $p = .004$). Whereas these stressful experiences did not affect somatic sensation thresholds at baseline in FNSD patients (childhood maltreatment: $r_s = .04$, negative life events: $r_s = -.25$, $p > .2$), somatic sensation was differentially affected by stress, in that perception threshold was higher after than before the KERF-Interview in FNSD compared to the other groups ($H(3) = 16.09$, $p = .001$) Yet, only the comparison of FNSD patients and HC was significant ($U = 236.5$, $p = .002$), indicating similar changes in patient groups.

3.5 Discussion

FNSD patients did not differ from the other patient groups in somatic sensation and discomfort thresholds at baseline, showing neither FNSD-characteristic somatic sensation per se (and disconfirming hypothesis 1) nor in dependence of symptom load, childhood adversities or experienced negative life events after the exposure to biographically relevant, acute stress (hypothesis 2 and 3a). Nevertheless (and conforming hypothesis 3b), perception thresholds were elevated after the acute stress (interview). Thus patients were less sensitive following the stressful confrontation with adverse experiences. This finding stands in line with findings that participants with high levels of somatoform dissociation were less body focused after being confronted with a traumatic film (D. Brown, 2010). The authors hypothesized that this could be due to the avoidance of bodily information upon traumatic content/stress – an alternative interpretation might be shutdown dissociation (for the results from both studies).

At first glance, present results seem to be contrary to findings by Fiess et al. (2015), that reported lowered discomfort but not perception thresholds after exposition to adverse

emotional stimuli in FNSD patients. However, the applied stimuli in the two studies were substantially different, which may account for the substantially different results: Fiess et al. used negative pictures of the international affective picture system (IAPS; (Lang, Bradley, & Cuthbert, 2005)) and patients were asked to actively down-regulate their emotional response upon certain cues. The biographically irrelevant stimuli may have led to sensitization, while the biographically relevant self-report applied here provoked shutdown dissociation – these possible relations seem to be worth further examinations.

Limitations have to be noted. Firstly, even though one study so far (Accarino, Azpiroz, & Malagelada, 1995) applied TENS as a measure of altered somatic sensation in patients with irritable bowel sydrome, compared to healthy controls, TENS is not yet established as a measure of somatic sensation. It may be useful to evaluate the influence of temperature, time of day and skin properties on somatic sensation measurement via TENS in HC to be able to standardize perception and /or discomfort thresholds measurements via this method. Furthermore, the confrontation with personal trauma may have led to a state of emotional dissociation (from affect and somatic sensation) in individuals experiencing high trauma loads (such as the FNSD group), whereas it may have been less effectfull for groups, that report lower trauma loads (such as HC).Further studies should consider a manipulation that allows for a differentiation of different (biographically relevant and irrelevant) stimuli (see above). Further it has to be noted, that all patient groups received medication. While unmedicated research in such severe disorders is ethically problematic, it seems yet possible, that medication may have influenced the results, especially somatic sensation. It also has to be noted, that all patient groups received medication. While unmedicated research in such severe disorders is ethically problematic, it seems yet possible, that medication may have influenced the results, especially somatic sensation.

Although altered somatic sensation could not be confirmed as specific feature in FNSD, since FNSD patients did not differ significantly in somatic sensation at baseline from the other patient groups, the result of blunted somatic sensation following the interview on traumatic experiences points in the direction of an important role of not only past traumatic experiences but also acute, biographically relevant stress on the generation of functional neurological symptoms and encourages the application of TENS to measure somatic sensation in patients with FNSD.

4 Variation of Functional Neurological Symptoms and Emotion Regulation with Time

4.1 Abstract

Introduction: The present study addressed the variation of emotion regulation in the context of functional neurological symptom disorder (FNSD) by examining changes of functional neurological symptoms (FNS), general psychological strain, alexithymia, emotion regulation strategies, and cortical correlates of emotion regulation in the context of a standard inpatient treatment program.

Methods and materials: Self-report data on FNS, general psychological strain, alexithymia, emotion regulation strategies, and cortical correlates of an experimentally induced emotion regulation task (participants either passively watched unpleasant and neutral pictures or regulated their emotional response to unpleasant pictures using pretrained reappraisal, while an electroencephalogram was recorded) were compared between 19 patients with FNSD and 19 healthy comparison participants (HC) before and after a 4-week standard treatment protocol that included a combination of (individual and group) psychotherapies and functional treatments (such as physiotherapy) or a 4-week interval in HC, respectively.

Results: General psychological strain did not decrease significantly in FNSD patients. Changes in emotion regulation in FNSD patients were constrained to an increase in self-reported use of cognitive reappraisal strategies. Subjective symptom intensity in FNSD patients varied with alexithymia pretreatment, but did not decrease significantly. Cortical activity in the time and frequency-domain distinguished passive watching of neutral and unpleasant pictures and regulating emotional responses upon unpleasant

pictures from passively watching them without difference between groups and/or time.

Discussion: Over the investigated time interval, augmented habitual cognitive emotion regulation suggests an alleviation of emotion processing deficits, but no significant symptom decrease. More controlled and prolonged treatment studies would be needed to determine whether and how a specific contribution of treatment-related changes of emotion regulation and FNS might be inferred.

4.2 Introduction

Functional neurological symptoms (FNS), that is, impaired voluntary motor or sensory function without verified neurological or medical basis (Association, 2013) cause pervasive suffer and often long-term treatment (Carson & Lehn, 2016; Carson et al., 2000). While the traditional concept of these symptoms as conversion of emotional conflicts and psychological strain into physical expression (Breuer & Freud, 1985) motivated the assignment of FNS to dissociative disorders (ICD-10), DSM-5 acknowledges the specific pattern of symptoms and factors contributing to their generation with the distinct category "functional neurological symptom disorder" (FNSD). Hypotheses on symptom generation still consider dissociation and conversion within the concept of aberrant emotion processing consequent upon emotionally upsetting or traumatic experiences and/or emotional conflicts (Hallett, 2017). Further clarification of emotion processing in FNSD should inform concepts and therapeutic procedures.

Framing FNSD as dissociative and conversion disorder linked emotion processing primarily to impairments in the perception and verbal expression of one's own feelings, as conceptualized by alexithymia (Gündel, 2000). Framing emotion processing in the context of stress and coping extended emotion regulation to cognitive and behavioral strategies that aimed at (explicit or implicit) control of unpleasant feelings in response

to external events; major strategies are described and measured as cognitive reappraisal of the upsetting event or suppression of rising unpleasant sensation (Gross, 2002; Gyurak, Gross, & Etkin, 2011). Both alexithymia and altered emotion regulation have been verified for patients with FNS: elevated levels of alexithymia (Demartini et al., 2014; Gulpek et al., 2014; Kienle et al., 2017) were explained as a transformation of emotional expressions into bodily symptoms or as a misperception of autonomic concomitants of emotion (i.e., increased heartbeat during the experience of fear) as signs of physical illness (Demartini et al., 2014). Altered emotion regulation was verified as stronger tendency for emotion suppression and less cognitive reappraisal in FNSD patients than in healthy controls (Steffen et al., 2015).

In addition to self-reported alexithymia and emotion regulation strategies brain dynamics measured in experimental emotion regulation tasks aimed at substantiating the role of emotion regulation in FNSD. Hemodynamic and electromagnetic imaging studies confirmed altered processing of emotional stimuli and emotion regulation in FNSD compared to controls in those frontocortical and parietal cortices that have been related to emotion regulation (Etkin, Buchel, & Gross, 2015; López-Pérez & Ambrona, 2015). In addition to frontal abnormality, augmented activity in movement-related cortical areas was reported for patients with conversion disorder compared to controls (Aybek, 2015; Blakemore, Sinanaj, Galli, Aybek, & Vuilleumier, 2016; Fiess et al., 2015; Voon et al., 2010). Similarly, (Fiess et al., 2015) reported less frontocortical but augmented sensorimotor electromagnetic activity in FNSD compared to controls in an emotion regulation task, in which participants implemented cognitive reappraisal strategies when watching unpleasant stimuli.

The contribution of emotion processing to FNS generation may be further probed in the context of treatment. Many treatment programs target emotion regulation in conflict

situations, considering symptoms as manifestation of dysfunctional emotion regulation or emotional conflict resolution by conversion into physical expression [brief psychodynamic interpersonal therapy (Howlett & Reuber, 2009; McCormack et al., 2014); enriching cognitive behavior therapy with emotion regulation (Kleinstauber et al., 2016)]. Thus, variation with treatment may test hypotheses on the role of emotion regulation in FNSD. Moreover, while so far an increasing research body on risk factors and/or comorbid symptoms and other characteristics of FNS(D) can be observed (see above), little is known of their interaction and/or variation over time—or even over treatment.

To this end, the present study combined self-reported alexithymia and emotion regulation strategies and cortical indices of experimentally induced emotion regulation in the time-domain (via event-related potentials; ERP) and in the frequency-domain between FNSD patients and healthy controls to gain further insight in altered emotion regulation in FNSD. In addition, the indices of emotion processing were examined before and after a standard clinical treatment program for FNSD that addressed emotion regulation, emotional conflict awareness, and analysis and resolution of learned stimulus-symptom contingencies as potential contribution to symptom generation.

Specific hypotheses were (1) FNSD patients express more alexithymia, psychological strain, and use less cognitive reappraisal and more suppression when downregulating emotions than healthy comparison participants (HC) prior to treatment. (2) FNSD patients recruit less frontal and more sensorimotor EEG activity than HC while applying cognitive reappraisal in an experimental emotion regulation task prior to treatment. (3) In FNSD, subjective and cortical indices of emotion regulation change across time in parallel to a change in symptom severity and overall psychological strain.

4.3 Materials and Methods

Participants

Twenty-six patients with FNSD were recruited at the neurological rehabilitation centers Kliniken Schmieder in Konstanz and Gailingen. Patients were diagnosed with ICD-10 diagnoses of a dissociative disorder (ICD-10 code F44.4: dissociative movement disorder, F44.6: dissociative sensibility disorder, F44.7: mixed dissociative disorder), which corresponds to the DSM-5 diagnosis FNSD. Individual diagnoses were given by at least two psychiatrists and neurologists according to ICD-10 guidelines. Patients with a history of central nervous lesion or disorder were excluded, and at least one core negative FNS (e.g., paresis or hypesthesia) was required for inclusion in the study. $N = 5$ of the 26 FNSD patients did not complete the study ($n = 3$ due to early discharge, $n = 2$ because of a change in diagnosis). In addition, data of two patients were excluded from analyses because of artifact-contaminated EEG data. Table 6 summarizes demographic and clinical data of the remaining sample of n = 19 FNSD patients ($n = 11$ with diagnosis F44.7, $n = 7$ with diagnosis F44.4, $n = 1$ with diagnosis F44.6).

Table 6: Sociodemographic information of study samples

	FNSD patients	**HC**	**FNSD patients vs. HC**
N	19	19	38
Gender (f/m)	13/6	12/7	$\chi^2 = 0.12$, $p = 0.73$
Age (M ± SD)	42.7 ± 14.2	50 ± 17.1	$t(36) = 1.38$, $p = 0.17$
Years schooling (M ± SD)	12.7 ± 4.5	14.3 ± 1.8	$t(36) = 1.34$, $p = 0.18$

FNSD = functional neurological symptom disorder; HC = healthy comparison participants;
f = female; m = male

Seven FNSD patients suffered from motor weakness or sensory disturbances of left-sided, $n = 5$ of right-sided limbs, in $n = 7$ both sides were affected. The average duration of

inpatient admission was 4 weeks (33 ± 5.8 range 27–45 days). At the time of data assessment, about half of the patients in the present sample (10/19) received analgesic medication (of different active substance groups, only two received the identical drug). Three patients were unmedicated, 7 out of 19 received medication against hypertension and/or thyroid hypofunction. Only 3 out of 19 patients received an antidepressant. Following neurological and neuropsychiatric assessment, patients accomplished a multidisciplinary treatment program to reinstall a functional interaction of body perception and emotion processing (following standards as postulated, e.g., by (Carson et al., 2012; Dallocchio, Tinazzi, Bombieri, Arno, & Erro, 2016)). This program included psychoeducation (1 h per week), functional therapeutic (i.e., daily physiotherapy, general movement therapy, and depending on individual needs ergotherapy, logotherapy, or neuropsychological training—on average 9.25 h per week) and different psychotherapeutic interventions (on average 7.5 h per week, i.e., once to twice a week individual and four times a week group cognitive behavioral therapy, moreover once or twice a week art and/or bodypsychotherapy). Psychotherapy comprised behavioral therapy with elements of schema-, psychodynamic, and systemic therapies, and addressed emotional regulation within these frameworks.

Twenty-four HC were recruited in the local community by flyer and oral advertisement. Exclusion criteria were a central nervous lesion or disorder, and any psychological disorder as screened with the MINI international neuropsychiatric interview (Ackenheil et al., 1999). After excluding $n = 2$ HC, who did not complete the study, and $n = 2$ with artifact-contaminated EEG, data of $n = 19$ HC were available for analyses. Groups did not differ in gender, age distribution, and years of education (see Table 6). All participants had normal or corrected to normal vision. Two healthy comparison participants were left-handed, patients diagnosed with FNSD were all right-handed.

Study Design

The study design was approved by the Ethics committee of the University of Konstanz and by the IRB of the Kliniken Schmieder. All participants provided written informed consent prior to assessment onset in accordance with the Declaration of Helsinki. The study design addressed the two main hypotheses by comparison of dependent measures (FNS severity, self-rating, and electrocortical emotion regulation indices) between groups (FNSD patients and HC) and across time (before and after the inpatient treatment period in FNSD patients and a respective time interval in HC).

Dependent measures were assessed on three separate days: In a first session (for FNSD within 1 week after admission) participants were introduced into the study design and filled in questionnaires on demographic information, FNS severity and general psychological strain, alexithymia and habitual emotion regulation strategies. Two subsequent assessments involving the experimental emotion regulation task, during which the EEG was monitored, were scheduled before and after completion of the treatment program (patients) or after approximately 4 weeks (HC). The mean time interval between the two laboratory sessions was 23 ± 8.3 days (range 14–45 days) for FNSD patients and 33 ± 5.8 days (range 27–45 days) for HC. The respective time interval was significantly different between groups [$T(36) = 4.5$, $p < 0.001$].

Data Aquisition and Analyses

Functional neurological symptoms were assessed with the Somatoform Dissociation Questionnaire (SDQ-20; (Nijenhuis, 1996), German version by Mueller-Pfeiffer et al. (Mueller-Pfeiffer et al., 2010)). The SDQ-20 is a 20-item self-report instrument, which assesses the frequency of somatoform dissociation experienced in the preceding 12 months. Good internal consistency (Cronbach's $\alpha = 0.92$) and test–retest reliability ($r_{tt} = 0.89$) are reported (Mueller-Pfeiffer et al., 2010). In consideration of the 4-week

treatment-interval assessment, a 1-week evaluation period was adopted for the present study, since changes were expected to be most pronounced in this time range. In addition, subjectively experienced symptom intensity was rated on an 11-point Likert scale with a range from 0 "no symptoms" to 10 "maximum intensity" pre and post each EEG session.

Psychological strain was evaluated with the Symptom-Checklist 90R (SCL 90R (Derogatis, 1986)). The SCL90R includes 90 items that are rated on a five-point Likert scale and combined to nine subscales: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism. The mean score of items per subscale represents the respective dimension, while the general psychological strain load is represented by the mean score of all 90 items (global severity index, GSI). Good reliability is approved for subscales (between $r = 0.75$ and $r = 0.87$ (Hessel, Schumacher, Greyer, & Brähler, 2001)) and global indices ($r_{tt} = 0.68$ to $r_{tt} = 0.80$ (Derogatis, 1986)).

Emotion regulation covered alexithymia, assessed with the Toronto Alexithymia Scale (TAS-26 (Bagby et al., 1994), German version (Kupfer et al., 2000)), and the Emotion Regulation Questionnaire (ERQ (Gross, 2002); German version (Abler & Kessler, 2009)). The TAS-26 includes 26 self-report items that measure alexithymia on three dimensions: "difficulty identifying feelings," "difficulty describing feelings," and "externally oriented thinking." Internal consistency ($\alpha = 0.84$) and convergent validity are evaluated as good (Kupfer et al., 2000). The ERQ includes six items addressing cognitive reappraisal and four items addressing emotion suppression, each rated on a 7-point Likert scale, with good convergent validity and internal consistencies (Abler & Kessler, 2009).

Differences between groups and assessments (pre-/posttreatment) in FNS- and emotion regulation indices were statistically evaluated by dependent-sample t-tests. Since the assumption of homogeneity of variance was not met, between-group differences were evaluated with non-parametric Mann–Whitney U tests. In FNSD patients, the relationships between changes in symptom severity and changes in emotion processing across the treatment period (post-pre difference scores of each scale) were probed using bivariate Pearson correlation analysis. To reduce the likelihood of a type I error, we applied a Bonferroni–Holm correction for multiple tests (Holm, 1979) and report only the corrected p-values.

Cortical correlates of emotion regulation were measured in an experimental emotion regulation task adopted from Fiess et al. (Fiess et al., 2015) and adjusted to EEG monitoring: 70 high-arousing unpleasant and 70 low-arousing neutral pictures from the International Affective Picture System (Lang et al., 2005) were presented on a screen about 90 cm from the participant's eyes. The 2-s picture presentation was preceded by a 2-s cue presentation (the capital letters A or R), indicating that participants should passively watch (A for the German word "Anschauen") the respective picture or downregulate their emotional response to the picture using cognitive reappraisal (R for the German word "Regulieren"). Across the total 210 trials, the three conditions (watch neutral pictures, watch unpleasant pictures, and regulate emotions upon unpleasant pictures) were arranged in pseudorandom order (70 trials per condition). Intertrial intervals were jittered between 2 and 2.5 s. Following standard procedures (e.g., (Moser, Hajcak, Bukay, & Simons, 2006)) cognitive reappraisal strategies were practiced prior to the experiment with individually selected examples like "it's a scene from a movie" or "help is coming." As manipulation check participants were asked after the experiment, which strategy they had implemented and whether this had been successful.

EEG Data Acquisition and Analysis

Data Recording and Preprocessing: The EEG was recorded from 128 electrodes with active shielding placed on a Waveguard cap with equidistant hexagonal layout (ANT Neuro) using a direct-coupled amplifier (ANT). Signals were sampled with 2048 Hz. A 40-Hz low pass 0-phase filter was applied offline. Impedances of all electrodes were kept below 20 $k\Omega$. Data were preprocessed using FieldTrip, a matlabbased open-source signal processing toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). Epochs of 9 s length were extracted from the continuous recording (5 s pre-stimulus), time-locked to picture onset and corrected for cardiac, blink and eye-movement artifacts via independent component analysis (Jung et al., 2001).

ERP Analysis: A cluster-based, dependent-sample F-test with Monte-Carlo randomization (38) was calculated for both groups in a time interval of 0.4–1 s after picture onset to identify sensor clusters indicating significant condition differences (NW: passively watch neutral pictures, UW: passively watch unpleasant pictures, UR: regulate emotion upon unpleasant pictures). Selection of time of interest (TOI) followed evidence on the electroencephalographic late positive potential (LPP) 400 and 700 ms after stimulus onset over posterior regions that distinguishe implementation of cognitive reappraisal strategies upon unpleasant stimuli and passive watching of unpleasant stimuli (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Hajcak & Nieuwenhuis, 2006; Moser et al., 2006; Schupp, Junghöfer, Weike, & Hamm, 2004). Regions of interest (ROI) were identified on the basis of this cluster procedure. Averaged power across those ROI and TOI was analysed in two separate repeated-measures ANOVAs with the within subject factors condition and time (pre/posttreatment) and the between subject factor group.

Spectral Analysis: Time-frequency representations of the measured signal were obtained using Hanning-tapered sliding window with a fixed window length of 0.5 s, re-

sulting in a 2 Hz frequency resolution. Stimulus evoked activity was expressed as change of power (in percent) relative to a cue-preceding baseline (-3 to -2.25 s) and averaged separately for group (HC, FNSD patients), conditions (NW, UW, UR), and time point (pre-/posttreatment or first–second assessment, respectively). Group differences in the modulation of oscillatory activity in a time-window from 0.3 to 2 s after picture onset in the frequency band of 8-12 Hz were evaluated using cluster-based dependent-sample t-tests with Monte-Carlo randomization[1] ($N = 1000$; allowing the control of type 1 error rate in the context of multiple comparisons) with a 5% significance threshold for activity differences between sensor clusters (Maris & Oostenveld, 2007). Time-window and frequency band were selected to be comparable to Fiess et al. (18) and Popov et al. (42). Posthoc planned comparisons confirmed the "emotion effect" as UW minus NW contrast, and the regulation effect as UR minus UW contrast. Group and time differences between were evaluated using independent-sample t-test statistics.

Source Analysis: Sources of activity that generated the effects at sensor level were determined by dynamical imaging of coherent sources beamformer on time-frequency windows that were defined based on the results at sensor level (DICS; (Gross et al., 2001)). Cross-spectral density matrices for a time period of 0.3-2 s after stimulus onset were calculated separately for conditions and groups using a multitaper method. The center frequency was set to 10 ± 2 Hz. A standard Montreal Neurological Institute-based (http://www.bic.mni. mcgill.ca/brianweb) boundary element method model (Oostendorp & van Oosterom, 1989) was used to create a realistic volume conduction model of the head. Electrodes were aligned using an ANT-specific template layout of the electrodes, based on averaged digitized electrode positions of 20 volunteers not included in the present report. Within-subjects, differences in source power for the "emotion effect" (NW - UW) and the "regulation effect" (UR - UW), were evaluated for the 0.3-2 s in-

terval as defined above using dependent-sample t-tests, and group differences for each effect was examined by independent-sample t-tests. All analyses were two-sided with an alpha-level set to 0.05. Relationships between changes in symptom severity scores, emotion regulation scores, and cortical emotion regulation indices across time/treatment were probed with bivariate Pearson correlation analysis.

4.4 Results

Pretreatment Group Comparison

Functional neurological symptom disorder patients reported higher FNS severity (SDQ-20: $U = 48.5$, $p < 0.00$) and higher psychological strain (SCL-90R: $U = 22$, $p < 0.00$) than HC. Emotion regulation in FNSD patients differed from HC with respect to more alexithymia than HC (TAS-26: $U = 41$, $p < 0.00$), less tendencies to use cognitive reappraisal (ERQ-R: $U = 87.5$, $p < 0.006$) but similar tendencies for emotion suppression (ERQS: $U = 167.5$, $p = 0.71$). In the entire sample (FNSD patients and HC), symptom and emotion regulation measures were related, in that TAS-26 scores varied with SDQ-20 ($r = 0.57$, $p < 0.001$), SCL-90R GSI ($r = 0.74$, $p < 0.001$), and subjective level of symptom intensity in FNSD patients ($r = 0.64$, $p < 0.001$). Group-specific relationships were confirmed for TAS-26–SCL-90R GSI ($r = 0.65$, $p = 0.003$) in FNSD patients.

Changes in the Context of Time/Treatment

Bonferroni–Holm adjusted effects confirmed significant changes over time/treatment only for increased use of cognitive reappraisal strategies in FNSD patients (ERQ-R, $t(16) = -3.9$, $p = 0.001$, here, the significant alpha-level after Bonferroni–Holm correction should be $p < 0.0035$), which did not differ from that in HC at the second assessment ($U = 129$, $p = 0.3$). A slight decrease in symptom severity (SDQ-20, $t(16) = 0.135$,

$p = 0.9$, following Bonferroni–Holm correction $p < 0.05$ would have been needed to reach significance), and psychological strain (SCL-90R from pre $M \pm SD.66 \pm 0.48$ to posttreatment $M \pm SD = 0.87 \pm 0.5$; $t(16) = 0.14$, $p = 0.018$, Bonferroni–Holm corrected $p < 0.004$ would have been needed) in FNSD patients did not reach significance. Hence, both symptom severity and psychological strain remained higher in FNSD than in HC (SDQ- 20: $U = 45.5$, $p < 0.001$ SCL-90R: $U = 46.5$, $p < 0.001$) at the second assessment.

In FNSD patients, no significant changes can be reported for subjective symptom report ($t(16) = 2.1$, $p = 0.05$, Bonferroni– Holm corrected $p < 0.007$ would have been needed). Similarly, alexithymia ($t(16) = 1.37$, $p = 0.19$, adjusted $p = 0.01$) and emotion suppression ($t(16) = -0.45$, $p = 0.66$, adjusted alpha-level: $p = 0.02$) did not vary with treatment and changes in symptom severity were not related with changes in emotion processing in FSND patients. For an overview on all reported Bonferroni– Holm adjusted alpha-levels please see Table 7 in Supplementary Material in Data Sheet S1 in Supplementary Material.

Cortical Indices of Emotion Regulation

Figure 7 illustrates the identified ROI and corresponding timecourse of the ERP during the stimulus–task interval separately for groups and conditions (passive watch, regulate). An "emotion effect" ($F(1, 36) = 107, 16$, $p < 0.001$) was indicated by the larger LPP in response to unpleasant compared to neutral stimuli in both groups. Similarly, a "regulation effect" was present in both groups ($F(1, 36) = 8, 62$, $p < 0.01$) with larger LPP during the regulation of unpleasant stimuli compared to the passive watching.

Frequency-domain analyses (see methods) indicated eventrelated decrease in the 8–12 Hz alpha power in the 0.3 - 2 s time-window after stimulus onset relative to baseline. Figure 8 illustrates the time-course of event-related alpha power decrease across a 3 s baseline

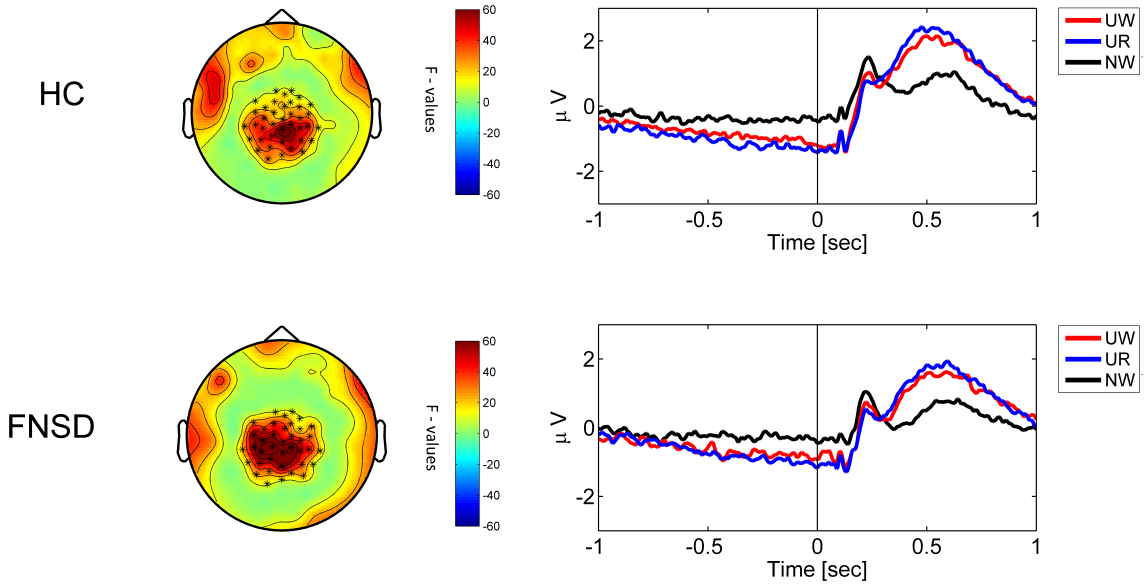

Figure 7: On the left part sensor clusters indicating significant condition differences (marked by asterics). On the right part corresponding time-courses of power of the maesured signal averaged seperately over conditions (UW – passively watch unpleasant pictures, UR – regulate emotions upon unpleasant pictures, NW – passively watch neutral pictures) and groups (HC – healthy comparison subjects and FNSD – patients with FNSD).

and 2 s stimulus interval separately for groups and conditions: In the pretreatment assessment, greater alpha power decrease during UW (watch unpleasant stimuli) than NW (watch neutral) trials characterized the "emotion effect" on sensor and source level in both groups (HC: $p < 0.001$, FNSD patients: $p < 0.01$). In the same time interval, the "regulation effect" was evident in both groups in marked alpha power decrease during UR compared to UW condition on sensor level (HC: $p < 0.01$; FNSD patients: $p < 0.01$).

Neither "emotion effect" nor "regulation effect" changed over time ($p = 0.34$), indicating response stability in HC, and no impact of the treatment period on cortical correlates of emotion regulation in patients. However, within the FNSD sample, changes of the

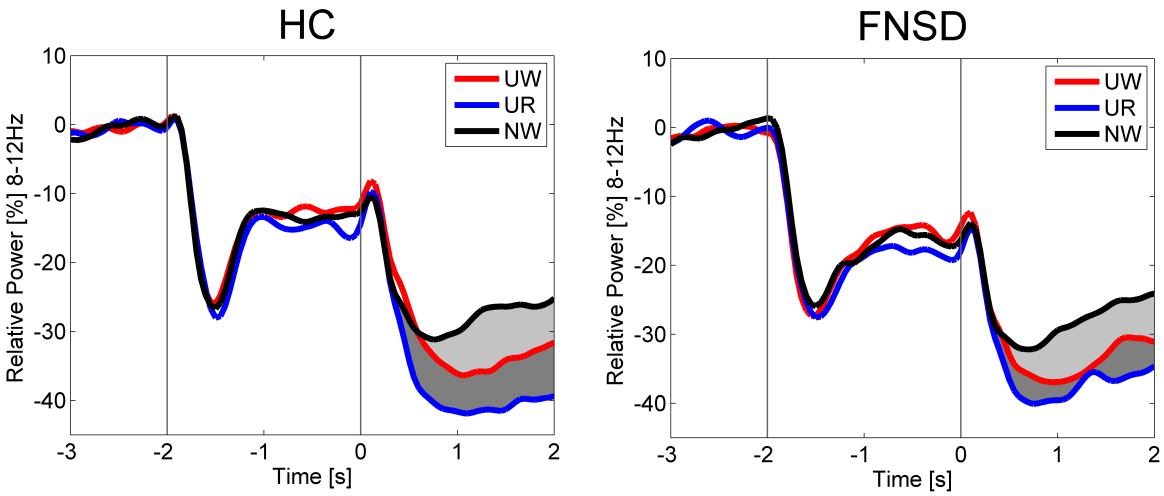

Figure 8: Grand average time-course of power in the 8-12 Hz band expressed as change (in percent) from pre stimulus baseline (-3 to -2.25 s) for healthy comparison subjects (HC) and patients with functional neurological symptom disorder (FNSD). Time-courses of power changes during the picture interval (0 s to 2 s) are averaged per group and condition (UW - passively watch unpleasant pictures, UR - regulate emotions upon unpleasant pictures, NW - passively watch neutral pictures). Light-gray shaded areas mark the emotion effect, dark-gray shaded areas mark the regulation effect.

"regulation effect" across time varied with changes in the subjectively rated symptom severity ($r = 0.52$, $p = 0.02$) in that larger (post-minus pre treatment) changes in power between the conditions "watch unpleasant" and "regulate unpleasant" varied with larger changes in experienced symptom severity.

4.5 Discussion

The present study evaluated indices of emotion regulation in relation to FNS by comparing these indices between FNSD patients and healthy controls and their variation with time and/or treatment. It was hypothesized (1) that groups differed in alexithymia, habitual emotion regulation style, and cortical responses during an experimental emotion regulation task before the treatment period and (2) that in FNSD patients changes in symptom severity and psychological strain after the treatment period varied with

changes in emotion regulation indices. In support of the first expectation and in line with previous reports (Demartini et al., 2014; Gulpek et al., 2014; Kienle et al., 2017), FNSD patients exhibited more alexithymia and used less cognitive reappraisal strategies on everyday emotion regulation than controls, Relationships between emotion regulation indices and symptom expression were confirmed for the entire sample, but only for alexithymia and general psychological strain for FNSD patients.

In addition, cortical correlates of "emotion" and "regulation" effects were replicated (Fiess et al., 2015), whereas frontal and more sensorimotor cortex involvement in emotion regulation in FNSD patients (Fiess et al., 2015; Voon et al., 2010) was not replicated. The present small sample size and interindividual variability may have resulted in electrocortical responses overlapping between groups, preventing group differences.

Event-related potential analyses confirmed "emotion" and "regulation effects" in the expected cortical regions. In contrast to previous reports of smaller LPP during regulation than during passive watching (Moser, Krompinger, Dietz, & Simons, 2009; Parvaz, MacNamara, Goldstein, & Hajcak, 2012) the LPP was enhanced during the regulation of the emotional response upon unpleasant pictures. Similar evidence of increased LPP under regulation instructions was recently reported by Ellis et al. (Ellis, Schroder, Patrick, & Moser, 2017), suggesting that this increase may reflect allocation of attention upon the instruction to actively regulate upcoming emotions.

The expected changes over a period that included a standard treatment program for FNSD patients were not confirmed. Robust changes were only confirmed for an increased tendency to use cognitive reappraisal as emotion regulation strategy. The tendency to use suppressive strategies of emotion regulation did not change over time and did not differ between groups. These results are in line with previous evidence of an association between reappraisal but not suppression with physic and psychic health (Cutuli, 2014;

John & Gross, 2004). Moreover, results on cortical emotion regulation indices indicated their stability, but did not vary with treatment in FNSD patients.

Different factors may have contributed to the lack of significant differences between groups and over time: in addition to larger sample sizes for adequate statistical power, the short 4-week treatment program (i.e., following the standard health insurance coverage in Germany) may be insufficient to prompt substantial and sustained changes. The present small sample size constrained the comparison of FNSD patients who benefited from treatment or did not change. Treatment effects on emotion regulation strategies and their cortical correlates may emerge only with longer treatment periods or may develop over time even after the end of treatment, as shown by (Goodman et al., 2014). Finally, more specific modules and targeted treatment may be a prerequisite for treatment-induced changes in emotion regulation on the different levels. So far, whether the self-reported increase of cognitive reappraisal to downregulate negative emotion reflects a substantial change in emotion regulation strategies or a trained reproduction of what was learnt in psychotherapy on how to (theoretically) regulate emotion without behavioral effects, remains unclear. Emotion regulation was just one target in the standard treatment program of the involved neurological rehabilitation center, and thus, the impact of intense treatment procedures focusing on emotion regulation remains to be evaluated. In consideration of these factors, the observed tendencies encourage hypotheses to be verified in future studies with longer, targeted treatment and follow-up assessment.

To conclude: probing the meaning of emotion regulation, measured on subjective and cortical level, in FNSD in the context of time/treatment offers first clues that need to be substantiated in powered, targeted studies: changes in the subjectively experienced symptom severity and psychological strain may vary with a tendency to adjust everyday

emotion regulation toward accentuated use of cognitive strategies, and to reduce alexithymia. If substantiated, this should be considered in designing the concept of FNS and their generation, as well as for the adjustment of remediation strategies.

4.6 Endnotes

[1] This procedure begins with a t-test between every combination of time point and channel in the actual data and between the two groups. Adjacent time-channel- combinations that showed significant group differences in the t-tests were clustered by summing the t-values. A 1000-fold repetition of this procedure after randomly assigning group associations of each subject can be described as "Monte Carlo permutation," resulting in a distribution with parallel results that is used for comparison with the original data: For each iteration, the t-value sum from the cluster with the highest t-value sum is added to a distribution reflecting the null hypothesis of no group difference. Finally, this hypothesis is evaluated by comparing the t-value sums of the actual data and the calculated distribution.

5 General Discussion

5.1 Trauma and stress in patients with FNSD

Patients with FNSD reported more trauma compared to HC (studies 1 + 3). However, study one illustrated the possible role of comorbid PTSD in this correlation: FNSD patients with comorbid PTSD reported the increased trauma load, but FNSD patients without PTSD did not differ from HC. Interestingly, FNSD patients with comorbid PTSD did not differ at all from patients with the primary diagnosis of PTSD concerning the total amount of traumatic experience during childhood. This matches the changes made in DSM-5, that allow for specification of FNSD with or without a preceding stressor.

Regarding trauma-type, FNSD patients with comorbid PTSD reported less sexual maltreatment than patients with the primary diagnosis of PTSD, which is consistent with the literature, suggesting sexual trauma as a strong factor for dissociative symptoms in PTSD (Putnam et al., 1995; Schalinski et al., 2011). FNSD in contrast, has been associated with emotional abuse/neglect rather than with sexual and physical abuse (Ludwig et al., 2018). This is also in line with the present findings, showing that emotional abuse/neglect distinguishes between FNSD patients with and without comorbid PTSD. FNSD patients without comorbid PTSD have higher levels of emotional abuse/neglect than those with comorbid PTSD. Emotional maltreatment seems to play a special role in FNSD that needs to be clarified in further research.

Examining the relationship between trauma and functional neurological symptom severity (Study 1) showed, that the severity of functional neurological symptoms was not explained by the pure number of traumatic or negative life events but by the severity of PTSD symptoms. This leads to the assumption that not the experience of traumatic

events per se, but the coping with such experiences may be crucial for the development of FNSD. Indeed, fewer coping skills are reported in patients with FNSD (Testa, Krauss, Lesser, & Brandt, 2012). One can only speculate about how these impairments in coping may arise: many patients report physical injury as a preceding event before the onset of FNSD (Stone, Carson, Aditya, et al., 2009; Wilshire & Ward, 2016). Furthermore it has been shown that patients with FNSD are more frequently confronted with illness of others (Hotopf, Mayou, Wadsworth, & Wessely, 1999). In case of PNES, 66% of patients report to have witnessed epileptic seizures before the onset of symptoms (Bautista, Gonzales-Salazar, & Ochoa, 2008). Still FNSD patients are more likely to have a profession in the medical field (Crimlisk et al., 1998).

The model of Edwards et al. stated in the introduction proposed the presence of abnormally strong internal (top-down) expectations in patients with FNSD that override "normal" bottom-up signals and bias the actual perception in direction of the expectation. It is possible, that the high personal confrontation with disease shapes those prior expectations/beliefs in patients with FNSD. This process could be further facilitated by the fact that patients with FNSD are reported to have a higher tendency for jumping to conclusion (compared to HC), that is, they request less information to make a decision and change this decision more frequently when represented with new evidence (Edwards, Fotopoulou, & Pareés, 2013). So abnormal prior beliefs/expectations may develop and be confirmed more easily.

Regarding traumatic and stressful experiences in patients with FNSD, it is important to note that the assessment of such experiences has to be conducted carefully. According to our experience, patients with FNSD have far more difficulties than patients with PTSD or MDD to talk about their traumatic experiences and their disorder in general. This may be due to the oftentimes negative experience background with doctors and medical

professionals and the scepticism on psychic explanations for their symptoms, as stated in the introduction. One should account for this by planning enough time for assessments and deliver a detailed explanation on study process and purpose.
Summing up, evidence does not allow for assumption of direct causality between trauma and FNSD. Yet, it seems convincing that trauma in combination with other predisposing factors, that will be entrained in the next chapters, can increase the risk for FNSD. The careful assessment of not only traumatic events but also general medical and learning history seems further mandatory.

5.2 Somatic Sensation in patients with FNSD

Study 2 showed that FNSD patients did not differ from other diagnostic groups in somatic sensation at baseline as measured by TENS. This finding may indicate that somatic sensation in general is unchanged in patients with FNSD. So we could not confirm the hypothesis of general abnormal somatic awareness in FNSD (in the sense of an endophenotype of the disorder), that has been stated in studies before (Almis, Cumurcu, Unal, Ozcan, & Aytas, 2013; Aybek, Apazoglou, Wegzyrk, & Mazzola, 2017). However, somatic sensation was different between FNSD patients and HC upon the stressful interview on adverse childhood experiences. Patients with FNSD reported significantly higher perception thresholds post-interview compared to pre-interview, indicating that they were less sensitive after the confrontation with stressful content than before.
Speculating about how these changes in body sensitivity may arise, literature advocates the consideration of attentional factors. A study of D. Brown (2010) reported alterations in body focused attention in participants with high levels of somatoform dissociation (after watching a neutral film), in a sense that they show disproportionate duration of attention to bodily cues. The observation that attention modifies somatic

symptoms is also the basis for Hoovers sign, a diagnostic tool used in FNSD which implies a return of normal functioning if attention is diverted away from the affected body part (Ziv, Djaldetti, Zoldan, Avraham, & Melamed, 1998). In line with this, further studies reported a change in frequency and character of functional tremor under manipulation of attention (Daum, Hubschmid, & Aybek, 2014; Stone & Carson, 2015) and showed that patients with FNSD have enlarged visual attention on their tremoring limbs compared to patients with epileptic seizures (van Poppelen et al., 2011). A recent study investigated attention in patients with FNSD compared to HC in a tactile cueing task and reported absence of cueing effects in FNSD patients on the affected side of the body. They suggest that this may be due to the enlargement of perceived symptoms (by attention) which is accompanied by a reduced sensory response (McIntosh, McWhirter, Ludwig, Carson, & Stone, 2017). Alterations in attention have also been demonstrated in non-clinical groups with high levels of somatform dissociative symptoms. The late somatosensory activity, a neural marker of attention towards the body, has been shown to be diminshed in the group of participants with high scores on the SDQ-20 (Karlinski, Jones, & Forster, 2019). In line with this, recent threapeutic approaches for FNSD, integrating the manipulation of body focused attention show promising results (Goldstein et al., 2010; Nielsen et al., 2017).

However, the relationship between attention and symptom expression in FNSD is complex. The present study included only patients with negative FNS, thus symptoms like paralysis, numbness etc. If an allocation of attention away from the body signifies a decrease in symptom severity, as suggested by various studies (see above), then a decrease in paralysis or numbness would imply an increase in sensitivity of the affected limbs. The present results however, showed a decrease in general sensitivity as measured by TENS. The effect of attention on negative FNS may manifest differently than in postive

FNS. In fact, to address the question about alterations of somatic sensation in FNSD in detail, future research should incorporate (besides the TENS as a general measure for sensitivity) a preferably objective measure of each individual symptom severity. This would allow for better conclusions on the impact of stress on symptom severity. However, the implementation of such a measure is challenging for the different subtypes of FNSD. Whereas some symptoms could be easily video-monitored (like nonepileptic seizures or tremor) others (like general weakness/slowness or Parkinsonism) may require more elaborated measures such as for example time needed to walk a certain distance.

Distinct personality traits or abnormalities may convey alterations in attention in FNSD patients. It has been shown that patients with FNSD have higher levels of neuroticism compared to HC (Ekanayake et al., 2017). Neuroticism in turn, has been associated with difficulties in the disengagement of attention from negative stimuli (Bredemeier, Berenbaum, Most, & Simons, 2011) and general deficits in attentional control (Wallace & Newman, 1997). Deficits in control are documented in FNSD patients not only in the domain of attention – various studies reported decreased sense of agency or control over their actions in patients with FNSD (Edwards et al., 2013; Kranick et al., 2013; Nahab, Kundu, Maurer, Shen, & Hallett, 2017). In line with this, traumatic experiences as frequently reported in patients with FNSD (view above) are situations of maximal loss of control. Such experiences may possibly contribute to deficits in sense of control in patients with FNSD. According to the consistency theory of Klaus Grawe, control is assumed as an essential psychological need, hence it might be promising for therapeuetic success to enable patients to the experience of control (for example by means of physiotherapeutic aids like electrically controllable splints).

Clear conclusions regarding the role of somatic sensation in FNSD can only be drawn from further research applying validated methods. Still, the present study encourages

the utilization of TENS to measure somatic sensation in FNSD and fosters the consideration of not only past traumatic but also acute stress in the development and maintenance of the disorder. Further research should also take attentional factors into account.

5.3 Emotion Processing in patients with FNSD

The present studies captured different aspects of emotion processing in FNSD patients. Study one replicated findings of higher levels of alexithymia in FNSD patients than in HC (Demartini et al., 2016; Gulpek et al., 2014). This result could be confirmed in study 3: Patients with FNSD showed less tendencies to use cognitive reappraisal than HC. Remarkably, emotion regulation strategies in FNSD patients seemed to be changeable across time and therapy, which was demonstrated in study 3 on behavioural and on cortical level. Taken together, the present findings match the current classification of altered emotion processing as an established factor in patients with somatic symptom and related disorders (Okur Güney, Sattel, Witthöft, & Henningsen, 2019).

Experiences of emotional abuse/neglect in patients with FNSD (discussed above) may contribute to these deficits in emotion processing. Furthermore, altered emotion regulation has been shown to be associated with neuroticism (Ng & Diener, 2009), a personality trait associated with FNSD (Ekanayake et al., 2017) and alterations in attention (view above). Personality traits are relatively stable and thus cannot be focus of therapy. According to the present results however, strategies of emotion regulation, probably mediating the relationship between neuroticism and FNSD, can be modified.

Taken together, these findings support the assessment of emotion processing in diagnosis and treatment of FNSD and encourage further research on the variability of cortical activity related to emotion regulation, thereby illuminating mechanisms of successful therapy.

5.4 Limitations

Despite the growing interest in FNSD, well-suited instruments for the assessment of the symptoms described by patients still appear to be missing. As such, operationalization of symptoms and their variability was challenging in the presented studies. As discussed in Study 2, the somatoform dissociation questionnaire (SDQ20) cannot fully capture FNS, since it does not account for the duration of symptoms. However, duration of symptoms is crucial when differentiating FNSD from other disorders showing somatoform dissociative symptoms (like PTSD). In PTSD, somatoform dissociative symptoms may last for minutes or hours, whereas they are permanent in patients with FNSD. Other scales, applied to measure treatment outcome in patients with FNSD capture either global concepts like hospital anxiety and depression (HADS; (Snaith, 2003)), work and social adjustment (WSAS; (Zahra et al., 2014)) or general somatic symptom load (SCL90-R, SOMS) or are focusing on movement disorders only (disabilities of the arm, shoulder and hand (DASH; Hudak96) (Nielsen et al., 2017), psychogenic movement disorder rating scale (FMDRS; (Hinson, Cubo, Comella, Goetz, & Leurgans, 2005)). An instrument on the assessment of changes in functional neurological symptom severity, incorporating the different forms of FNSD is urgently needed. It would allow specific, yet generalizable conclusions for this patient group. We suggest to amplify the SDQ-20 by an additional item, capturing duration of symptoms. The results of study 2 advocate TENS as a symptom-close measure for somatic sensation in FNSD, however, further validation studies are mandatory. TENS was applied on the right forearm as a general measure of sensitivity, independent of affected limbs. So we were unable to hypothesize on eventual stress related changes of individual FNS severity. As a further shortcoming, it has to be noted, that the present studies included only patients with negative FNS. So, findings cannot be generalized to all patients suffering from FNSD.

5.5 Final Conclusion

Summing up the findings discussed above, the answer to the question: "Is Functional Neurological Symptom Disorder (FNSD) a (somatic) stress disorder with altered emotion processing?" has to be "No". Stressfull and traumatic experiences may increase the risk for the development of FNSD but they are no prerequisite for the disorder. First hints suggest alterations in somatic sensation by accute stress in FNSD, yet further powered studies need to investigate this in more detail, especiallay focusing on differences between positive and negative FNS. Alterations in emotion processing could be confirmed as important feature of FNSD and should be targeted in treatment approaches. Comming back to the triangular model stated in the introduction, we suggest an amplification by two factors: Learning history and coping may influence emotion processing and attention seems to have a strong impact on somatic sensation. The following model could form a basis for further research in the field of FNSD.

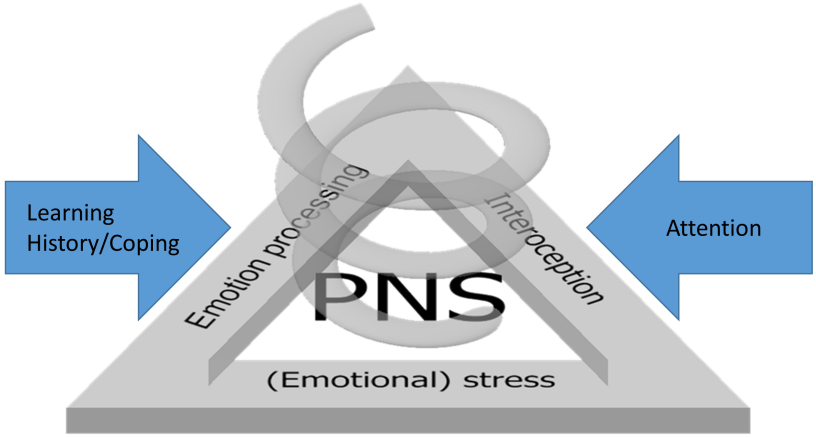

Figure 9: Hypothetical model on the interplay of (emotional) stress, emotion processing and interoception (somatic sensation) in the generation and maintenance of FNSD, extended by the factors learning history and attention.

6 Supplemetal material (Study 3 / Chapter 4)

Table 7: Mean and standard-deviation of alexithymia and emotion regulation (i.e. cognitive reappraisal and emotion suppression), pre-treatment.

	FNSD patients	**HC**
N	19	19
Alexithymia (TAS-26)	2.89 ± 0.53	2.15 ± 0.35
Cognitive reappraisal (ERQ_R)	3.45 ± 1.54	4.75 ± 1.35
Emotion suppression (ERQ_S)	3.57 ± 1.93	3.26 ± 0.88

FNSD = functional neurological symptom disorder; HC = healthy comparison participants

Table 8: Bonferroni-Holm corrected alpha level and original p-values for the reported measurements.

Dimension (scale)	**Bonferroni-Holm corrected alpha level**	***p* - value**
Symptom severity (SDQ-20)	0.05	0.89
Subjective symptom report (self report, Likert scale)	0.007	0.053
Psychological strain (SCL-90R_GSI)	0.004	0.018
Alexithymia (TAS-26)	0.01	0.19
Cognitive reappraisal (ERQ_R)	0.0035	0.001
Emotion suppression (ERQ_S)	0.02	0.65

SDQ-20 severity of somatoform dissociative symptoms, verified by the Somatoform Dissociation Questionnaire; SCL-90R_GSI = Symptom Checklist-90-Revised; TAS-26 = Alexithymia, assessed with the Toronto Alexithymia Scale; ERQ_R = Emotion Regulation Questionnaire Regulation; ERQ_S = Emotion Regulation Questionnaire Suppression;

7 Conducted studies and own research contributions

The co-authors of the studies in the present dissertation are listed below, as well as my own contributions to each study.

Study 1: Somatoform dissociation and posttraumatic stress syndrome – two sides of the same medal? A comparison of symptom profiles, trauma history and altered affect regulation between patients with functional neurological symptoms and patients with PTSD

Published as: Kienle, J., Rockstroh, B., Bohus, M., Fiess, J., Huffziger, S., and Steffen-Klatt, A. (2017). Somatoform dissociation and posttraumatic stress syndrome – two sides of the same medal? A comparison of symptom profiles, trauma history and altered affect regulation between patients with functional neurological symptoms and patients with PTSD. BMC Psychiatry 17(1), 248. doi: 10.1186/s12888-017-1414-z.

My Contributions: I contributed to the development of the study protocol and to the data collection. I analysed the data and pre-prepared the manuscript and the figures.

Study 2: Body Sensation in Functional Neurological Symptom Disorder – typical or specific feature?

Authors: Beckh, J., Steffen-Klatt, A., Fiess, J., Rockstroh, B.

My Contributions: I contributed to data collection. I analysed the data and prepared the manuscript and the figures.

Study 3: Variation of Functional Neurological Symptoms and Emotion Regulation with Time Published as: Kienle, J., Rockstroh, B., Fiess, J., Schmidt, R., Popov, T., and Steffen-Klatt, A. (2018). Variation of Functional Neurological Symptoms and Emotion Regulation with Time. Frontiers in Psychiatry 9(35). doi: 10.3389/fpsyt.2018.00035.

My contributions: I collected and analysed the data and prepared the figures. I contributed to the preparation of the manuscript.

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