Psychosocial and somatic resilience factors of patients with fibromyalgia syndrome (FMS)

Psychosoziale und somatische Resilienzfaktoren bei Patienten mit dem Fibromyalgie Syndrom (FMS)

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mich und hältst deine Hand über
mir.

Psalm 139, 5

Abstract

Background: In recent years, health care has increasingly become the focus of public interest, politics, health insurance companies, and research. This includes the development of therapeutic concepts that can respond individually to patients' resources in order to improve coping with chronic diseases. Research into psychosocial and biological resilience factors is very important and the basic objective of the present work. I studied patients with fibromyalgia syndrome (FMS), who suffer among others from chronic pain, fatigue, sleep and gastrointestinal problems. This patient cohort is characterized by a pronounced heterogeneity in terms of clinical outcome, degree in disability and coping. FMS has a prevalence of 3 – 8 % in the Western population and has a significant socio-economic impact. Validated psychosocial resilience factors include optimism, humor, coherence, self-efficacy, awareness with one's own resources and the ability to apply them profitably (coping), and a healthy social environment with positive relationships. Studies in patients with cancer revealed religiosity as positive and negative factor on the health outcome, but there is little data on religious aspects of pain resilience. Various genetic polymorphisms and anti-inflammatory cytokines are known as biological resilience factors. Various microRNA (miRNA) were detected to contribute to resilience in the context of stress and psychiatric disorders.

Objective: The underlying research question of this work is to understand the factors that make some FMS patients resilient and others not, even though they suffer from the same disease. The long-term aim was to understand mechanisms and influencing factors of resilience to design preventive and resource-oriented therapies for FMS patients.

Material and Methods: Three studies examined religious, physiological, biological, and psychosocial factors which may contribute to resilience in FMS patients. Study one combined data of questionnaires, a psychosocial interview, and regression analyses to investigate the relevance of religiosity for coping and resilience. Study two examined variance explaining factors and defined clusters among FMS patients by their differences in coping, pain phenotype and disability. The factor analysis used variables derived from questionnaires and qPCR of cytokines in white blood samples (WBC) of patients and healthy controls. Study three assessed cluster-wise miRNA signatures which may underly differences in behaviour, emotional and physiological disability, and resilience among patient clusters. A cluster-specific speculative model of a miRNA-mediated regulatory cycle was proposed and its potential targets verified by an online tool.

Results: The data from the first study revealed a not very religious patient cohort, which was rather ambivalent towards the institution church, but described itself as a believer. The degree of religiosity played a role in the choice of coping strategy but had no effect on psychological parameters or health outcomes. The coping strategy "reinterpretation", which is closely related

to the religious coping "reappraisal", had the highest influence on FMS related disability. Cognitive active coping strategies such as reappraisal which belongs to religious coping had the highest effect on FMS related disability (resilience) and could be trained by a therapist. Results from the second study showed high variances of all measured cytokines within the patient group and no difference between patient and control group. The high dispersion indicated cluster among patients. Factor analysis extracted four variance-explaining factors named as affective load, coping, pain, and pro-inflammatory cytokines. Psychological factors such as depression were the most decisive factors of everyday stress in life and represented the greatest influence on the variance of the data. Study two identified four clusters with respective differences in the factors and characterized them as poorly adapted (maladaptive), well adapted (adaptive), vulnerable and resilient. Their naming was based on characteristics of both resilience concepts, indicated by patients who were less stress-sensitive and impaired as a personal characteristic and by patients who emerged as more resilient from a learning and adaptive process. The data from the variance analysis suggests that problem- and emotion-focused coping strategies and a more anti-inflammatory cytokine pattern are associated with low impairment and contribute to resilience. Additional favorable factors include low anxiety, acceptance, and persistence. Some cluster-specific intervention proposals were created that combine existing concepts of behavioral and mindfulness therapies with alternative therapies such as vitamin D supplementation and a healthy intestinal flora. The results of the third study revealed lower relative gene expression of miR103a-3p, miR107, and miR130a-3p in the FMS cohort compared to the healthy controls with a large effect size. The adaptive cluster had the highest gene expression of miR103a-3p and tendentially of miR107, which was correlated with the subscale score "physical abuse" of the trauma questionnaire. Further correlations were found in particular with pain catastrophizing and FMS-related disability. MiR103a-3p and miR107 form a miRNA-family. Based on this, we proposed a miR103a/107 regulated model of an adaptive process to stress, inflammation and pain by targeting genetic factors which are included in different anti-inflammatory and stress-regulating pathways.

Conclusion: All three studies provide new insights into resilience in FMS patients. Cognitive coping (reappraisal/reinterpretation) plays a central role and thus offers therapeutic targets (reframing in the context of behavioral therapy). Religosity as a resilience factor was only partially valid for our patient cohort. Basically, the use of resource-oriented therapy in large institutions still requires research and interdisciplinary cooperation to create a consensus between the humanities, natural sciences and humanism.

Zusammenfassung

Hintergrund: Die Gesunderhaltung ist in den letzten Jahren mehr und mehr in den Fokus des Interesses der Öffentlichkeit, Politik, Krankenkassen und Forschung gerückt. Dazu zählt auch die Entwicklung von Therapiekonzepten, die individuell auf die Bedürfnisse und Ressourcen der Patienten zugeschnitten sind, um den Umgang mit insbesondere chronischen Erkrankungen zu verbessern. Die Erforschung von psychosozialen und biologischen Resilienzfaktoren ist hierfür sehr wichtig, und das grundlegende Ziel der vorliegenden Arbeit. Zielgruppe sind Patienten mit Fibromyalgiesyndrom (FMS). Symptome des FMS sind u.a. chronischer Schmerz, Erschöpfung, Schlaf und Magen-, Darmprobleme. Die Patientengruppe erscheint in der Klinik als sehr heterogene mit unterschiedlichen Beeinträchtigungsgraden und verschiedenen Strategien, mit den Auswirkungen der Erkrankung umzugehen. Die Prävalenz des FMS liegt bei 3 – 8% in der westlichen Bevölkerung und ist somit von erheblicher gesellschaftlicher und sozioökonomischer Bedeutung. Validierte psychosoziale Resilienzfaktoren sind u.a. Optimismus, Humor, Kohärenzgefühl, Selbstwirksamkeit, Bewusstsein der eigenen Ressourcen und die Fähigkeit diese gewinnbringend anzuwenden (Coping) und ein gesundes soziales Umfeld mit positiven Beziehungen. Studien an Krebspatienten ergaben unterschiedliche Effekte von Religiosität als Copingstrategie und Resilienzfaktor. Im Allgemeinen liegen wenige Daten vor zum Thema Religiosität / als Schutzfaktor bei Schmerzpatienten. Als biologische Resilienzfaktoren sind verschiedene genetische Polymophismen, anti-inflammatorische Zytokine und microRNA (miRNA) bekannt, die zur Resilienz bei chronischem Stress und psychiatrischen Krankheitsbildern beitragen.

Ziel: Die zugrundeliegende Forschungsfrage dieser vorliegenden Arbeit ist, welche Faktoren dazu beitragen, dass manche Patienten resilienter sind als andere, obwohl sie unter derselben Erkrankung leiden. Das langfristige Ziel dieser Forschung ist es, Mechanismen und Einflussfaktoren der Resilienz zu verstehen, um präventive und gezielte Ressourcen-orientierte Therapien für FMS Patienten zu entwickeln.

Material und Methoden: Insgesamt drei Studien untersuchten explorativ eine Reihe von religiösen, physiologischen, biologischen und psychosozialen Faktoren und ihre Rolle als Schutzfaktor bei Patienten mit FMS. Studie 1 kombinierte Daten von Fragebögen, einem psychologischen Interview und Regressionsanalysen, um die Relevanz von Religiosität für das Coping und Resilienz zu untersuchen. Studie 2 versuchte mit einer explorativen Faktorenanalyse Einflussfaktoren zu ermitteln, die für die heterogene Datenlage der Patienten verantwortlich sind. Mithilfe einer Clusteranalyse wurden Subgruppen anhand ihrer Unterschiede in mentaler Gesundheit, Coping, Schmerzphänotyp und Beeinträchtigung definiert. Die Faktorenanalyse verwendete Daten der Fragebögen und Genexpressionsanalysen ausgewählter Zytokine aus Blutproben der Patienten und einer

gesunden Kontrollgruppe. Zuletzt wurden Cluster-spezifische Therapievorschläge auf der Basis bereits bekannter Therapien zusammengestellt. Studie 3 bestimmte Cluster-charakteristische miRNA Signaturen, die verantwortlich für die Cluster-spezifischen Unterschiede in Verhalten (coping), emotionaler und körperlicher Beeinträchtigung, und Resilienz sein können. Die Ergebnisse wurden in einem Regulationsschema zusammengefasst und schlagen einen möglichen miRNA-regulierten Mechanismus von adaptivem Verhalten vor. Die potentiellen genetischen Targets wurden mittels eines online Tools „Target Scan Human“ verifiziert.

Ergebnisse: Die Daten der ersten Studie zeigten eine wenig religiöse Patientenkohorte, die der Institution Kirche eher ambivalent gegenüberstand, sich jedoch dennoch als gläubig beschrieb. Der Grad der Religiosität spielte eine Rolle bei der Wahl der Copingstrategie, hatte jedoch keinen Einfluss auf psychologische Parameter oder die Gesundheit. Die Copingstrategie „Reinterpretation“, welche auch nah verwandt mit dem religiösen Coping „reappraisal“ ist, hatte einen signifikanten Einfluss auf die Beeinträchtigung, und könnte innerhalb einer Verhaltenstherapie erlernt werden. Ergebnisse der zweiten Studie zeigen hohe Varianzen aller gemessenen Zytokine innerhalb der Patientengruppe und keinen signifikanten Unterschied zwischen Patienten- und Kontrollgruppe. Die hohe Streuung deutete auf Subgruppen innerhalb der FMS Kohorte hin. Mittels einer Faktorenanalyse wurden vier Faktoren ermittelt, die dieser Varianz zugrunde liegen, welche absteigend als affektive Belastung, Coping, Schmerz und pro-inflammatorische Zytokine benannt wurden. Interessant ist, dass psychische Faktoren wie Depression den höchsten Einfluss auf die Belastung im Alltag darstellten und auch den größten Einfluss auf die Varianz der Daten abbildete. Studie 2 konnte vier Subgruppen mit jeweiligen Unterschieden in den charakterisierten Faktoren ermitteln und diese als schlecht angepasst (maladaptive), gut angepasst (adaptive), vulnerabel und resilient charakterisieren. Ihre Benennung basierte auf Charakteristika beider Resilienzkonzepte. Es gab Anzeichen für Patienten, die weniger stresssensibel und beeinträchtigt waren aufgrund von Persönlichkeitsstrukturen sowie Patienten, die aus einem Lern- und Anpassungsprozess nun resilienter hervorgingen. Die Daten der Varianzanalyse legten nahe, dass problem- und emotionsfokussierte Copingstrategien und ein eher antiinflammatorisches Zytokinmuster mit einer niedrigen Beeinträchtigung assoziiert sind und eher zur Resilienz beitragen. Zusätzliche begünstigende Faktoren sind niedrige Angstwerte, Akzeptanz und Durchhaltevermögen. Basierend auf diesen Erkenntnissen wurden einige Subgruppen-spezifische Interventionsvorschläge vorgestellt, welche bereits existierende Konzepte der Verhaltens- und Achtsamkeitstherapien mit alternativen Therapien wie Supplementierung von Vitamin D und eine gesunde Darmflora miteinander kombinieren. Die Ergebnisse der dritten Studie zeigten eine niedrigere relative Genexpression von miR103a-3p, miR107 und miR130a-3p in der FMS Kohorte verglichen mit der gesunden Kontrollkohorte mit

einer großen Effektstärke. Die höchste relative Genexpression zeigte miR103a im adaptiven Cluster, das Cluster mit der niedrigsten Beeinträchtigung. MiR107 tendierte zu einer leicht erhöhten relativen Expression im adaptiven Cluster und war mit dem Subskalenscore „körperlicher Missbrauch“ des Traumafragebogens korreliert. Weitere Korrelationen fanden sich insbesondere mit den Variablen psychologischer Fragebögen zu Schmerz Katastrophisieren und FMS-bezogene Beeinträchtigung. MiR103a-3p und miR107 bilden zuammen eine miRNA Familie mit gleichen physiologischen Funktionen. Basierend auf diesen Erkenntnissen, schlugen wir ein Model der miR103a/107 regulierten Anpassung an Stress, Entzündung und Schmerz unter Einbezug verifizierter Gene, vor.

Schlussfolgerung: Zusammenfassend geben alle drei Studien neue Einblicke in die Resilienzfaktoren von FMS Patienten. Dabei kommt dem kognitiven Coping (reappraisal / reinterpretation) eine zentrale Rolle zu, was therapeutische Ansatzpunkte (reframing innerhalb einer Verhaltenstherapie) bietet. Religiosität konnte sich in der hier untersuchten Kohorte als Schutzfaktor nur bedingt validieren. Grundsätzlich benötigt der Einsatz von ressourcenorientierter Therapie innerhalb großer Kliniken noch einiges an Forschung und interdisziplinärer Zusammenarbeit, die einen Konsens zwischen Geisteswissenschaften, Naturwissenschaften und Humanismus schafft.

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Abbreviations

A	ACR	American College of Rheumatology
	ADS	Allgemeine Depressions Skala
	ASP	Aspects of Spirituality Questionnaire
	APA	American Psychological Associations
B	BSC	Biological Sensitivity to Context
	BDNF	Brain Derived Neurotrophic Factor
C	CNS	Central Nervous System
	CRH	Corticotropin Releasing Factor
	CRHR1	CRH Type 1 Receptor Gene
	COMT	Catechol-O-methyltransferase
	ConA	Concanavalin A
	CCM	Corneal Confocal Microscopy
	CTQ	Childhood Trauma Questionnaire
	CSQ	Coping Strategies Questionnaire
	CDK	Cyclin-Dependent Kinases
	CT	Cycle Threshold
D	DHEA	Dehydroepiandrosterone
E	ELISA	Enzyme-Linked Immunosorbent Assay
	EVS	European Values Study
	ESS	European Social Survey
	EMG	Electromyography
F	FMS	Fibromyalgia Syndrome
	FS	Fibromyalgia Symptom Scale
	FIQ	Fibromyalgia Impact Questionnaire
G	GR	Glucocorticoid Receptor
	GE	Genotype Environment (interaction)
	GCPS	Graded Chronic Pain Scale
H	HPA	Hypothalamic-Pituitary-Adrenal (axis)
	5-HT	5-Hydroxytryptamine
	5-HTTLPR	Serotonin Transporter Linked Polymorphic Region
I	ICD	International Statistical Classification of Diseases and Related Health Problems
	IASP	International Association for the Study of Pain
	IL	Interleukine
	IENFD	Intraepidermal Nerve Fibre Density
	ISSP	International Social Survey Programme
J		

K

L

LC	Locus Coeruleus
LPS	Lipo-Polysaccharid

M

mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
MBSR	Mind-Based Stress Reduction
MBCT	Mind-Based Cognitive Treatment
mRNA	Messenger Ribonucleic Acid
miRNA	Micro Ribonuleic Acid

N

NF-κB	Nuclear Factor Kappa B
NPY	Neuropeptide Y
NGFI-A	Nerve Growth Factor Inducible Protein A
NA	Nucleus Accumbens
NPSI	Neuropathic Pain Scale Inventory

O

P

PTSD	Post-Traumatic Stress Disorder
PFC	Prefrontal Cortex
PREP	Pain Related Evoked Potentials
PCS	Pain Catastrophizing Score
PAI	Positive Activity Intervention
PCR	Polymerase Chain Reaction

Q

QST	Quantitative Sensory Testing

R

ROS	Reactive Oxygen Species
RS-13	Resilience Scale (short version, 13 items)

S

SS	Symptom Severity
SNRI	Serotonin Norepinephrine Reuptake Inhibitors
SOC	Sense of Coherence
SNP	Single Nucleotide Polymorphism
STAI	State Trait Anxiety Inventory
SF-12	12-Item Short Form Survey
SNRK	Sucrose Non-Fermentable Kinases

T

TNF-α	Tumor Necrosis Factor Alpha
TLR4	Toll-like Receptor 4

U

V

Val66Met	Methionine (Met) substitution for valine (Val) at codon 66
Val158Met	Methionine (Met) substitution for valine (Val) at codon 158

W

WPI	Widespread Pain Index
WHO	World Health Organization
WVS	World Values Survey
WBC	White Blood Cells

X

Y

Z

1 General Introduction

1.1 Fibromyalgia Syndrome (FMS)

1.1.1 Definition and clinical symptoms

A long time ago, FMS was called “psychoneurotic rheumatism”, a term that tried to summarize the somatic and psychological symptoms of a cohort of mainly middle-aged women in pain, that physicians had no clinical explanation for [1, 2]. This missing exact explanation for the diffuse wide range of symptoms and the controversy about classification and pathophysiology made it hard to find an exact definition for what FMS really is and it remains a problematic fact. *Fibrositis* [3] was the first term patients were described with to differentiate them from patients suffering from rheumatic disorders [4]. For the first time, the term *fibromyalgia* (Latin for *fibro*- “fibrous tissue”, Greek for *myo*- “muscle” and *algia*- “pain”), which literally means *“pain in fibrous tissue and muscles”*, appeared 1976 in Hench’s “review of a common rheumatologic syndrome” [5]. Afterwards it gave grounds for discussion, but was generally accepted from most experts [6].

FMS is characterized by chronic widespread pain, pain attacks, numbness, allodynia, neuropathic pain, weakness of limbs or palpitations [7]. Associated symptoms are often fatigue, sleep and functional bowel disturbances, morning stiffness, cognitive dysfunction (“fibro fog”), anxiety, and depressive mood [8]. Pain and associated symptoms can persist for some weeks followed by painless episodes and then a phase lasting further weeks with highly intensive pain and depressive symptoms or exist every day as a low to medium dose of pain. Comorbidities could be interstitial cystitis, irritable bowel syndrome, migraine, temporomandibular joint dysfunction, osteoporosis, arthritis, multiple allergies or other autoimmune disorders [9].

1.1.2 Diagnosis

Since the first thoughts of understanding the “fibrositis” syndrome, some authors tried to establish diagnostic criteria for this diffuse syndrome, and finally, in 1986, the first multicentre study proposed criteria that could rather be used for clinical trials than function as diagnostic criteria [6]. But the topic of fibromyalgia started to be more in focus and 1990 the American College of Rheumatology (ACR) published a first guide with criteria to diagnose FMS based on widespread pain in combination with tenderness at over 11 to 18 tender points [6]. These criteria had more focus on physiological symptoms and less on psychological associations that could also be observed in the “typical” FMS patient. Furthermore, the examination of tender points often made problems during clinical performance, the revised criteria of 2010 excluded

the tender points and added two scores (WPI, widespread pain index; SS, symptom severity) rating the number of pain locations, the most discriminative symptoms and an estimate of the overall degree of somatic symptom severity [10]. Even the revised criteria caused problems in clinical practice, therefore further modifications excluded the estimate of pain extent done by the physician instead of another scale (FMS symptom scale, FS) [11]. In 2016, the revision of the 2010/11 criteria was published and concluded that the diagnosis of FMS could be made if generalized pain and symptoms are present for at least three months, if the WPI and SS scores reach certain limits, and if other rheumatic disease are excluded, but including the presence of other illnesses [12]. FMS is actually classified in ICD-11 (International Statistical Classification of Diseases and Related Health) under “chronic primary pain” after the work of a task force from the International Association for the Study of Pain (IASP) [13]. The diagnosis remains exclusive and many issues still need to be discussed [14].

1.1.3 Pathophysiology

The pathophysiology of FMS has not been entirely solved, but many influencing factors have been identified. There are controversial opinions on which potential pathophysiological agent underlines the FMS symptoms. One group of clinicians consider FMS to be a symptom complex characterized by amplification of pain by the central nervous system (CNS) titled “pain sensitization” or “centralization” [7, 15-17]. The concept of FMS as a “centralized pain state” can include damage of peripheral nerves or inflammation which contributes to nociceptive peripheral input and amplify pain, but the central sensitization remains as a potential origin of the pain [17]. The centralization is supported by the fact that FMS patients often fail in response to opioids [18].

The finding of an impairment of small nerve fibers and the resulting phenotype of “small-fiber pathology” gave objective evidence for further factors which contribute to the symptom complex of FMS patients and are localized in the peripheral nervous system [19, 20]. It remains unclear whether the small nerve pathology is the cause or the consequence, but nociceptive input is being detected by sensory nerves in the peripheral tissues which will lead in the end to the perception of pain in humans [15].

Specialists in psychosomatic medicine, conceptualize the FMS symptom complex as a type of somatoform disorder [21], while many psychiatrists see it as a type of affective disorder [22]. These specialists assert that the inappropriate "medicalization of misery" [23] as a rheumatological disease construct implies that some sort of non-demonstrable rheumatic process exists in the muscles and connective tissue, and might be responsible for the condition. The psychosomatic conception of FMS leads to a recommendation for treatment with psychotherapy [24], while the psychiatric conception leads to a recommendation for treatment with psychotropic medications [25]. Many patients reject a reduction of this condition

to purely somatic causes. Furthermore, there are lots of associations with pain and symptom intensity. There is broad evidence that maltreatment and experience of traumatic events during childhood are associated with the symptom intensity [26] and could lead to the development and chronification of pain [27]. Stress is a huge influencing factor that have immense consequences on physical health [28]. Chronic stress leads to de-synchronization of all stress axes (e.g. HPA, hypothalamic-pituitary-adrenal axis) resulting in increased resource usage and need of water, natrium, oxygen, neuroendocrine mediators such as cortisol, adrenaline, tyrosine or melatonin, and also an active immune system on duty with increased levels of immune mediators like pro-inflammatory cytokines [29-32].

The risk to be diagnosed with FMS is increased when one or more family members have the diagnosis of FMS suggesting a genetic influence. Candidate gene genetic association studies discuss the genetic predisposition and association of pain with some genes known to be involved in biological pathways of painful syndromes [26, 33-36]. Environmental factors like infections by specific viruses like Epstein-Barr virus, viral hepatitis or Lyme disease, and traumatic accidents are known to be linked with FMS [37, 38]. A wide range of miRNA as small regulatory items was found to be associated with FMS symptoms and the small nerve fiber pathology [39-42].

1.1.4 Therapy and outcome

Based on the multifaceted syndrome FMS, the treatment plan includes pain subtype and psychosocial profile, incorporating pharmacotherapy, self-management modalities, and a multimodal biopsychosocial management approach which is recommended in the German guideline [43].

Pharmacological therapies with a wide consensus on effectiveness in FMS patients are Amitriptyline, Duloxetine and Pregabaline [44]. Recommended non-pharmacological therapies are exercise and awareness therapies [45], advanced education and cognitive behavioral therapy [44, 46, 47]. In the last years, the need for complementary and alternative therapies become more and more important, and several studies showed the effectiveness of yoga, Thai Chi or acupuncture for FMS patients [48, 49]. Nevertheless, missing clarity about the diagnosis, pathophysiology and effectiveness of therapies is still persistent with consequences for clinicians and especially for patients. Every patient has its own individual method to cope with that insecurity and every one has its own medical history and experiences with clinicians and the the syndrome. This heterogeneity makes it highly difficult to offer generalized therapies and highlights cluster studies for classification of FMS patients to offer subgroup-specific therapies.

1.2 Coping in the context of health

The most popular definition of health was given by the World Health Organization (WHO) that defined health […] as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” [50]. In 2011, a group of researchers challenged the common understanding of health by suggesting that the WHO definition of health no longer fits the needs of people living with chronic conditions [51]. The “state of complete physical, mental and social well-being” is an impossibility for chronic pain patients who must manage symptoms (e.g. chronic pain, fatigue, and cognitive limitations) and the consequences of the chronic condition (e.g. limited working and social life). The alternative definition of health was proposed as “the ability to adapt and self-manage in the face of social, physical and emotional challenges” [51]. The underlying concept of this newly proposed health definition is related to the concept of “Salutogenesis” by Antonovsky [52]. This thesis would like to highlight and emphasize this holistic concept as necessary for patients with extensive chronic conditions.

Coping is understood as all those attempts that people use to deal with and manage internal and external demands during stressful events and periods in life that challenge the resources of the person [53]. Functional coping and an adequate stress response play a central role in the process of controlling the homeostasis and allostasis in the body and refers to resilience [54]. Stress offers the opportunity to become flexible and to develop strategies that make individuals less susceptible to stress and diseases [55]. During the time course and the experience of different stressful events, the allostatic load can accumulate. A hyper exposition to stress (neuronal, endocrine or immune stress) means the overload of allostasis and has negative effects on different organic systems. When the stress exceeds the ability to bounce back to homeostasis and coping is dysfunctional, (chronic) diseases arise [56].

Coping is a mixture of attributional (e.g. source of stress) and personal characteristics (e.g. risk tolerance, optimistic or pessimistic outlook). The personal aspects are relatively fixed, but the coping strategies can be improved by e.g. behavioral therapies. The effects of stress are depending on the reactivity phenotype that can be measured by the biological sensitivity of context (BSC) [57]. The BSC is partly determined by environmental factors and experiences during childhood. This calibrates the dynamics of stress reactions in crosstalk with polygenetic variations. In general, it is expected that individuals who experienced high stressful events during early life have a higher stress reactivity in later life. But even individuals with the low burden and intensive supportive relationships can develop high-reactive stress profiles because of the missing exposition to stress and missing diversity of stressors. Most stable profiles were developed by individuals with moderate exposition to stressors during early life in the continuum between independence and supportive social environment. The exposition to a stressor isn’t only a risk, it is also the opportunity to develop the ability to recognize environmental risks to learn an adequate reaction [57].

Many different coping styles have been identified and categorized as avoidant, attention, active, passive, and cognitive coping [53].

Problem-focused strategies are mainly active rational strategies to solve the problem, might be information seeking, trying to get help, seeking social support by professionals, family or friends, turning to religion, increasing of the activity or active distraction [53]. Social support is a key factor and people who can use active self-management approaches are rather resilient than people who use only passive strategies, such as catastrophizing or wishful thinking [58]. Exclusion and social defeat can promote the same neuronal and physical effects as infections or injuries. Positive supportive relationships influence the reward system with an inhibiting effect on stress reactivity. Social defeat makes sensitivity for physical trauma and injuries (e.g. predator). Social support and connection within a group protect of direct physical violence and reduce the risk of inflammation [59]. Problem-focused coping focuses on changing or modifying the fundamental cause of the stress. This can be an effective method of coping when it is practical, and the stressor is changeable or modifiable. The overarching goal for this type of coping is to reduce or remove the cause of the stressor [60].

Emotion-focused coping strategies are effective in the management of unchangeable stressors [61, 62]. These strategies try to work on the inner setting of a problem, e.g. accepting borders, making compromises or thinking of the problem to get different solutions. These coping mechanisms involve a cognitive reappraisal process that includes self-reflection to regulate and take control of emotions. Compared to problem-focused strategies, emotion-focused coping analyses the emotional response to the stressor rather than changing the problem, which has a positive effect on psychiatric disorders [63]. Especially reappraisal can facilitate expressing and processing emotions which promotes resilience and affective adaptation to chronic conditions [64].

1.3 Resilience

The worldwide prevalence of FMS is cited as 1 to 4 % [65] or 1 to 8% [17] depending on the analysed population. About half a billion people are taken ill with psychological diseases every year worldwide [66]. But despite high traumatic stressors, not everyone develops a chronic disease or long-lasting psychological disability [67]. There is significant variation in the way individuals react and respond to extreme stress and adversity. This phenomenon of psychological resistance is called “resilience” related to the Latin word “*resilire*” meaning “bouncing back” [68] and was first studied in the popular “Kauai study” examining the influence of biopsychosocial risk and protective factors of children living in difficult circumstances on the isle of Hawaii [69]. Despite poverty or psychopathologies within their families, one-third of the children became successful, psychologically strong personalities. To understand why some individuals, exhibit characteristics of a resilient profile, the interplay between neurochemical,

genetic, and epigenetic processes needs to be explained [70]. Identification of the underlying neurobiological components related to resilience may offer a contribution to improved approaches toward prevention and treatment.

1.3.1 Concepts

Definitions and concepts of resilience differed in the last years of resilience research [67, 71-73]. In the beginning, resilience was defined as a natural predisposition or stable personal characteristic [73]. In the last few years, resilience is seen as a result of a dynamic adaptive process to stressors influenced by many psychosocial and neuro-biological factors including personal characteristics [67, 73]. By now, resilience is understood as a dynamic changeable process and adaptation during coping with stress. People change their minds, opinions and views and grow in the face of adversity using these newly generated competences and resources, and are partly immunized to consequences of future stress or epigenetic changes [73]. Resilience can be defined as the dynamic life-long process in the interplay of environment and individual which may also change in different spheres and stages in life [74].

1.3.2 Evaluation

There is scientific consensus that resilience needs a meaningful stressor and this stressor must be handled by successful strategies [75]. Stress and the evaluation of the extent of stress and stress exposition is very important, but it is very difficult to evaluate it with objective measurements because the perception of stress is very individual [67]. Nevertheless, resilience defined as an adaptation to stress needs an evaluation of the type, extent and effect of stress to the individual. As a reference guide function some studies that evaluate the effect of a variety of stressors [76].

So far, there is no gold standard to evaluate resilience, but many resilience scales exist that are based on each concept of resilience, e.g. scales that evaluate personal resources and characteristics [71]. The brief resilience scale [77] evaluates the ability to return to mental health and bounce back after stressful events. This scale is the only instrument that is not only focused on personality and also exists in a German version [78]. Valid scales or instruments that base on the actual definition of resilience as a process or result are still missing. The only score that might evaluate resilience as a dynamic process over a time course was proposed as the “R score” [79]. This score assumes that an individual is resilient if less psychological dysfunctions are developed between two specific time points with a high stressful load. But also, this “R score” needs to be evaluated in longitudinal studies. Now, resilience research also considers neurobiological aspects and is more interested in integral and translational concepts [80, 81]. This new orientation also needs to be considered in the evaluation process of resilience and is still missing.

The definition of resilience in this thesis is combining both concepts – the consideration of specific personal characteristics but also the definition of resilience as a dynamic process of adaptation. In the published studies, summarized in this thesis in point *"4. Manuscripts",* resilience I tried to evaluate resilience by different aspects like disability, traumatic events in childhood, pain intensity, and cytokine state.

1.3.3 Critiques

Resilience research and the possibility to operationalize resilience in science were mainly criticized in these four categories [82]:

1. Definitions and operationalization
2. The discrepancy between resilience as a trait and as a dynamic concept
3. Instability in the phenomenon of resilience
4. Theoretical concerns about resilience as a scientific construct

The first research in the field of resilience was focused on personal characteristics [83], that was further broadened to other external factors like social environment or economical state that have an influence on resilience [84]. Now, the focus is on an underlying neurobiological mechanism [85]. There is still a missing consensus about definitions, operationalization, and missing instruments to measure resilience especially based on today's definition of a dynamic process. This heterogeneity may also be something positive when studies synchronously determined similar resilience factors although they were based on different designs and concepts.

Second, the biggest discrepancy exists in the controversy between resilience as a trait versus as a process. The most popular reflections about the topic resilience as trait were given by Jeanne and Jack Block [86] who coined the term "ego-resiliency" that means a general set of traits and flexibility in response to environmental changes. Opposed to resilience, ego-resiliency is a personal trait and characteristic. Following, ego-resiliency can be a trait of someone who was never exposed to any kind of adversity, whereas resilience includes the fact of being resilient in the face of adversity [87]. This discrepancy is reinforced in the context of "resilient children" [88].

Third, the instability or multidimensional character of resilience remains a critical term in resilience research. Studies showed that children defined as resilient showed competences in specific areas whereas they had simultaneously problems in other areas [89]. This variability across domains led speculate some scientists on resilience as a veridical construct [90]. Consequently, it is important that scientists must specify their findings regarding the particular spheres to which their data apply. It must be clarified that success in these domains by no

means implies positive adaptation across all important areas [91]. Additionally, these implications make resilience more complex than it is.

Fourth, some critical voices point out the robustness of evidence on resilience. This shortly means that no study can determine that every study participant had the same level of adversity. Even there is a life circumstance that defines a high risk there might be another aspect which contributes to the maintenance of health. This means that this person is not “originally resilient” because despite the high risk there was another healing aspect [85]. This describes the discrepancy between “statistical” risk versus “actual” risk [92] and between “subjective” versus “objective” ratings of risk [93].

1.4 Resilience factors

Some psychosocial, neurobiological, theological, and anthropogenic factors are well known protective factors, just like coping with stressful periods and physical symptoms has an important impact on stress, pain, and the fact to stay healthy [94]. The physical and psychological inside of everyone is in dialogue with the context. Especially social and anthropogenic factors in the context of school, work, communication with colleagues, parents, friends, and especially reactions of others or the western lifestyle have an impact on the continuum between illness and health, and at least (pain) behavior [95]. Cognitive factors like ruminating have an immense negative influence on pain and can lead to anxiety disorder or depression [96, 97]. Focusing on pain and physical symptoms can elevate pain perception whereas distraction and ignoring are well established coping strategies to reduce pain [98]. There is growing evidence that also theological factors like believing in god leading to a high sense of coherence and might have a positive effect on pain intensity and health [99]. Placebo- and nocebo effects on pain base on expectations and imagination and are firmly fixed in patients. All these cognitive aspects are the aim of pain management therapies like deep learning, reframing or mindfulness therapies [100].

1.4.1 Psychosocial resilience factors

Self-esteem, positive emotions, optimism, hope, the expectation of self-efficacy, the internal conviction of control, sense of coherence (SOC), hardiness, and positive relationships are examples for psychological factors with high validity in functioning as protective factors [1, 59, 74, 85].

The SOC was first mentioned in the salutogenesis concept by Antonovsky and consists of the three terms comprehensibility, manageability, and sense or meaning in life [101]. People with high SOC take less ill with chronic diseases and are better in using the best fitting coping strategies to reduce pain [102]. Self-esteem [103] is the evaluative and affective component of

the conscious perception of “the self”. People with high self-esteem were protected from getting depressed or addicted [104]. Positive emotions like pleasure, satisfaction or confidence have a general protective effect on health. Positive affect is strongly associated with low pain and stress, whereas negative affect overweighs when people go through a period of intensive stress [104]. The negative affect increases pain, whereas positive emotions have a suppressive effect on pain. Supportive friendships and social networks are the empirical best determined protective factors [105].

1.4.2 Anthropogenic resilience factors

Anthropogenic factors can be an artificial environment and their side effects, as well as related lifestyles with an entirely negative impact on human health. Anthropogenic factors are predominantly risk factors, but the opposite of these anthropogenic factors – e.g. lifestyle changes and trying to avoid plastics, synthetic materials and toxic environments including social life – might function as protective factors. Epidemiologic analyses are mainly concentrated on risk factors (such as blood tension or lipids) and proximal factors, but less attention to distal factors with influence on lifestyle (e.g. social, political, ecological and economic conditions). Distal factors are e.g. quality and affordability of food, supply for physical activity or environmental pollution with hormones and other toxic chemicals but also the inner environment of the human body (microbiome). Such factors are often the result of political, economic, and social circumstances which were often not included in the medical history but can have an immense contribution to chronic diseases. So far less analyzed factors are the influence of social media (including psychopathological effects of “cyber-mobbing”) and new communication technologies, consumption of drugs especially of recreational drugs and less restful sleep [106]. The percentage of chronic diseases within a society can also reflect a general problem in the structure of society.

1.4.3 Theological resilience factors

Religiosity and believing in the existence of something higher had positive effects on pain and health outcomes in some studies [107]. The results of other studies showed the opposite, even demonstrated religiosity as a risk factor. This inconsistency makes it very difficult to categorize religiosity as protective or as a risk factor. Religiosity interplays with other factors like social support or positive emotions. For example, one study on terroristic attacks 2005 on the underground in London showed that believing had an emerged effect on the protective factor “positive emotions” [108]. Another study showed that religious people have a bigger and stronger social network with qualitatively higher support [109]. Another interesting point is, that religious people tend to use active coping strategies and additionally in highly intensive stressful situations, e.g. short and hurried prayer. There is also a general difference between

coping with life events and chronic burdens. Religious patients with breast cancer used effective religious coping compared to chronic pain patients who seem to be more disabled every day [99, 110]. Religious coping can be “passive”, “cooperative” or kind of “religious self-management” [111]. The most challenging aspect of religiosity is operationalization [112].

1.4.4 Somatic resilience factors and neuro-immunological circuits

Over the years, resilience research became focused on the interplay between neurochemical, genetic, and epigenetic processes as a basis that some individuals exhibit a resilient profile. This development was accompanied by fundamental changes in the assumption of the interplay between the immunological, nervous and endocrinological systems and emotional circuits with its center in the brain. Robert Ader experimentally demonstrated in “behaviorally conditioned immunosuppression” 1974 that the immune system cooperates with the central nervous system and described the neuroplasticity of the brain with the ability to learn [113]. Since then, psychoimmunology has become one of the most important areas of modern medical research. In general, messenger substances of the nervous system act on the immune system and vice versa. Interfaces of the control circuits are the brain with the pituitary gland, the adrenal glands, and the immune cells. This basis provides an explanation of why psychological and psychotherapeutic processes have a demonstrable effect on physical functions (psychosomatics). Stress can negatively affect immune factors. Many of these elements involved in these psycho-neuro-immunological circuits are also involved in processes that promote resilience.

During stress, the autonomic nervous system and the HPA axis play a key role in orchestrating behavior and physiological changes [114]. Differences in the function, balance and interaction of these factors underlie inter-individual variability in stress resilience. Glucocorticoids can enhance amygdala activity, increase mRNA (messenger ribonucleic acid) concentrations of the corticotrophin releasing hormone (CRH) in the central nucleus of the amygdala [115], increase the effects of CRH on conditioned fear [116], and facilitate the encoding of emotion-related memory [117]. Early life stress has been linked to chronically high levels of CRH in human and animal studies [118]. Chronically elevated cortisol level is linked with different diseases and symptoms [119], but a short-term increase of cortisol has an adaptive effect in CRH receptor activity resulting in atrophic effects in certain types of neurons in the brain [120] that promotes resilience. Dehydroepiandrosterone (DHEA) is also released in response to stress and has anti-glucocorticoid effects in the brain. In a study of male veterans with post-traumatic stress disorder (PTSD), higher DHEA levels were associated with symptom improvement [121]. Brain parts that are involved in the serotonergic and noradrenergic neuronal network are known to contribute to resilience. Raphe nuclei within the brainstem have

5-hydroxytryptamin (5-HT) receptors functioning as autoreceptors and decrease serotonin release during stress.

The best-studied gene-environment interaction involves a naturally occurring variation in the promoter of the human serotonin transporter gene (5-HTTLPR). The short allele of 5-HTTLPR is associated with decreased serotonin transporter availability and resulting lower reuptake of serotonin from synaptic clefts. Carriers of the short allele show elevated risk for depression on exposure to stressful life events, including childhood maltreatment, compared with long-allele homozygotes in some studies [122, 123]. Locus coeruleus (LC) is mainly releasing noradrenaline during stress resulting in increased noradrenergic stimulation of numerous forebrain areas implicated in emotional behavior, such as the amygdala, the nucleus accumbens, the prefrontal cortex (PFC) and the hippocampus. Chronic hyperresponsiveness of the locus coeruleus noradrenergic system is associated with anxiety disorders and cardiovascular problems. The blockade of β-adrenergic receptors in the amygdala can oppose the development of aversive memories in animals and humans [124]. This suggests that reduced responsiveness of the locus coeruleus noradrenergic system could promote resilience.

Neuropeptide Y (NPY) has anxiolytic-like effects in rodents and is thought to enhance cognition under stressful conditions. Veterans with PTSD had an elevated level of NPY compared to veterans without PTSD. These findings are consistent with recent studies in rats that showed increased fear after the central administration of NPY mediated by the amygdala and reduced anxiety-like behavior (resilience to stress) after the intra-amygdala administration of NPY [125, 126]. The brain-derived neurotrophic factor (BDNF) is a nerve growth factor that is expressed at high levels in the brain and is best known in its role for resilience. During chronic stress, the expression of BDNF is increased in the nucleus accumbens (NA) in rats that showed depression-like behavior [127]. This increase in BDNF is comparable to humans with depression [128]. The gene that encodes BDNF in humans – the single nucleotide polymorphism (SNP) (Val66Met) - is associated with reduced BDNF function in mice that express the Met66 BDNF allele. These mice show greater anxiety-like behavior and impaired hippocampus-dependent learning but are more resilient to chronic stress [128]. Social support reduced the risk of depression that is elevated for individuals with 5-HTTLPR and BDNF Val66Met genotypes [129].

There are some HPA axis related genes that contribute to resilience. Polymorphisms and haplotypes of the CRH type 1 receptor gene (CRHR1) moderate the influence of child abuse on depressive symptoms in adulthood, with certain alleles and haplotypes resulting in a protective effect [130]. Functional variants of the brain mineralocorticoid and glucocorticoid receptor (GR) genes, which are respectively involved in setting the threshold and regulating

the termination of the HPA axis response to stress, have also been identified in humans [131]. Another polymorphism that is relevant to resilience (Val158Met) is found in the gene that codes for catechol-O-methyltransferase (COMT), an enzyme that degrades dopamine and noradrenaline. Individuals with the low-functioning Met158 allele have higher circulating levels of these neurotransmitters. Possibly, as a result, they tend to exhibit higher anxiety levels, increased plasma adrenaline levels in response to stress, lower resilience to negative mood states, and increased limbic reactivity to unpleasant stimuli [132].

Epigenetic mechanisms are known to be involved in the generational transfer of resilience or vulnerability. A popular example of epigenetic processes that of was experiments with female rats and their offspring. Some rats showed high nurturing behaviors (e.g. licking, grooming) whereas others displayed low levels of such behaviors. Consequences of these different behaviors were the lower risk for highly nurtured offspring to get depression. These behavioral changes were also detected in the corticosterone response to stress and expression level of GR in the hippocampus. This enhanced GR expression is mediated in part by the transcription factor nerve growth factor-inducible protein A (NGFI-A). Offspring that received little nurturing show increased methylation of the GR gene promoter at the NGFI-A binding site in the hippocampus, an epigenetic change that is associated with reduced GR expression [133] and persists into adulthood.

MiRNA are also well-known regulatory targets in resilience to chronic stress [134]. Inflammation-regulating miRNA like miR-124 in the hippocampus was detected to promote resilience in stressed mice [135]. MiR126a-3p and miR708-5p levels were higher in the mPFC (medial PFC) of vulnerable compared to resilient rats [134]. Several studies analyzing the miRNA profile in FMS patients and found some aberrantly expressed miRNA associated with different parameters [41, 42].

There are also so-called “peripheral mechanisms of resilience” like the adaptive and innate immune system, gut microbiota, and neuroimmune interactions. Pathways like the microbiota-gut-brain axis have an immense influence on the brain, the production of neuronal metabolites and the behavior within stress situations [136]. Furthermore, the immune system and its innate response is the first line of defence e.g. during an infection. Like the response to a pathogen, during chronic stress, the immune system also releases pro-inflammatory components like interleukine-6 (IL-6) or tumor necrosis factor-alpha (TNFα) [137]. There is also a difference in blood levels of inflammatory markers between resilient or stress susceptible mice [138].

2 Research questions and outline of the thesis

The research in this thesis is centered on the psychosocial and somatic resilience factors in FMS patients. The central question was, which biological, life historical and psychosocial factors contribute to resilience in FMS patients, resulting in different coping with FMS and FMS related aspects.

Each manuscript is addressing specific research questions:

Manuscript 1:

- Does religiosity play a role for pain patients, more specifically for FMS patients?
- Which effects has religious coping on FMS related disability and might it function as a resilience factor?
- Are there subgroups regarding pain phenotype, depression and religiosity, which define different coping types resulting from a different outcome in resilience?

Manuscript 2:

- Are there subgroups regarding pain phenotype, depression and religiosity, which define different coping types resulting from a different outcome in resilience?
- Are there differences between the defined subgroups due to systemic pro- / anti-inflammatory immune pattern?
- Is there a correlation between subgroup-specific immune pattern and skin innervation?
- Is there a difference in the function of central pain-conducting nerves depending on the immune pattern?
- What significance do these patterns have for coping, clinical outcome and resilience?

Manuscript 3:

- Do the previously defined subgroups have different miRNA expression pattern?
- What significance do these patterns have for coping, clinical outcome and resilience?
- Is there a miRNA-dependent regulatory cycle?

Cumulative thesis – outline

Manuscript 1

Religiosity, coping and resilience

Background and objectives: Coping strategies are essential for the outcome of chronic pain. There was little known about religious aspects of pain resilience. The first study analyzed and defined the relevance and need of different dimensions of religiosity in FMS patients and its impact on coping, FMS related symptoms, disability, and health outcome.
Material and methods: Religious dimensions and psychological variables were evaluated by questionnaires, and a subgroup of 42 patients participated in a face-to-face interview that analyzed social environment, values and personal understanding of religion, problem solving and learning, as well as stress in life. The relevance of religiosity and spirituality to chronic pain patients for coping was evaluated by correlation and regression analyses.
Results: A few patients described themselves as traditionally religious, but the majority believed in a higher reality and was convinced of transcendence. Three religious dimensions were significantly correlated with at least one coping strategy regardless of degree of religiosity. Intense religiosity was negatively associated with the choice of coping "ignoring". Depression and affect-related variables had the highest impact on disability.
Conclusion: In this cohort, negative affection, pain intensity and reinterpretation as a coping strategy had a high influence on FMS-related disability. Reinterpretation as a religious coping strategy might be of interest to some FMS patients.

Manuscript 2

Multivariate analysis of subgroups

Background and objectives: The clinical outcome of FMS patients is very heterogenous, which was also seen in our cytokine analysis suggesting subgroups. The second study aimed to identify psychosocial and somatic factors contributing to different coping and resilience levels among FMS patients.
Material and methods: Questionnaires assessed coping strategies, pain and psychosocial variables. Quantitative PCR measured gene expression of selected pro- and anti-inflammatory cytokines in WBC samples among patients and a healthy control group. Multivariate analyses defined variance explaining factors and clustered the patient cohort into subgroups.
Results: Four variance explaining factors could be termed as (1) affective load, (2) coping, (3) pain, and (4) pro-inflammatory cytokines. In particular, psychopathological variables had a high impact on the cohort and seemed to be crucial for subgrouping. 118 FMS patients were classified into four clusters which were named as “maladaptive”, “adaptive”, “vulnerable” and

“resilient”, considering differences in the emerged factors, coping strategies, cytokine profiles, resilience, and disability level. The adaptive cluster was characterized by low impairment in everyday life as a result of active problem- and emotion-focused coping. The vulnerable cluster significantly contrasted to the adaptive and resilient cluster caused by massive physical and psychological impairment as well as severe catastrophizing ($p < 0.05$). The cluster, named "resilient", showed remarkably frequent coping "reinterpretation", a form of reappraisal, which is used as an emotion-regulating behavioural strategy that is well known as a resilience factor. In addition, the cytokine profile was less pro-inflammatory ($p < 0.05$).

Conclusion: Overall, the data suggest that active problem- and emotion-focused coping strategies and an anti-inflammatory cytokine profile with low disability might promote resilience. Additional resilience factors such as low scores in anxiety, the ability for acceptance and patience as well as perseverance promote a resilient phenotype. Subgroup-specific therapies might change a vulnerable and severe phenotype respecting the heterogeneity of FMS patients.

Manuscript 3

MiRNA and resilience

Background and objectives: MiRNA regulate gene expression of specific targets by post-transcriptional inhibition. Based on the previous classification of the FMS patient cohort into different subgroups characterized by different disability level, the third study aimed to identify miRNA signatures that discriminate between the FMS patient cluster.

Material and methods: MiRNA were selected based on literature search with the search terms “inflammation”, “resilience”, and “chronic stress”. The relative gene expression of the miRNA miR103a-3p, miR107, miR130a-3p, and miR125a-5p were determined in white blood cell (WBC) RNA of 31 FMS patients from the previously clustered cohort and 16 healthy controls. Clinical scores taken by questionnaires were correlated with the relative gene expression of all four miRNA. A cluster-specific speculative model of a miRNA-mediated regulatory cycle was proposed, and its potential targets verified by the online tool “*target scan human”*.

Results: MiR103a-3p, miR107 and miR130a-3p were lower expressed in FMS patients compared to healthy controls. MiR103a-3p showed the highest peak of expression in the adaptive cluster, and correlated with the questionnaire score "FMS related disability”. MiR107 did not show any clear differences in expression pattern but correlated with the CTQ score of "physical abuse" ($p < 0.05$). Using the online tool "TargetScanHuman" targets of the miRNA family miR103/107 were identified, and a possible molecular mechanism between highly regulated gene expression of miR103a (tendentious also of miR107) and adaptive coping in FMS patients was proposed.

Conclusion: We show a connection between upregulated gene expression of miR103a, tendentially of miR107, and the adaptive coping in a cluster of FMS patients. Further validation of miR103a or miR107may aid to identify them as biomarker or a somatic resilience factor in FMS.

3 Study subjects and experiments

This thesis was part of a currently larger study on FMS at the Department of Neurology of the University Hospital Würzburg and approved by the Würzburg Medical School Ethics Committee (No. 135/15).

3.1 Study criteria and procedure

The study included male and female patients who were at least 18 years old, had a diagnosis that met ACR criteria for FMS of 1990 and 2010, and agreed to participate in all tests during the study day. Potential participants with other possible differential diagnoses that did not explain pain (e.g. rheumatologic, orthopedic) or with other and additional pain sources (e.g. pain due to arthritis) were excluded. Further exclusion criteria were diabetes, polyneuropathies, psychiatric conditions, cancer, epilepsy, drug and alcohol abuse, the permanent wearing of hard contact lenses, eye surgery and diseases, allergies to local narcotics, ongoing legal proceedings (e.g. regarding health assurance) and abnormalities in routine blood tests.

All patients provided written informed consent before enrollment. 156 FMS patients fulfilling the diagnostic criteria for FMS of the American College of Rheumatology published in 2010 [139], and 48 healthy controls were recruited between 2015 to 2018. The recruiting process was separated into two steps. The first step was the examination of the study criteria. If a participant was eligible for inclusion into the study, the second step was another phone call including the verification of the diagnosis by sending the medical letter, making an individual appointment for the study day and education about the tests on the day of study.

3.2 Study design

One week before the appointment, all questionnaires were sent to the patients and were brought back filled in on the study day. After a detailed history taking that collected demographic data, starting date of FMS, family history, a clinical examination and a skin punch biopsy (intraepidermal nerve fiber density, IENFD) in upper and lower leg was conducted followed by the psychological interview. Afterward, electrophysiological measurements examined data on small nerve fibers by quantitative sensory testing (QST) and pain-related evoked potentials (PREP). Final tests conducted at the ophthalmic clinic included an

examination of small nerve fibers on the cornea of both eyes by corneal confocal microscopy (CCM) and test of the quantity of tear fluid by Schirmer test. Data on clinical examination, electrophysiological and laboratory measurements and the tests in the ophthalmic clinic were published elsewhere [140, 141], and only used for the statistical evaluation in the factor and cluster analysis. In this thesis, data of questionnaires, blood, and psychological interview were included in the manuscripts (see section 4.1. – 4.2).

3.3 Evaluation of life historical, religious and psychosocial data

All study participants filled in the German versions of a set of standardized questionnaires collecting data on religiosity and spirituality (Aspects of Spirituality questionnaire, ASP) [142], coping strategies (Coping Strategies Questionnaire, CSQ) [143], pain (Graded Chronic Pain Scale, GCPS; Neuropathic pain scale inventory, NPSI) [144-146], pain catastrophizing (Pain Catastrophizing Questionnaire, PCS) [147], depression (General Depression Scale (German: Allgemeine Depressionsskala, ADS) of the Center of Epidemiological Studies) [148], anxiety (State-Trait Anxiety Inventory, STAI) [149], quality of life due to FMS (Fibromyalgia Impact Questionnaire, FIQ) [150], self-reported quality of life (short form of the self-report of health, SF-12) [151] and traumatic events in early childhood (Childhood Trauma Questionnaire, CTQ) [152]. A different number of patients and controls were included in each study, because the questionnaires CTQ, ASP, SF-12, CSQ, STAI and the data of the psychological interview were added later into the larger study.

The psychosocial interview was created to have an actual overview of the psychological condition of patients on the study day, to generate a private impression, to verify the results of the questionnaires, to avoid differences and biases that often are generated by analytical instruments like questionnaires and to evaluate additional data on resilience (e.g. problem-solving, learning to describe the adapting process after experiencing stress/life events). The protocol contained elements of the Life History Calendar [153], questions on morality and religion adapted on an interview form developed by the Department of Psychology of the University of Würzburg and self-developed items to evaluate problem-solving and learning behavior.

3.4 Evaluation of biological data

In general, WBC fractions asservated from blood samples were used to measure relative gene expression of selected cytokines. Data on structure and function of peripheral and central afferent nerves (skin punch biopsies, QST, PREP, tests in opthalmic clinic) were used in cooperation with another project for the biostatistical analysis of the current study.

For the examination of neuro-immunological circuits and particularly determination of the relative gene expression of mRNA, proteins and inflammation-regulatory miRNA the anti-inflammatory cytokines Interleukin (IL)–10, IL–4, IL–13 and the pro-inflammatory cytokines IL–6 and the tumor necrosis factor (TNF)–α were selected. Gene expression of mRNA and miRNA were measured by real-time PCR (polymerase chain reaction) andof proteins by an enzyme-linked immunosorbent assay (ELISA).

Protocols and detailed information on the preparation of biological material are described in all manuscripts (see section 4. Manuscripts).

In the following, experiments that were planned, performed and then not included into the manuscripts or could not be performed are listed and reasons for excluding data or the cancel of the experiment are described.

Measurement of relative gene expression of interleukin-13 (IL-13) via qRT-PCR

Originally, IL - 13 was measured by the PCR expression analyses, but no ct (cycle threshold) value was measurable because the quantity of IL-13 mRNA was too low in the WBC samples of patients and controls. Therefore IL-13 was excluded from further evaluation.

Measurement of protein levels via ELISA

ELISA analyses were planned and performed to evaluate the selected cytokines at the protein level. A previous factor analysis (data presented in manuscript 2, see 3.2.) defined among others “pro-inflammatory cytokines” as fourth of the four variance explaining factors. Raw values of TNF had the strongest discrepancy between the highest and lowest value, therefore we grouped each 12 serum samples of 24 FMS patients into two groups labelled as “high TNF” and “low TNF”. Serum samples of 12 healthy controls serves as reference samples. The ELISA data showed no intergroup differences, therefore no further ELISA were performed.

In vitro cell stimulation

Furthermore, lymphocyte stimulation and cytokine measurement were planned after isolation of the WBC and incubation of the cells in vitro with concanavalin A (ConA; T cell stimulator) and lipopolysaccharide (LPS; as an inflammatory stimulus). After an optimized incubation period (preliminary tests), the WBC should be harvested, and the gene expression of selected pro- and anti-inflammatory cytokines determined compared to unstimulated samples by means of quantitative real-time PCR (qRT-PCR). In addition, the respective elected amount of cytokine protein should be determined from the cell culture supernatant by means of ELISA. Unfortunately, it remained only in the preparation of the protocols, whilst it had to be determined that the protocol of WBC extraction was not suitable for working with living cells.

Instead of these three tests, further additionally experiments were created and described in 3.5. as supplementary data.

3.5. Supplementary data

Saliva collection for cortisol measurements

A protocol for the collection of saliva samples was created to define differences in stress levels that might have an influence on the individual profile of coping, resilience and pain. The first protocol provided a two-time saliva collection before and after the skin biopsy, which was considered a stressor. Salivettes (Sarstedt, Nümbrecht, Germany) were used for saliva collection and hold to the edge of the suspended vessel, the plug and the cotton roller were removed, and the patient instructed to chew at least 1 minute on the cotton roller. The cotton roller must put back into the hanging vessel, the salivette firmly closed with the plug and centrifuged for 5 minutes at 2800 rpm to get at least a saliva volume of 1.1 x 0.3 ml. Saliva samples must be transported as fast as possible on dry ice and stored at 4°C after sampling. Long-term storage is possible at -20°C and preferred at -80°C, if available. The measurements of free cortisol in saliva were done by means of a commercial chemiluminescence immunoassay (CLIA, IBL-Hamburg, Germany) at the Department of Endocrinology in the Department of Internal Medicine I in Würzburg. After measuring 15 samples, the protocol was adjusted twice, as the data did not show the expected peak after the stressor, but instead even lingered in the reference area with the controls. With an adjusted protocol, five additional saliva samples at five different time points were collected: once upon registration at 8:30 a.m., once right after blood withdrawal, EMG (electromyography) and once before and after skin biopsy which was defined as stress-inducing event (stressor). After a further five samples yielded the same results as the previous ones measured with the previous protocol, the saliva collection for cortisol measurements was discontinued.

Comparison of white and grey matter volume of two different FMS patient groups derived from the same entire cohort

Another study that is part of the current larger study at the neurology department is conducting MRI (magnetic resonance imaging) measurements of specific pain and emotion processing brain areas of selected FMS patients who have already participated in the main study and are partially presented in study 1 to 3 of this thesis. Studies 1 and 2 confirmed “reinterpretation” as coping with a positive impact on disability and pain relief. Reinterpretation is a cognitive coping strategy. We hypothesized, that the volume of cognition and emotion processing brain areas were different in the resilient and adaptive cluster compared to the unfavorable cluster (maladaptive and vulnerable). However, no significant difference was found between the clusters.

Cluster illustration as a 3D (three-dimensional) model

In study 2, the clusters were presented in a 2D figure. For a convenient illustration of the differences of each cluster in the emerged factors, a 3D model was created by the Postdoc Jeremy Signoret-Genest using MATLAB (*MATrix LABoratory*, The MathWorks Inc., Natick, Massachusetts, USA) [154].

3.6. Statistical analyses

IBM SPSS Statistics software (IBM, Ehningen, Germany) was used for statistical analysis and GraphPad Prism (San Diego, CA, USA) for the graphical design of all figures of study 3. A detailed description of statistical analyses is given in the manuscript section 4 (see 4.1. to 4.3., page 21 - 60).

4 Manuscripts

4.1 Relevance of religiosity for coping strategies and disability in patients with fibromyalgia syndrome.

4.2 Clustering fibromyalgia patients: Specific combination of psychosocial and somatic factors lead to resilient coping in a subgroup of FMS patients.

4.3 MiR103a-3p and miR107 are related to adaptive coping in a cluster of FMS patients.

Manuscript 1

Relevance of religiosity for coping strategies and disability in patients with fibromyalgia syndrome.

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Journal of Religion and Health

Manuscript 1 **Braun A, Evdokimov D, Frank J, Wabel T, Pauli P, Üçeyler N, Sommer C. Relevance of Religiosity for Coping Strategies and Disability in Patients with Fibromyalgia Syndrome. J Relig Health (2021). https://doi.org/10.1007/s10943-020-01177-3.**

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ORIGINAL PAPER

Relevance of Religiosity for Coping Strategies and Disability in Patients with Fibromyalgia Syndrome

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Abstract

Coping strategies are essential for the outcome of chronic pain. This study evaluated religiosity in a cohort of patients with fibromyalgia syndrome (FMS), its effect on pain and other symptoms, on coping and FMS-related disability. A total of 102 FMS patients were recruited who filled in questionnaires, a subgroup of 42 patients participated in a face-to-face interview, and data were evaluated by correlation and regression analyses. Few patients were traditionally religious, but the majority believed in a higher existence and described their spirituality as "transcendence conviction". The coping strategy "praying–hoping" and the ASP dimension "religious orientation" ($r=0.5$, $P<0.05$) showed a significant relationship independent of the grade of religiosity ($P<0.05$). A high grade of belief in a higher existence was negatively associated with the choice of ignoring as coping strategy ($r=-0.4$, $P<0.05$). Mood and affect-related variables had the highest impact on disability ($b=0.5$, $P<0.05$). In this cohort, the grade of religiosity played a role in the choice of coping strategies, but had no effects on health and mood outcome.

Keywords Fibromyalgia syndrome · Religiosity · Coping · Disability

Supplementary Information The online version of this article (https://doi.org/10.1007/s10943-020-01177-3) contains supplementary material, which is available to authorized users.

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Introduction

Fibromyalgia syndrome (FMS) is an incompletely understood chronic pain condition accompanied by symptoms like sleep disturbance, depression or fatigue (Clauw 2015; Clauw et al. 2011; Häuser et al. 2015). Pathophysiological mechanisms in the central and peripheral nervous system as well as psychological factors have been shown to play a role (Afari et al. 2014; Clauw 2015; Leinders et al. 2016; Paiva et al. 2008; Park and Lee 2017; Sluka and Clauw 2016; Staud and Smitherman 2002; Üçeyler et al. 2013; Zimmermann 1991). There is large heterogeneity of patient profiles in FMS patients, in particular regarding coping strategies (Alok et al. 2014; Kengen-Traska et al. 2012; Loevinger et al. 2012; Stoffel et al. 2013; Tommaso et al. 2014; Triñanes et al. 2014; Yim et al. 2017). Some patients cope very well with the symptoms, while others are heavily affected in their daily life with passive and negative coping styles like catastrophizing, ignoring, and helplessness (Baastrup et al. 2016).

A large body of evidence shows that religious involvement is related to better psychological well-being, enhanced social support, less depression, and reduced substance abuse (Baetz and Bowen 2008; Basiński et al. 2013; Büssing et al. 2005, 2009, 2010, 2014, 2013 ; Dedert et al. 2004; Dezutter et al. 2009; Kendler et al. 1997; Mishra et al. 2017; Wachholtz et al. 2007). Only few studies have analyzed the influence of religiosity on pain sensitivity or intensity in chronic pain patients (Basiński et al. 2013; Fehring et al. 1997; Gilbert 2009), and even less so in FMS (Anema et al. 2009; Biccheri et al. 2016; Moreira-Almeida and Koenig 2008). The evaluation of the impact of religiosity is difficult because of the variety of possible definitions of religiosity. Religiosity is a multidimensional construct including cognition, feelings, and behavior with institutional affiliation (Huber 2003; Koenig et al. 2001). Beside this definition there are others, but all of them are commonly based on religious practice and doctrine as opposed to spirituality (Park et al. 2013). The definition of spirituality which we follow in this study was given 2009 by the International Consensus Conference as "aspects of humanity that refer to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred" (Puchalski et al. 2009). Whether religiosity and spirituality might have a positive impact on health and on coping with disease has been discussed controversially (Berthold and Ruch 2014; Klein and Albani 2007; Koenig 2012; Reis and Menezes 2017; Wachholtz et al. 2007). Believing and hoping are important factors that may improve mental strength in aversive situations (Berthold and Ruch 2014; Nejat et al. 2017; Paloutzian and Park 2013), and the relationship to God as an abstract social support might replace lacking family connections (Anson et al. 1990; McIntosh et al. 1993) and might function as a strong resilience-driving element.

In this study, we first examined whether FMS patients have specific spiritual or religious needs, and whether they use religious strategies to cope with emotional aspects of FMS and every day pain. This was achieved by assessing religiosity with specific questionnaires and in a subgroup of patients with an additional

semi-structured interview. We then asked whether religiosity is helpful or disadvantageous for coping with FMS and which would be the impact of different aspects of religiosity on FMS-related disability. In the long-run, our findings might contribute to improving therapies by considering the religiosity of patients.

Methods

Study Participants

This study is part of a currently larger study on FMS at the Department of Neurology of the University Hospital Würzburg that included 148 FMS patients (Wolfe et al. 2010) and 46 healthy controls who were recruited between 2015 and 2018. Inclusion and exclusion criteria were published elsewhere (Üçeyler et al. 2013). Our study was approved by the Würzburg Medical School Ethics Committee (No. 135/15). All patients provided written informed consent before enrollment. Data on clinical examination, electrophysiological, and other laboratory measurements will be published elsewhere.

Questionnaires used for Correlation and Regression Analyses

All study participants filled in a set of standardized questionnaires collecting data on religiosity and spirituality (Bössing et al. 2007), coping strategies (Verra et al. 2006), pain (Sommer et al. 2011; Türp and Nilges 2000), depression (Meyer and Hautzinger 2001), anxiety (Laux et al. 1981), and quality of life due to FMS (Offenbaecher et al. 2000). Because some questionnaires were added during the ongoing study, we present data for 102 patients (Supplementary Fig. 1).

Convictions and Attitudes Related to the Dimension of Religiosity/Spirituality

The Aspects of Spirituality (ASP) questionnaire examines a wide range of aspects of spirituality on a scale from 0 to 4 with "does not apply at all" to "applies very much". Four subscales reflect dimensions such as religious orientation, search for insight/wisdom, conscious interactions and transcendence conviction. "Religious orientation" includes traditional religious activities like praying to God or attending religious services. "Transcendence conviction" indicates spirituality, belief in the existence of higher realities and rebirth. The dimension "search for insight/wisdom" includes a mindful spirit of broad awareness and developing wisdom. The dimension "conscious interactions" describes compassion and generosity. Subgroups of each dimension are defined as low grade, i.e., sum scores < 50 and as high grade, i.e., sum scores ≥ 50 (Bössing et al. 2007).

Psychological Interview

A subgroup of 42 patients additionally participated in a semi-structured 20-minute face-to-face interview consisting of three parts: early life stress (part 1), parameters of religiosity including morality (part 2), and parameters of problem-solving behavior including learning (part 3; supplementary Fig. 2). The protocol contained elements of the Life History Calendar (Freedman et al. 1988), questions on morality and religion adapted on an interview form developed by the Department of Psychology of the University of Würzburg and self-developed items to evaluate problem solving and learning behavior. These items are known resilience promoting psychological factors in literature (Navrady et al. 2018; Niitsu et al. 2018; Rutter 1985; Treichler et al. 2019).

Coping Strategies

The Coping Strategies Questionnaire (CSQ) consists of 8 subscales (distraction of attention, reinterpretation, self-instructions, ignoring, praying and hoping, catastrophizing, increase in activity, pain behavior) on a 1 to 6 scale ranging from "never" to "always" and two sum items indicating self efficacy. The maximum possible value for each coping strategy sum score is 36 (Verra et al. 2006).

Depression, Pain Catastrophizing, and Anxiety

The German Version of the Center of Epidemiological Studies General Depression Scale (CES-D) examines the severity of depressive symptoms on a 0 to 3 scale from "rare" to "mostly". A score of CES-D $\geq$ 16 indicates depressive symptoms that may be of clinical relevance (Meyer and Hautzinger 2001). The German version of the Pain Catastrophizing Scale (PCS) uses 13 items to examine the strength of catastrophizing thoughts and behavior on a 0 to 4 scale from "never" to "always" (Meyer et al. 2008). We used the State-Trait Anxiety Inventory (STAI-G) to examine anxiety as a trait (STAI-T) and as a state (STAI-S) on a 1 to 4 scale from "almost never" to "almost always" (Laux et al. 1981).

Pain and FMS Questionnaires

The Graded Chronic Pain Scale (GCPS) examines the current severity of pain, pain in the last six months with influence on daily activities, free time, and job on a 0 to 10 scale from "no disability" to "no activity possible". A grade of disability was calculated (Türp and Nilges 2000). To assess neuropathic pain components, the German Version of the Neuropathic Pain Scale Inventory (NPSI-D) was used (Sommer et al. 2011). FMS symptom severity and impact were measured by the

Fibromyalgia Impact Questionnaire (FIQ) that examines physical and emotional functioning and related disability of FMS patients (Offenbaecher et al. 2000).

Study Design

One week before the appointment, all questionnaires were sent to the patients and were brought back filled in on the study day. After a detailed history taking that collected demographic data, starting date of FMS, and family history, the psychological interview was conducted.

Statistical Analysis

SPSS Statistics 24 software (IBM, Ehningen, Germany) was used for statistical analysis. Data distribution was tested with the Shapiro–Wilk test and by observing data histograms. Results of the non-normally distributed data are given as median and range, normally distributed data are given as mean and standard deviation. Differences in mean scores were tested by the Wilcoxon test for nonparametric-related samples. Correlation was analyzed by the Spearman correlation coefficient to select potentially relevant variables for regression analysis and p values were corrected with Benjamini–Hochberg correction. For subgroup analyses on religiosity and the preference for a specific coping strategy, we applied the Chi-square test. A hierarchical multiple regression analysis was conducted to determine the contribution of variables and coping strategies in the outcome variable "FMS impact in life". $P < 0.05$ was considered significant.

Results

Demographic Characteristics

Demographic characteristics of 102 study participants (96 women) are listed in Table 1. On average, patients had suffered from FMS for 14.71 years in median. A total of 47 out of 102 (47.94%) patients had a family history of pain-related diseases and 85/102 (86.70%) patients of affective mood disorders. A total of 50 out of 102 (51%) patients had experienced a traumatic life event which was, for example, the death of a close relative or sexual, physical or emotional abuse and neglect. Among the 42 patients who participated in the psychological interview, 17/42 (7.14%) patients were catholic, 13/42 (5.46%) protestant, 1/42 (0.42%) muslim, and 11/42 (4.62%) without any confession (Table 1).

Religiosity and Spirituality According to the Four Dimensions of the ASP Questionnaire

We used the ASP questionnaire (maximum sum scores for each dimension 100) to evaluate the religiosity in our patient cohort and to differentiate between the

Table 1 Sociodemographic characteristics

Variables	*N*
Sample size	102
Age[a]	50.5 ± 53.2
Female/male	96/6
Ø Weight[b]	75.0 ± 15
Height[c]	166.3 ± 7.4
BMI	25.3 ± 5.1
Disease duration[d]	14.7 ± 11.2
Highest level of education[e]	
University diploma	14
A-level	14
0-level	55
Secondary school only	19
Current employment status	
Regularly working	57
Sick leave all/sick leave because of pain	15
Retired all/retired because of pain	23
Unemployed	5
Psychological/psychiatric treatment	
Never	40
Currently	39
In the past	23
Family history of diseases	
Chronic pain	47
Neurological disorder	84
Affective disorders	85
Life Event	
Yes	50
No	52
Confession (*N* = 42)	
Catholic	17
Protestant	13
Islamic	1
None	11

N number

[a]Year (in median and range)

[b]Kilogram in mean ± SD

[c]Centimeter in mean ± SD

[d]Year (in mean ± SD)

[e]Highest level of education: A-level: High school diploma allowing university access (12–13 years of school), O-level: O-level diploma after 10 years of school, Secondary school only: lower secondary school diploma after 8–9 years of school

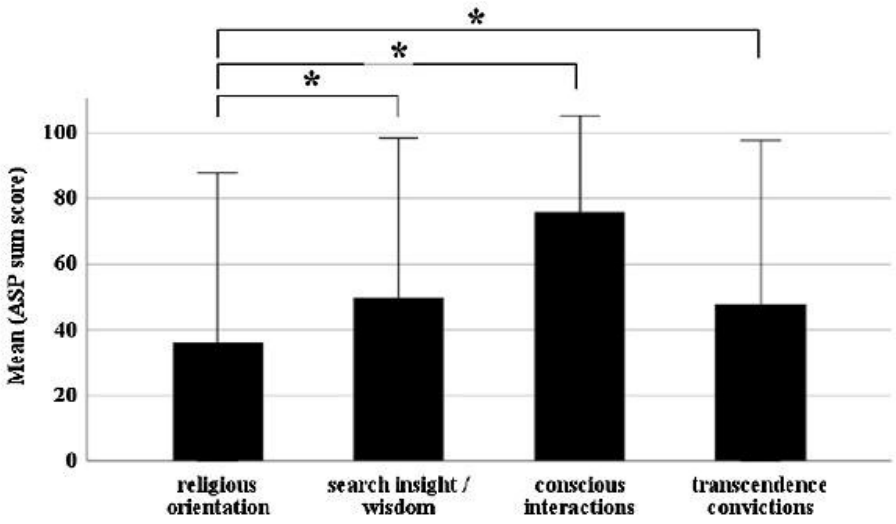

Fig. 1 Religiosity according to the ASP questionnaire. Bar graphs show mean scores of all four religious' dimensions. The first dimension "religious orientation" ($M = 36.2$, SD = 25.8) shows a significantly lower mean score than conscious interactions (75.8 ± 14.7, $P < 0.001$). This combined with high values for "transcendence convictions" ($M = 47.7$, SD = 25.0, $P < 0.001$), suggests a more spiritual than traditionally religious patient cohort

four dimensions of religiosity and spirituality. Patients on average reported relatively low scores in the dimension "religious orientation" (36.2 ± 25.8, Fig. 1) and higher scores in the dimension "conscious interactions" (75.8 ± 14.7; $z = -8.8$, $P < 0.001$, $r = -0.8$, Wilcoxon test). However, we have no reference values but this outcome suggests that most patients frequently interact in a conscious way with the environment and other people. The mean scores for (1) "search of insight/wisdom" and (2) "transcendence conviction" were 49.7 ± 24.3 and 47.7 ± 25.0, respectively, and both significantly differed from religious orientation ($z_{(1)} = -4.9$, $P < 0.001$, $r = -0.5$; $z_{(2)} = -4.6$, $P < 0.001$, $r = -0.4$; Fig. 1).

Religiosity and Spirituality According to the Interview

During the psychological interview, patients were asked to characterize their religious preferences (supplementary Table 1). Five patients defined their believing type as "spiritual", 9/42 (21%) as "religious", 4/42 (10%) as "atheistic", 1/42 (2%) as "agnostic" and 1/42 (2%) as "not determined", but 22/42 (52%) defined their belief with their own words. This comes as no surprise, given the highly subjective character of religious and spiritual self-description (Eisenmann et al. 2016). In order to operationalize this heterogeneity, we decided to use only the parameter "belief in a higher existence" with grading from "none" to "intense" (Supplementary Table 2), knowing that this means a certain degree of simplification. 27/42 (11.34%) patients had moderate to strong beliefs in a higher existence, while only 15/42 (6.30%) had none to low belief.

Influence of Religiosity on Coping and Health Outcomes

Spearman correlations were applied to assess associations between religiosity and demographic variables, health outcomes and coping strategies. All coefficients had a low or moderate strength, so that no clear conclusion can be reached; however, these values provide information and hints about suspected connections. The correlation between the coping strategy "praying—hoping" and the ASP dimensions of "religious orientation" ($r=0.5$, $P<0.05$) might suggest a higher use of "religious coping" in those with higher scores in the religious and spiritual dimensions, as expected (Table 2). After Benjamini–Hochberg correction the correlation between coping "praying-hoping" and "transcendence conviction" ($r=0.3$, $P<0.05$) remained only a trend.

To examine whether the patients used a specific coping strategy related to their grade of belief in a higher existence, we created two subgroups with high or low agreement for each of the four ASP dimensions performed a Chi-square test. Patients with high or low agreement for any of the ASP dimensions did not differ in their coping strategies. However, when a Chi-square test was done with the subgroups of "none to low" versus "moderate to intense" religiosity as derived from the interview, we found that patients with higher belief in a higher existence preferred the coping strategies "ignore", "catastrophizing" and "pain behavior" ($P<0.05$).

Influence of Psychological, Physical, Spiritual and Demographic Variables on FMS-Related Disability

A hierarchical multiple regression analysis was conducted to analyze whether some FMS-related variables, choice of coping type or religiosity had an influence on the impact of FMS on daily life. The sum score of the FIQ (Offenbaecher et al. 2000) was set as dependent variable to indicate FMS-related disability. The hierarchical multiple regression model contains five models with gradually added variables (supplementary Table 3). The results of 99/102 (97%) patients were valid to be involved into the regression analysis.

Table 2 Correlation between ASP dimensions and predicting variables

Predicting variable	ASP dimension	*r*	*p*	Corrected *p*
Distraction	Transcendence convictions	0.268	0.007	0.149
	Search insight wisdom	0.210	0.037	0.4736
Praying hoping	Religious orientation	0.476	0.000	0.000*
	Search insight wisdom	0.208	0.039	0.416
	Transcendence convictions	0.306	0.002	0.064
Pain duration	Religious orientation	–	–	
GCPS grade	Search insight wisdom	0.225	0.025	0.4

R Spearman's Rho, correlation coefficient

ASP aspects of spirituality, *GCPS* graded chronic pain scale

*Correlation is significant at the 0.05 level (2-tailed) after Benjamini–Hochberg correction

Table 3 The summary of the regression model and the variance explained by every added predictor variables

Model[a]	R^2	Adjusted R^2	R^2 change	F change	Significant F change	Durbin Watson
1	0.027	−0.0	0.0	0.7	0.6	
2	0.384	0.3	0.4	17.6	0.0	
3	0.616	0.6	0.2	13.2	0.0	
4	0.660	0.6	0.0	1.0	0.5	
5	0.710	0.6	0.0	0.6	0.7	1.7

[a]Dependent variable: FMS impact in life; squared R: R^2 shows how much of the variability in the outcome is accounted for by the predictors

Model one, which included demographic variables, explained only 2.7% of the variance, indicating minor importance to the impact of FMS on daily life (Table 3). Model two, in which three pain-related variables were added, explained 38.4% of the variance. In model three, the R^2 was doubled after adding variables of psychopathology. By adding the variables depression, anxiety (trait/state) and pain catastrophizing, 61.6% of the variance could be explained. This shows that variables related to affect and mood have a high impact on disability. After adding coping variables to the model, the variance explaining R^2 was increased to 66%. Finally, after adding the four dimensions of religiosity to the model, the squared R minimally increased (67.1%), which reflects the lower importance of any dimension of religiosity for disability in our cohort. The entire model showed a moderate cross validity (Durbin Watson = 1.7) (Table 3). The F ratio of every model (except model 1) showed a value > 1, which indicates a significant improvement of predicting the outcome (FMS impact in life) compared to not fitting the model (supplementary Table 4).

The b-values give a measure of the individual contribution of each predictor to the final model (Table 4). Positive b-values indicate a positive relationship between the outcome and the predictor. The variables "reinterpretation" as coping, "pain intensity", "GCPS grade" and "depression" made a significant contribution ($P < 0.05$) to the model with the largest impact made by the variable "depression" ($t = 3.2$, $P < 0.05$). All four dimensions of religiosity had little influence on the model, as well as most of the coping strategies except reinterpretation and two pain variables. When we also looked at the standardized b-values (β-values), we could see the same effect for especially the variable "depression" (Table 4).

Discussion

The aim of our study was to assess the relevance of religiosity and spirituality on health outcome in a patient cohort suffering from chronic pain. Our cohort of 102 patients seemed to be less religious than expected, at least when considering religiosity in the traditional way (regarding religious institutions and traditional practices) (Fig. 1). However, spirituality, in the way it was modelled here,

Table 4 Individual contribution of each predictor to the chosen model five and the relationship between the FMS impact in life and each parameter

Category	Predictor variable[a]	Unstandardized b	Standardized β	*T*	Significance
Constant		**36.9**		**1.4**	**0.2**
Demographic variable	Age	−0.0	−0.0	0.1	0.9
	Height	−0.1	0.1	−0.7	0.5
	BMI	0.0	0.0	0.1	0.9
	Pain duration	0.1	0.1	0.7	0.5
Pain variables	Neuropathic pain	2.4	0.0	0.4	0.7
	Pain intensity	**0.2**	**0.2**	**2.0**	**0.0**
	GCPS grade	**4.0**	**0.2**	**2.4**	**0.0**
Psycho-pathological variables	Pain catastrophizing	−0.2	−0.2	1.1	0.3
	Depression	**0.5**	**0.4**	**3.2**	**0.0**
	State anxiety	−0.0	−0.0	−0.3	0.8
	Trait anxiety	0.2	0.2	1.0	0.3
Coping strategies	Distraction	−0.0	−0.0	−0.1	1.0
	Reinterpretation	**0.3**	**0.2**	**2.1**	**0.0**
	Self-instructions	−0.2	−0.1	−1.0	0.3
	Ignore	0.2	0.1	1.0	0.4
	Praying hoping	0.1	0.1	1.0	0.5
	Catastrophizing	0.1	0.1	0.5	0.6
	Activity increase	−0.2	−0.1	−1.0	0.3
	Pain behavior	−0.1	−0.0	−0.4	0.7
Dimension of religiosity	Religious orientation	−0.0	0.0	0.1	0.9
	Search insight/wisdom	0.0	0.0	0.2	0.8
	Conscious interaction	−0.1	−0.1	−1.4	0.2
	Transcendence convictions	0.0	0.1	0.6	0.6

Bold values are statistically significant (Data significance at $p < 0.05$)

FMS fibromyalgia syndrome, *GCPS* graded chronic pain scale

[a]Dependent variable: FMS impact in life

was a frequent finding, and most participants believed in a higher existence (supplementary Table 2). The reason for the low traditional religiosity might be the setting of our study in the more secular region of Western Europe compared to, e.g., Latin America or Africa. The world values survey association published a report in 2014 on the degrees of secularization where the percentage of people that consider themselves religious varied widely from 12.9% in China to 99.8% in Pakistan and 95.8% in Nigeria (Inglehart et al. 2010—2014). Another study analyzed religious coping in 54 women in Tanzania with the diagnosis of an obstetric fistula for 14.9 years, comparable to the median disease duration of 14.7 years in

our cohort (Table 1) (Watt et al. 2014). 48.1% of these women considered themselves as very religious, 40.7% moderately religious and 0% not religious. These reports confirm that the grade, definition and the performance of religiosity is dependent on the region where patients live.

The relevance of religiosity to coping strategies in chronic pain was another aspect that was examined in our study. The correlation tests demonstrated a significant relationship between the dimension "religious orientation" with the coping "praying hoping" (Table 2). However, this might be a chance association, since the regression analysis demonstrated no significant impact of any ASP dimension neither on physical, mental symptoms nor on a specific coping strategy (Table 4). An aspect related to the lower importance of religiosity on coping with FMS could be that chronic pain patients are not confronted to a lethal disease such as cancer. One study analyzed spiritual needs of patients suffering from cancer compared to patients with chronic back pain using the Spiritual Needs Questionnaire (SpRQ) and showed that patients with cancer had higher scores in the SpRQ than chronic pain patients (Büssing et al. 2010). Moreover, as shown by a comparative study on patients with chronic pain in patients with breast cancer, it may be the initial stress of being diagnosed with a serious disease that arouses religious and spiritual needs (Appel et al. 2010). Furthermore, we should have in mind that religious coping is only considered in a few items of the CSQ, which might not be enough to evaluate multidimensional religious aspects (Verra et al. 2006). Nevertheless, the connection between at least one coping type, especially "praying and hoping" shows that a small part of our cohort uses an element of religion to cope with their symptoms. We also see some indirect religious coping in our FMS cohort. The coping strategy "reinterpretation" belongs to spiritual and religious coping strategies and may be positive as well as negative (Pargament et al. 2000). In our cohort, reinterpretation significantly contributed to disability (Fig. 2). Furthermore, patients who reacted aversively to questions about religiosity during the interview sessions, often added comments like "why should God exist when I suffer from pain all day long". This indicates that religion is not only a positive source of strength (Klein and Berth 2011; Pargament 1997), but doubts and the feeling of being abandoned by God are closely associated to the

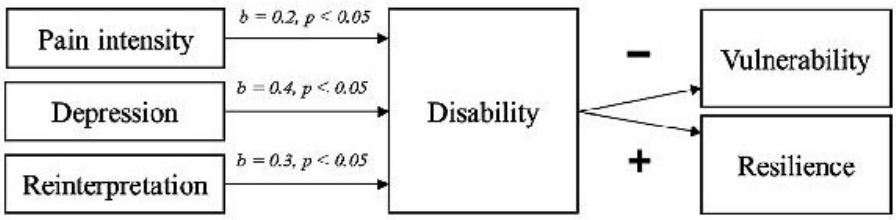

Fig. 2 Summary model of disability and resilience. B values present the individual contribution of each predictor to the model and the relationship between life quality and each parameter. Depression has the highest impact on disability ($b = 0.427$, $P < 0.05$). The higher the b value of depression the higher is the resulting disability in life with effects which could result in resilience or vulnerability. Besides depression, the active coping strategy "reinterpretation" and pain intensity have a significant impact on disability

personal journey to God (Gauthier et al. 2006). Thus, negative connotations of religiosity may also influence the success of coping strategies.

The final purpose of this study was to assess the influence of psychological, physical, spiritual and demographic variables on FMS-related disability. The b-values of the hierarchical regression analysis we applied on 99 valid patient data represent the individual contribution of each predictor to the model and the relationship between each parameter and FMS-related disability. We propose the following model (Fig. 2): Depression, coping "reinterpretation" and pain intensity had a significant impact on FMS-related disability. Depending on the grade of disability, and in combination with other factors like personal characteristics (i.e., sense in life, ability to accept), coping with stress and experienced life events, these three factors may increase or decrease either resilience or vulnerability. Previous studies demonstrated that among other factors active problem- and emotion-focused coping (e.g., reinterpretation) problem solving ability, acceptance and optimism leads to resilience (Denny and Ochsner 2014; Rutter 1985). As expected, and confirming previous data (White et al. 1999), pain intensity had a significant effect on disability. If ineffective coping is used, high pain intensity leads to high disability which promotes vulnerability rather than resilience. The same concept is valid for depression and reinterpretation as an active coping strategy. Reinterpretation belongs to the coping tactic reappraisal—an emotion regulatory skill that is a well-defined and an effective strategy to reduce negative affect and perceived stress (Denny and Ochsner 2014). Redefinition itself is a type of religious coping strategy both positive (benevolent religious reappraisal) and negative (demonic or punishing religious reappraisal) (Pargament et al. 2000). Redefinition is assumed to be effective in pain control, but patients need instructions by a psychologist to use it as a coping for mental and physical symptoms (Denny and Ochsner 2014).We suggest that trained by a coach, patients might achieve a positive effect on their symptoms, resulting in less disability in their daily activities with a positive effect on resilience. They may cope more effectively, adapt to the situation, and may be less vulnerable in stressful situations (Rutter 1985).

Conclusion

Our patient cohort was moderately religious and disconnected or consciously aversive to classic religious symbols and the church, which might be signs of living in a secular society. The grade of believing in a higher existence plays a role in the choice of coping strategies but has no effects on the outcome of health and mood. Depression, pain catastrophizing and anxiety have a high impact on disability due to FMS, which is highly connected to being resilient or not. Therapies that offer stress-reducing strategies like reappraisal have the potential to increase adapting on stressful situations in the context of pain.

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Compliance with Ethical Standards

Conflict of interest All authors declare they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Würzburg Medical School Ethics Committee (No. 135/15)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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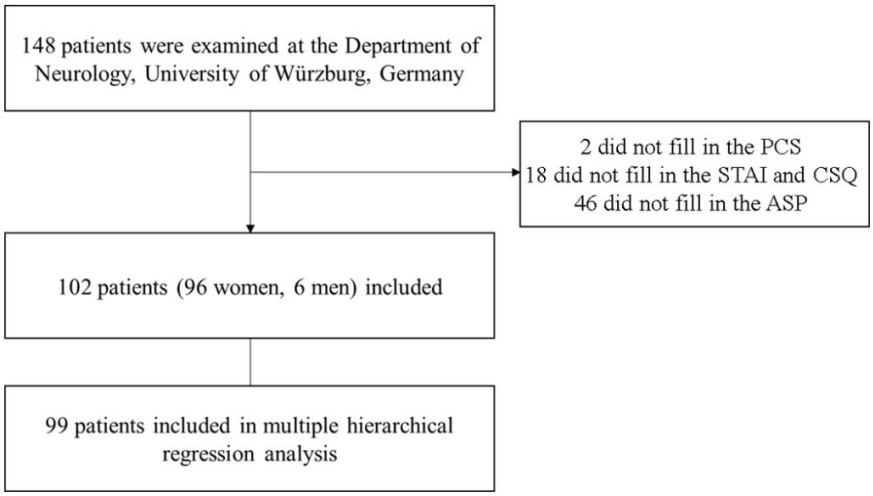
Supplementary information

Supplementary Figure 1



Supplementary Figure 2

Standardized protocol: psychological interview [20 min]

- Good morning Mrs. / Ms., Mr. ….. ? How are you? What is bothering you today?
- How do you estimate your coping competence with pain as well as daily problems on a scale from 0 as no competence to 9 best competence?

Part I - childhood and sociality

Evaluation: 2 = burdensome, 0 = neutral, 1 = positive

nr.	Life event item	age [years]	burdensome	neutral	positive
1	serious disease / injury / accident of yourself				
2	serious disease / injury / accident of a close person				
3	death				
4	break up / divorce				
5	serious problem with a good friend / neighbor / relatives (arguments)				
6	unemployness / aimlessness				
7	loss (job / person / theft)				
8	serious financial problems				
9	problems with the police and subpoena				
10	move				
11	intensive care of an old / ill person				
12	abortion / misscarriage / complications				
13	abuse (physical / emotional)				

Part II – faith / belief and values

1. Confession:
2. Independent from your opinion on the church and other religious organizations: Do you believe on a higher existence, that one could name, e.g. God, Jahwe, Allah, higher being, sth. / sb. divine, sth. / sb. absolute?

   ☐ none ☐ low ☐ moderate ☐ high ☐ intense
3. Which of the following terms best characterize your religious attitude?

   ☐ spiritual ☐ religious ☐ atheistic ☐ agnostic ☐ undetermined

   ☐ others: _____
4. How important are religiosity and belief in your life at the moment?

   ☐ not ☐ low ☐ moderate ☐ high ☐ intense
5. Which part in your life gives you power, sense and energy?

   ☐ family ☐ religion ☐ sports ☐ nature ☐ friends ☐ job ☐ meditation ☐ activity

Part III – problem solving and learning

Evaluation: 1 = no, 2 = little bit, 3 = high, 4 = intense

Nr.	question	no	little bit	high	intense
1	Do you sometimes think „Why me?" ?	1	2	3	4
2	Did your disease positively contribute to your personal development?	1	2	3	4
3	Do you ask for help when you have problems?	1	2	3	4
4	Can one solve every problem?	1	2	3	4
5	Can you well take account of your physical and emotional needs?	1	2	3	4
6	Can you maintain these needs towards others?	1	2	3	4

Supplementary Tables

Supp. Table 1: Characterization of the religious preferences in a subgroup of patients.

	N*	%
Sample size	42	100
Spiritual	5	3.4
Religious	9	6.1
Atheistic	4	2.7
Agnostic	1	0.7
Not determined	1	0.7
Other	22	14.9

*N: number

Supp. Table 2: Count of patients related to the grade of believing in a higher existence (interview data, N = 42).

Grade of believing in a higher existence	Count [N]
None	10
Low	5
Moderate	6
High	15
Intense	6
Total	**42**

Supp. Table 3: Descriptive statistics of the predictive variables used for the regression analysis.

Model	Categories	Predictor variables	M	SD
1	**Demographic variables**	Age	50.9	9.4
		Weight	75.0	14.6
		Height	166.5	7.7
		BMI	25.4	4.9
		Pain duration	14.1	10.1
2	**Pain variables**	Neuropathic pain	0.4	0.2
		Pain intensity	67.2	11.8
		GCPS grade	1.8	0.7
3	**Mental variables**	Pain catastrophizing	22.1	10.8
		Depression	23.3	11.1
		State anxiety	47.6	13.1
		Trait anxiety	48.4	11.9
4	**Coping strategies**	Distraction	15.5	7.0
		Reinterpretation	6.6	6.6
		Self-instructions	21.1	6.8
		Ignore	15.5	7.1
		Praying hoping	10.0	5.7
		Catastrophizing	17.1	7.8
		Activity increase	18.7	5.4
		Pain behavior	19.9	5.4
5	**Dimensions of religiosity**	Religious orientation	36.2	25.8
		Search insight / wisdom	49.7	24.3
		Conscious interactions	75.8	14.7

		Transcendence conviction	47.7	25.0

SD: standard deviation; M: mean

Supp. Table 4: The ANOVA presents the accuracy of the regression model and the improvement due to the model.

Model[a]		**Sum of squares**	**df**	**Mean square**	**F**	**Significance**
1	Regression	323.5	4	80.9	0.7	0.6
	Residual	11526.5	94	122.6		
	Total	11850.0	98			
2	Regression	4.550.6	7	650.1	8.1	0.0
	Residual	7.299.4	91	80.2		
	Total	11.850.0	98			
3	Regression	7.303.9	11	664.0	12.7	0.0
	Residual	4.546.1	87	52.3		
	Total	11.850.0	98			
4	Regression	7.824.3	21	372.6	7.1	0.0
	Residual	4.025.7	77	52.3		
	Total	11.850.0	98			
5	Regression	7.954.2	25	318.2	6.0	0.0
	Residual	3.895.8	73	53.4		
	Total	11.850.0	98			

[a] = dependent variable: FMS impact in life; df: degree of freedom; F: F - value

Manuscript 2

Clustering Fibromyalgia patients: Specific combination of psychosocial and somatic factors lead to resilient coping in a subgroup of FMS patients.

Alexandra Braun, Dimitar Evdokimov, Johanna Frank, Nurcan Üçeyler, Claudia Sommer

PLoS ONE (2020)

Manuscript 2 **Braun A, Evdokimov D, Frank J, Pauli P, Üçeyler N, Sommer C. Clustering fibromyalgia patients: A combination of psychosocial and somatic factors leads to resilient coping in a subgroup of fibromyalgia patients. PLoS One. 2020 Dec 28;15(12):e0243806. doi: 10.1371/journal.pone.0243806. PMID: 33370324.**

Abstract

Background: Coping strategies and their efficacy vary greatly in patients suffering from fibromyalgia syndrome (FMS).

Objective: We aimed to identify somatic and psychosocial factors that might contribute to different coping strategies and resilience levels in FMS.

Subjects and methods: Standardized questionnaires were used to assess coping, pain, and psychological variables in a cohort of 156 FMS patients. Quantitative real-time polymerase chain reaction (qRTPCR) determined gene expression of selected cytokines in white blood cells of 136 FMS patients and 25 healthy controls. Data of skin innervation, functional and structural sensory profiles of peripheral nociceptive nerve fibers of a previous study were included into the statistics. An exploratory factor analysis was used to define variance explaining factors, which were then included into cluster analysis.

Results: 54.9% of the variance was explained by four factors which we termed (1) affective load, (2) coping, (3) pain, and (4) pro-inflammatory cytokines ($p < 0.05$). Considering differences in the emerged factors, coping strategies, cytokine profiles, and disability levels, 118 FMS patients could be categorized into four clusters which we named “maladaptive”, “adaptive”, “vulnerable”, and “resilient” ($p < 0.05$). The adaptive cluster had low scores in disability and in all symptom categories in contrast to the vulnerable cluster, which was characterized by high scores in catastrophizing and disability ($p < 0.05$). The resilient vs. the maladaptive cluster was characterized by better coping and a less pro-inflammatory cytokine pattern ($p < 0.05$).

Conclusion: Our data suggest that problem- and emotion-focused coping strategies and an anti-inflammatory cytokine pattern are associated with reduced disability and might promote resilience. Additional personal factors such as low anxiety scores, ability of acceptance, and persistence further favor a resilient phenotype. Individualized therapy should take these factors into account.

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PLOS ONE

RESEARCH ARTICLE

Clustering fibromyalgia patients: A combination of psychosocial and somatic factors leads to resilient coping in a subgroup of fibromyalgia patients

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Abstract

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number is not available. The study was in part funded by Else Kröner-Fresenius-Stiftung (available from: https://www.ekfs.de/en). N.Ü. was the recipient of the grant with the grant number 2014_A129. Further funding came from internal research funds of the Department of Neurology of the University hospital Würzburg. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. There was no additional external funding received for this study.

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cluster was characterized by better coping and a less pro-inflammatory cytokine pattern ($p < 0.05$).

Conclusion

Our data suggest that problem- and emotion-focused coping strategies and an anti-inflammatory cytokine pattern are associated with reduced disability and might promote resilience. Additional personal factors such as low anxiety scores, ability of acceptance, and persistence further favor a resilient phenotype. Individualized therapy should take these factors into account.

Introduction

Fibromyalgia syndrome (FMS) is a chronic pain syndrome with specific associated symptoms [1]. FMS patients show heterogeneity in symptoms and in coping with the disease's impact on daily activities and professional life [2–7]. Some patients deal actively and effectively with pain and accompanying FMS symptoms, while others are vulnerable and severely disabled [8]. Activating resources and using effective coping with the disease might also be named resilience. The term resilience stems from the Latin word "*resilire*" meaning "bouncing back" from difficult experiences and is related to the phenomenon of psychological resistance despite intense distress and high risks [9, 10]. One definition of resilience is a flexible ability to adapt to every situation in the best fitting biopsychosocial way [11, 12]. Other definitions understand resilience as a personal trait or characteristic [13] that allows to activate resources. Better knowledge of the factors involved in resilience might guide individualized therapies.

Psychosocial factors that are well known to contribute to a resilient profile are among others solution-focused and active coping strategies and supportive social contacts [14]. Resilient people show low scores in depression, anxiety, and pain catastrophizing and remain with low disability after traumatic events and stressful life periods [15].

Decades of research in the field of resilience found biological determinants, which allowed to identify neural circuits and signaling pathways that mediate resilient phenotypes [16, 17]. Previous studies from our group showed that patients with widespread chronic pain have lower levels of the anti-inflammatory cytokines interleukin (IL)-4 and IL-10 compared to healthy controls [18]. Accordingly, in patients with polyneuropathies, higher blood levels of IL-4 and IL-10 were associated with a painless phenotype [19]. Recently, we showed that a subgroup of FMS patients with markedly reduced skin innervation, i.e. with pathological peripheral nociceptors, has more severe FMS symptoms [20, 21]. Here we wanted to assess, whether psychosocial factors, the cytokine profile, or the state of peripheral nociceptive nerve fibers as measured by functional and structural tests, are associated with successful coping and resilience in FMS.

Given the wide range of variables, we used an exploratory factor analysis of this clinically well-defined FMS patient cohort with the aim to find independent factors explaining the high variance within the cohort. The following hierarchical clustering aimed to identify subgroups with differences in these predefined factors and characterize them regarding biopsychosocial aspects, severity levels, and resilient or vulnerable phenotypes, with the goal to identify resilient coping patterns.

Several authors have performed cluster analyses to identify subgroups among fibromyalgia patients characterized by symptom severity, objective or subjective measures of physical and mental health with different outcomes [22–27]. One study stands out with a large cohort of

947 FMS patients assessed with the FIQ-R sum score variable, resulting in four clusters with differences in clinical, economical and somatic outcomes like inflammatory markers and grey matter volume [28]. In contrast to this study [28], which did clustering only with a single sum score variable, our approach was to cluster the cohort by previously emerged validated factors, a method that is supposed to make data more transferrable on other cohorts independently on regional differences. In the long run, these identified coping patterns might be used to develop individualized therapies for the subgroups.

Materials and methods

Subjects and ethics

This study is part of a current larger study on FMS at the Department of Neurology of the University Hospital Würzburg, in course of which 156 FMS patients fulfilling the diagnostic criteria for FMS of the American College of Rheumatology published in 2010 [29], and 48 age and gender matched healthy controls were recruited between 2014 to 2018 [20]. Exclusion and inclusion criteria were as specified elsewhere [30] (see S1 Table). All patients provided written informed consent and filled in a series of questionnaires before enrollment. An overview of the examination plan of the main study is included (see S1 Fig). Data on clinical examination, electrophysiological and laboratory measurements, and the tests in the ophthalmology department were published elsewhere [20, 21]. Details among clusters are summed up in S2 Table. Our study was approved by the Würzburg University Ethics Committee (No. 135/15).

Psychosocial and symptom specific questionnaires as variables for clustering

Psychosocial variables. All questionnaires were available as standardized validated German versions as indicated by an added "D" at the end of the questionnaire abbreviation.

The Center of Epidemiological Studies General Depression Scale (CES-D) is a 20-items questionnaire that examines the severity of depressive symptoms. A total score of CES-D $\geq$ 22 is supposed to indicate clinically relevant depressive symptoms [31]. The State-Trait Anxiety Inventory (STAI-G) examines anxiety on a 1 to 4 scale as a trait (STAI-T) and as a state (STAI-S) shown by two sum scores [32]. The STAI-S sum score is created by the scores of item 1 to 20, and the STAI-T sum score by the items 21 to 40. The Pain Catastrophizing Scale (PCS-D) examines the strength of catastrophizing feeling and behavior [33]. The PCS sum score was created with the sum of all 13 items. The short form of the Childhood Trauma Questionnaire (CTQ-D) is a 28-items questionnaire that examines the experience (as frequency) and severity of traumatic events summarized in the five sub scales "sexual abuse", "emotional abuse", "emotional neglect", "physical abuse", physical neglect, and an additional scale of trivialization. The sum score of every subscale is 5 to 25 which is indicated as "severe" traumatic event [34, 35].

Coping. We used the Coping Strategies Questionnaire (CSQ-D) and its 8 subscales (distraction of attention, reinterpretation, self-instructions, ignoring, praying and hoping, catastrophizing, increase in activity, pain behavior) plus the effectiveness ratings on pain control and pain reduction) to examine different strategies to cope with pain. The maximum sum score was 36 for each coping strategy and 6 for the effectiveness ratings [36].

Pain and FMS related disability. Three questionnaires assessed different aspects of pain and disability due to pain. The Neuropathic Pain Symptom Inventory (NPSI-D) examines the severity and characteristics of pain in the last 24 hours, which results in the NPSI sum score [37]. The Graded Chronic Pain Scale (GCPS-D) is a 7-item questionnaire that calculates 3 sub

scores showing pain intensity, disability due to pain and the grade of disability, which is constructed from a combination of a disability scale from 0 to over 70 and days of disability from 0 to 31 days [38]. The Fibromyalgia Impact Questionnaire (FIQ-D) examines physical functioning, working status, well-being of FMS patients, and their impact on daily life [39]. The Short-Form Health Survey (SF-12) is the shorter version of the SF-36 questionnaire and a screening tool for measuring health-related quality of life [40, 41]. The Physical Component Summary (PCS) scale represents general health perception, physical function and role function as well as pain. The Mental Component Summary (MCS) scale represents emotional role function, mental well-being, negative affect and social functioning. The FIQ sum score and both subscales of the SF-12 (PCS, MCS) represent physical disability and quality of life. All three scores were used as components to define the severity level resulting in low or high resilience in our cohort by plotting them among all clusters and calculating the effect size.

Somatic data as variables for clustering

Blood withdrawal, white blood cell extraction, and RNA isolation. Venous blood was collected from all patients and 25 healthy controls between 8:00 AM and 9:00 AM after overnight fasting. Subjects were instructed not to consume alcohol, not to smoke and not to perform strenuous physical activity 24 h before the study day. Two serum monovettes (4.7 ml) and three ethylendiamine-tetra-acetic acid-containing tubes (EDTA, 9.0 ml; Sarstedt AG & Co., Nümbrecht, Germany) were taken. After incubation for 30 minutes on ice, the white blood cell (WBC) fraction was extracted and 9 falcon tubes were filled with 1.5 ml EDTA blood each and 7.5 ml erythrocyte lysis buffer (EL buffer; Qiagen, Hilden, Germany) was added and gently mixed. Afterwards the second incubation on ice for 30 minutes was interrupted for 3 times vortexing. All 9 falcon tubes were centrifuged (400 g) for 10 minutes at +4˚C, supernatant was discarded, and each cell pellet resuspended in 3 ml EL buffer. The same centrifugation step was conducted, and the supernatant discarded. The total white blood cell (WBC) fraction of 8 falcon tubes was resuspended in RNA Protect Cell Reagent (Qiagen, Hilden, Germany) and stored at -80˚C until PCR analyses. 1 ml EL buffer was added to the 9th falcon tube and 1 μl of the content was added to a Neubauer improved cell chamber (Bürker, 0.100 mm depth, 0.0025 mm^2; BLAUBRAND®, Brand GmbH & Co.KG, Wertheim, Germany), and cells were quantified. After extraction, plasma and serum samples were frozen at -80˚C, and the mRNA was isolated from 136 WBC samples following the manufacturer's protocol using the miRNeasy Mini kit (Qiagen, Hilden, Germany).

cDNA synthesis. For reverse transcription of 250 ng of the isolated mRNA to cDNA, TaqMan Reverse Transcription Reagents® (Applied Biosystems, Darmstadt, Germany) were used as previously describedKlicken oder tippen Sie hier, um Text einzugeben. The cycler (ABI PRISM 7700 Cycler, Applied Biosystems, Darmstadt, Germany) was set as annealing at 25˚C for 10 minutes, reverse transcription at 48˚C for 60 minutes and enzyme inactivation at 95˚C for 5 minutes.

TaqMan qRT–PCR. 5 μl of transcribed cDNA was used for qRT-PCR performed in GeneAmp 7700 sequence detection system® (Applied Biosystem, Darmstadt, Germany) as previously described [19]. Gene specific TaqMan primers for IL-6 (assay-ID: Hs00174131_m1), tumor necrosis factor (TNF) (assay-ID: Hs00174128_m1), IL-4 (assay–ID: Hs00174122_m1), IL-10 (assay-ID: Hs00174086_m1), and endogenous control 18sRNA as well as a WBC control from human blood of a healthy person were used for the TaqMan Gene Expression Assays® (Applied Biosystems, Darmstadt, Germany). Samples on each PCR plate were run as triplicates, endogenous control samples were run as duplicates. Each plate contained a negative control (RNA free water) to exclude genomic contamination. Before the samples run, control

samples were used to verify a calibrator as a standard sample on each plate to guarantee inter-plate comparability. For evaluation of relative gene expression of all four target genes compared between patients and controls we used the comparative deltaCT method (lower deltaCT values express higher gene expression). As a more convenient visualization of the results we calculated 1/deltaCT to illustrate higher values as higher gene expression (compare [42]).

Further physiological data. Data of quantitative sensory testing (QST), pain-related evoked potential (PREP) measurements, data from clinical examination and history, and data of intraepidermal nerve fiber density (IENFD) derived from skin biopsies of upper and lower leg were collected in the main study and here used as variables for multivariate variance analyses (factoring and clustering). These data were published elsewhere [20, 21] and summarized in S2 Table regarding patient cluster of the current study (see S2 Table).

Statistical analysis. IBM SPSS Statistics 25 software (IBM, Ehningen, Germany) was used for statistical analysis. Data distribution was tested with the Shapiro-Wilk test and by observing data histograms. Results of the non-normally distributed data are given as median (MED) and range, and of normally distributed data as mean (M) and standard deviation (SD).

Z transformation. Sum scores of the questionnaires and somatic data used in factor analysis were saved as standardized values to make all variables comparable independent of scaling in the total data sheet within SPSS.

Higher order principal factor analysis (PFA). Extraction method was a principal axis factoring with oblimin rotation. We checked the anti-image correlation matrix if the data set is representable as factors. Derived from this the Kaiser–Meyer–Olkin (KMO = 0.77) measure verified sampling adequacy for the analysis and the Bartlett's test of sphericity (χ^2 (253) = 1322.276, $p < 0.001$) indicated that correlations between items were sufficiently large and not multicollinear for PFA (see S3 Table). The determinant of the R correlation matrix was higher than 0.00001, which implies no severe multicollinearity [43]. An initial analysis was run to obtain eigenvalues for each factor. Seven factors had eigenvalues of at least one verified by Kaiser's criterion and in combination explained 70% of the variance (see S4 Table). The scree plot was slightly ambiguous and showed less inflexions starting at factor 3 to 7 (see S3A Fig). Given the large variable size of 23, and the convergence of the scree plot and Kaiser's criterion on four factors, this is the number of factors that were retained in the final analysis (overall Cronbach' alpha = 0.7, which is suitable for items regarding ability tests [44]). Variable loadings of < 0.30 were suppressed in the PFA. Factor scores were created by regression within the SPSS software. Internal consistency of factors was analyzed by Cronbach's α. Missing cases were excluded listwise.

Cluster analysis. Using factor scores a hierarchical cluster analysis with Ward's method was conducted to group the entire cohort to clusters specified by previous defined factorial characteristics. Visual inspection of the dendrogram (see S4 Fig) was done to indicate the number of clusters that should be considered. The decision on the number of clusters was additionally made following Rehm et al. [45] and van Leeuwen et al. [46] by practical considerations (i.e. the least frequent cluster should include a minimum of 15% of the total sample) and by heuristic interpretability of mean factor scores within clusters (i.e. agglomeration schedule within SPSS software). By using this combination of interpretability, the developed cluster solution minimizes the within-group variability and maximizes the between-group differences [47, 48]. With a defined number of four clusters, the hierarchical method was run again with fixed and saved cluster solution (range 2 to 5 cluster). The 3D illustration model of these cluster and their differences in the emerged factors were created by MATLAB (*MATrix LABoratory*, The MathWorks Inc., Natick, Massachusetts, USA) [49].

Differences between patient profiles. A one-way analysis of variance (ANOVA) and Games-Howell post-hoc analyses of the pairwise comparisons of the ANOVA were used to detect between-cluster differences in all variables included into the multivariate analyses.

Grades of severity. For symptom severity and evaluation of subgroups, we calculated effect sizes using Cohen's d [50] to choose the resilient and the vulnerable profiles (using the mean and standard deviation of these two subgroups). The calculated effect sizes were interpreted as small (0.2), medium (0.5) or large (0.8) [51]. Level of significance was set at $p < 0.05$.

Results

Data availability

Questionnaire data were available for 136 patients except for the CTQ-D and SF-12-D, which was only available from 112 patients. Some questionnaires were added at a later stage, therefore only data of 118 patients were valid for the multivariate analyses (see S2 Fig). Controls were only included to validate the PCR data, the other parts of the study focuses on differences among FMS patients. Sufficient data of 136 patients and 25 healthy controls were available to include them into the PCR study. Overall, fewer patients and controls could be included in the PCR analysis because not all patients had blood samples available.

Variance within psychosocial data, coping strategies, pain variables, and immune agents

Psychosocial data (CES-D, STAI-G-D, PCS-D, CTQ-D), coping strategies (CSQ-D), pain variables (GCPS-D, NPSI-D), skin innervation, and relative cytokine gene expression of all gene targets showed a large variability. As an example, the relative gene expression of all analyzed cytokines showed no intergroup difference between FMS patients and controls but had high within group variabilities (Fig 1).

This overall huge variance and the clinical experience with this FMS patient cohort led us to assume the existence of more than two subgroups within the entire patient cohort. Due to the differences in a high amount of variables we aimed to exploratively test a range of variables to group the cohort.

Mental health, coping, symptom disability and cytokine profile is responsible for variance

First, a factor analysis was performed on the data of 118/156 (75.6%) patients valid for multivariate analysis (see S4 Fig).

An initial run of the PFA was applied on 53 z -standardized variables to reduce the number of variables and to search for factors that explain the variance within the data field. 29 variables were identified as not responsible for the variance and not sufficient to be included in the final analysis. Factors related to nociceptor structure and function like proximal and distal IEFND did not emerge in the factor analysis. Data of quantitative sensory testing (QST) and evoked potentials nonspecifically loaded on two factors and could not be interpreted resulting in the decision to exclude them. After exclusion of these 29 variables, we ran a second PFA with 23 variables. The decision about the number of factors was based on inspection of the scree plot (see S3B Fig). Table 1 shows the factor loadings after rotation.

The items that load on the same factors suggest that factor 1 represents "affective load", factor 2 "coping strategies", factor 3 "physical functioning" and factor 4 "pro-inflammatory cytokines". The loadings are given in descending order representing that anxiety and catastrophizing are the items that have the most decisive influence on variance (Table 1).

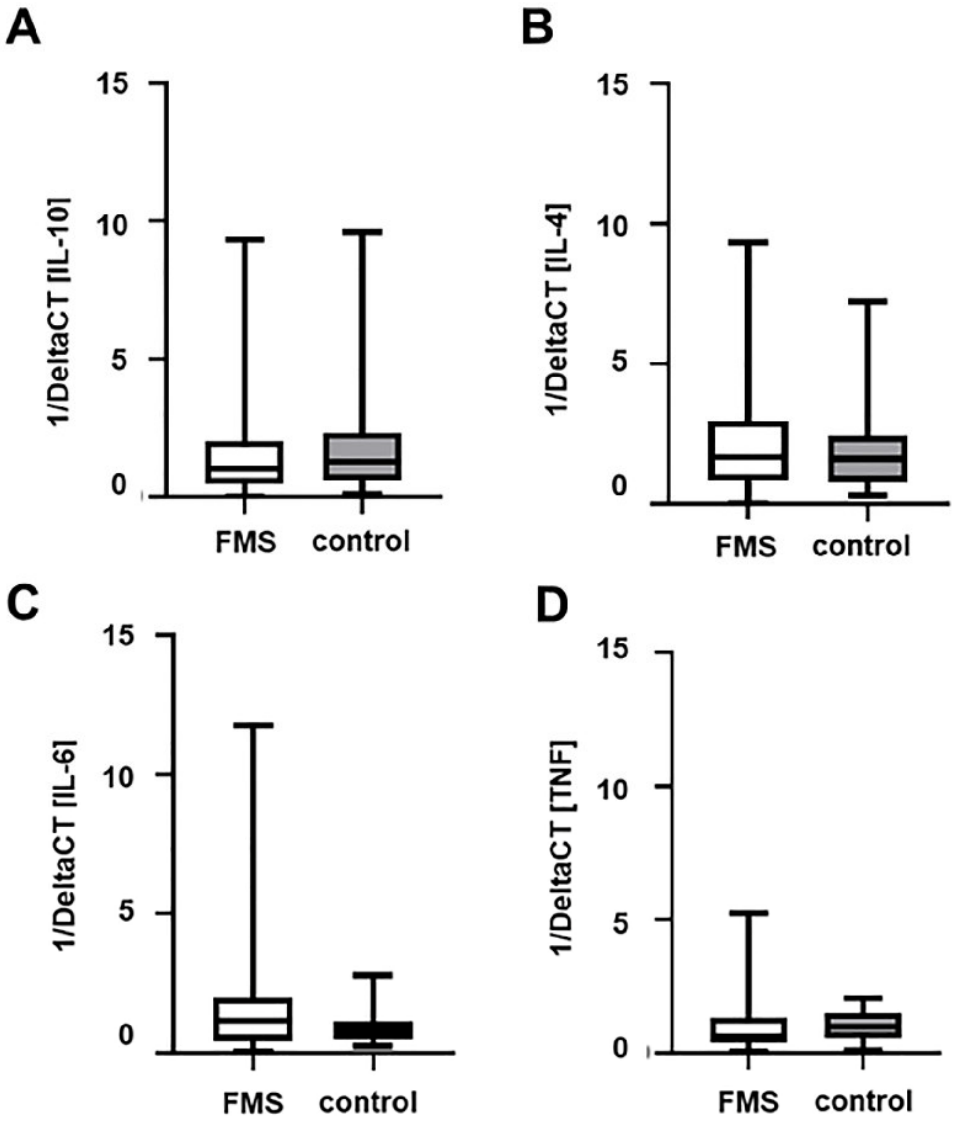

Fig 1. Relative gene expression of selected anti- and pro-inflammatory cytokines in FMS patients and healthy controls. Boxplots show deltaCT values, i.e. relation of the CT value of the target normalized to the housekeeping gene 18sRNA, of IL-10 (A), IL-4 (B), IL-6 (C) and TNF (D) of patients with FMS and healthy controls. Data are presented as 1/ΔCT. No intergroup difference was found for any of the investigated targets. Note the high variability within the patient group. Abbreviations: CT = cycle threshold; FMS = Fibromyalgia syndrome; IL = Interleukine; TNF = Tumor necrosis factor-alpha.

https://doi.org/10.1371/journal.pone.0243806.g001

Followed by self-instructions / reinterpretation / praying and hoping, pain intensity and pain behavior.

Affective load, coping, physical functioning and cytokine profile cluster patients into four subgroups

A hierarchical cluster analysis was performed on the individual factor scores to distinguish patient subgroups. We decided to interpret a four-cluster solution as the best fit for our cohort

Table 1. Pattern matrix with factor loadings of every variable of the principal factor analysis (PFA).

	factor			
z score variables	**1**	**2**	**3**	**4**
STAI-T[a] sum score	0.9			
CSQ-D[b] catastrophizing	0.9			
CES-D[c] sum score	0.8			
PCS-D[d]	0.8			
STAI-S[e] sum score	0.8			
rel. gene expression IL10[f]				
CSQ-D[b] self-instructions		0.8		
CSQ-D[b] distraction		0.7		
CSQ-D[b] ignore		0.7		
CSQ-D[b] reinterpretation		0.6		
CSQ-D[b] praying hoping		0.5		
CSQ-D[b] activity increase		0.5		
CSQ-D[b] pain control		0.4		
CSQ-D[b] pain reduction		0.3		
GCPS-D[g] pain intensity			-0.7	
GCPS-D[g] grade			-0.6	
GCPS-D[g] disability			-0.6	
NPSI-D[h] sum score			-0.6	
rel. gene expression IL4[i]				
CSQ-D[b] pain behavior				-0.6
rel. gene expression TNF[j]				0.5
rel. gene expression IL6[k]				0.3
α[l]	0.9	0.8	0.7	0.5

[a]STAI-T = subscale trait-anxiety of the German version of the state/trait anxiety inventory

[b]CSQ-D = subscales of the German version of the coping strategies questionnaire

[c]CES-D = German version of the center of epidemiological studies general depression scale

[d]PCS-D = German version of the pain catastrophizing scale

[e]STAI-S = subscale state-anxiety of the German version of the state/trait anxiety inventory

[f]IL10 = interleukin 10

[g]GCPS-D = three subscales of the German version of the graded chronic pain scale

[h]NPSI-D = German version of the neuropathic pain scale inventory

[i]IL4 = interleukin 4

[j]TNF = tumor necrosis factor

[k]IL6 = interleukin 6

[l]α = Cronbach's alpha for each factor

https://doi.org/10.1371/journal.pone.0243806.t001

(see S4 Fig). Finally, we characterized and labeled these clusters based on differences regarding the factor scores as following: Cluster A as "maladaptive", cluster B as "adaptive", cluster C as "vulnerable" and cluster D as "resilient". The differences in the mean factor scores at the four profiles are illustrated in Fig 2 and their scores are compared in S2 Table.

A 3D model provides a more convenient illustration of the four clusters characterized by four factors and is available from following link: https://drive.google.com/file/d/14r8DXQN1akmftBSYWWFRNv3sZlTQvtpI/view?usp=sharing [49].

The cluster labels are based on the differences and characteristics of each individual cluster which described in the following. The maladaptive cluster A (N = 35) is characterized by negative affect, maladaptive coping, low scores in physical functioning and a higher gene expression

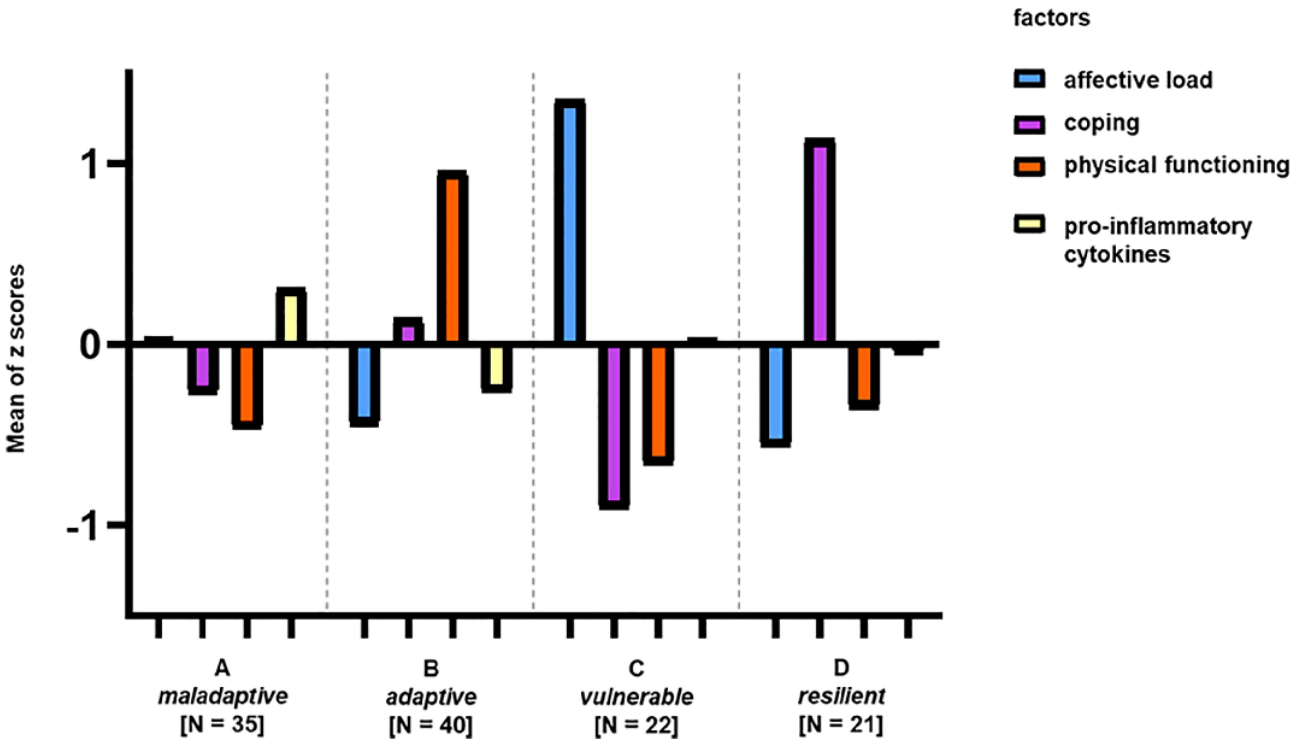

Fig 2. Four clusters differentiated by four factors explaining the variance in somatic and psychosocial data within the patient group. Bars symbolize positive or negative difference of this cluster in one specific factor to the mean value in this factor of the entire group. No bar symbolizes no difference of the group in this factor to the mean value of the factor of the entire group. Cluster A (named "maladaptive") consists of 35 patients, Cluster B the "adaptive" cluster of 40, Cluster C the "vulnerable" cluster of 22 FMS patients and cluster D (named "resilient") of 21 patients. Significant differences between factors and groups are marked ($p < 0.05$). Abbreviations: FMS = Fibromyalgia Syndrome.

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of pro-inflammatory cytokines ($p < 0.05$, compared to cluster B). Maladaptive coping might be dysfunctional and not effective to maintain physical functioning. The adaptive cluster B (N = 40) includes patients with a low negative affect who are using adaptive coping to deal with the highest pain scores ($p < 0.05$ compared to the vulnerable cluster C; see S2 Table), and lower values for pro-inflammatory cytokines. The active way of coping has positive effects on physical functioning. Cluster C ("vulnerable", N = 22) is characterized by high negative affect and destructive coping ($p < 0.05$). Cluster D ("resilient", N = 21) has the lowest scores in affective load ($p < 0.05$) and is the cluster with highest rate of active coping strategies ($p < 0.05$).

Clusters differ in disease impact

To assess the impact of disease in the four different clusters, we examined differences regarding clinical disease characteristics with one-way ANOVAs (see S5 Table), followed by pairwise post-hoc comparisons (see S6 Table), and we calculated effect size values (Table 2).

One-way ANOVAs revealed that clusters differed in "impact of FMS on daily activities" according to the FIQ-D sum score and in mental health according to the MCS scores ($p < 0.05$, Fig 3).

The follow-up tests revealed significant differences with large effect sizes (r = -0.8; see Table 2) between cluster B vs. C, and D vs. C regarding FMS impact ($p < 0.09$, Fig 3A), whereas the daily life of cluster C was highly affected by FMS related symptoms and patients in

Table 2. Cohen's d and calculated effect size r between adaptive and resilient cluster B and D and the vulnerable cluster C regarding factors and some outcome variables.

	cohen's d[a]	effect size r[a]	comment[b]
factor "affective load"			
BC[c]	-2.8	-0.8	large
DC	-2.6	-0.8	large
factor "coping"			
BC	1.5	0.6	medium
DC	3.0	0.8	large
factor "physical functioning"			
BC	2.9	0.8	large
DC	0.6	0.3	small
factor "pro-inflammatory cytokines"			
BC	-0.3	-0.2	small
DC	-0.1	-0.1	small
FIQ[d]			
BC	-2.3	-0.8	large
DC	-1.3	-0.5	medium
SF-12 –MCS[e]			
BC	1.4	0.6	medium
DC	0.6	0.6	medium

[a]Cohens's d and effect size r were calculated with the Cohen's d and effect size r calculator of the University of Colorado: https://www.uccs.edu/lbecker/

[b]classification of effect size r: 0.2 = small, 0.5 = medium, 0.8 = large

[c]cluster labels: A = maladaptive, B = adaptive, C = vulnerable, D = resilient; BC = between cluster B and cluster C (other comparisons labelled likewise)

[d]FIQ-D = German version of the Fibromyalgia Impact Questionnaire

[e]SF-12 = Short-Form 12-items Health Survey; MCS = Mental Component Summary.

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this cluster had the highest disability ($p < 0.05$). The mental health score differed between cluster B vs. C, and D vs. C with medium effect sizes ($p < 0.05$), but the cluster did not differ in the physical component score.

Coping seems to be crucial for the main difference between the resilient cluster D and the vulnerable cluster C, with a large effect size between both clusters in factor 2 "coping" (r = 0.8; Table 2), whereas the effect of coping between the adaptive cluster B and the vulnerable cluster C was only medium (r = 0.6). Interestingly, the resilient cluster D had higher FIQ scores than the adaptive cluster B, suggesting that adaptive coping may be more successful than "resilient" coping. Overall, the adaptive cluster and the vulnerable cluster showed the lowest and the highest impact of disease and mental health (Fig 3, $p < 0.05$).

One cluster uses reinterpretation as highly effective coping and might activate natural resources to cope with FMS

Cluster specific coping patterns, which might indicate vulnerable or resilient coping, were evaluated based on the mean using frequencies of the eight different behavioral and cognitive coping strategies and their subjective efficacy as assessed with the CSQ-D (Fig 4).

The group differences between all coping strategies including pain control and pain reduction were significant ($p < 0.05$) except for "pain behavior". The coping type of patients within cluster C might be described as vulnerable coping, since this cluster had the highest frequency in catastrophizing (M = 25.9, SD = ±5.0) and passive negative coping strategies with less effect on pain control (MED = 2.0 (0–3) and symptom reduction (MED = 2.0 (0–4) (S2 Table).

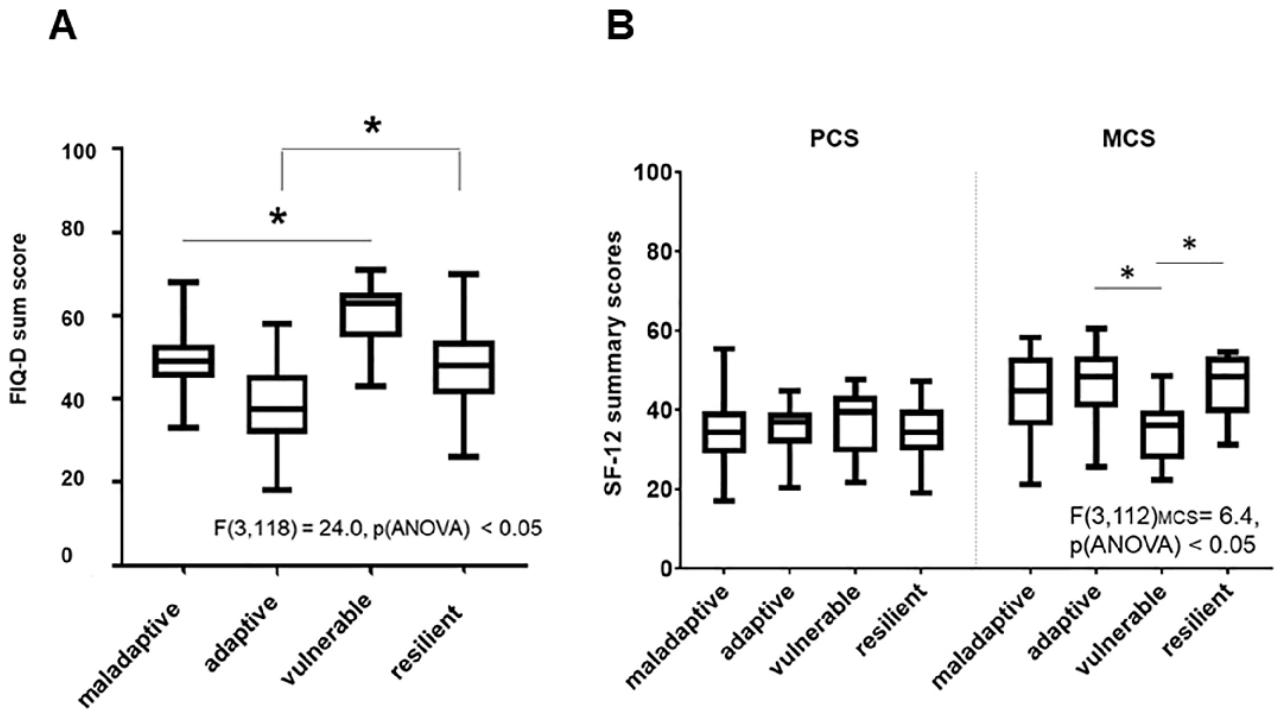

Fig 3. Differences of the clusters in FMS impact in life (A) and self-reported quality of life (B). Boxplots of all clusters show differences in all plotted sum score variables resulting in different severity level of the clusters. Significant differences are marked ($p < 0.05$). Abbreviations: FIQ = Fibromyalgia Impact Questionnaire; FMS = Fibromyalgia Syndrome; SF-12 = 12-items Short-Form Health Survey; PCS = Physical Component Summary; MCS = Mental Component Summary.

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Resilient coping might be seen in cluster D, which had the highest values in all active coping strategies especially in reinterpretation with the most positive effect on pain control (MED = 4.0 (0–5)) and pain reduction (MED = 2.0 (0–4)) compared to the maladaptive and vulnerable cluster (Fig 4, Table 2, S2 Table; $p < 0.05$). Reinterpretation or reappraisal is a well-known cognitive technique to modulate and control negative emotions resulting in reduced subjective experience of emotions and physiological response. The ability to cope with this technique normally needs professional support. Thus, cluster D seemed to be naturally prepared to cope effectively with pain and other symptoms indicating the ability to activate resources which is also defined as resilience.

Cluster specific cytokine pattern

Effect sizes of factor 4 ("pro-inflammatory cytokines") between the adaptive (B) and the vulnerable cluster C (BC; r = -0.2), and between the resilient cluster (D) and the vulnerable cluster C (DC; r = -0.1) were small, suggesting that differences in gene expression of all measured cytokines regarding the cluster categories were minor (Table 2), which was confirmed by the data in Table 2. Searching for a specific cytokine pattern related to resilience, we only found differences between cluster D versus C and cluster D versus A regarding the anti-inflammatory gene target IL-10 (Fig 5; $p < 0.05$).

All other comparisons only revealed a trend toward lower levels of pro-inflammatory cytokines in the adaptive and the resilient cluster, such that a specific cytokine pattern related to resilience could not be verified.

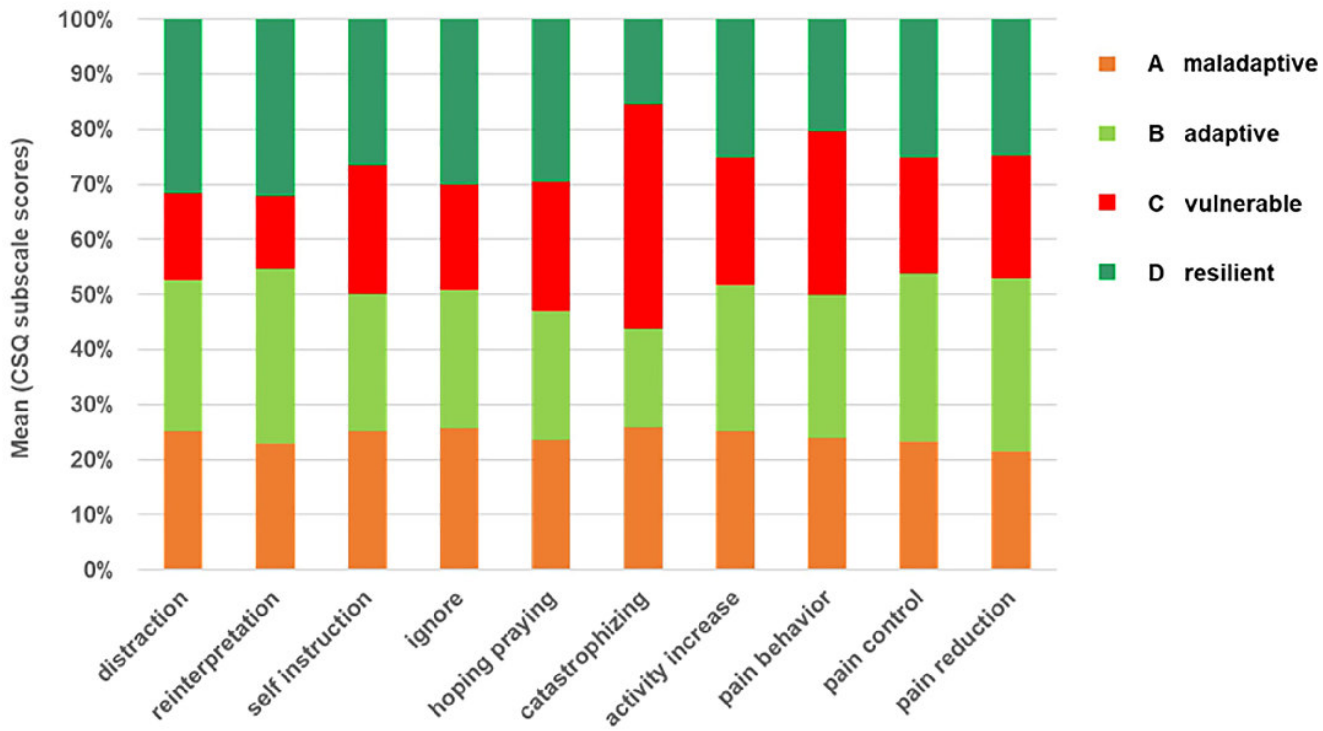

Fig 4. Differences between clusters regarding coping strategies. Bars illustrate the different proportion of the clusters A to D on the mean value of 8 subscale scores of the CSQ-D questionnaire indicating different coping strategies and 2 scores indicating efficiency of these strategies. The coping pattern of the vulnerable cluster is characterized by the high impact of catastrophizing ($p < 0.05$), the coping of the maladaptive cluster shows higher values in less effective passive strategies with relatively high values in catastrophizing, the adaptive clusters copes with effective problem and emotion-focused strategies with high values in pain control and reduction ($p < 0.05$) and the resilient cluster uses cognitive based coping strategies with high efficiency in pain control. Abbreviations: CSQ = Coping Strategies Questionnaire.

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Cluster–specific case description

To illustrate the findings in our cluster analysis, we selected one typical patient per cluster and described their social environment and socio-demographic data. The case descriptions underline and discuss the cluster labels (Fig 6).

Additional comments describing the subjective personal impression on each patient were taken during the medical history and the psychological interview on the study day (see S1 Fig).

Mrs. B. is a 52-year-old woman who was categorized to the maladaptive group. She reported experiencing neck, shoulder, and lower back pain of medium intensity for 12 years following no specific incident. She is overwhelmed by requirements with slight to moderate degree of difficulty, resulting in somatic symptoms and anxiety. Pain attacks, depressive mood, and the lack of resilient handling of stress resulting in sick leave in her job. The patient was always trying to obtain treatment (such as psychotherapy) but resolved to unhealthy and dysfunctional coping like eating and smoking.

Mrs. Z. is a 53-year-old woman who was categorized to the adaptive group. After 10 years experiencing pain and accompanying symptoms like irritable bowel, headache, or concentration problems, she was referred to a pain clinic. During her treatment there, she learned various techniques to deal with the pain. She considers herself "a positive personality", and also gets a lot of support from her family. She reported that it demands a lot of strength to daily fight against the pain, but she was well able to handle her daily life. She does a lot of sports and listens to her needs.

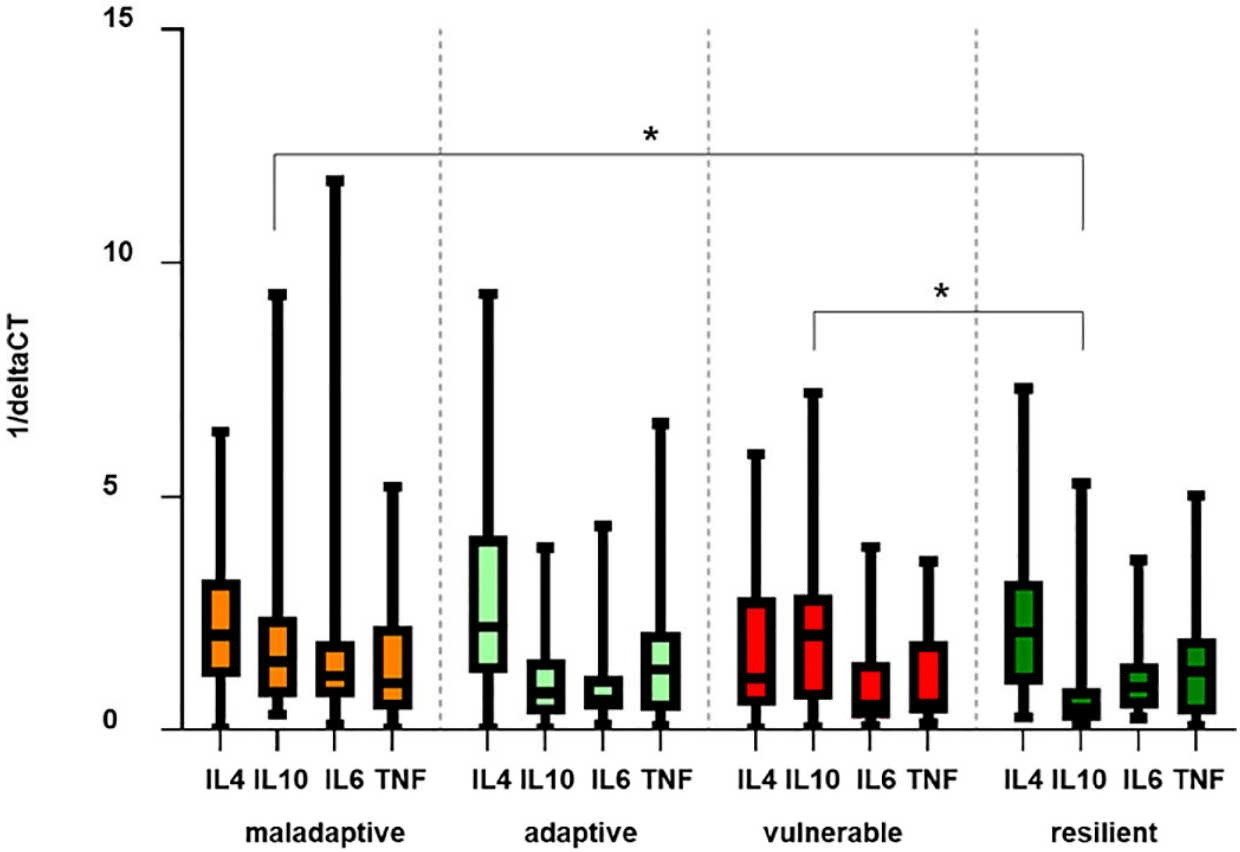

Fig 5. Cluster specific cytokine profiles. Bars illustrate mean deltaCT values of the target normalized to the housekeeping gene 18sRNA, of IL-4, IL-6, IL-10 and TNF of patients with FMS organized by the four defined clusters. Results are presented as 1/ΔCT. Relative gene expression of IL-10 between cluster A and D, and between cluster C and D are marked as significant ($p < 0.05$). Abbreviations: FMS = Fibromyalgia Syndrome; IL = Interleukine; TNF = Tumor necrosis factor-alpha.

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Mrs. W. is a 48-year old woman who was categorized to the vulnerable group. The recruitment process was difficult, the patient was very anxious about the study tests. She came to the hospital with a big backpack although she lived only 30 minutes away. She seemed to be lost with her symptoms and was complaining about how bad the doctors were, that no one is helping her, and everything would no longer make sense. She reported pain intensity on the highest possible scores. She was currently in psychological therapy that she described as exhausting since she had to do all the work instead of the therapist. She was not active in her life, did no sports, was undergoing divorce and had lots of conflicts with her family.

Mrs. A. is a 50-year old woman who was categorized to the resilient group. This patient reported intense pain and high impairment, but during history taking, the story of her symptoms fades into the background. Rather, she tells of the sweltering conditions during her childhood and the horrific abuse by her uncle experienced repeatedly. She says she turned to uncontrolled eating habits that led to obesity which she experienced as shelter against environmental challenges. Despite her adverse experiences, she easily achieved good grades at school and was basically happy in her life. She works as a social educator to give back some of her life experience to young people and seems to be reflective and calm.

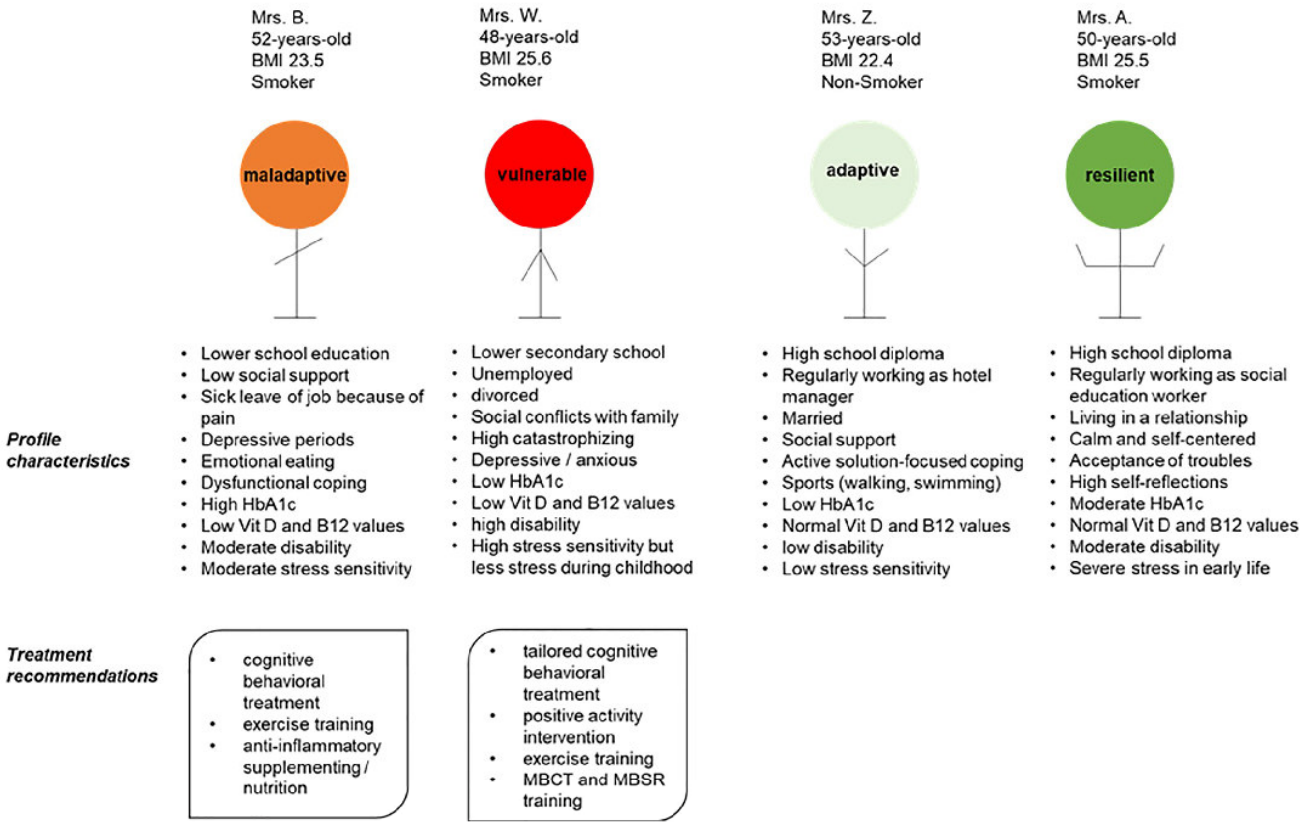

Fig 6. Cluster-specific case description and treatment options. Four profiles of FMS patients per cluster were selected, and possible interventions are listed based on cluster characteristics and missing resources of the vulnerable and maladaptive cluster to improve the severe and maladaptive phenotypes. Abbreviations: MBCT = Mindfulness-Based Cognitive Therapy. MBSR: Mindfulness-Based Stress Reduction.

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The commonality in each of these four cases is that the individual is experiencing pain and further symptoms that have an impact on daily life. The way to cope strongly modulates the impact.

Discussion

We determined four factors potentially contributing to the heterogeneous clinical profiles in a well-defined cohort of 118 FMS patients. Based on these factors we were able to categorize the patients into four clusters distinguished by FMS related disability, coping, psychosocial and somatic factors, which we suggest may be related to resilience or vulnerability.

Despite advances in the understanding of pain mechanisms, chronic pain patients are still treated as a homogeneous group, with insufficient treatment success. Several attempts have been made to categorize chronic pain patients. Most cluster studies were focused on psychosocial parameters and personality traits.

Several authors have performed cluster analyses to identify subgroups among fibromyalgia patients [22–27]. Most of the previously published cluster studies in FMS patients performed clustering without previous factoring [23, 27, 28]. We carried out PFA to reduce the number of variables, to focus more on the factors that might be responsible for vulnerability or higher

resistance to adversity in our cohort, and to identify valid factors that might be responsible for the variability within the cohort.

We included a wide range of psychosocial and somatic variables, because resilience is composed of a variety of small-scale aspects. Initially, more physiological data were included into the analysis, derived from QST, PREP measurements, clinical examination and history, and skin biopsy (IENFD). In the first run, only QST and PREP appeared to have an influence on within-group variability. Unexpectedly, IENFD derived from proximal and distal leg did not emerge as loadings on any factor, although they were previously shown to relate to disease severity [58]. It could be that nerve pathology has an influence on the severity of the disease, but that the way to cope with this severity is decisive for the functioning in everyday life. Therefore, coping and mental parameters statistically emerge as variance influencing factors.

Despite the small effect sizes between the clusters in factor "pro-inflammatory cytokines", these data influenced the variability of the cohort and were important enough to exclusively load on factor 4. If indeed higher levels of IL-4 and IL-10, as in cluster B and D, had a protective influence on pain, only cluster B would benefit from this constellation, with low disability scores and low pain scores. One caveat is that we only assessed cytokine mRNA and not protein.

With a four-factor solution including the factors (1) "affective load", (2) "coping", (3) "physical functioning", and (4) "pro-inflammatory cytokines", we achieved a clear separation of the factor loadings to thematic groups in the final run of the PFA. The highest loadings on factor 1 were anxiety and pain catastrophizing that are well-known risk factors and promote vulnerability [52, 53]. Coping items were the loadings of factor 2, leading to the name "coping strategies". Factor 3 was clearly determined by a combination of items regarding impact of pain and FMS symptoms on daily activities resulting in the label "physical functioning". Interestingly, the active coping strategy "pain behavior" loaded on the same factor as the pro-inflammatory cytokines, supporting the connection between pain behavior and pro-inflammatory cytokines as shown in animal models [54, 55] and in pain patients [56].

The following clustering divided the cohort into four clusters. A four-cluster solution provided the best fit for our data as in most other studies [4, 6, 7, 22, 28, 57, 58]. The al-Ándalus project [24] classified 486 FMS patients based on eight factors into five clusters named by the grade of performing as adapted, fit, poor performer, positive and maladapted. Our analysis resulted in a maladaptive, adaptive, vulnerable and resilient cluster, distinguished by the factors affective load, coping, physical functioning and pro-inflammatory cytokines. Most studies used symptom severity and variability of psychological factors to separate groups differing in resilience [25, 59], whereas in our study affective load and its control by specific coping and the cytokine balance determined the difference between resilient and vulnerable clusters. Coping is a variable that might be changed by a specific therapy and has a huge influence on physiological and psychological variables, in turn [60, 61]. The factors affective load and coping were the most discriminative factors in our cohort and decisive for a low or high FMS related disability and quality of life, confirmed by moderate to large effect sizes, indicating a minor role of somatic factors.

The choice of the right type of coping is the key to increase quality of life and resilience in aversive life periods [62, 63]. Problem-focused coping like increasing activity or seeking of social support and emotion-focused coping (e.g. positive reinterpretation) are two types of coping resulting in higher quality of life. Cluster B combines these two effective strategies (activity increase, self-instructions, ignore) resulting in low disability and ultimately in adaptation on FMS symptoms. High scores in negative affect including anxiety, depression and pain catastrophizing and the missing control of these negative emotions by coping strategies that are focused on emotions, behavioral or mental disengagement [64] suggest vulnerability in

cluster C. The reason for combining specific coping strategies also depend on peoples' experiences in childhood, on personality, inflammatory state, gender and age [62, 65–68].

Traumatic events during childhood are a well-known risk factor for FMS that also has the potential to alter brain activation patterns [69]. Cognitive coping mechanisms including reappraisal were identified to contribute to resilience in children with a history of maltreatment [70]. Patients in cluster D showed the highest scores in almost all types of psychoemotional stress the CTQ-D is evaluating and exclusively most frequently used reinterpretation as coping strategy. Reinterpretation or reappraisal is a well-known cognitive technique to modulate and control negative emotions resulting in reduced subjective experience of emotions and physiological response [71]. Positive emotions and cognitive reappraisal promote adaptive coping strategies and resilience [72]. The ability to cope with this technique normally needs professional support. Most patients within cluster D (8 of 21) and cluster B (18 of 40) never had an intervention by a psychotherapist or psychiatrist (see S2 Table). Thus, the subjects in cluster D who were exposed to stressful events in early life had resources to activate resilient coping strategies, therefore this cluster was termed as able to cope in a "resilient" way with the experienced adversity.

Resilience is a complex phenomenon. Many scientists regard resilience as a personality trait [73], whereas others consider it as a process of adaptation during a critical time [74, 75]. We speculate that cluster D has personal resources to actively deal with intense pain and high traumatic events, indicating a resilient trait, whereas cluster B might be best adapted and has learned how to effectively cope with FMS. The chosen labels might be debatable, but in our judgement, they reflect the different emerged profile groups in the best way. In contrast to [24], we did not include a predefined factor "resilience" by factor loadings of questionnaires such as emotional repair (TMMS-24), positive affect (PANAS) and optimism (LOT-R), focusing on the psychological ability of resistance. Our strategy was to define resilient strategies of coping with FMS that might be used to change a "non-resilient" into a more resilient phenotype and open new potential ways of treatment.

Clusters may offer the possibility for individualized therapies. Based on profile specific characteristics of the unfavorable clusters, we suggest individualized treatment options based on known effects on the immune system and on mental health. Besides drug therapy, there are potential alternative anti-inflammatory and microbiome-influencing therapies [12, 53, 62, 76–80] to support the immune system and mental health, cognitive behavioral and mindfulness based (MBSR / MBCT) therapies to support adaptive coping [81, 82], and exercise training with beneficial effects on fatigue, pain and mood [83, 84]. Positive activity interventions (PAI) that promote positive affect, acceptance, feeling of support and coherence and show a long-term persistent effect on pain relief and FMS related symptoms like depressive mood might be helpful [85].

A general limitation of the study may be that although patient recruitment followed strict criteria, our cohort might exclude the very vulnerable individuals who were not willing or who were not able to participate in this series of tests on a specific day and far away from their familiar environment.

Conclusions

Our FMS patient cohort consists of four clusters defined as maladaptive, adaptive, vulnerable, and resilient. Crucial for the resilient cluster were resilient coping with focus on cognitive strategies like reappraisal, associated with low depression scores, low values in other psychopathological symptoms despite the high frequent experience of high traumatic stress in early life, and high relative gene expression of the anti-inflammatory cytokine IL-10 compared to

the vulnerable cluster. Resilient coping seems to consist of a combination of personal characteristics and learned behavior and might be trained based on the described coping pattern of the resilient cluster.

Supporting information

S1 Fig. Overview of the measurements during the larger study on FMS.
(TIF)

S2 Fig. Flow chart of patient recruitment of this study.
(TIF)

S3 Fig. Scree plot (A) before and (B) after predefining the number of factors.
(TIF)

S4 Fig. Dendrogram of the cluster analysis and the marked four cluster.
(TIF)

S1 Table. Exclusion and inclusion criteria of patient recruitment.
(DOCX)

S2 Table. Sociodemographic, electrophysiological, laboratory, psychosocial, and somatic characteristic differences among cluster.
(DOCX)

S3 Table. Adequacy tests of the principal axis factoring analysis.
(DOCX)

S4 Table. Data of variance of emerged factors with eigenvalues more than 1 observed between predicting variables.
(DOCX)

S5 Table. One-way ANOVA to test the significance between factors between the subgroups.
(DOCX)

S6 Table. Post-hoc analysis between subgroups and factors.
(DOCX)

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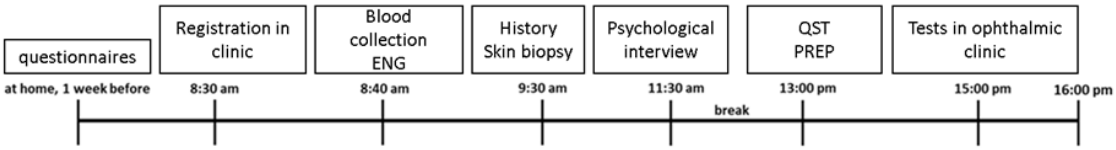
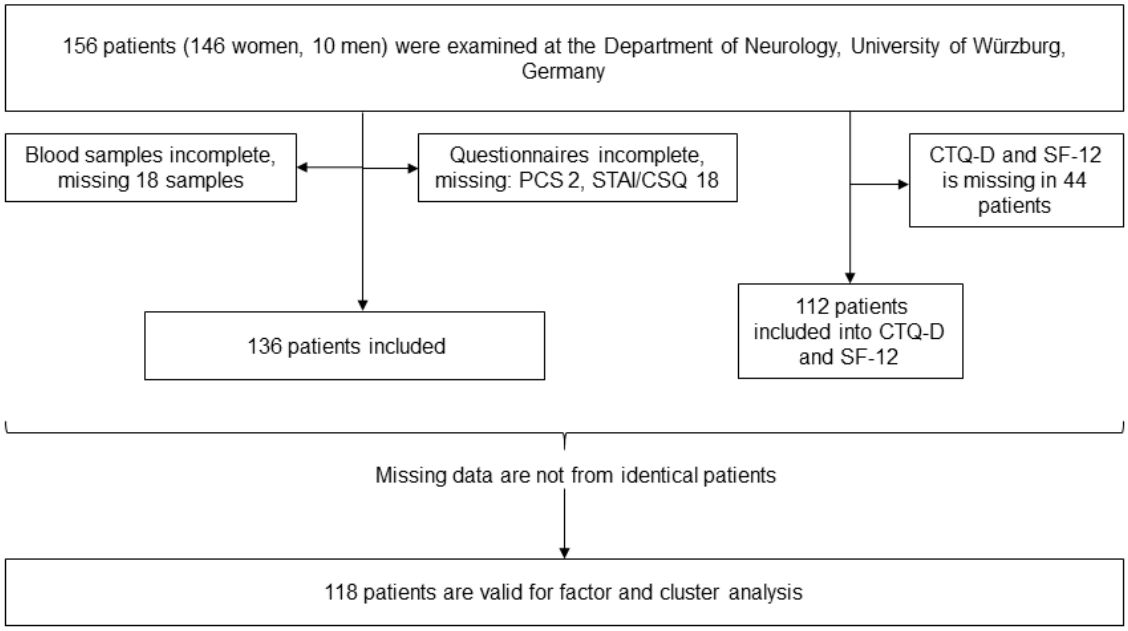
Supporting information

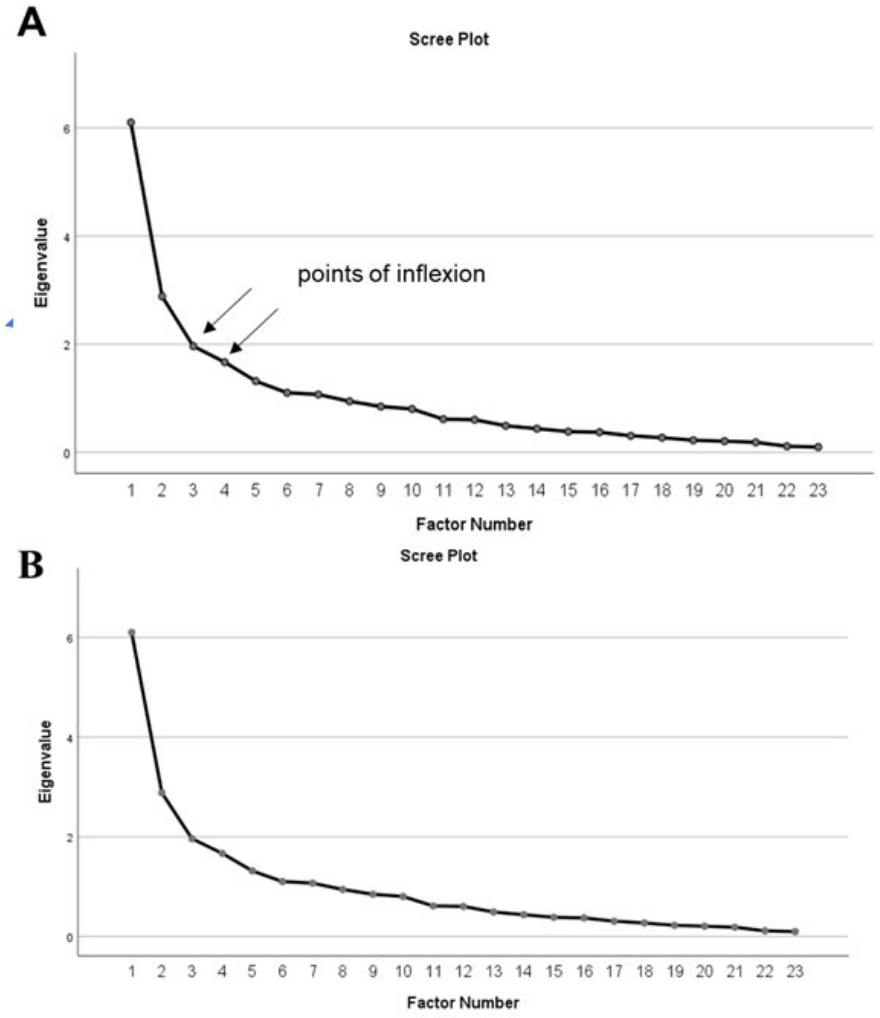
S1 Fig: Overview of the measurements during the larger study on FMS.



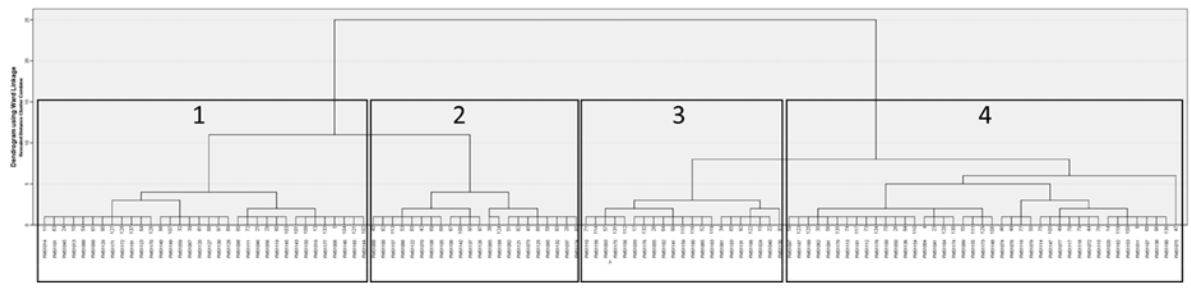
S2 Fig: Flow chart of patient recruitment of this study.



S3 Fig: Scree plot (A) before and (B) after predefining the number of factors.



S4 Fig: Dendrogram of the cluster analysis and the marked four cluster.



S1 Table: Exclusion and inclusion criteria of patient recruitment.

inclusion criteria
• male and female patients • at least 18 years old • medically confirmed diagnosis of fibromyalgia syndrome according to the ACR criteria of 1990 and 2010 • willingness to participate in all tests during the study and to travel to the neurological clinic in Würzburg
exclusion criteria
• other possible differential diagnoses excluded explaining the pain (e.g. rheumatologic, orthopedic) • other and additional pain sources (e.g. pain due to arthritis) • abnormalities in routine blood tests • diabetes • polyneuropathy • ongoing legal proceedings (e.g. regarding health assurance) • psychiatric diseases • cancer (in the last 5 years) • permanent wearing of hard contact lenses • eye surgery / eye diseases • allergies to local narcotics • drug or alcohol abuse • epilepsy • pacemaker

S2 Table: Sociodemographic, electrophysiological, laboratory, psychosocial, and somatic characteristic differences among cluster.

characteristics	**maladaptive cluster A**		**adaptive cluster B**		**vulnerable cluster C**		**resilient cluster D**	
	M[a]	**SD[b]**	**M[a]**	**SD[b]**	**M[a]**	**SD[b]**	**M[a]**	**SD[b]**
N[c]	**35**		**40**		**22**		**21**	
Sociodemographic data								
gender[d]	3♂/ 38♀		4♂/ 30♀		20♀		22♀	
age [years]	52.1	10.0	52.4	9.6	48.5	9.6	50.0	6.4
Weight [kg][e]	69.8	10.6	66.3	9.8	75.8	14.3	75.5	15.7
Height [cm][f]	163.0	5.0	164.4	6.6	168.1	3.9	164.9	7.9
BMI[g]	23.6	3.6	22.4	3.3	25.6	4.8	25.5	5.3
Highest graduation								
Lower secondary school	7		6		6		3	
Secondary school	19		20		12		14	
High school	5		7		2		3	
University	4		7		2		1	
Employment status [N][c]								
Regularly working	15		27		7		10	
Sick leave	3		2				2	
Sick leave because of pain	3		2		4		3	
Retired	5		6		3		1	
Retired because of pain	5		1		5		5	
Unemployed	4		1		3			
Time since diagnosis [years]	6.4	4.6	5.4	5.1	3.9	3.0	5.5	4.5
Duration of pain due to the disease [years]	14.0*	38.0*	6.0*	25.0*	12.0*	45.0*	11.0*	42.0*

Smoker [N][c]	6		5		6		3	
Family history [N][c]								
Chronic pain	13		22		11		9	
Neurological disorder	4		5		7		5	
Affective disorder	8		3		3		3	
Psychological/psychiatric treatment [N][c]								
Never	12		18		6		8	
Currently	11		12		14		7	
In the past	12		10		2		6	
pain duration [years]	14.0*	38.0*	6.0*	25.0*	12.0*	45.0*	11.0*	42.0*
Questionnaire data								
NPSI-D sum score[h]	0.4*	0.7*	0.3	0.1	0.4	0.2	0.5	0.1
GCPS-D pain intensity[i]	74.4	8.8	54.3	9.1	73.4	8.1	70.5	7.9
GCPS-D disability[i]	61.4	16.0	39.5	16.1	69.2	14.7	54.5	19.0
GCPS-D grade[i]	2.0*	3.0*	1.0*	1.0*	2.0*	2.0*	2.0*	2.0*
PCS-D sum score[j]	20.9	6.9	17.9	9.7	35.6	8.0	13.0*	31.0*
CES-D sum score[k]	23.1	7.1	16.0	8.7	36.6	8.8	19.0*	38.0*
FIQ-D sum score[l]	48.2	8.1	36.6	9.8	57.4	8.4	50.5	8.8
STAI-S sum score[m]	48.2	10.2	38.0*	38.0*	64.6	9.1	42.0	9.8
STAI-T sum score[m]	48.1	9.0	43.4	9.7	62.9	7.6	42.2	11.4
CSQ-D distraction[n]	13.5	6.2	17.0	5.4	9.1	5.3	22.0	7.2
CSQ-D reinterpretation[n]	3.5*	21.0*	4.0*	22.0*	1.0*	9.0*	10.5	7.4
CSQ-D self instructions[n]	20.0*	32.0*	23.0*	25.0*	17.2	6.1	27.8	3.4
CSQ-D ignore[n]	13.3	6.5	15.8	7.4	11.1	5.8	24.0*	17.0*
CSQ-D hoping praying[n]	7.9	4.6	9.6	4.6	9.0	6.9	15.0*	21.0*
CSQ-D catastrophizing[n]	16.2	6.1	14.4	7.4	25.9	5.0	12.9	9.1

CSQ-D activity increase[n]	18.0*	25.0*	19.4	4.6	14.8	3.9	21.5	5.5
CSQ-D pain behavior[n]	19.5*	25.0*	20.9	4.7	18.5	32.0	19.6	5.0
CSQ-D pain control[n]	2.1	1.3	3.0*	3.0*	2.0*	3.0*	4.0*	5.0*
CSQ-D pain reduction[n]	2.0*	4.0*	3.0*	3.0*	2.0*	4.0*	2.0*	4.0*
CTQ-D emotional neglect[o]	8.0*	18.0*	7.0*	14.0*	13.8	6.1	12.8	5.6
CTQ-D sexual abuse[o]	6.0*	6.0*	5.0*	15.0*	7.5*	16.0*	9.3	4.2
CTQ-D physical abuse[o]	5.0*	22.0*	5.0*	1.0*	5.0*	20.0*	8.8*	6.5*
CTQ-D emotional abuse[o]	10.9	4.8	10.4	3.9	18.0	6.0	14.7	5.5
CTQ-D physical neglect[o]	7.0	2.4	6.0*	5.0*	11.6	5.0	10.2	3.7
CTQ-D trivialization[o]	0.0*	3.0*	0.0*	3.0*	0.0*	1.0*	0.0*	2.0*
PCR results of cytokines								
rel. gene expression IL6[p]	2.0*	1.2*	2.3*	8.7*	1.0*	5.9*	2.0*	1.2*
rel. gene expression TNF[p]	1.2*	11.7*	1.6*	6.5*	0.5*	3.4*	1.4*	4.9*
rel. gene expression IL4[p]	1.5	9.0	0.9*	3.8*	2.1*	7.2*	0.7	5.2
rel. gene expression IL10[p]	1.1*	5.2*	0.6*	4.3*	0.6*	3.9*	0.6*	3.4*
Laboratory measurements								
HbA1c [%][q]	5.4	0.3	5.3	0.2	5.4	0.5	5.5	0.5
oGGT[r]								
Before oGGT [mg %]	95.6	11.2	93.2	8.8	100	0.19	98.3	8.8
oGGT (1h value) [mg %]	148.1	39.4	153.7	38.1	146.7	37.8	145.8	28.3
oGGT (2h value) [mg %]	127.0	31.3	116.9	19.6	124.9	23.7	119.9	15.6
Vitamin B12 [pg/ml]	449.5	140.5	536.6	206.5	560.9	391	554.7	242
TSH [mIU/l][s]	3.2	8.9	1.7	1.3	1.6	0.8	2.1	1.4
Vitamin D [µg/l]	27.5	8.9	33.6	10.7	25.6	7.1	26.2	9.9

Clinical examination								
Pain character [%]								
Tearing	3		4		2		2	
Pressing	12		12		13		13	
Burning	19		13		11		4	
Muscle sourness	9		12		4		5	
Stabbing	12		9		3		5	
Pain distribution type								
Proximal	10		10		7		3	
Distal	1		0		2		0	
Whole body	23		30		11		17	
Paresthesia								
Current pain intensity [NRS scale 0 - 10][t]	6.0	1.6	4.2	1.5	5.8	1.8	5.6	1.8
Electrophysiological data - QST[u]								
CDT	-2.7	2.1	-2.9	4.0	-4.2	2.7	-4.0	2.7
WDT	6.6	3.8	7.6	3.8	7.2	3.7	7.8	2.4
TSL	10.6	7.2	12.0	6.8	11.8	5.6	12.0	4.5
PHS	0.4	1.0	0.4	1.0	0.7	1.1	0.0	0.8
CPT	18.3	7.6	17.9	6.6	16.3	6.1	16.2	7.2
HPT	44.1	3.3	45.7	2.9	44.8	2.9	46.0	1.9
MDT	3.9	4.8	3.9	3.8	4.0	4.5	2.1	3.5
MPT	62.3	58.5	151.4	156.6	63.9	111.3	74.5	59.1
MPS	5.0	9.5	3.9	5.4	4.4	4.7	3.7	5.5
DMA	0.5	2.0	0.0	0.1	0.3	1.1	0.0	0.0
WUR	2.9	1.7	3.1	1.8	2.8	1.5	3.7	3.1

VDT	6.0	1.1	6.4	0.9	6.4	1.2	6.3	1.4
PPT	336.2	87.9	384.1	171.9	380.6	157.6	477.7	133.7
PREP[v]								
Face N1 [ms]	137.0	10.3	135.2	12.4	136.2	14.5	121.4	36.4
Face P1 [ms]	184.9	10.7	183.3	12.6	178.6	18.1	161.4	49.8
Face PPA [mV]	-	-	-	-	-	-	-	-
Foot N1 [ms]	144.9	57.9	132.5	55.7	143.3	61.4	118.4	66.7
Foot P1 [ms]	182.7	73.4	162.1	66.3	179.1	76.1	149.1	88.4
Foot PPA [mV]	-	-	-	-	-	-	-	-
NFD [no/mm2]	22.1	6.8	25.9	6.2	23.5	6.6	22.7	7.4
NBD [no/mm2]	64.8	34.7	76.4	40.3	85.1	38.1	77.7	32.8
NFL [mm/mm2]	12.8	3.6	14.2	3.1	13.8	3.5	13.6	3.7
skin biopsy[w]								
IENFD lower leg [fibers/mm]	8.5	3.5	9.2	3.4	8.2	3.4	7.4	3.0
IENFD upper thigh [fibers/mm]	7.1	2.7	7.8	3.1	6.4	2.7	5.7	3.6

[a] M = mean; [b] SD = standard deviation; [c] N = number; [d]gender: ♂: men; ♀: women; [e]weight in kg = kilogram; [f]height in cm = centimetre; [g]BMI = body mass index; [h]NPSI-D = German version of the neuropathic pain scale inventory; [i] GCPS-D = three subscales of the German version of the graded chronic pain scale; [j]PCS = German version of the pain catastrophizing scale; [k] CES-D = German version of the center of epidemiological studies general depression scale; [l]FIQ-D = German version of the fibromyalgia impact questionnaire; [m]subscales trait (T) and state (S) of the German version of the state/trait anxiety inventory (STAI-G); [n] CSQ-D = ten subscale scores of the German version of the coping strategies questionnaire; [o]CTQ-D = six subscale scores of the German version of the childhood trauma questionnaire; [p]relative gene expression values of four cytokines: IL = interleukin, TNF = tumor necrosis factor; [q]HbA1c = glycosylated haemoglobin; [r]oGTT = oral glucose tolerance test; [s]TSH = thyroid-stimulating hormone; [t]NRS = numeric rating scale; [u] twelve values of QST (= quantitative sensory testing): CDT = cold detection threshold, WDT = warm detection threshold, TSL = capability to identify temperature alterations, thermal sensory limen, PHS = paradoxical heat sensation, CPT = cold pain threshold, HPT = heat pain threshold, MDT = mechanical detection threshold, MPS = mechanical pain sensitivity, DMA = dynamic mechanical allodynia, WUR = wind up ratio, VDT = vibration detection threshold, PPT = pressure pain threshold

[v]three values for PREP (= pain-related evoked potential measurements), each for face and foot: N1 = first negative peak, P1 = first positive peak, PPA = peak-to-peak amplitudes; [w]IENFD = intraepidermal nerve fibre density (derived from skin biopsies of lower and upper leg). [*]All not normally distributed data are given as median (MED) and range (R) respectively.

S3 Table: Adequacy tests of the principal axis factoring analysis.

Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy		0.8
Bartlett's test of sphericity	**chi[2]**	1322.3
	df[a]	253
	p[b]	0.0

[a]df = degree of freedom; [b]p value of significance

S4 Table: Data of variance of emerged factors with eigenvalues more than 1 observed between predicting variables.

		initial Eigenvalues	
factor	**total**	**% of variance**	**cumulative %**
1	6.1	26.5	26.5
2	2.9	12.5	39.1
3	2.0	8.5	47.6
4	1.7	7.3	54.9
5	1.3	5.7	60.6
6	1.1	4.8	65.4
7	1.1	4.7	70.0

Extraction method: principal axis factoring.

S5 Table: One-way ANOVA to test the significance between factors between the subgroups.

factor		sum of squares	df[a]	mean square	F[b]	p[c]
affective load	between groups	55.1	3	18.4	38.1	0.001[d]
	within groups	54.9	114	0.5		
	total	110.1	117			
coping	between groups	48.3	3	16.1	33.9	0.001[d]
	within groups	54.1	114	0.5		
	total	102.4	117			
Physical functioning	between groups	55.2	3	18.4	55.9	0.001[d]
	within groups	37.6	114	0.3		
	total	92.8	117			
pro-inflammatory cytokines	between groups	5.9	3	2.0	3.4	0.05[e]
	within groups	66.8	114	0.6		
	total	72.7	117			

[a]df = degree of freedom; [b]F = value of test statistic ; [c]p = level of significance; [d]Level of significance is p < 0.001; [e]level of significance is p < 0.05.

S6 Table: Post-hoc analysis between subgroups and factors.

Cluster		Games - Howell, * p < 0.05			
A	**B**	*		*	*
	C	*	*		
	D	*	*		*
B	**A**	*		*	
	C	*	*	*	
	D		*	*	
C	**A**	*	*		
	B	*	*	*	
	D	*	*		
D	**A**	*	*		
	B		*	*	
	C	*	*		
factor		**affective load**	**coping**	**physical functioning**	**pro-inflammatory cytokines**

** significant differences are marked.*

Manuscript 3

MiR103a-3p and miR107 are related to adaptive coping in a cluster of fibromyalgia patients.

Alexandra Braun, Dimitar Evdokimov, Johanna Frank, Claudia Sommer, Nurcan Üçeyler
PLoS ONE (2020)

Manuscript 3: **Braun A, Evdokimov D, Frank J, Sommer C, Üçeyler N. MiR103a-3p and miR107 are related to adaptive coping in a cluster of fibromyalgia patients. PLoS One. 2020 Sep 17;15(9):e0239286. doi: 10.1371/journal.pone.0239286. PMID: 32941517; PMCID: PMC7498021.**

Abstract

Background: MicroRNA (miRNA) mainly inhibit post-transcriptional gene expression of specific targets and may modulate disease severity.

Objective: We aimed to identify miRNA signatures distinguishing patient clusters with fibromyalgia syndrome (FMS).

Subjects and methods: We previously determined four FMS patient clusters labelled "maladaptive", "adaptive", "vulnerable", and "resilient". Here, we cluster-wise assessed relative gene expression of miR103a-3p, miR107, miR130a-3p, and miR125a-5p in white blood cell (WBC) RNA of 31 FMS patients and 16 healthy controls. Sum scores of pain-, stress-, and resilience-related questionnaires were correlated with miRNA relative gene expression. A cluster-specific speculative model of a miRNA-mediated regulatory cycle was proposed, and its potential targets verified by the online tool "target scan human".

Results: One-way ANOVA revealed lower gene expression of miR103a-3p, miR107, and miR130a-3p in FMS patients compared to controls ($p < 0.05$). Follow-up post-hoc tests indicated the highest peak of gene expression of miR103a-3p for the adaptive cluster ($p < 0.05$), i.e. in patients with low disability in all symptom categories. Gene expression of miR103a-3p correlated with FMS related disability and miR107 with the score "physical abuse" of the trauma questionnaire ($p < 0.05$). Target scan identified sucrose non-fermentable serine/threonine protein kinase, nuclear factor kappa-b, cyclin dependent kinase, and toll-like receptor 4 as genetic targets of the miR103a/107 miRNA family.

Conclusion: We show an association between upregulated gene expression of miR103a, tendentially of miR107, and adaptive coping in FMS patients. Validation of this pair of miRNA may enable to identify a somatic resilience factor in FMS.

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PLOS ONE

RESEARCH ARTICLE

MiR103a-3p and miR107 are related to adaptive coping in a cluster of fibromyalgia patients

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Competing interests: The authors have declared that no competing interests exist.

Conclusion

We show an association between upregulated gene expression of miR103a, tendentially of miR107, and adaptive coping in FMS patients. Validation of this pair of miRNA may enable to identify a somatic resilience factor in FMS.

Introduction

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain and additional symptoms such as depressive mood, sleep disorders, and gastrointestinal problems [1]. The pathophysiology of FMS is incompletely understood, but there is evidence that higher expression of pro-inflammatory cytokines and experience of traumatic events during childhood may be associated with the development and severity of FMS [2, 3].

MicroRNA (miRNA) are small noncoding RNA that mostly function in post-transcriptional regulation by translational inhibition, silencing and mRNA destabilization of specific target genes [4]. MiRNA are involved in the pathophysiology of inflammation, pain, and mood disorders [5] and may characterize patient subgroups in heterogeneous disorders [6].

In FMS patients, the expression of miRNA has been investigated in body fluids [7–10]. For instance, miR107 and miR103a-3p expression was reduced in blood samples of FMS patients compared to healthy controls, and miR103a-3p correlated with pain and sleep duration [11]. Given the vast phenotypic heterogeneity of FMS, we previously conducted a factor analysis and labelled clusters as "maladaptive", "adaptive", "vulnerable", and "resilient" [12]. The main characteristics of these clusters were "dysfunctional coping and pro-inflammatory cytokine pattern", "active coping and low disability", "high catastrophizing and high negative affect", and "resilient coping (reappraisal) with high traumatic stress". We now asked whether miRNA signatures might distinguish these clusters.

Studies in patients suffering from inflammatory (e.g. preeclampsia) and (post-traumatic) stress-related syndromes (e.g. post-traumatic stress disorder) identified some miRNA and their genetic targets, e.g. the miR103a/107 miRNA family as involved in different pathways, e.g. the STAT6/IL4 anti-inflammatory pathway [13] or the SNRK / NF-κB / p65 signaling pathway [14]. MiR107 is linked to childhood trauma [15] and has a regulatory role in inflammation [16, 17] by targeting cycline dependent kinases (CDK) and toll like receptors (TLR) [18, 19]. Activated TLR4 was shown to induce secretion of tumor necrosis factor-alpha (TNF) in patients with renal sepsis [20] and to attenuate adaptive thermogenesis in obese mice via endoplasmatic reticulum stress. Pro-inflammatory processes are known to be a driver of chronic pain [21] and have an impact on mental issues [22].

Based on these findings, we hypothesized that an upregulation of miR103a-3p, miR107, miR130a-3p, and miR125a-5p might promote adaptive coping in the adaptive and resilient cluster of our FMS cohort. We report on higher gene expression of miR103a-3p and miR107 in the adaptive cluster of FMS patients compared to the maladaptive, vulnerable, and resilient cluster. Our data may facilitate the discovery of somatic factors of resilience and adaptation in FMS patients in further studies.

Materials and methods

Subjects and ethics

FMS patients and healthy controls were recruited between 2014 and 2018 at the Department of Neurology of the University Hospital Würzburg, Germany for a large-scale study [23]. For our study, we firstly included 32 FMS patients (8 per cluster) and blood samples of 25 healthy controls that were available from the large-scale study. During the analysis, only data of 31 patients and 16 controls were valid. We included male and female patients ≥18 years, who were diagnosed with FMS according to the ACR criteria of 1990 and 2010 [1, 24]. Subjects with other possible differential diagnoses for pain (e.g. rheumatologic, orthopedic) or with other and additional pain sources (e.g. pain due to arthritis) were excluded. Further exclusion criteria were diabetes mellitus, polyneuropathy, psychiatric conditions, cancer, epilepsy, drug and alcohol abuse, allergies to local anaesthetics, abnormalities in routine blood tests, and ongoing legal issues (e.g. regarding health assurance). Our study was approved by the Würzburg Medical School Ethics Committee (No. 135/15). All study participants provided written informed consent before enrollment. Data on clinical examination, detailed laboratory and electrophysiological measurements are summarized in S1 Table (see S1 Table).

Questionnaire assessment for clinical data

All patients and controls underwent neurological examination and were assessed with questionnaires for pain, impairment due to FMS symptoms, and psychopathological variables such as depression, anxiety, and pain catastrophizing. We used the German versions of the following questionnaires: The Neuropathic Pain Symptom Inventory (NPSI-G) [25], the Graded Chronic Pain Scale (GCPS) [26], the Fibromyalgia Impact Questionnaire (FIQ) [27], the Center of Epidemiological Studies General Depression Scale (CES) [28], the State-Trait Anxiety Inventory (STAI-G) [29], the Pain Catastrophizing Scale (PCS) [30], and the Childhood Trauma Questionnaire (CTQ) [31].

Blood withdrawal, white blood cell extraction, and miRNA isolation

Venous whole blood was drawn from all patients and 25 healthy controls as previously described in [12]. Data of 31 patients and 16 controls were valid for the analysis. After the extraction of the white blood cell (WBC) fraction, all samples were stored at -80˚C until further processing. The manufacturer's protocol of the miRNeasy Mini kit (Qiagen, Hilden; ermany) was followed to isolate miRNA from WBC samples and the RNA concentration was measured by Nanodrop Photometer Pearl® (Implen, München, Germany).

Selection criteria for candidate miRNA

MiRNA were selected based on literature search. We used "inflammation", "chronic stress", and "resilience" as search terms and cross-compared results for miR103a-3p, miR107, miR130a-3p, and miR125a-5p in public data bases (miRbase [32], NCBI [33]). We then compared our results with those of a previous miRCURY LNA miRNA array taken by the profiling service of Exiqon (Exiqon Services, Vedbaek, Denmark) [9] and decided on four miRNA that had survived Benjamini-Hochberg correction ($p < 0.05$) and showed ≥ 60fold log-fold change.

cDNA synthesis and SYBR green real-time PCR (qRT–PCR)

Five ng of the isolated miRNA was appropriate for the cDNA synthesis which was conducted by following the manufacturer´s protocol of the miRCURY LNA RT Kit (Qiagen, Hilden,

Germany). Before starting the SYBR Green qRT-PCR, four mL of synthesized cDNA was diluted (1:80). The miCURY LNA miRNA PCR Assay (Qiagen, Hilden, Germany) provided specific reference primer sets for amplification of the selected miRNA. Specific miCURY LNA assays were labeled with the following assay IDs (in brackets) for all miRNA assessed: hsa-miR 107 (5′AGCAGCAUUGUACAGGGCUAUCA, MIMAT0000104), hsa-miR 103a-3p (5′AGCAGCAUUGUACAGGGCUAUGA, MIMAT0000101), hsa-miR 130a-3p (5′CAGUGCAAUGUUAAAAGGGCAU, MIMAT0000425), hsa-miR 125a-5p (5′UCCCUGAGACCCUUUAACCUGUGA, MIMAT0000443). Five seconds rRNA (5S) was used to normalize the expression level of the derived miRNA and was received as PCR assay (YP00203955). Each target sample was quantified in triplicate, the 5sRNA was measured in duplicate. RNA free water was used as negative control. A previous run of the control samples determined a calibrator as reference sample to ensure the inter-plate comparability. The relative gene expression was evaluated by the delta-delta CT method [34]. This method directly uses the CT value (threshold cycle at which the fluorescence level reaches a certain amount) to calculate fold changes in miRNA gene expression among groups related to its reference sample and normalized by its individual 5sRNA expression. Lower deltaCT values represent sample detection at earlier PCR cycles and indicate higher gene expression. We calculated 1/deltaCT to illustrate higher values as higher gene expression (compare [35]).

Statistical analysis

IBM SPSS Statistics 26 software (Ehningen, Germany) was used for statistical analysis and GraphPad Prism (San Diego, CA, USA) for the graphical design. Data distribution was tested with the Shapiro-Wilk test and by observing data histograms. Non-normally distributed data of the questionnaires NPSI, GCPS, CTQ (subscales "sexual abuse", "physical abuse", and "trivialization"), and of the gene expression analysis are given as median (MED) and range (R). The normally distributed data of all other questionnaires are presented as mean (M) and standard deviation (SD). Spearman correlation tests analyzed correlation between relative gene expression and selected clinical scores of questionnaires. One-Way ANOVA and post-hoc tests (Games-Howell) analyzed group differences between patients and controls, and among cluster. Data are significant at $p < 0.05$.

Results

Complete data sets of 31 patients and 16 controls were suitable for PCR analysis and questionnaire assessment (see S1 Fig).

Group characteristics

Table 1 summarizes demographic characteristics and questionnaire data of the study cohort.

Relative gene expression of miR103a-3p, miR107, miR125a-5p, and miR130a-3p in FMS patients and healthy controls

One-way ANOVA and post-hoc tests revealed that miR103a-3p, miR107, miR125a-5p and miR103a-3p were differently expressed when comparing FMS patients and healthy controls ($p < 0.05$, Fig 1).

Relative gene expression of miR103a-3p, miR107, and miR130a-3p was lower in patients with a large, small and medium effect size, while the relative gene expression of miR125a-5p was higher in FMS patients with a medium effect (Table 2 and Fig 1).

Table 1. Demographic characteristics and questionnaire data.

	Maladaptive cluster	Adaptive cluster	Vulnerable cluster	Resilient cluster
N	8	8	7	8
Age	52.4	53.7	47.2	49.4
NPSI-D*	47 ± 0.52	28 ± 0.21	42 ± 0.34	48 ± 0.18
FIQ-D	50.1 ± 9.8	35.8 ± 3.4	54.9 ± 9.4	48.9 ± 5.6
GCPS_grade*	2 ± 2	2 ± 2	2 ± 2	2 ± 0
CES-D	21.1 ± 8.9	13.0 ± 7.4	30.2 ± 8.3	17.1 ± 3.5
PCS-D	21.9 ± 6.8	8.5 ± 6.8	29.6 ± 6.0	10.2 ± 3.2
STAI-S	47.0 ± 8.6	39.5 ± 7.3	63.6 ± 7.3	38.7 ± 9.7
STAI-T	47.1 ± 8.2	43.3 ± 7.5	62.2 ± 8.3	37.8 ± 7.7
CTQ-D				
[N = 22][a]	[7]	[4]	[5]	[6]
emotional neglect	10.3 ± 5.4	7.3 ± 1.3	12.4 ± 6.0	8.33 ± 2.7
sexual abuse*	7 ± 17	5.5 ± 4	7 ± 11	5.7 ± 8
physical abuse*	9.7 ± 7.0	5.0 ± 0.0	6.2 ± 2.7	5.7 ± 1.0
emotional abuse	13.6 ± 3.3	10.5 ± 4.2	16.0 ± 4.1	14.2 ± 3.2
physical neglect	7.4 ± 2.1	6.5 ± 2.4	8.8 ± 4.3	8.5 ± 1.8
trivialization*	0 ± 1	0 ± 0	0 ± 0	0 ± 0

*not normally distributed data, MED (= median) ± R (= range); [a] CTQ-D questionnaire was added during the study and represents data of 22 patients.
Based on data obtained in our previous study [12], a cluster classification is included in Table 1 reflecting cluster-specific differences.

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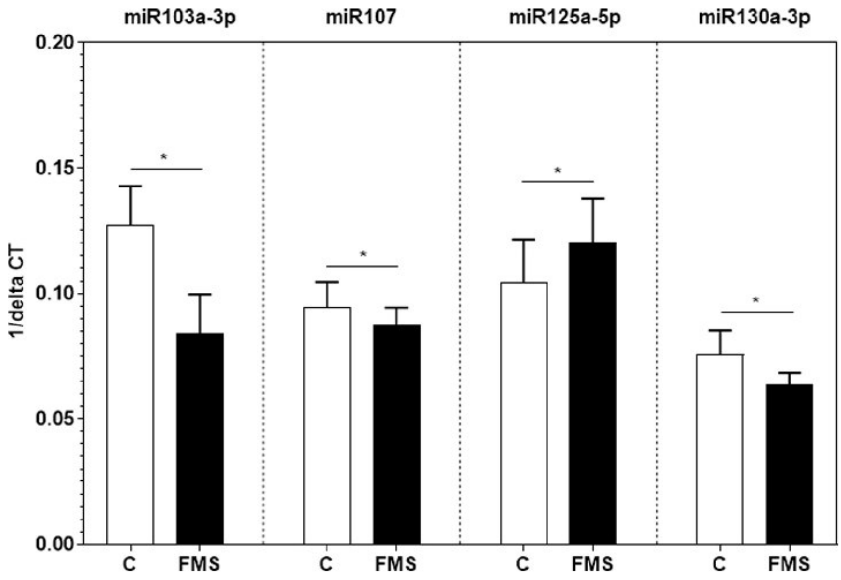

Fig 1. Relative gene expression of four selected miRNA in WBC samples of FMS patients and healthy controls. Boxplots show ΔCT values of miR103a-3p, miR107, miR125a-5p, and miR130a-3p of patients with FMS and healthy controls normalized to the housekeeping gene 5sRNA. Data are presented as 1/ΔCT. Intergroup differences were seen for miR103a-3p, miR107, miR125a-5p and miR130a-3p ($p < 0.05$). Abbreviations: C = controls; CT = cycle threshold; FMS = patients with fibromyalgia syndrome.

https://doi.org/10.1371/journal.pone.0239286.g001

Table 2. Effect sizes underline the large differences in miR103a-3p between unfavorable and favorable cluster.

	d	r	Comment**
Cluster*			
miR103a-3p			
BC*	3.6	0.9	large
AC*	2.9	0.8	large
DA*	-3.0	-0.8	large
BD*	3.6	0.9	large
DC*	-0.3	-0.2	small
miR107			
A*control	-1.2	0.5	medium
FMS vs. control			
miR103a-3p	-2.8	-0.8	large
miR107	-0.8	-0.4	small
miR125a-5p	1.0	0.5	medium
miR130a-3p	-1.6	-0.6	medium

*Capitals symbolizing cluster A (maladaptive), B (adaptive), C (vulnerable), and cluster D (resilient) and the calculated effect size r and Cohen's d between them

**Evaluation of effect size regarding following grades: 0.2 = small, 0.5 = medium, 0.8 = large

Calculated with effect size calculator of the University of Colorado, https://lbecker.uccs.edu/

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The effect sizes show a large effect for the difference in gene expression of miR103a-3p among all cluster, except for the resilient and the vulnerable cluster. Even the effect between the entire cohort and the control group was calculated as large. The slight decrease in miR107 of the maladaptive cluster differed to the control group with a medium effect but was small between the patient and control group. It is of note that the variance of relative gene expression for all measured miRNA was high in the patient cohort.

Relative gene expression of miR103a-3p, miR107 and miR130a-3p in FMS cluster

Post-hoc tests revealed that only miR103a-3p was differently expressed among FMS patient clusters (Fig 2).

For miR107 and miR130a-3p only differences were apparent between the control group and individual clusters. Relative gene expression of miR125a-5p was different between patients and controls with a medium effect size (Table 2), while no intergroup differences were detected among clusters. Patients assigned to the adaptive cluster had higher miR103a-3p gene expression (MED = 0.1, R = 0.03) than patients in the vulnerable cluster (MED = 0.07, R = 0.01, $p < 0.05$) and the resilient cluster (MED = 0.07, R = 0.02, $p < 0.05$). Patients in the maladaptive cluster had a higher expression of miR103a-3p (MED = 0.09, R = 0.03) compared to those in the vulnerable cluster (MED = 0.07, R = 0.01) and the resilient cluster (MED = 0.07, R = 0.02, $p < 0.05$). In contrast, miR107 expression was lower in patients within the maladaptive cluster (MED = 0.09, R = 0.01) compared to the control group (MED = 0.1, R = 0.03, $p < 0.05$) with a medium effect size of 0.5 (Table 2). The differences in relative gene expression of miR130a-3p between the control group and each cluster ($p < 0.05$) were of a medium effect size (Table 2).

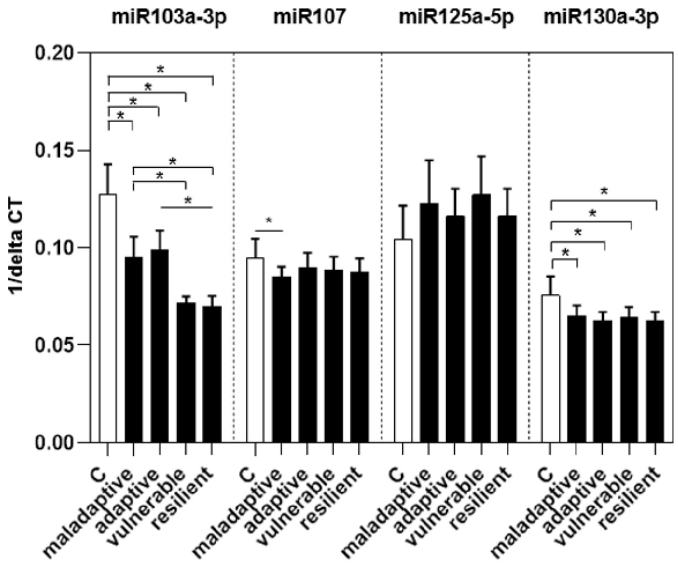

Fig 2. Relative gene expression of four selected miRNA in WBC samples of FMS patients illustrated regarding their cluster division in maladaptive, adaptive, vulnerable, and resilient cluster. Data are presented as 1/ΔCT. Differences among cluster are detected for miR103a-3p ($p < 0.05$). Abbreviations: C = controls.

https://doi.org/10.1371/journal.pone.0239286.g002

Association between miRNA expression and clinical scores

Spearman correlation analysis indicated an association between the expression of miR103a-3p with the FIQ sum score ($r = -0.4$, $p < 0.05$), and the expression of miR107 and the subscale "physical abuse" of the CTQ-D questionnaire ($r = -0.5$, $p < 0.05$; Table 3).

Discussion

We report a subgroup-specific miRNA signature in a cluster of FMS patients that is associated with adaptive coping in terms of active, problem-focused, and cognitive coping resulting in flexibility and adaptability during aversive life periods. After validation and further extension, this signature may serve as an identification code in research of further resilience factors in FMS.

Our data show lower expression levels of miR103a-3p, miR107, and miR130a-3p in patients compared to healthy controls, except for miR125a-5p. Several other studies on miRNA

Table 3. Correlation between relative gene expression of miRNA and clinical scores within the patient cohort (N = 22).

miR	Clinical score	r*
miR103a-3p	FIQ	-0.4**
miR107	CTQ physical abuse	-0.5**
miR125a-5p	PCS	0.4**

*Spearman coefficient r

**Significance level $p < 0.05$

Gene expression of miR125a-5p was associated with the sum score of the PCS questionnaire ($r = 0.4$, $p < 0.05$).

https://doi.org/10.1371/journal.pone.0239286.t003

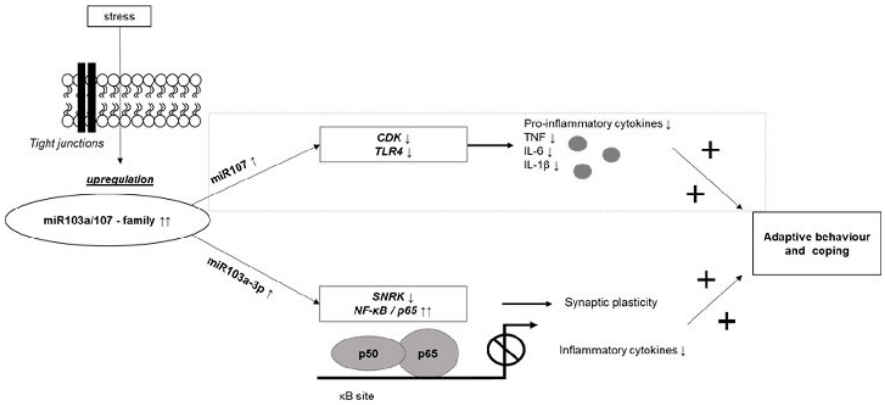

Fig 3. Synopsis of a speculative regulatory process of adaptive behavior in a cluster of FMS patients. Upregulated miRNA expression of miR103a-3p might be responsible for a regulatory cascade of SNRK and NF-κB signalling leading to adaptation on FMS symptoms in a subgroup of FMS patients. Based on the fact of forming a miRNA–family with miR103a-3p and the slight increased gene expression in our adaptive FMS cluster, the speculative potential signalling cascade of miR107 is included and marked as only based on literature data and a trend in our data. Abbreviations: ↑ symbolizes upregulation, ↓ symbolizes downregulation; + symbolizes the positive and resilience / adaptation promoting effect; CDK = cyclin dependent kinases; IL6 = interleukin 6; IL-1β = interleukin 1beta; NF-κB = nuclear-factor kappa B subunit protein 65; SNRK = sucrose non-fermentable serine/threonine-protein kinase; TLR4 = toll-like receptor 4; TNF = tumor necrosis factor-alpha."

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expression in biomaterial obtained from FMS patients revealed lower expression levels in FMS patients compared to healthy controls [7–9, 11, 36]. Here we focused on cluster-specific differences in gene expression, which were found for miR103a-3p. However, since the differences in gene expression for miR130a-3p were seen between the control group and each cluster, but not exclusively among clusters, and no intergroup differences among cluster for miR125a-5p were detected, we focused on miR103a-3p and miR107. Mean miR107 gene expression did not differ among clusters but tended to be higher in the adaptive cluster. Since miR107 forms a family with miR103 with similar physiological functions [37], we included miR107 to the proposed regulatory model.

In our previous study [12], the adaptive profile was characterized by active problem- and emotion-focused coping resulting in low scores in disability, depression, anxiety, pain catastrophizing, and early life stress (Table 1). The current study shows an association between the adaptive character and a higher expression of miR103a-3p in this cluster. In a speculative model, we outline the relationship between adaptive behavior and the increased expression of miR103a-3p by targeting specific genes that are involved in resilience promoting and inflammatory pathways supported by literature, correlation, and expression data (please see Fig 3).

Early life stress and inflammation may have a huge impact on the development of chronic pain and is reported in several studies among FMS patients [38, 39]. MiR107 is associated with childhood traumatization [15] and plays a regulatory role in inflammation [16, 17] by targeting CDK and TLR4 [18, 19]. Pro-inflammatory cytokines i.e. TNF, interleukin 6 (IL-6), or IL-1β are released by this process [20]. We speculate that higher miR107 gene expression may lead to lower expression of CDK and TLR4 resulting in low pro-inflammatory cytokine levels. A pro-inflammatory profile may lead to depressive behavior [40] whereas low levels of pro-inflammatory cytokines favor permissive behavior [41, 42].

Despite the lacking increase of miR107 gene expression in our patient cohort, we decided to include miR107 into the synopsis. Both form a miRNA family and there are valid data on the influence of miR107 via TLR4 and CDK signalling on adaptation and inflammation. We

can only speculate which potential reasons it might have that although miR107 and miR103a-3p belong to the same family, miR107 seems not to have the same influence in our cohort as miR103a-3p. As illustrated in Fig 3, miR107 is influenced by TLR4 and CDK signalling. It might be that both genetic targets are differently expressed in our patient cohort resulting in a less prominent role of miR107 here. As one of our study limitations, we stated that we only did verify the genetic targets by an online tool.

MiR103a-3p is linked to stress and inflammation by regulating the SNRK / NF-κB / p65 signaling pathway [43]. Higher gene expression of miR103a-3p may lead to suppression of sucrose non-fermentable serine/threonine protein kinase (SNRK) and ultimately lead to an over-activation of the transactivating subunit protein 65 (p65) of nuclear factor kappa B (NF-κB). NF- κB was reported to be linked to epigenetic resilience promoting mechanisms [44] and synaptic plasticity resulting in adaptive processes [45].

We report on higher relative gene expression of the miR103a/107 family in an adaptive cluster of FMS patients compared to the vulnerable / maladaptive cluster. This regulatory process may be responsible for adaptation via SNRK / NF-kB and via CDK/TLR4 signalling (Fig 3).

Our study has some limitations: the study cohort is small which was due to the availability of patient biomaterial. The selection of miRNA candidates was based on previously published research [9] and also the endogenous control for the PCR was adopted and not further verified. We did not assess the four proposed genetic targets SNRK, CDK, TLR4, and NF-κB, but stayed with *in silico* verification as genetic targets of the miR103a/107 family by the online tool *TargetScanHuman* [46, 47]. Our findings including the expression level of the suggested genetic targets of the miR103/107-family need to be confirmed in an independent FMS patient group.

Conclusion

We show an association between higher gene expression of miR103a-3p and miR107 and adaptive coping in a cluster of FMS patients. This miRNA signature might function as a diagnostic profile of FMS subgroups and enable further research on somatic parameters of adaptation and resilience in FMS.

Supporting information

S1 Fig. Flow chart of patient recruitment.
(TIF)

S1 Table. Data of clinical examination, laboratory, and electrophysiological measurements. BMI = body mass index; NCV = nerve conduction velocity.
(DOCX)

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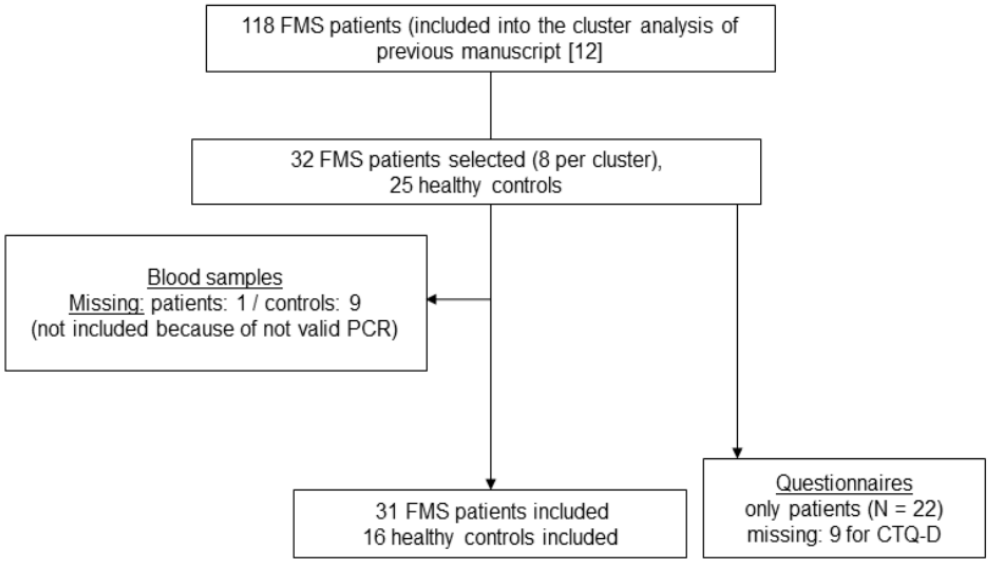
Supplementary materials

S1 fig: Flow chart of patient recruitment.



S1 table: Data of clinical examination, laboratory, and electrophysiological measurements.

	Maladaptive [8]	**Adaptive [8]**	**Vulnerable [8]**	**Resilient [8]**
Clinical examination				
Gender				
Female	8	8	8	8
Weight [kg]	67.6	66.69	74.5	73.5
Height [cm]	159.6	163.3	167.8	164.9
BMI	22.9	22.5	25.2	24.8
Employment status				
Regularly working	3	5	5	3
Sick leave because of pain	-	-	1	3
Retired because of pain	2	-	1	2
Time since diagnosis [years]	4.2	8.5	2.8	6.8
Duration of pain due to the disease [years]	12.8	16.4	12.5	11.5
Pain distribution type				
Proximal	3	1	4	1
Distal	-	-	-	-
Whole body	4	7	3	6
Current pain intensity [scale 0 - 10]	6.8	4.5	6	6.3
Pain character [%]				
Tearing	6	25	9	-
Pressing	25	25	50	58
Burning	25	25	25	8

Muscle sourness	25	-	8	17
Stabbing	19	25	8	17
Psychological/psychiatric treatment				
Never	3	3	3	4
Currently	2	2	5	-
In the past	3	3	-	4
Electrophysiological measurements				
Sural nerve				
Peak to peak amplitude [µV]	24.5	23.3	21.5	25.4
NCV [m/s]	49.3	45.7	50.0	48.6
Tibial nerve				
Proximal amplitude [mV]	14.7	15.1	16.4	16.5
distal amplitude [mV]	19.1	20.3	22.0	21.5
dmL [ms]	3.8	3.3	3.6	3.4
NCV [m/s]	47.6	47.1	45.8	46.5

BMI = body mass index; NCV = nerve conduction velocity.

5 General discussion

The present cumulative thesis compromises three studies analyzing theological, psychosocial and somatic factors that might function as resilience factors in patients with FMS. Validated standardized questionnaires and a face-to-face interview were used to evaluate theological and psychosocial factors. qRT - PCR analyzed selected cytokines and microRNA as potential biological factors contributing to resilience. Variance analyses were used to categorize the FMS cohort into subgroups to characterize different coping and resilience phenotypes. The findings and implications of each study are critically discussed in a general context and highlights carefully translated into prospects.

Manuscript 1

Religiosity, coping and resilience

Study 1 evaluated religiosity and its effect on coping, pain, health outcome, FMS related disability, and resilience. We examined how our cohort defines religiosity, which religious dimension might be relevant for their coping with FMS and if religiosity has an influence on the health outcome.

The complexity of all three terms - religion, religiosity and spirituality - makes it difficult to be operationalized by any instruments, like questionnaires. For an appropriate evaluation of the relevance of religiosity for a cohort, religiosity must be defined before further examinations were done, and the study must be referred to a specific definition of religion, religiosity and spirituality. Hill and Hood [155] presented an extensive review of more than 100 scales for measuring a wide range of domains related to religiosity, such as religious orientation, religious experiences, concepts of god, moral values and religious coping [156]. Campbell and Coles recognized religiosity and religious affiliation as “independent dimensions” and pointed out the need to study differences of religious attitudes and beliefs between the religiously affiliated and unaffiliated [157]. We agreed with the definition of religiosity as a multidimensional construct including cognition, feelings, and behavior with institutional affiliation which was made by König [158] and with the definition of spirituality which was given by the International Consensus Conference as “aspects of humanity that refer to the way individuals seek and express meaning, and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred” [159].

Religious dimensions were assessed by questionnaires. The literature on the different dimensions of individual religiosity and the scales for their measurement is extremely vast. Already 1964, Glock and Stark proposed five dimensions of religiosity: “belief”, “practice”,

“experience”, “knowledge”, and “consequences” [160] that were validated within a cohort of undergraduate students [161]. Allport and Ross proposed the religious orientation scale (ROS) [26] that measures two dimensions of religious orientation - “intrinsic” (I) and “extrinsic” (E) religious orientations which were further improved [162]. Saroglou proposed a scale called “The Big Four Religious Dimensions” which are “Believing” (cognitive), “Bonding” (emotional), “Behaving” (moral) and “Belonging” (social) [163]. “Believing” refers to belief in some kind of transcendence, “Bonding” captures the emotional effect of rituals, either public (participation in religious ceremonies, etc.) or private (prayer and meditation), “Behaving” is related to moral behavior and “Belonging” refers to self-identification with a religious denomination or group.

The Aspects of Spirituality (ASP) questionnaire that was used in our study was developed by Arndt Büssing [164], a medical doctor at the department of human medicine at the University of Witten/Herdecke (Germany) [142, 165]. His interdisciplinary research is mainly focused on spirituality as a resource in the course of a disease. The different aspects that are evaluated by this questionnaire were built by asking experts of different spiritual orientations which aspects might be relevant for them [166]. The ASP questionnaire is a reliable and valid instrument that is often used in health care research. It was perfectly suited for our FMS cohort, because mainly elderly women are suffering from this syndrome and the questionnaire measures a wide variety of vital aspects of spirituality in secular societies that are easily understood by nonreligious and religious people independently on their cultural belonging. Nevertheless, there are further limiting aspects of questionnaires (even they are valid and standardized). Questionnaires are often incorrectly or illegibly filled out and missing answers have an inevitable influence on the quality of the data obtained and have the potential to further lower the number of useable questionnaires. The structure of the method itself is also limiting. Fixed-choice questionnaires generally assume an unstated general knowledge of the topic being investigated, and force the respondent to answer questions that she or he might be ignorant of, have a different understanding in base on personal perception, or which are influenced by exogenous factors such as education, culture, age, or societal status [167]. A questionnaire has no means of correcting this; the outcome might thus be slightly biased at best, or plainly misleading. Saunders and colleagues [168] also describe the limitations of questionnaires with regards to the expected outcome, for example they might highlight trends or attitudes, but may fail to explain the underlying reasons for the outcome. The ASP is a validated and standardized method to evaluate a wide range of religious and spiritual aspects. Further quality criteria for the choice of a questionnaire are empirical validity, reliability, and ability to represent the entire population as normative value, economical (evaluation, costs) and comprehensibility by patients that are all fulfilled by the ASP. A ‘multi-method’ approach, where the researcher combines questionnaires with, for instance, interviews to explain the results, is therefore proposed. This approach we applied in our study 1.

Data of the interview revealed a highly varianble subjective definition of religiosity by each FMS patient who participated in the interview but a relatively low score in the ASP dimension “religious orientation” that illustrates the traditional religiosity which is shown in classic religious symbols and practices. In general, large multinational surveys such as the World Values Survey (WVS) [169], the European Values Study (EVS) [170], the International Social Survey Programme (ISSP) [171] or the European Social Survey (ESS) [172] prove the regional differences in the importance of religiosity for daily life, for coping with diseases, and also for the subjective definition of religiosity we have seen in our data. This may be a sign of living in a secular society that has this kind of aversive past with religious affiliations in the middle of Europe [158, 164].

The lower importance of all religious dimensions on the choice of coping was discussed as missing urgency in a cohort of chronic pain patients compared to patients with cancer. Studies in chronic pain patients revealed a lower religiosity when compared with patients suffering from cancer. Cancer patients are more often in contemplation of death than chronic pain patients, which was supported by several studies [164, 173, 174]. FMS patients belong to chronic pain patients but have a specific state within the chronic pain cohort, because the diagnosis is still made by exclusion of other diseases with legal, financial or social consequences in daily life. Such patients have lost their identity, strength, and sense of coherence because many of them are not able to do their job, sports, hobby or housekeeping as before and struggle with the difference between the functioning ego versus the sick FMS-ego independently on how resilient they are. Chronic pain patients predominantly reported needs like “inner peace”, “call for help” or “generative relatedness on a personal level” [164], which also show needs like sense of coherence, acceptance, self-love, and identity and shows frustration factors that go hand in hand with chronic diseases with less effect therapies and less acceptance in society or even in medical personal.

One further study aim was to assess the influence of religious dimensions and the grade of religiosity on the choice of coping strategies. The regression analysis revealed no influence of all four religious dimensions on coping or health outcome. After correction for multiple comparisons, the coping strategy “praying – hoping” and the ASP dimension “religious orientation” ($r = 0.5$, $p < 0.05$) showed a significant relationship independent of the grade of religiosity ($p < 0.05$). The correlation between coping “praying – hoping” and “transcendence conviction” showed a trend to be related ($p = 0.064$). All coefficients had a low or moderate strength, so that no clear conclusion can be reached, however, these values provide information and hints about suspected connections. Furthermore, the CSQ only evaluate religious coping via a few items that might contribute to this result. But nevertheless, also the low number of patients who uses kind of religious coping show that religiosity might be relevant

for some of the FMS patients. For a therapeutical application of religiosity, the individual importance and definition of any religious aspect must be assessed, such that patients are enough open-minded for the therapy, and that this has a successful effect on the relief of pain and accompanying symptoms.

The effect of religious dimensions on the choice of coping strategies and health outcomes is low but not absent, as the data of the regression analysis also showed. Reinterpretation - a cognitive, spiritual and religious coping strategy with positive and negative effects - had a significant contribution to disability. These data might show an indirect religious coping, which is not categorized into the field of “religiosity” by the patients, but has a well-defined effect in different diseases and disorders [111]. Nevertheless, there are many indices that confirm both sides of the effect on health – positive as well as negative. We assume that negative associations with religion might overweigh in our Western society that often associates religion with negative headlines made by the religious institutions. This is supported by the impressions during the face-to-face interviews with FMS patients, which indicate that religion is not only a positive source of strength [111, 175]. Doubts and the feeling of being abandoned by God are closely associated with the personal journey to God [176]. Thus, negative connotations of religiosity may also influence the success of coping strategies.

The study proposed a model that shows the impact of depression, pain intensity and coping “reinterpretation” on FMS related disability that might promote either resilience or vulnerability depending on other extrinsic or intrinsic factors (like personal characteristics, life circumstances and experiences). Previous studies demonstrate significant effects on disability, life quality and resilience for all three variables [177]. No religious dimension that was analyzed by the regression analysis had any significant influence on FMS related disability. But, coping “reinterpretation” is an emotion regulatory coping technique that belongs to the coping strategy reappraisal that is a religious practice that can be used in a positive (benevolent religious reappraisal) as well as negative (demonic or punishing religious reappraisal) way of coping [178]. This indicates that the cohort is using a coping strategy with a reducing effect on disability that is also known as a religious technique of coping. Probably, when not trained by a coach or supported by any therapy, religiosity itself is not consciously used by nonreligious people. The advantage of this regression model may be that we know that some of the patients who reported low religious importance and showed aversive reactions to religious symbols and institutions, might already non-consciously using religious coping like reinterpretation. It is clear, that not everybody is open to every kind of therapy and not every concept is appropriate for every patient. But, when a patient reports low relevance of religion but shows coping which belongs to redefinition, reappraisal or reinterpretation, the therapist might promote this hidden resource. This model might motivate therapists to try out some spiritual and religious concepts

of therapy even in patients who seem to be nonreligious. It should be clear, that no therapy has its effect when the patient is not freely-minded or has negative associations with. The best way to apply religion into the clinic might be to sensitize patients for their own values and to find their inner peace.

Resilience was not measured directly in this study. We did not use a specific resilience scale because of our understanding of resilience. In our mind, resilience cannot be exclusively operationalized by one scale because this complex process is based on different contributing factors like psychosocial, theological or personal factors. To give a substantial reply to the question “might religion function as resilience factor?” and its relevance for education and therapy, we first must analyze existing concepts in prevention and educational programs for children and youths, and discuss different opinions.

Several existing educational concepts have no religious elements except for one song called “Kindermutmachlied” [179], which is supposed have a reassuring effect on children. This faith and trust of a baby that its need will be taken care of, is the positive effect that religion might have on children and people. Religious education is seen as a kind of school that prepares children to be open-minded, strong and faithful for the long and partly aversive journey of life [180]. Fritz Oser sees religion as a protecting factor and religious education as important to strengthen the religious belief and the trust in children, and that they have something that gives them strength during aversive periods in their life [179]. The sociologist Antonovsky understands resilience as a concept that is based on the sense of coherence (SOC) as a protecting element for identity. This sense is essential for children and it is then possible to build SOC from their own religious beliefs. Children need trust in their families, in society, and their social environment to get a positive feeling for themselves and the environment. This development is dependent on their experiences and cognitive abilities and interpretations. Values, ethics, moral, religious belief, and stories about God or a higher being as embracing element plays an important role [181]. From an early age, people have gained experiences in which they encounter transcendent dimensions that refer to God (e.g. questions after death). Children have hopes and fears, seek protection and security, and desire to be recognized by their fellow human beings. These are dimensions that happen interpersonally. The influence on children in terms of their faith depends very much on their environment and how they handle it. Part of the child's need for love can be fulfilled with a positively lived interpersonal religious lifestyle. FMS patients often experienced traumatic events in their early childhood and not everyone lived within an intact family, resulting in lower trust in themselves and others. This circumstance makes it conclusive that our FMS cohort is markedly aversive against religious symbols and has less trust in God or does not use religious belief in their daily life and for coping with pain and accompanying symptoms. Anxious children (later anxious FMS patients)

who do not dare to discover their world will not explore the world, because, among other things, they lack the necessary confidence in people and things. Hope is the base for trust to others and to see the world positive and not adversely and to have the strength to cope with difficult situations, because in the end everything will be good. This is supported by studies defining optimism as a resilience factor as opposed to depression. In our proposed model, depression had an effect on FMS related disability. We assume that depression has an elevating effect on pain and disability which promotes vulnerability rather than resilience. It might be interesting to study whether the small group within the FMS cohort with high values in transcendence conviction and religious orientation experienced healthy family structures and could thus develop trust. Resilience is tightly connected with belief and hope, which needs solace and trust.

Manuscript 2

Multivariate analysis of subgroups

Study 2 evaluated variance explaining factors which cluster FMS patients into different subgroups. The aim was to define cluster discriminating factors that promote resilience.

The heterogeneity of FMS patients is independently present in almost every cohort [182]. For the definition of variance underlying factors, we carried out a factor analysis that determined four factors that were found as a predictor for the differences between four clusters within the FMS cohort of 118 patients. Correlation between variables of questionnaires that evaluate psychosocial data and somatic variables of gene expression of selected cytokines were to be attributed to a few factors assumed behind the variables. An exploratory factor analysis was applied to find factors that contribute to the variability within the data set and to reduce the number of variables. Factor analyses also have their limitations, but in our mind, done carefully it is a valid method to extract factors as the base for further clustering. Most cluster studies did not carry out factor analysis before the clustering [183, 184]. Pérez-Aranda [184] published a cluster study of a large cohort of FMS patients only with a single sum score variable without a previous factoring. We clustered the cohort by four emerged validated factors, a method that is supposed to make data more transferrable to other cohorts, independent of regional differences. Of course, some aspects must be considered during the factoring process, which have an impact on the results. The choice of extraction method, e.g. main axis or main component analysis, the choice of number of factors to be extracted, e.g. specifying a certain number of factors based on theoretical considerations or using cancellation criteria, such as Kaiser criterion or scree plot, and the choice of rotation algorithm, e.g. skewed angle (oblique) or orthogonal rotation [185]. Unfortunately, exploratory factor analyses are often carried out

uncritically without being aware of the possible methodological problems. For example, a problem with exploratory factor analysis may also be that, in addition to substantial factors, sham factors are also extracted as a result of items with similar item difficulties or similar symmetry properties which can form its own factor [186, 187]. After several critical analyses of the data set, the four-factor solution was chosen as the best to interpret as (1) “affective load”, (2) “coping strategies”, (3) “pain”, and (4) “pro-inflammatory cytokines”. The factor loadings were clearly separated into thematic groups, and the only double-loading was seen for the sum score variable of the FIQ questionnaire on factors 1 and 3, which is plausible because the content of FIQ items measures depressive symptoms as well as pain [188]. There is always a bias due to questionnaires and statistical analyses. This also illustrates a general problem of such analyses. In the end, conclusions were made based on numbers and data extracted by questionnaires that have their own methodological problems even when they are valid and standardized. This might create a discrepancy between the reality of living beings and the created statistical reality that is described by data extracted of questionnaires and other analyses. Thus, data must be carefully and consciously interpreted and set into the context of each study. Maybe this is the main limiting aspect to create an individualized therapeutic concept that should be transferrable to every patient cohort.

FMS patients are an appropriate cohort for clustering because the patient profiles are highly variable. Several authors tried to illustrate a typology and individual profile by clustering fibromyalgia patients by symptom severity, objective or subjective measures of physical and mental health with different outcomes [189-198]. A four cluster solution was the best fit for most studies including our study [189, 199-205]. Additionally, to the illustration of the clusters and their different factoring scores, we created a 3D model to illustrate the clusters three-dimensionally rotating in space [154]. Similar to factor analysis, the cluster analysis provides some methodological problematic aspects. The choice of the cluster method has an influence on the number of clusters that emerge, which need to be interpreted by the scientist. This interpretation is vulnerable to preoccupations and subjectivity. Furthermore, the results are based on mathematical modeling that try to illustrate the living reality. The most crucial step is the naming of the clusters. An outstanding study - the al-Ándalus project [193] - classified 486 FMS patients based on eight factors into five clusters named by the grade of performing as adapted, fit, poor performer, positive and maladapted. Our analysis resulted in a maladaptive, adaptive, vulnerable and resilient cluster, distinguished by the factors affective load, coping, pain, and pro-inflammatory cytokines. In contrast to [193], we did not include a predefined factor “resilience” by factor loadings of resilience scales. The categorization of cluster D as “resilient” was done by the definition of resilient strategies of coping with FMS that might be used to change a “non-resilient” into a more resilient phenotype. The choice of the right type of coping is the key to increase quality of life and resilience in aversive life periods [206, 207].

In our cohort coping was a crucial factor and decisive for being adapted, resilient or not that might function as therapeutic target. Resilience is a complex phenomenon which is criticized to be difficult for operationalization [90]. As previously mentioned in (1 General Introduction – 1.3 Resilience - 1.3.3 Critique) many definitions exist that complicate the evaluation of resilience. In our mind, resilience is formed by several influencing factors of which all of them cannot be analyzed by only one scale. The combination of different questionnaires captures several of these influencing factors but repeatedly reaches their limits. It is essential to give a definition of resilience before the results are explained and discussed. We followed the definition of resilience as a dynamic process of adaptation in the face of adversity [208, 209] but also included the concept based on personal aspects [210]. We see both concepts within our cohort. Cluster D was speculated to have personal resources to actively deal with intense pain and high traumatic events, indicating a resilient trait, whereas cluster B might be best adapted and has learned how to effectively cope with FMS. Interestingly, reappraisal – a cognitive emotion-regulatory coping strategy that has relation to the religious strategy "redefinition" that has a positive effect on stress, depression and physical symptoms [211, 212] – was also found to be used in the small religious orientated group of FMS patients investigated in study 1. In study 2, reappraisal is used by the as "resilient" defined patients of cluster D. Reappraisal belongs to active emotion-regulatory coping strategies that promote resilience [213] and has a good potential to be learned during a therapy supported by a therapist or coach.

The variables which were included in the factor analysis present FMS related disability, psychopathological symptoms, coping strategies and gene expression of four cytokines. The weighting of the variables is more due to the importance of the psyche rather than the neurobiological or somatic variables. The importance of psychological factors might increase the longer the patients are suffering from FMS symptoms. The average pain duration of the cohort was at 12.5 years suggesting the immobility and loss of function became a higher impact on disability. When we classified the clusters into severity grades, cluster B had the lowest disability, cluster C the highest disability, and cluster A and D were in an intermediate position. Nevertheless, the cytokine data influenced the variability of the cohort and were important enough to exclusively load on factor 4. Only results of cytokine mRNA were included in the analysis because the ELISA of TNF revealed no difference between patient and control protein (thus the results were not included in the manuscript, please see section 3 Materials and methods, 3.4 Evaluation of biological data, page 18). The overload of psychosocial data might create a bias within the data set but cannot be avoided and are naturally there in such statistical analyses. Initially, more physiological data were included in the analysis, derived from QST and PREP measurements, and skin biopsies. None of these variables emerged as loadings on any factor. We thus did not include QST, PREP, and data of skin biopsies into the factor

analysis and only focused on cytokines. This shows the discrepancy between natural reality and statistical reality, again. Another limiting aspect is that psychosocial factors are well researched, but the few somatic ones I have studied are also based on known results (always the same cytokines are studied), which creates a bias by fact, which unfortunately cannot be changed because the scientist has to rely on already known facts and can only fill the existing data into the analysis. The general limitations of every study depend on suitable study participants who are willing to appear on the study day and participate in every test. Our cohort might exclude the very vulnerable individuals who were not willing or who were not able to participate in a series of tests on a specific day in the clinic far away from their familiar environment. This limiting aspect is present for every study because every study has its limited cohort-specific cultural or environmental influences that make it difficult to universally transfer the results.

During the data collection of study two, a pilot study was carried out, taking saliva samples from the patients to create the cortisol profile based on the stressor “skin biopsy” during the study day. The samples of the 25 patients who participated in this pilot study were fully in range with the healthy reference samples, and no patient indicated hypo- or hypercortisolism. One of the reasons might probably be that the stressor was not stressful enough. The saliva removal was no longer taken. Chronic and traumatic stress is well known to be associated with FMS related disability and the increase of pain intensity [214, 215]. Stress is a natural driver of adaptation. Several experienced stressful events lead to an accumulated allostatic load. Regarding different BSC phenotypes and stress reaction profiles, the system can bounce back to homeostasis that describes the mechanism of a resilient organism. When the stress exceeds the ability to bounce back, probably the vulnerable and maladaptive phenotype is built [56]. For further analyses, the study design of this pilot test needs to be revised. It might be interesting to include the cortisol results in the multivariate analysis to see the impact on the different stress reactive phenotypes and the emerging cluster characteristics.

Another study that is part of the main FMS study is performing brain MRI measurements. The FMS patient group was a popular group to perform MRI based on the assumption of central sensitization as the cause of pain and hyperalgesia [216]. There are some studies that show an alteration in volume of the grey and white matter, and other brain areas involved in emotion, cognition, and pain processing [217]. Results of the study at our department also indicated altered volume in grey and white matter in FMS patients. We additionally compared the brain volume of the white and grey matter regarding the cluster classification, but the volumes were not different between the clusters. Resilient coping seems to have no effect on the volume of white and grey matter in our cohort. For future analyses, it would be interesting to include more neurobiological data, e.g. individual stress responses, MRI data or miRNA.

Study 2 described the social environment and socio-demographic data of cluster-specific cases. The case description makes it easier to create specific therapy suggestions. There are many cluster studies, but only few suggest individualized therapeutic concepts for FMS patients. In contrary, the number of patients without trust in drug therapies is increased because the effectiveness is reduced and combined with side effects. Such case descriptions and proile-based therapeutic suggestions also have the potential to improve the confidence in therapy. Alternative therapies like supplementation with minerals or vitamins [206, 218-228], cognitive-behavioral and mindfulness-based (MBSR / MBCT) therapies to support adaptive coping [229, 230], and exercise training with beneficial effects on fatigue, pain and mood [231, 232] are more in focus now. Exercise and stress management are essential especially in this century and the meritocracy of the western population. Sedentary and western lifestyle produces lots of diseases [233]. A structural general rethinking is necessary to really prevent the endemic increase of chronic diseases. Exercise (more than the officially recommended 30 minutes three times per week) is the best therapy for many diseases of civilization [234], because we are adapted to long-distance runs by evolution. The non-pharmacological and alternative therapies are a promising start resulting in a higher awareness for the natural needs of the human body. More therapists and coaches are needed to offer individualized therapies for chronic pain patients and the education of people who work in the health industry needs to include more content on nutrition, exercise, and physiology of the human body. Some specific resilience promoting therapies are known, e.g. positive activity interventions (PAI) that show a long-term persistent effect on pain relief and FMS related symptoms like depressive mood [235].

But, since the pathophysiology of FMS is still incompletely understood, more research is necessary to offer an adequate therapy for FMS, and resilience is still a complex phenomenon. All these unresolved aspects raise questions of whether it is even possible to offer therapies aimed at strengthening resilience, especially when resilience remains a complex phenomenon. First, a general screening tool independent of culture, country, and patient cohort is necessary and still missing. The development and establishment of such a screening tool as diagnostic tool for vulnerable patients is the major challenge. The biggest factor to overcome will be the dependence of each study cohort to local influences. This study might offer a concept to categorize FMS patients to one of the four clusters and sensitize for the needed inter-disciplinary concept that must be applied in the clinical practice.

Manuscript 3

MiRNA and resilience

Since now, the diagnosis and therapy of FMS remains a major challenge for clinicians and scientists. Despite the recommendation of a multimodal therapeutic approach, these therapies are often not appropriate for the heterogenous clinical outcome of FMS patients, however an objective diagnostic tool for clinical application is still missing. This study described a subgroup-specific miRNA signature that after further validation might function as somatic resilience factor to physical and emotional stress and might be useful as a diagnostic tool.

Previously research of our group concluded that the findings suggest a deregulated expression of miRNAs in chronic pain patients which were associated with the degree of pain resulting in an individual profile which might be used as a diagnostic profile for FMS subgroups. Additional research was called to be required to identify if these miRNA profiles are expressed individually in patients, and to advance understanding about the factors that generate these differences ultimately resulting in adequate anti-pain medication based on miRNA profiles [42].

Several studies including FMS patients tried to find diagnostic biomarkers in several different body fluids [40, 236, 237]. Numbers of patients were limited due to price and time for miRNA analyses especially when using microarrays. Our study measured the relative gene expression by qRT-PCR of four miRNA that were selected based on literature search by the terms “resilience”, “inflammation”, and “chronic stress” and those of a previous miRNA array of our research group [42]. 25 controls and 32 patients were selected from the previously clustered cohort of 118 FMS patients [238]. The subgroups were labelled “maladaptive”, “adaptive”, “vulnerable”, and “resilient”. Data of 31 patients and 16 healthy controls were valid after the PCR run. This number is on average a higher number compared to the published articles except for the study of Leinders et al. [42].

MiRNA gene expression of miR107, miR103a-3p, and miR130a-3p were lower in patients than in controls, as seen in almost every study screening for miRNA differences between a patient and control cohort [41, 237]. One study reported 20% downregulation of all screened miRNA in patients. These congruent results are interesting because the methods among all published studies are highly variable. Our main interest was on differences in the miRNA profile among clusters, which we see only for miR103a-3p. The mean expression level of miR107 was almost the same, but the expression level tended to be higher in the adaptive cluster. We included miR107 into the proposed regulatory model because both form a miR family with similar physiological functions [239]. The miR103/107 family is validated to be involved in several regulating processes resulting in different types of cancer, inflammation but also psychiatric disorder such as Alzheimer’s disease or schizophrenia [240].

We reported on an upregulation of the relative gene expression of the miR103a/107 family and suggested a miR103a/107 regulated adaptation to FMS symptoms via SNRK / NF-kβ and via CDK/TLR4 signaling in a cluster of FMS patients. The adaptive FMS profile was characterized by active problem-, and emotion-focused coping resulting in low scores in disability, depression, anxiety, and pain catastrophizing and low scores in all other symptom categories [238].

MiR107 is confirmed to be associated with childhood traumatization [241] and play a regulatory role in inflammation [242, 243] by targeting CDK and TLR [244, 245] resulting in the induction of TNF-α secretion [246]. CDK are protein kinases that are involved in control of cell division and modulate transcription in response to several extra- and intracellular cues. TLR are a class of pattern-recognition-receptors, which recognize pathogens via PAMPs (pathogen-associated-molecular-pattern) and play a central role in the innate immune response. Besides PAMPs, in general all alarmins (e.g. EAMPs (emotional associated molecular pattern) might be detected by TLRs, which is relevant for stress associated diseases as FMS [247]. We proposed the following signalling concept of miR107: We speculated that the upregulation of miR107 gene expression might lead to low expression of its genetic targets CDK and TLR4 resulting in a low-proinflammatory profile which has an impact on behaviour [248]. Low-grade inflammation is responsible for many non-communicable diseases as depression [249] and favor permissive behavior [250].

MiR103a-3p is linked to stress and inflammation by regulating the SNRK / NF-κB / p65 signaling pathway [251]. We proposed the following signalling concept of miR103a-3p: The upregulated gene expression of miR103a-3p leads to suppression of SNRK and ultimately to an overactivation of the transactivating subunit p65 of NF-κB that induces inflammation. NF-κB hasbeen reported to be linked to epigenetic resilience promoting mechanisms [252] and synaptic plasticity resulting in adaptive processes [253]. The SNRK (sucrose nonfermentable serine/threonine kinase) gene family is known to be involved in the modulation of stress responses, inflammation and energy homeostasis in mice and humans [254]. In SNRK deficient mice the interacting pathways are dysregulated and insulin resistance in adipose tissue is promoted. The SNRK family is also evolutionarily implicated and already known to be an important regulatory target in plants and vertebrates [255]. NF-κB (nuclear factor kappa beta) is a protein that acts as a switch to turn inflammation on and off in the body. In response to pathogens, pro-inflammatory cytokines, ROS (radical oxidative substances) or even another extrinsic stressor like a traumatic accident or the daily excessive demands, NF-κB “turns on” the genes that produce inflammation. As we age, NF-κB expression in the body increases, provoking widespread chronic inflammation and setting the stage for diseases ranging from atherosclerosis, Alzheimer’s disease or chronic pain. Interesting, the average age of our FMS

cohort is around 50 years. Both factors are included into the SNRK / NF-κB / p65 signaling pathway, which is regulated by miR103a-3p in the context of stress and inflammation [251]. When NF-κB is activated, the interaction with SNRK leads to an anti-inflammatory effect. This has an promoting effect on adaptive behavior, because pro-inflammatory conditions promote a psychopathological state. The adaptive cluster is characterized by low values of pro-inflammatory cytokines [238].

As support of these theoretical networks, we applied a simple Spearman correlation, however with significance between the expression profile of the total patient cohort and clinical scores. The correlation analyses were even done between clusters and each evaluated clinical score of the questionnaires, but no score was correlated with any miRNA expression of any cluster. But in return, we detected significant correlations between the entire patient cohort and clinical scores of pain catastrophizing, FMS-related disability and traumatic stress scores. The expression of miR107 was negatively associated with the subscale “physical abuse” of the CTQ-D in our cohort. We are not able to interpret these correlations in an absolute way, but the results of the correlation studies might give a hint to the association of emotional processes and their regulation by miR107. The relative expression of miR103a-3p was associated with the clinical score “FMS-related” disability” and might give a hint to the relevance of this miRNA for adaptation and resilience promoting processes, as scetched in our synopsis.

The adaptive process of the adaptive cluster is described as adaptation on FMS symptoms by active coping resulting in low scores of every symptom category. Adaptive behavior is a process to conform with the context that surrounds a person, organism or even a plant [256]. Pain itself is an adaptive process that signals danger to the body and triggers a protective response via behavior to extrinsic stimuli. This might be behavior at a molecular level. Behavior is influenced by genes, environment, intrauterine experiences, culture but also events in previous generations. Factors such as parenting, schooling, trauma, and the prenatal environment play critical roles in the development of social behavior [257]. Even the most highly heritable traits, such as height, are influenced by environmental factors, as demonstrated by malnourished children that are very short despite having tall parents [257]. In this example, environmental factors such as nutritional intake have altered the way in which genetically influenced characteristics are expressed. Contrary to a common misconception, genes do not cause behavioral or personality traits, they only influence them. Although genes may be linked to certain traits, it is unlikely that researchers will ever find a single gene that is entirely responsible for most complicated behaviors. Many genes work in concert to influence most behaviors, meaning the genetic aspects of a particular trait are the result of small effects over hundreds of individual genes.

This is important to know, because this is a huge limiting aspect of studies, especially of miRNA studies. We are dependent on previous knowledge and it is impossible to find in one study every single miRNA that probably has an influence on the behavior. Therefore, although these two influences are often presented in an either/or-way, as in the commonly used phrase “nature versus nurture,” evidence suggests that behavior and other characteristics do not have one clearly identifiable cause. More probable is that both factors are always at work and that for the cause of any given trait researchers should not be asking, “Genes or environment?” but rather, “What is the contribution of each and how do they work together?” [258]. This collaboration was illustrated in a model that proposed the potential interplay between environment, genes and regulatory elements in FMS cluster. Another limiting factor was that we did not measure the level of SNRK, NF-κb, TLR4 or CDK in our patients, but we confirmed them as real targets for the miR103/107 miRNA family by the tool T*argetScanHuman* [259]. This useful tool is a quantitative model that considers size types and features to predict targeted mRNAs and provides to place miR into gene-regulatory networks [260].

Furthermore, for individual target verification, we tested 5S and snord44 as endogenous controls, although 5S was set as endogenous control because our study is based on the previous study [261]. U6, snord48, snord44, and 5sRNA were tested as endogenous controls and 5S as the most stable in both groups used for further analyses. On the one hand, our study was limited to previous results and methods (endogenous control, patient material), but on the other hand we also have a confirmation of the results generated by the previous study. We used the delta-delta CT (cycle threshold) method as devised by Livak and Schmittgen [262] to evaluate the relative fold gene expression of samples after performing the real-time PCR. This method consists of several security steps by using the ct values that are distinguishable from the background noise and the delta CT (the difference between the gene of interest and the untreated control) ensures a normalization of the samples to a gene which is not affected by the experiment itself.

As already mentioned, it is now widely held that both nature and nurture simultaneously influence traits and the environment can influence the expression of genes which is called the genotype-environment (GE) correlation. This might be also related to the newest concept of resilience as a dynamic process of adaptation that includes personality, environmental and neurobiological factors. MiRNA that contributes to resilience against chronic stress has been already defined in resident intruder paradigms with rats in the context of chronic stress but not chronic pain as well as in the special case “FMS” [134, 135, 263, 264]. All of the selected miRNA for this study were found as relevant for stress, traumatic stress or other psychiatric symptoms like anxiety, panic or depression [265-267]. The WBC samples of patients who were categorized to cluster D that was termed as “resilient”, had no striking increase or decrease in

relative gene expression of all four miRNA compared to all other clusters. Based on a subjective experience during the interviews, most patients had to undergo a process in order to be able to adapt to the physical symptoms. This is generally referred to as an adjustment process, which has been favored or complicated by various factors. In this context, we need to describe and define resilience more in the sense of an adaptation by adaptive coping.

Finally, the benefits of all these studies need to be addressed. We do not need to discuss the urgent need for effective therapies for chronic pain patients. But besides all the research, something must reach the patients, and if it is only a paradigm shift that will be introduced into the hospitals like the shift from pathogenesis to salutogenesis. Possible treatment options may directly interfere with miRNA regulation via miRNA antagonists or mimetics. This can furthermore be targeted towards a single miRNA or multiple miRNAs simultaneously. There are still great challenges in understanding the differential regulation of target genes and the role of miRNAs in various diseases and their contribution to the chronification of pain which must be done in future research to use miRNA - based drugs in the treatment of chronic pain. Several difficulties in missing knowledge on effectivity, possible side effects or specificity of miRNA therapeutics contribute to the largely unexplored field of miR based drugs. But miRNA has the potential to be useful as diagnostic tools targeted for more effect treatment.

In our knowledge, no research exists analyzing the connection between miRNA and resilience in FMS patients. This study might function as the first step, which can further lead to more detailed results on a miRNA regulated resilience in FMS patients.

6 The concept of resilience in clinical practice

The growing interest in resilience was initiated by the paradigm shift in the human and social sciences from the pathogenetic approach to the concept of salutogenesis [268] that includes the perspective of the emergence and maintenance of health. In 1986, the WHO Ottawa Charta called for programs to promote health and prevent diseases [269]. Over the last ten years, resilience support programs have been developed, particularly in the Anglo-American countries. In Europe, however, there is a lack of science-based programs. Nevertheless, the market for training for resilience is booming in Germany, but rarely are these programs embedded in a theoretical concept or empirically verified. A German Resilience Centre was established to develop and evaluate empirically substantiated preventive measures. These programs usually start with behavioral prevention, i.e. on the person himself, but are also applied for relationship prevention (e.g. in companies) [74].

The Bavarian and Federal State Medical Association requested to identify patients with low resilience and to provide psychosocial support to these patients for more effective coping and therapy [270]. Furthermore, they recommend short forms of the resilience scale, such as the RS-13, that can be used as a reliable, valid and time-economic measuring instrument for the identification of these patients [271, 272]. The scale measures the expression of resilience as a positive personality trait in the sense of a personal resource that promotes individual adaptability. But there is no existing statistic that has an overview of the concept is still less applied or is already used in practice. Another critical point is that research has gone so far, and several neurobiological factors are known to have a major impact on the response profile to stress [80]. The recommended resilience scales only cover patients who have a resilient personality, but not those who are physiologically resilient. In order to determine these, further measuring instruments are needed, such as screening for certain SNPs or various genes known to contribute to resilience.

In general, there are four approaches for already existing resilience promoting programs [74]:

1. Mass media approaches that promote public health awareness through information transmission. One example is the American Psychological Association's (APA) "The road to resilience" campaign which presents mainly online-based ten ways to develop resilience [273].

2. Structured prevention programs aimed at the general population (e.g. programs for kindergartens, schools, businesses, students).

3. Structured prevention programs aimed at specific high-risk groups for the development of diseases (e.g. rescue workers e) or who already have a disease (e.g. diabetes patients) or who have been exposed to trauma (e.g. war veterans).

4. Multi-level programs involving the different levels of intervention, such as programs for school children involving children as well as their parents and teachers, or in the enterprise sector, which are at the organisational level (e.g. management level (e.g. management skills) and individual level (e.g. strengthening of personal resilience).

The focus of the healthcare industry and medicine has been on health-preserving factors for several years. However, the increasing number of patients suffering from mental disorders (e.g. depression, burnout) [274] led us to assume that these already existing concepts of resilience are still not applied in clinical practice or do not find their target for different reasons. Maybe the concept of resilience must also include the education of new medical staff. This might be a very subjective impression, but many FMS patients or patients with mental diseases still reporting that doctors and medical staff did not take them seriously and named them as “simulating”. This clearly shows maladministration in the education of medical staff.

Risk factors have already been known for decades, but the new social structures (including anthropogenic factors like social media, high workload and insecurities in the future) and the missing deceleration within society cause new problems combined with its diseases (e.g. burnout). However, there is a very different question: why should resilience to disease-causing systemic factors be strengthened and not simply change the disease-causing structure towards more humanity? Calm, leisure, devotion to oneself should be firmly established, in everyday life and in the houses that are dedicated to becoming healthy. The application in the clinic must include the creation of valuable awareness of health. Health is a rare commodity and is often taken for granted. The training of health staff should be reconsidered in terms of nutrition, awareness, and exercise. Various disciplines such as physiotherapists, human scientists, economic health scientists, physicians, psychiatrists and psychologists need to work more closely together, develop respect for each other and put people and health at the center. We do not need new concepts, because all the knowledge is already there. The existing concepts must be implemented and carried into the clinics.

This thesis is an attempt to bring these areas into dialogue productively with each other, to take unusual paths and to bring back some humanity.

7 Conclusion

The central question of the outlined thesis was to find biological, life historical and psychosocial factors that contribute to resilience in FMS patients resulting in different coping. Changing the vulnerable into a resilient phenotype with individualized and preventive therapies was defined as longterm aim. Altogether, the studies provide novel insights into the resilience of FMS patients. Coping seems to be the most crucial target for any therapy. Although the FMS cohort was found to be only moderately religious, disconnected and consciously aversive to classic religious symbols, a small group that was identified as religious orientated used the coping strategy “reappraisal”. This method was also identified as central coping within the resilient phenotype with a moderating effect on depression and other psychopathological symptoms as well as traumatic stress. Cytokines and miRNA also seemed to contribute to an adaptation to stress and inflammation, thus the resilient phenotype was characterized by high relative gene expression of the anti-inflammatory cytokine IL-10 compared to the vulnerable phenotype and the adaptation to stress might be regulated and promoted by the miR103a/107 family. This study made the first step in the analysis of miRNA regulated resilience in FMS patients which might help to develop diagnostic tools to identify vulnerable patients by their miRNA signature. Additional research is required to identify further neurobiological aspects of resilience in FMS patients and to create appropriate therapies for chronic pain patients and the prevention of chronic diseases to promote a positive lifestyle and health care.

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9 Appendix

Appendix A: List of Figures and Tables

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Manuscript 2

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Manuscript 3

Table 1: Demographic characteristics and questionnaire data.

Table 2: Effect sizes.

Table 3: Correlation between relative gene expression of miR and clinical scores within the patient cohort (N = 22).

Figure 1: Differences in relative gene expression of four selected microRNA in WBC samples of patients and controls normalized to 5S as housekeeping gene.

Figure 2: Differences in relative gene expression of four selected microRNA in WBC samples of patients clustered in four different subgroups normalized to 5S as housekeeping gene.

Figure 3: Association between resilience, immune system, behavior and selected four microRNA.

S1 Fig: Flow chart of patient recruitment.

S1 Table: Data of clinical examination, laboratory, and electrophysiological measurements.

Appendix B: Affidavit

I hereby confirm that my thesis entitled ***Psychosocial and somatic resilience factors in patients with Fibromyalgia syndrome (FMS)*** is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

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-

Place, Date Signature

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation ***Psychosoziale und somatische Resilienzfaktoren bei Patienten mit dem Fibromyalgie Syndrom (FMS)*** eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

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Ort, Datum Unterschrift

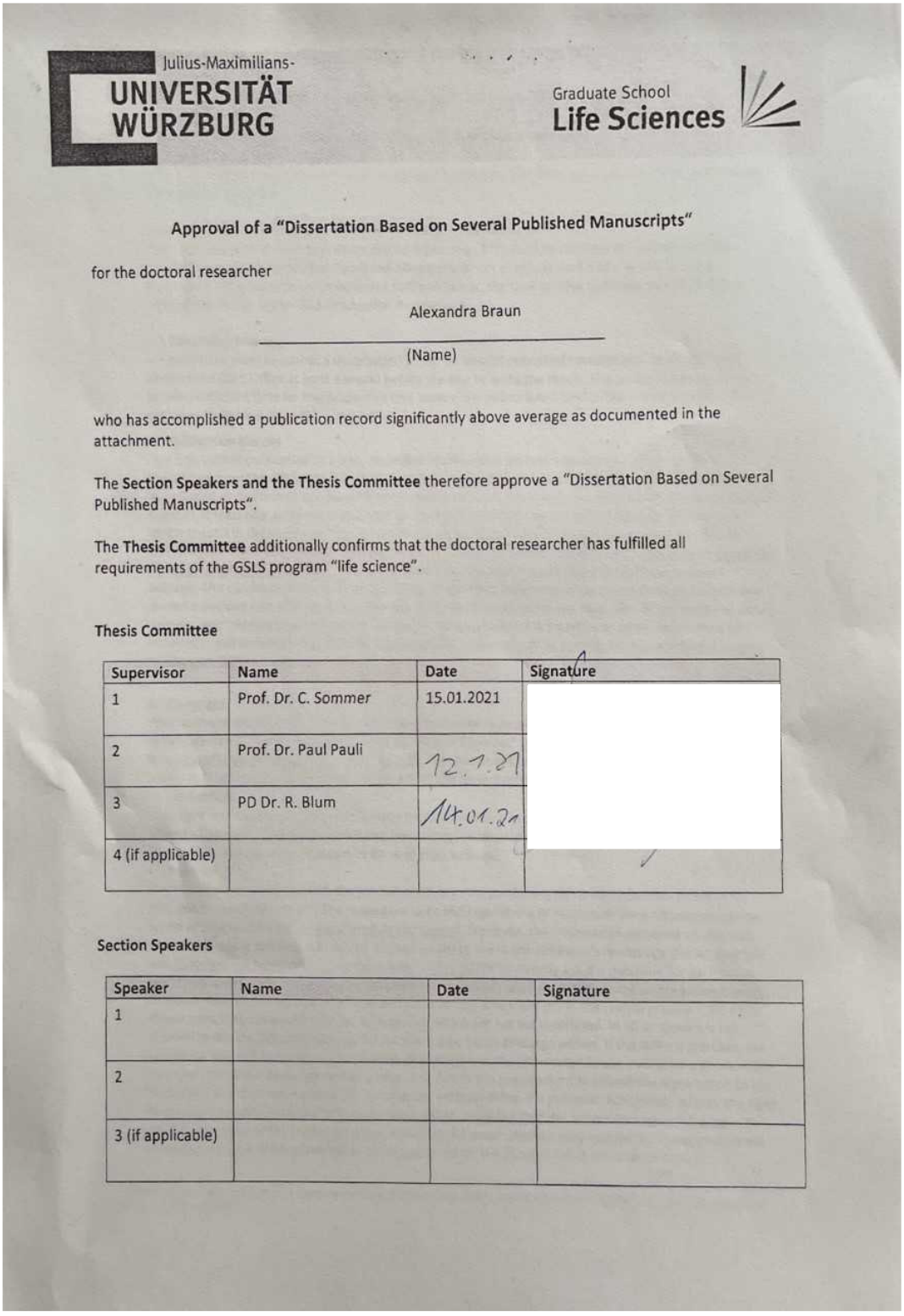
Appendix C: List of Publications with full reference

Braun A, Evdokimov D, Frank J, Wabel T, Pauli P, Üçeyler N, Sommer C. Relevance of Religiosity for Coping Strategies and Disability in Patients with Fibromyalgia Syndrome. *J Relig Health* (2021). https://doi.org/10.1007/s10943-020-01177-3

Braun A, Evdokimov D, Frank J, Pauli P, Üçeyler N, Sommer C. Clustering fibromyalgia patients: A combination of psychosocial and somatic factors leads to resilient coping in a subgroup of fibromyalgia patients. PLoS One. 2020 Dec 28;15(12):e0243806. doi: 10.1371/journal.pone.0243806. PMID: 33370324.

Braun A, Evdokimov D, Frank J, Sommer C, Üçeyler N. MiR103a-3p and miR107 are related to adaptive coping in a cluster of fibromyalgia patients. PLoS One. 2020 Sep 17;15(9):e0239286. doi: 10.1371/journal.pone.0239286. PMID: 32941517; PMCID: PMC7498021.

Appendix D: Approval of a “Dissertation Based on Several Published Manuscripts”



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WÜRZBURG

Graduate School
Life Sciences

Approval of a “Dissertation Based on Several Published Manuscripts“

for the doctoral researcher

Alexandra Braun

(Name)

who has accomplished a publication record significantly above average as documented in the attachment.

The **Section Speakers and the Thesis Committee** therefore approve a “Dissertation Based on Several Published Manuscripts“.

The **Thesis Committee** additionally confirms that the doctoral researcher has fulfilled all requirements of the GSLS program “life science”.

Thesis Committee

Supervisor	Name	Date	Signature
1	Prof. Dr. C. Sommer	15.01.2021	
2	Prof. Dr. Paul Pauli	12.1.21	
3	PD Dr. R. Blum	14.01.21	
4 (if applicable)			

Section Speakers

Speaker	Name	Date	Signature
1			
2			
3 (if applicable)			

Appendix E: Statement on Individual Author Contributions

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WÜRZBURG

Graduate School
Life Sciences

"Dissertation Based on Several Published Manuscripts"

Statement of individual author contributions to figures/tables/chapters included in the manuscripts

(If required please use more than one sheet)

Publication (complete reference):
Braun A, Evdokimov D, Frank J, Wabel T, Pauli P, Üçeyler N, Sommer C. Relevance of Religiosity for Coping Strategies and Disability in Patients with Fibromyalgia Syndrome. *J Relig Health* (2021). https://doi.org/10.1007/s10943-020-01177-3

Figure	**Author Initials**, Responsibility decreasing from left to right				
1	AB	CS			
2	AB				
Suppl. Figure*	**Author Initials**, Responsibility decreasing from left to right				
1	AB	CS			
2	AB				
Table*	**Author Initials**, Responsibility decreasing from left to right				
1	AB				
2	AB				
3	AB				
4	AB				
Suppl. Table*	**Author Initials**, Responsibility decreasing from left to right				
1	AB				
2	AB				
3	AB				
4	AB				

Explanations (if applicable): ***Three extra rows were added, "Suppl. Figure". "Table", and "Suppl.Table" to illustrate all present Figures and Tables within the manuscripts.**

Publication (complete reference):
Braun A, Evdokimov D, Frank J, Pauli P, Üçeyler N, Sommer C. Clustering fibromyalgia patients: A combination of psychosocial and somatic factors leads to resilient coping in a subgroup of fibromyalgia patients. PLoS One. 2020 Dec 28;15(12): e0243806. doi: 10.1371/journal.pone.0243806. PMID: 33370324.

Figure	**Author Initials**, Responsibility decreasing from left to right				
1	AB	NÜ			
2	AB	PP	CS		
3	AB				
4	AB	NÜ	CS		
5	AB				
6	AB				

Suppl. Figure*	Author Initials, Responsibility decreasing from left to right				
1	AB	CS			
2	AB	CS			
3	AB				
4	AB				
Table*	**Author Initials, Responsibility decreasing from left to right**				
1	AB				
2	AB				
Suppl. Table*	**Author Initials, Responsibility decreasing from left to right**				
1	AB	CS			
2	AB				
3	AB				
4	AB				
5	AB				
6	AB				

Explanations (if applicable): *Three extra rows were added, "Suppl. Figure", "Table", and "Suppl.Table" to illustrate all present Figures and Tables within the manuscripts.

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Figure	Author Initials, Responsibility decreasing from left to right				
1	AB	NÜ	CS		
2	AB	NÜ	CS		
3	AB				
Suppl. Figure	**Author Initials, Responsibility decreasing from left to right**				
1	AB	CS	NÜ		
Table	**Author Initials, Responsibility decreasing from left to right**				
1	AB				
2	AB				
3	AB				

Explanations (if applicable): *Three extra rows were added, "Suppl. Figure", "Table", and "Suppl.Table" to illustrate all present Figures and Tables within the manuscripts.

I also confirm my primary supervisor's acceptance.

Alexandra Braun 21.01.2021 Nürnberg

Doctoral Researcher's Name Date Place Signature

Prof. Dr. C. Sommer 20. Jan 2021 Würzburg

Supervisor

"Dissertation Based on Several Published Manuscripts"

Statement of individual author contributions and of legal second publication rights

(If required please use more than one sheet)

Publication (complete reference):

Braun A, Evdokimov D, Frank J, Wabel T, Pauli P, Üçeyler N, Sommer C. Relevance of Religiosity for Coping Strategies and Disability in Patients with Fibromyalgia Syndrome. *J Relig Health* (2021). https://doi.org/10.1007/s10943-020-01177-3

Participated in	**Author Initials**, Responsibility decreasing from left to right				
Study Design Methods Development	AB AB	CS CS	NÜ NÜ	TW PP	
Data Collection	AB				
Data Analysis and Interpretation	AB	TW	CS		
Patient recruitment and assessment*	JF	DE	AB	NÜ	CS
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	 AB AB AB AB	 CS CS CS CS	 TW		

Explanations (if applicable): ***An extra row was added, "patient recruitment and assessment". These authors were involved in the recruitment and assessment of patients of the multiple pain centers. These persons however did not participate in any of the other listed points.**

Publication (complete reference):

Braun A, Evdokimov D, Frank J, Pauli P, Üçeyler N, Sommer C. Clustering fibromyalgia patients: A combination of psychosocial and somatic factors leads to resilient coping in a subgroup of fibromyalgia patients. PLoS One. 2020 Dec 28;15(12): e0243806. doi: 10.1371/journal.pone.0243806. PMID: 33370324.

Participated in	**Author Initials**, Responsibility decreasing from left to right				
Study Design Methods Development	AB AB	CS NÜ	NÜ CS		
Data Collection	AB				
Data Analysis and Interpretation	AB	CS	NÜ		
Patient recruitment and assessment*	JF	DE	AB	NÜ	CS
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	 AB AB AB AB	 CS CS CS CS			

Explanations (if applicable): ***An extra row was added, "patient recruitment and assessment". These authors were involved in the recruitment and assessment of patients of the multiple pain centers. These persons however did not participate in any of the other listed points.**

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Participated in	**Author Initials**, Responsibility decreasing from left to right				
Study Design	AB	NÜ	CS		
Methods Development	AB	NÜ	CS		
Data Collection	AB				
Data Analysis and Interpretation	AB	NÜ			
Patient recruitment and assessment*	JF	DE	AB	NÜ	CS
Manuscript Writing					
Writing of Introduction	AB	NÜ	CS		
Writing of Materials & Methods	AB	NÜ	CS		
Writing of Discussion	AB	NÜ	CS		
Writing of First Draft	AB	NÜ	CS		

Explanations (if applicable): ***An extra row was added, "patient recruitment and assessment". These authors were involved in the recruitment and assessment of patients of the multiple pain centers. These persons however did not participate in any of the other listed points.**

The doctoral researcher confirms that she/he has obtained permission from both the publishers and the co-authors for legal second publication.

The doctoral researcher and the primary supervisor confirm the correctness of the above mentioned assessment.

Alexandra Braun	21.01.2021	Nürnberg	
Doctoral Researcher's Name	Date	Place	Signature

Prof. Dr. C. Sommer	20. Jan. 2021	Würzburg	
Primary Supervisor's Name	Date	Place	Signature