PROFESSOR ANNE ECKERT

Resilience and vulnerability in schizophrenia

A research consortium of neurobiologists and psychiatrists led by **Professor Anne Eckert** aims to improve understanding of schizophrenic psychoses, which may lead to novel therapeutic targets

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First, could you outline your plan to create a stronger understanding of resilience and vulnerability in schizophrenia?

In recent years, ideas of the aetiopathogenesis of psychotic disorders based on the concept of 'vulnerability' have been gaining increasing ground. The publications of Zubin and associates above all have contributed to a 'vulnerability stress model'. According to this descriptive model, schizophrenic psychoses develop as a result of underlying vulnerability, which seems to be a genetic one in most cases, and triggers such as stress factors under modulation of the social and physical environment, which finally lead to the outbreak of frank psychosis. The increased vulnerability which gives rise to this is perceived as a threshold descensus of the individual towards stimuli. Furthermore, multi-causality of vulnerability is assumed as the starting point, whereby there is the possibility of several therapy approaches.

On the contrary, protective factors against the effects of stress might be the key to the development of optimal interventions by improving resilience and reducing vulnerability. Thus, a more favourite disease outcome seems to be associated, among others, with less vulnerability and greater resilience. The vulnerability-resilience model differentiates temporarily relatively stable trait markers with generally unaltered expressivity at the pre-, intra-, and post-psychotic stages in contrast to episode (state) markers. The goal of the present study is the identification of resilience and vulnerability factors using a multilevel approach from psychopathology, neuropsychology and neuroimaging to neurobiology.

Why is it important to look at this disorder through different levels: psychopathology, neuropsychology and neuroimaging to neurobiology ?

We want to relate disturbances in several patient groups in brain structure, brain function, information processing, and mitochondrial abnormalities at the molecular and cellular level to each other and to psychopathology in an interdisciplinary research setting, addressing a translational approach. Linking psychopathology to functional aspects of mitochondria and brain structure and function might represent an advantage with regard to a better characterisation of vulnerability and resilience factors in patient groups compared to single approaches. One important step in taking this novel approach is to differentiate and characterise trait and state markers for schizophrenic psychoses. Psychotic symptoms alone are not adequate for determining the genetic and neural basis of schizophrenia. Future studies should underscore whether and to what extent the enduring trait markers for these psychoses are modifiable and how they are related to state markers for frank psychosis. Knowledge acquired from our study will eventually be applied to unravel the pathophysiology and to inform prevention and intervention strategies.

Could you expand on the main methods you employ? Have you developed any innovative techniques specifically for this study?

Very little is known about the nature of structural and neurofunctional brain correlations of liability to psychosis. The objective of the present project is to develop a better understanding of the neurobiological mechanisms of liability and resilience factors for these disorders. This will be achieved by using state of the art neuroimaging methods such as Magnetic Resonance Imaging (MRI) to examine brain structural and functional correlates and correlating them with blood biomarker findings. The innovation lies in the fact that the team wants to link results gained from different innovative techniques on an individual level to identify a potentially important set of factors that, when combined, yield high sensitivity, specificity, and positive predictive value for identifying individuals at high risk for schizophrenia.

How important is forming partnerships to the success of your research?

The research team recognises the challenge of such a complex project which requires collective action, involving a range of stakeholders working in partnership. Very

Sculpting schizophrenia

Work underway at the **University of Basel** in Switzerland takes an unprecedented approach to understanding schizophrenic psychoses by combining neurobiological methods, neuroimaging, neuropsychological and clinical methods to investigate well-defined patient groups

SCHIZOPHRENIC PSYCHOSES CAN be long-term mental health conditions; the most common form being the paranoid type which is characterised by the presence of prominent delusions or auditory hallucinations. Commonly, the onset of schizophrenic psychoses in men peaks at around age 20, whereas the onset peak is later in women, at around their mid-twenties. Approximately 4 per cent of all cases of schizophrenia experience the onset of the disorder before the age of 18. Subtle prodromal symptoms frequently present in individuals, on average five years prior to onset of frank psychosis.

It is being increasingly recognised that schizophrenia is a pleiotropic disorder. The past decade has witnessed an abundance of studies focusing on the broad spectrum of different psychopathologies (including misinterpretations of perceptions or experiences, disorganised thinking and behaviour, affective symptoms, but also dysfunction in cognition) as well as brain structure and function. Magnetic resonance spectroscopy has led to a better understanding of the disease suggesting that schizophrenia is a disease of brain energetics characterised by abnormalities in mitochondrial function and oxidative stress levels. Although different schizophrenia types are similar in symptom presentation and many neurobiological aspects, there is evidence of different disease variations with diverse etiologies and pathomechanisms as articulated in the endophenotype concept of schizophrenia. Furthermore, there is evidence that improved patient outcomes are associated, among other things, with less vulnerability and greater resilience.

However, exact pathogenetic mechanisms are not yet known, although genetic vulnerability seems to underly most disorders. There are currently discrepancies in published data, which might be the result of investigating different patient populations by using different methods, e.g. different tissues. For example, in many cases investigated, patient groups are not well defined with regard to factors such as type of schizophrenia, course of illness and medication, age of onset, impact of gender, and neurobiology.

WELL-DEFINED PATIENT GROUPS

A team at the University of Basel in Switzerland is currently undertaking research designed specifically to deal with these limitations, using well-defined and highly specific patient groups which sets their project apart from all previous investigations in this field. Led by project coordinator Professor Anne Eckert, the consortium's three co-investigators are: Stefan Borgward, MD; Anita Riecher-Rössler, MD; and Marc Graf, MD. Funded with a grant from the Swiss National Science Foundation, the project is a collaboration between the Neurobiology Laboratory For Brain Aging and Mental Health (Professor Anne Eckert who is responsible for the neurobiological methods and biomarker research), the Department of Forensic Psychiatry at the University (Marc Graf, MD), which deals with the most severe forms of schizophrenia, and the FePsy (Früherkennung von Psychosen, early detection of psychosis) Clinic (Professor Anita Riecher-Rössler). This project has established the methodology and experience of exactly characterising patients with a predisposition to schizophrenia and patients in the very early phase of schizophrenia – not only in the clinical domain of psychopathology and risk factors but also in the domain of neuropsychology and neuroimaging (the latter led by Professor Stefan Borgwardt).

This unique collaboration opens up a great opportunity to study a broad range of patients, from individuals with an at-risk mental state, to first episode patients and patients with a chronic course, as well as age-matched controls. "For the first time, a direct comparison between distinct patients groups usually merged under the term 'schizophrenia' by using identical laboratory methods will be possible," Eckert reveals.

The project is investigating the patient groups and the healthy controls using a multilevel approach addressing working hypotheses in three areas: neurocognition and resilience; neurobiology; and neuroimaging. They are aiming to use this interdisciplinary setting to relate disturbances in brain structure and function, psychopathology and information processing with abnormalities in energetic homeostasis. The research is expected to contribute to a better understanding of resilience and vulnerability factors in schizophrenia than has previously been achieved.

THE CORE HYPOTHESIS

An important hypothesis is the question of whether an increase of cognitive deficits is related to an increased vulnerability and a reduced resilience as expressed by abnormalities in cellular energetics and/or structural and neurofunctional abnormalities. The investigators will verify this hypothesis by using a neuropsychological test

important national collaborations have been established with the Medical Image Analysis Centre (MIAC); the Departments of Radiological Physics and Department of Neuroradiology of the University Hospital Basel (Ernst-Wilhelm Radü and Christoph Stippich); and with the Interdepartmental Research Platform of the University of Basel (Andreas Papassotiropoulos). Internationally, close collaborations exist with King's College London (Philip K McGuire) for development of new imaging methods as well as with the Department of Pharmacology, University of Frankfurt (Walter E Müller) for the optimisation of biomarker research with the focus on bioenergetics.

What ultimate impacts do you hope the project has?

This study should clarify the understanding of the pathogenetic mechanisms of schizophrenic psychoses with respect to vulnerability and resilience factors. Increased understanding of these pathophysiological mechanisms may lead to novel therapeutic targets for schizophrenic psychoses.

VULNERABILITY AND RESILIENCE FACTORS OF SCHIZOPHRENIA: AN APPROACH COMBINING NEUROIMAGING, NEUROPSYCHOLOGICAL AND NEUROBIOLOGICAL METHODS

OBJECTIVES

- To relate disturbances in patient groups with schizophrenic psychoses in brain structure and function, with mitochondrial abnormalities at the molecular and cellular level
- Characterisation of associations between parameters of brain structure and function, defects in mitochondria and energy homeostasis and psychopathology
- Identification of resilience/vulnerability factors in different patient collectives
- Characterisation of putative endophenotypes

KEY COLLABORATORS

Professor Klaus Schmeck, Kinder- und Jugendpsychiatrische Klinik, Psychiatric University Clinics • **Professor Andreas Papassotiropoulos**, Division of Molecular Psychology, University of Basel • **Professor Walter E Müller**, Department of Pharmacology, Biocenter, University of Frankfurt am Main • **Professor Ernst-Wilhelm Radü,** Medical Image Analysis Centre (MIAC) and **Professor Christoph Stippich,** Department of Neuroradiology of the University Hospital Basel • **Professor Philip K McGuire**, King's College London, Institute of Psychiatry

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ANNE ECKERT studied Pharmacy at the University of Marburg, Germany, and received her PhD in 1994. As a postdoc fellow she joined the Institute for Brain Aging, UCI, USA, working on cell death mechanisms and mitochondria. She then moved to the Department of Pharmacology at the University of Frankfurt, as Assistant Professor. Since 2004 she has served as Head of the Neurobiology Laboratory at the UPK Basel.

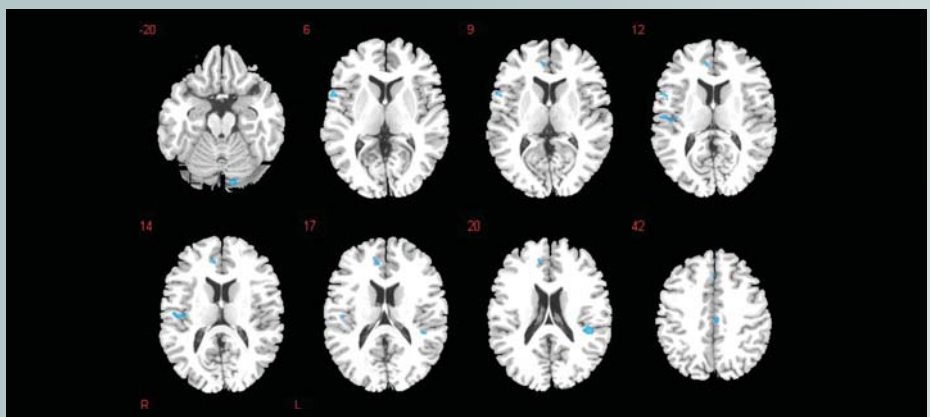

FIGURE 1. Structural neuroimaging in prodromal psychosis, gray matter reductions associated with vulnerability and transition to psychosis. Gray matter probability maps for comparison of all subjects with an At-Risk Mental State (ARMS), first-episode patients and healthy controls.

battery, which covers the domains of general intelligence, executive functions, memory and attention as well as the Resilience and Social and Functioning Assessment Scale. The aim of this part of the study is to compare the profile and severity of cognitive deficits indicating vulnerability or resilience in patients with chronic schizophrenia, first episode schizophrenia as well as in at-risk mental state.

For neurobiology, on the basis of current research and the consortium's preliminary study findings, the group expects changes in mitochondrial function as well as abnormalities in oxidative stress and energy levels to be found in blood cells of all these patients. This hypothesis will be verified by using a combined approach ranging from gene profiling to functional aspects of mitochondria. Lymphocytes are not only easily accessible but, unlike postmortem brain tissue, can also be subjected to experimental manipulations. The work will also go beyond gene expression profiling from freshly drawn blood to culture lymphocytes of patients and healthy controls under stress conditions related to energy homeostasis. This approach will allow for a more comprehensive view of the complex interplay between genes and cellular function, and give way to characterising patterns of mitochondrial vulnerability and resilience in blood cells from different schizophrenic patient groups.

It has recently been accepted that schizophrenia is associated with neuroanatomical abnormalities. However, the extent to which these are related to the vulnerability of the disorder, rather than the illness itself, is less certain. Within the FePsy project it has recently been shown for the area of neuroimaging that subjects with an at-risk mental state show brain structural and neurofunctional abnormalities relative to controls that are qualitatively similar to those in patients with first episode schizophrenia and that these abnormalities progress with transition to frank psychosis. In this project the scientists can now compare them to chronic patients with schizophrenia and expect to find a linear trend for more structural and neurofunctional abnormalities. Furthermore, and most importantly, they can correlate these neuroanatomical with the corresponding biomarker findings.

UNDERSTANDING SCHIZOPHRENIA

By the end of the project, four main aims are expected to be addressed: identification of resilience and vulnerability factors that are specific for a single patient collective; identification of differences or similarities between the different patient groups versus controls; characterisation of associations between parameters of brain structure and function, defects in mitochondria and failure in bioenergetics demands and psychopathology; and characterisation of putative endophenotypes.

This collaborative project provides a unique approach to understanding schizophrenia, especially because links between psychopathology and functional aspects of mitochondria and brain structure and function assessed by structural and functional MRI with specific regard to vulnerability and resilience factors in schizophrenia have never been documented before. Determining the mechanisms of structural and neural abnormalities will hopefully improve knowledge of the processes that are implicated in biological vulnerability or resilience to mental illness. In the long term it is hoped that the study will contribute to clear rationales for specific treatments aimed at improving brain energy metabolism in disorders like schizophrenia.

For the first time, a direct comparison between distinct patients groups usually merged under the term 'schizophrenia' will be possible

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