Claudia Schilling
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1. Academic Profile

Claudia Schilling is a psychiatrist, neurologist and sleep specialist, head of the sleep laboratory at CIMH and of the research group Neuropsychiatric Sleep Disorders. Her research focusses on the contribution of sleep disturbance and sleep microstructure to aetiological models of mental illness. At the centre of her studies are neurophysiological sleep-related aspects of schizophrenia, insomnia disorder and, more recently, the post-COVID syndrome.

Her vision is to use sleep as a window to the neurobiology of mental disorders. Sleep physiology is affected in almost all mental illnesses. The study of sleep holds the unique opportunity to investigate the functioning of the brain of people with mental disorders without this investigation being influenced by behavioural aspects and cooperation. Knowledge of sleep physiology allows conclusions to be drawn about the structures and neurotransmitters involved. For example in schizophrenia altered activity of sleep spindles, a characteristic feature of NREM sleep, which is one of Claudia Schilling's main fields of study, points to thalamo-cortical network dysfunction.

Already early in her career, the functioning of the thalamo-cortical network was subject of her research in investigating NMDA neurotransmission in this network in an animal model of absence epilepsy during her doctoral thesis. Her work showed that shifting this network's NMDA transmission in either direction by agonists or antagonists prevents it from producing oscillatory activity characteristic for this network. During her time at the department of neurology at the University of Heidelberg, she continued using neurophysiological methods for the investigation of intracortical excitability in neuroimmunological and vascular brain disease.

At the CIMH she continues her interest in studying the neurophysiology of the brain by investigating sleep to contribute to the understanding of neuropsychiatric disorders. Consisting of three doctoral students and her colleague Michael Schredl, her research group performs its research in humans combining neurophysiologic methods such as polysomnography and electroencephalography with clinical, psychometric and genetic data. 38 peer-reviewed articles so far cover her research findings.

One of Claudia Schilling's main research interests are sleep spindles, their involvement in the pathophysiology of mental and sleep related disorders and their role for cognitive processes. Sleep spindles are brief bursts of oscillatory EEG activity within the 9-16 Hz range of NREM sleep, originating in the thalamo-cortical network. In a hierarchical interaction with other sleep-related oscillations they provide optimal conditions for synaptic plastic processes underlying memory formation, supporting the transformation of labile memory traces into stable long-term representations. In schizophrenia, deficient sleep spindle activity is a stable finding and correlates with cognitive functions and positive symptoms. Claudia Schilling could show that the spindle deficit also can be found in healthy first-degree relatives compatible with a genetic background and that it was associated with decreased memory performance. Further studies addressed the association of the altered spindle activity with genetic risk constellations for schizophrenia.

The second research area is the study of pathophysiological mechanisms including sleep spindles in insomnia disorder. Central nervous hyperarousal is as a key component of current pathophysiological concepts of insomnia and discussed as a transdiagnostic feature in mental illness. Using the VIGALL (Vigilance Algorithm Leipzig) algorithm, the group found evidence for daytime hyperarousal in insomnia. This resembles the hyperstable vigilance regulation found in patients with depression. In contrast to these, however, insomnia patients do not remain in high vigilance stages, but show a decreased tendency to produce spindles at the transition to sleep. Reduced spindle activity has been shown to be predictive for poorer response to cognitive behavioral therapy for insomnia. However, the literature regarding the integrity of spindle activity in insomnia disorder so far is inconclusive as other studies failed to show a spindle deficit. This may be due to insomnia being a heterogenous disorder. Thus, in another project the group currently investigates sleep spindle activity in a large sample of patients with insomnia disorder distinguishing potential subtypes regarding objective sleep disturbances. Further, the group evaluates whether Claudia Schilling's insomnia psychotherapy program, having been offered to 105 insomnia patients and showing very high effect sizes, differs in treatment response with respect to differences in objective sleep disturbance, spindle activity, sleep-related metacognitions or stress reactivity.

The third research topic since recently is the post-COVID syndrome. In the COVID-19 pandemic-related experiences of the last two years, it quickly became clear that a proportion of patients have not yet recovered after overcoming acute infection. Sleep-wake disturbances and cognitive disorders play an important role in this context, as they are among the most prevalent symptoms within the post-COVID syndrome. The mechanisms underlying these symptoms are still largely unknown and are the subject of research projects of the group. As a first step, Claudia Schilling established an outpatient clinic for patients with post-COVID syndrome. Affiliated research projects benefit from the outpatient clinic in recruiting patients, while clinical work benefits from the research projects, for example with respect to growing knowledge about treatable sleep features in post-COVID improving fatigue and daytime functioning. This is the case for new onset central nervous hypersomnia or sleep-related breathing abnormalities. Other projects focus on autoimmunity, cell energy metabolism and endothelial dysfunction in post-COVID syndrome. In addition, Claudia Schilling is a member of the EPILOC consortium, a collaborative research network of all four Baden-Württemberg universities to study the epidemiology and clinical symptoms of post-COVID syndrome. Within the consortium, Claudia Schilling is in charge of the neuropsychiatric topics across all four sites. Together with her colleague Michael Schredl she could show that in the EPILOC population-based sample of more than 11.000 persons tested positive for SARS-CoV-2, disordered sleep before the infection was one of the strongest risk factors for developing long lasting sequelae. The interest in post-COVID syndrome is not only related to the disorder itself, but the vision is to learn from post-COVID syndrome for a better understanding of other conditions with leading symptom fatigue such as other post-viral syndromes with neuropsychiatric manifestation or post cancer fatigue.

A strength of the research group Neuropsychiatric Sleep Research is its location at two interfaces: The close connection of experimental sleep research with clinical sleep medicine, given by the location of the research group in the sleep laboratory with sleep outpatient clinic, results in important impulses for clinically relevant questions and in access to a large amount of clinical-neurophysiological data sets of various disorders. Similarly, the connection of sleep medicine and sleep research with clinical psychiatry at CIMH offers the opportunity to approach the pathophysiology of mental disorders from a sleep medicine perspective, in line

with the central vision of the research group, and also to facilitate an implementation of sleep medicine services in psychiatric care.

2. Key output of the years 2020 to now

Altered spindle activity in schizophrenia

To elucidate the genetic background of impaired spindle activity in schizophrenia, we investigated the association of fast sleep spindle density with polygenic risk for schizophrenia (SCZ-PGS) in healthy subjects. In view of the important role of spindle activity for intelligence and cognition we further analyzed the effect of stratification of genetic variance for SNPs concordant and discordant for intelligence and schizophrenia-related risk on this association. We found (1) a positive correlation of SCZ-PGS with fast spindle density and (2) that this association was predominantly driven by the subset of SNPs concordant for schizophrenia and intelligence.
Our results fit the considerations about genetically driven cognitive heterogeneity of schizophrenia. In this context, integrity of spindle activity might represent an easily accessible biological marker for a favorable cognitive outcome in schizophrenia. This should stimulate further research on the prognostic value of sleep spindle parameters for clinical subtypes of schizophrenia.

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Insomnia pathophysiology

Insomnia research often focusses on sleep, however, there are clinical indicators of hyperarousal in insomnia patients also occurring during waking. Therefore, we studied waking state hyperarousal in insomnia by the perspective of resting-state vigilance dynamics using the VIGALL algorithm. Insomnia patients showed enhanced EEG vigilance stability as compared to controls. The pattern of vigilance hyperstability differed from that reported previously in depressive patients. Thus, hyperarousal is a common feature in insomnia and depression, however its nature differs between both disorders.

Sleep-related metacognitions are a typical feature in insomnia disorder and typically drive hyperarousal in bed. To be able to investigate sleep-related metacognitions in insomnia patients, Claudia Schilling together with her colleague Michael Schredl developed and published a German short version of a questionnaire about sleep-related metacognitions.

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Sleep research in clinical psychiatry
As a member of the Sleep Medicine taskforce of the DGPPN, Claudia Schilling has been involved in several studies aiming at improving sleep medicine care for psychiatric patients. Studies on the prevalence of sleep-related disorders, here restless legs syndrome, within psychiatric patient populations intend to raise awareness of the topic of sleep. Moreover, given a lack of insomnia-related psychotherapy services, digital treatment services, which were the subject of a review, help to fill this gap.

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Neuropsychiatric manifestation in post-COVID syndrome
As a clinical care offer for patients with post-COVID syndrome and at the same time as a basis for associated research projects, Claudia Schilling set up a post-COVID outpatient clinic at the CIMH in May 2021. In the course of the last year, about 130 patients with post-COVID syndrome were treated there. The outpatient clinic is very much in demand and the strong public interest is reflected in the press in the form of 6 daily newspaper articles over the last year.

Claudia Schilling's expertise on post-COVID syndrome was reflected in an invited review article on sleep and cognition in post-COVID syndrome.

In the EPILOC consortium, Claudia Schilling is responsible for the neuropsychiatric topics across all sites. The data from phase I have already been published as a preprint, phase II is about to be completed. In a separate own research project on post-COVID syndrome with a focus on sleep, cognition and autoimmunity, the recruitment of 52 patients and healthy subjects has been completed and the evaluation is currently underway.

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