Etiology and pathophysiology of fibromyalgia syndrome

Background and goals

There is extensive scientific literature on the etiology and pathophysiology of fibromyalgia syndrome (FMS) which makes it difficult for the individual practitioner to stay up-to-date. Recent review articles focus either on biological or psychological aspects. The classification of FMS (physical illness vs. mental disorder), contents of patient education, and the preferred treatment methods are closely related to the identified etiologic and pathophysiologic factors. Therefore, we decided to perform a literature review and a formal consensus process on the pathogenesis and pathophysiology of FMS and chronic widespread pain (CWP). We aimed to analyze the content and quality of published studies on these topics in order to identify possible risk factors for the development of FMS and CWP and also to identify factors that are unrelated to the two syndromes.

Methods

The methodology of the literature search and analysis, and preparation of recommendations are presented in the article "Methodological fundamentals used in developing the guideline".

Results

Preliminary note

The following findings apply to adults. For the etiology and pathophysiology of FMS and CWP in children and adolescents please refer to the chapter "Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents".

Etiology

Risk indicators and factors

Evidence-based observation
Current evidence does not allow definite conclusions to be drawn about the etiology of CWP/FMS. It is unclear whether the risk indicators of CWP and FMS described in the following observations are risk factors. Strong consensus

Comment. Risk indicators are characteristics whose presence indicates a greater risk of illness without playing a causative role. Risk factors (etiologic factors) are characteristics that are causally associated with an increased risk of disease. Risk indicators and risk factors for disease are identified by retrospective and prospective cohort studies. The design of these studies, however, do not allow proof of a causal relationship. The following criteria increase the likelihood of a causal relationship: dose–effect relationship and experimental evidence, i.e., randomized-
controlled trials that demonstrate elimination of risk when the risk factor is eliminated.

The literature search yielded 3,107 hits. There were 6 prospective cohort studies with a follow-up duration ranging from 15 months to 45 years on biopsychosocial risk indicators for the development of CWP. There were 2 prospective cohort studies with a follow-up duration ranging from 11–24 years on biopsychosocial risk indicators for the development of FMS and 2 systematic reviews of case–control studies. There were no studies on dose–effect relationships. Experimental studies on risk factors for CWP and FMS were not found.

### Risk indicators of CWP

**Evidence-based observation**

The following biologic, mechanical, and psychosocial factors are associated with the development of CWP (risk indicators):

- **biological factors:** gene polymorphisms (β2-adrenergic receptors, ACTH precursor receptor, corticosteroid binding globulin), dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis (EL 2b);
- **mechanical factors:** uncomfortable postures at work (crouching, repetitive movements of wrist), monotonous work (EL 2b);
- **psychological factors:** increased physical complaints and illness behavior; low physical health-related quality of life; sleep disorders (EL 2b); permanent threat to life (EL 2c);
- **childhood:** hospitalization after traffic accident; institutionalization; maternal death; financial need (EL 2b).

### Strong consensus

**Comment.** The results of prospective cohort studies are summarized in **Tab. 1.** A study from Israel [1] compared 1,024 people from a town (Sderot) that was repeatedly attacked by rocket fire with 1,006 people who lived in another town (Ofakim) with a similar socioeconomic and demographic profile, but who were not exposed to rocket fire. Trauma-related symptoms and physical complaints were more frequent and the point prevalence of CWP was higher in Sderot (11.1%) than in Ofakim [8.3%; odds ratio (OR) 1.37].

### Tab. 1  Predictors of chronic widespread pain (CWP) in prospective population-based cohort studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk indicator (statistical predictor)</th>
<th>Risk (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective population-based cohort study of 1,658 adults between 25–65 years of age; follow-up after 36 months</td>
<td>Repetitive movements of wrists</td>
<td>OR 1.8 (1.2–2.7)</td>
<td>[25, 26, 27]</td>
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<td></td>
<td>Increased illness behavior</td>
<td>OR 9.0 (3.7–22.2)</td>
<td></td>
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<tr>
<td></td>
<td>Regional pain at baseline measurement</td>
<td>OR 2.1 (1.3–3.3)</td>
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<tr>
<td></td>
<td>Increased physical symptoms</td>
<td>OR 3.3 (1.5–7.4)</td>
<td></td>
</tr>
<tr>
<td>Prospective cohort study of 1,081 newly employed individuals at 12 different work places; follow-up after 24 months</td>
<td>Crouching activity &gt;15 min</td>
<td>OR 2.0 (1.1–3.6)</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>Monotonous work</td>
<td>OR 1.9 (1.1–3.2)</td>
<td></td>
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<tr>
<td>Prospective population-based cohort study; 3,171 adults without CWP between 25–65 years of age; follow-up after 15 months</td>
<td>Increased physical symptoms</td>
<td>OR 1.8 (1.1–3.1)</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Increased illness behavior</td>
<td>OR 3.3 (2.3–4.8)</td>
<td></td>
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<tr>
<td></td>
<td>Sleep disorder</td>
<td>OR 2.7 (1.6–3.2)</td>
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<tr>
<td>Prospective cohort study of 768 individuals without CWP but with a profile indicating increased risk for CWP, out of a population-based sample of 11,000 individuals; follow-up after 15 months</td>
<td>HPA axis dysfunction</td>
<td>OR 8.5 (1.5–47.9)</td>
<td>[28]</td>
</tr>
<tr>
<td>EPIFUND: 2,509 patients from three British general practitioners between 25–65 years of age; follow-up after 15 months</td>
<td>Gene polymorphisms affecting the HPA axis</td>
<td>OR 1.61 (1.0–2.6)</td>
<td>[19]</td>
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<tr>
<td></td>
<td>ACTH precursor-receptor</td>
<td>OR 1.2 (1.0–1.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SERPINA6, rs941601, genotype CT</td>
<td>OR 2.2 (1.1–4.4)</td>
<td></td>
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<tr>
<td></td>
<td>Genotype TT</td>
<td>OR 2.2 (1.2–4.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroid-binding globulin MC2R rs11661134, genotype AG and AA</td>
<td>OR 2.2 (1.1–4.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased health-related quality of life</td>
<td>RR 4.0 (2.6–6.2)</td>
<td>[33]</td>
</tr>
<tr>
<td>1958 British Cohort Study: 18,558 individuals; follow-up after 45 years</td>
<td>Teacher reports of persistent behavioral abnormalities at ages 7, 11 and 16 years of age</td>
<td>RR 2.1 (1.4–3.2)</td>
<td>[34]</td>
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<tr>
<td></td>
<td>β2-adrenergic receptor (ADRB2) combinations, e.g. H2-H2</td>
<td>RR 1.8 (1.1–2.9)</td>
<td>[18]</td>
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<td></td>
<td>Hospitalization after traffic accident</td>
<td>RR 1.5 (1.1–2.1)</td>
<td>[30, 31]</td>
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<td></td>
<td>Institutionalization</td>
<td>RR 1.7 (1.3–2.4)</td>
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<td></td>
<td>Maternal death</td>
<td>RR 2.0 (1.1–3.7)</td>
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<td></td>
<td>Financial need</td>
<td>RR 1.6 (1.3–1.9)</td>
<td></td>
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<td></td>
<td>Multiple physical symptoms at the age of 7 years</td>
<td>RR 1.5 (1.0–2.3)</td>
<td></td>
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</tbody>
</table>

ACTH adrenocorticotropic hormone; CI confidence interval; CWP chronic widespread pain; HPA hypothalamic–pituitary–adrenal; OR odds ratio; RR relative risk.
Risk indicators for FMS

Evidence-based observation
The following biological and psychosocial factors are associated with the development of FMS:
- biological factors: inflammatory-rheumatic diseases (EL 2b),
- gene polymorphisms of the SHT2-receptor (EL 3a),
- life style: smoking, overweight, lack of physical activity (EL 2b)
- psychological factors: physical abuse in childhood and adulthood, sexual abuse in childhood and adulthood (EL 3a), stress at the workplace (EL 3b).

Strong consensus

Comment. See Tab. 2. Genetic factors are likely present since FMS tends to cluster in families [38]. Candidate genes in the serotonergic, dopaminergic, and catecholaminergic systems may play a role. However, this is also the case in other chronic pain syndromes and therefore these findings are not specific for FMS [3, 4].

In a retrospective cohort study of 62,000 members of a U.S. health insurance association with FMS was found for rheumatoid arthritis [RR (relative risk) for women 4.5 (95% CI 3.6–5.5), RR for men 6.1 (95% CI 4.2–8.8)] and with systemic lupus erythematosus [RR for women, 5.8 (95% CI 4.2–8.0); RR for men not significant; [46]).

Out of 9,739 patients with rheumatoid arthritis without FMS (U.S. National Data Bank for Rheumatic Diseases) on average 19.8% met the criteria for FMS at least once during 4.4 years of observation; 7.4% met the criteria at the end of the observation period. Poverty [HR (hazard ratio) 1.64 (95% CI 1.47–1.82)], overweight [HR 1.60 (95% CI 1.43–1.79)], depressive symptoms [HR 2.28 (95% CI 1.97–2.64)], numerous physical comorbidities [HR 2.53 (95% CI 2.36–2.71)], and low physical activity [HR 2.53 (95% CI 2.36–2.71)] predicted FMS [47].

In a 2-year prospective observational study of 4,791 hospital employees (4,250 women, 541 men), increased bullying in the workplace, low freedom of action, and high workload increased the risk of physician-diagnosed FMS [22]. Due to problems with the study design (no detection of pain using validated instruments at the beginning and end of the study), the level of evidence was downgraded for this study.

Etiology and pathophysiology of fibromyalgia syndrome

Abstract

Background. The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinäre Vereinigung für Schmerztherapie", DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycInfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine.

Results. Current data do not identify distinct etiologic or pathophysiological factors mediating development of FMS. The development of FMS is associated with inflammatory rheumatic diseases (EL2b), with gene polymorphisms of the 5-hydroxytryptamine (HT2) receptor (EL3a), lifestyle factors (smoking, obesity, lack of physical activity; EL2b), physical and sexual abuse in childhood and adulthood (EL3a).

Conclusion. FMS is most likely the result of various pathogenic factors and pathophysiological mechanisms. The English full-text version of this article is available at Springer-Link (under “Supplemental”).

Keywords

Fibromyalgia syndrome · Guideline · Systematic review · Etiology · Pathophysiology

Zusammenfassung

Hintergrund. Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom (FMS; AWMF-Registernummer 041/004) wurde ab März 2011 vorgenommen.


Ergebnisse. Die aktuelle Studienlage erlaubt keine eindeutigen Aussagen zur Ätiologie und Pathophysiologie des FMS. Die Entwicklung eines FMS ist mit entzündlich-rheumatischen Erkrankungen (EL2b), Genpolymorphismen des 5-Hydroxytryptamins (HT2)-Rezeptors (EL3a), Lebensstilfaktoren (Rauchen, Übergewicht, mangelnde körperliche Aktivität; EL2b), körperlicher Misshandlung und sexuellem Missbrauch in Kindheit und Erwachsenenalter (EL3a) assoziiert.

Schlussfolgerung. Das FMS ist wahrscheinlich die Endstrecke verschiedener ätiopathogenetischer Faktoren und pathophysiologischer Mechanismen.

Schlüsselwörter

Fibromyalgiesyndrom · Leitlinie · Systematische Übersicht · Ätiologie · Pathophysiologie
Vitamin D deficiency, infectious diseases, and accidents

Evidence-based observation
Data on the association between FMS and vitamin D deficiency, infectious diseases, and accidents are inconsistent.
EL 3b. Strong consensus

Comment
Vitamin D deficiency: In population-based studies [29] and in case–control studies [17], an association of CWP with decreased vitamin D levels has been reported. However, in case–control studies no difference in vitamin D levels were found between patients with FMS and healthy controls [10, 42].

Infections: Prospective studies are not available. In case–control studies, the association of chronic hepatitis C and FMS is contradictory. The results of two case–control studies showing an increased prevalence of FMS in patients with chronic hepatitis B and HTLV-1 infection, respectively, have not been replicated [38, 39]. Case–control studies investigating the association of Lyme disease with FMS are not available. In a large single-center observational study of 287 patients, 22 patients (8%) developed FMS. Fifteen patients diagnosed with FMS participated in the 4.5-year observational study. Symptoms of Lyme disease improved in 14 of 15 patients following antibiotic therapy but FMS symptoms persisted in all patients [11]. Following Lyme disease, 5% of patients report persistent musculoskeletal pain, fatigue, and difficulties in concentrating [6].

Accidents: Data are contradictory. A total of 154 patients who were hospitalized after a whiplash injury were examined after 1.5 and 3 years for the presence of FMS; 53 patients with fractures served as a control group. After 3 years of follow-up, 3 of 126 patients with whiplash injury and 1 of 53 patients with fracture were diagnosed with FMS [43]. A prospective cohort study of 957 members of a health insurance who had recently suffered an automobile accident examined the occurrence of widespread pain (WP) after 12 months of follow-up; 7.8% of patients had WP. Physical symptoms after the accident (RR 2.5, 95% CI 1.2–5.1), high utilization of health care services prior to the accident (RR 3.6, 95% CI 1.6–7.9), somatization prior to the accident (RR 1.7, 95% CI 0.99–2.8), and older age (RR 3.3, 95% CI 1.5–7.1) predicted WP [48].

In a prospective cohort study of 7,462 members of a health insurance company with whiplash injuries of the cervical spine, 266 individuals had localized pain after the accident and were followed-up at 4, 6, and 12 months. The cumulative incidence of CWP was 21%. CWP was reported most commonly in the early time period after the accident. The risk of developing CWP was greater in individuals with depressive symptoms at baseline measurement (OR 3.2, 95% CI 1.6–6.3) [20]. CWP at 12 months was rare (49).

The examination of 53 of 153 survivors 3.5 years after a major train accident demonstrated that 15% fulfilled FMS criteria [5].

Pathophysiology

Altered central pain processing, dysfunction of the HPA axis, peripheral pain generators

Evidence-based observation
It is possible that the following pathophysiological mechanisms play a pathogenic role in FMS:

- altered central pain processing (EL 3b),
- dysfunction of the HPA axis (EL 2b), and
- peripheral pain generators (EL 3b).

Strong consensus

Comment. The literature search yielded 763 hits. These included a systematic review of biomarkers [9], no other systematic reviews of other pathophysiological mechanisms, and numerous narrative review articles (e.g., [2, 3, 13, 35, 37, 38, 40]). Systematic reviews completed by members of the working group regarding cytokines [44] and central nervous system im-
The neurotransmitter hypothesis is unclear [9]. The role of cortisol secretion and individual tests of the HPA axis are inconsistent and the role they are confounded by other variables (e.g., changes in cytokine patterns because of depression).

2. Confounding of the results due to comorbidities: due to the frequent comorbidity of FMS with other psychiatric disorders and functional disorders, it is difficult to define a “pure FMS” group [36]. The potential influence of these comorbidities has not been sufficiently controlled in these studies. One study that controlled for comorbid depression disorder found no consistent differences in the gray matter between FMS patients and healthy controls [21].

3. Lack of specificity of findings: in most studies on pathophysiology, the healthy control subjects were healthy individuals of the same age and sex as the affected individuals, but not patients with other chronic pain syndromes and mental disorders. It is unclear whether the described pathophysiological abnormalities are specific for FMS.

4. Methodological problems: the heterogeneity of analysis makes a comparison of study results difficult [35]. The sample sizes of most studies are small (<25 individuals per group). In addition, the quality of these studies is mostly low.

5. Ignoring the probable heterogeneity of the FMS population.

Because of the problems mentioned, we chose not to summarize the numerous studies presented—neither in a narrative fashion nor in the form of a meta-analysis. Instead a few pathophysiological mechanisms for which the data are largely consistent are discussed.

**HPA axis**: Dysfunction of the HPA axis as a pathophysiological factor is discussed in many review articles (e.g., [3]). Data on cortisol secretion and individual tests of the HPA axis are inconsistent and the role of comorbid depression is unclear [9].

The best evidence for the role of a disturbed HPA axis derives from a prospective population-based study. Out of 11,000 individuals, 768 were chosen because their psychosocial profile indicated an increased risk for the development of CWP. Then, 463 subjects were randomly selected and 267 (58%) eventually agreed to participate in the study, of whom 241 completed the study. After 15 months, 12% of these individuals had newly developed CWP. A lack of suppression in the dexamethasone suppression test (OR 3.53, 95% CI 1.17–10.65), low morning serum cortisol levels, and high evening salivary cortisol levels were associated with the development of CWP [28].

**Autonomic nervous system**: A number of differences in the function of the autonomic nervous system among patients with FMS and healthy subjects have been described (e.g., decreased heart rate variance, a tendency for syncope, altered cutaneous capillary responsiveness). However, a causal relationship could not be proven [38].

**Immune system**: Many studies addressed the issue of immune dysfunction in FMS. Some groups detected autoantibodies whose significance is still unclear [9]. Among the cytokines, interleukin-6 is increased in the plasma or serum of patients with FMS [44]. In one longitudinal study, elevated cytokine levels normalized after multimodal therapy [45].

**Neurotransmitter**: The neurotransmitter substance P is increased in the cerebrospinal fluid (CSF) of patients with FMS, but also in other chronic pain syndromes, so that substance P is more of a marker for chronic pain than for FMS specifically. Serotonin levels in CSF and serum are decreased. The CSF levels of the neurotrophic factors nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are increased, but the significance of these findings is unclear. Data for other neuropeptides and neurotransmitters are inconsistent [39].

**Peripheral nervous system** and **muscle**: It was hypothesized that peripheral pain generators contribute significantly to the initiation or maintenance of FMS [41]. In a subgroup of patients with FMS, polyneuropathy was present [7]. Modulation of muscle afferent fibers may play a role [38].

**Altered central pain processing**: The studies on central pain processing in FMS cannot be reliably interpreted due to the use of different methods (e.g., PET, fMRI, EEG), different study designs (e.g., measurement while resting or during stimulation), the lack of longitudinal studies, and the low quality of the methods used and of data analysis. Augmentation of pain processing and a tendency for altered structures and functions of brain areas that are important for the cognitive–emotional processing of pain and descending pain inhibition have been reported. However, due to the general lack of patients with other chronic pain syndromes in the control groups, these findings cannot be interpreted as being FMS specific [35].

**Disorders of the thyroid hormone system, disorders of the female sex hormones, disorders of the renin–angiotensin–aldosterone system, structural muscle changes, cosmetic breast implants**

**Evidence-based observation**
The following statements from the first version of the guidelines still apply: there is no evidence of a link between FMS and disorders of the thyroid hormone system, disorders of the female sex hormones, disorders of the renin–angiotensin–aldosterone system, structural muscle changes, and cosmetic breast implants.

**EL 2c, strong consensus**

**Comment**: See [39]

**Mechanisms of learning**

**Evidence-based observation**
The following statements from the first version of the guidelines still apply: learning mechanisms such as operant conditioning, and sensitization play a role in the chronicity of FMS.

**EL 2b, strong consensus**

**Comment**: See [39]
Biopsychosocial model

Evidence-based observation
A biopsychosocial model with respect to predisposition, initiation, and chronicity of FMS is postulated. Physical and/or biological and/or psychosocial stressors in the context of an appropriate genetic predisposition and learning history produce autonomic, endocrine, and central nervous system reactions that result in the symptoms of FMS, such as pain, fatigue, and sleep disorders, autonomic and psychological symptoms. There is heterogeneity in the genetic predisposition, learning history, and in the autonomic, endocrine, and central nervous system reactions. FMS is a final pathway of various pathogenetic factors and pathophysiological mechanisms. Strong consensus

Comment. See [39]

Discussion

It is difficult to summarize the evidence on the etiology and pathophysiology of CWP and FMS due to several factors. There is an extensive literature on individual factors that are related to CWP or FMS and which may play a role in the etiology or pathophysiology of these conditions. Since the publication of the first version of these guidelines, multiple other factors have been examined, including gene polymorphisms, smoking, overweight and nutrition, vitamins, neuroendocrine factors, immunologic factors, mitochondrial function, different infections, central pain processing, and individual biographical aspects.

Unfortunately, for the majority of these studies, due to limitations in methodology and design, it remains unclear whether the findings indicate random associations, factors inherent to the conditions studied, consequences of disease, or if they indeed represent relevant factors in etiology or pathophysiology.

As was mentioned in the first version of these guidelines, there are some factors for which there is definitely no relationship with FMS. These conclusions are still accurate and apply to the thyroid hormone system, the renin–angiotensin–aldosterone system, female sex hormones, structural muscle changes, Lyme disease, and cosmetic breast implants.

The best evidence for positive correlations of causative factors with the development of CWP or FMS has been obtained from prospective cohort studies. Several biologic factors could be identified, including the presence of inflammatory–rheumatic diseases, genetic factors, lifestyle factors such as smoking, overweight, and decreased physical activity, and psychological factors, such as physical abuse or sexual abuse. Additional prospective, population-based studies with an analysis of dose–effect relationships, and interactions of presumed risk factors are required.

Conclusion for clinical practice

Several factors reduce the meaningfulness of many studies on pathophysiology, such as their sectional design, the lack of consideration of confounding comorbidities, the small number of study subjects, and the use of very heterogeneous methods. The pathophysiologic factors that are probably associated with FMS have been listed above. However, because of the aforementioned limitations, it is difficult to assess a causal relationship. There is an urgent need for further research. Future research should employ standardized methods, control for current medication use and psychological comorbidities, and include adequate control groups consisting of healthy individuals and individuals with other chronic pain syndromes. In addition, studies with larger sample sizes are required to simultaneously examine different potential neuroimmunological and neurobiological factors, and their reciprocal relationships.

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Conflict of interest. See Tab. 5 in “Methodological fundamentals used in developing the guideline” by W. Häuser, K. Bernandy, H. Wang, and I. Kopp in this issue.

References


Tab. 5

Schwerpunkt