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Concept and Results of the German Research Network on Schizophrenia

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Abstract

Background: The German Research Network on Schizophrenia (GRNS) was funded by the Federal Ministry of Education and Research (BMBF) from 1999 to 2011. The aim was to obtain a better horizontal and vertical networking of German research and care facilities on schizophrenia, in order to investigate open research questions, to transfer the results into clinical practice and after all to improve care and quality of life in patients with schizophrenia.

Objectives / Methods: This paper describes the concept and functioning of the GRNS as well as its results on the basis of selected research projects.

Results: The GRNS comprised about 25 clinical trials of high practical relevance, which were closely interrelated regarding content, methodology and organization. The trials primarily served the development and evaluation of new and established diagnostic and therapeutic approaches, the assessment of the status quo of clinical care as well as its improvement, together with the investigation of basic scientific questions. Many substantial results to highly relevant issues could be obtained, which led or will lead to an improvement in mental health care.

Conclusions: Quantitative and qualitative evaluation parameters such as scientific publications and raising of additional grants, as well as promotion of young scientists, public relations activities, congress activities and foundation of the European Scientific Association on Schizophrenia and other Psychoses (ESAS) prove the successful work of the network. The successful grant raising will allow continuing cooperative schizophrenia research in Germany as initiated by the GRNS.

Background

The German Research Network on Schizophrenia (GRNS) (also called "Competence Network Schizophrenia") was funded by the German Federal Ministry of Education and Research (BMBF) from 1999 to 2011. Initiated and chaired by the authors WG (Düsseldorf) and HJM (Munich), it was one of nine medical competence networks that were selected for funding in 1999 from a total of 160 applications from the entire field of medicine. The GRNS was funded by the BMBF with a total of approx. 15 million euros over 12 years (1999-2011). Additional funds (<10% of the budget) were provided by various pharmaceutical companies for research projects or for public relations activities.

Aims and Structure of the Network

The structural aim of the funding program was to obtain a better horizontal and vertical networking of German research and care facilities, in order to investigate open research questions, to transfer the results into clinical practice and in the end to improve care and quality of life in patients with schizophrenia. The GRNS comprised 25 research projects, which were closely coordinated with regard to content, methodology and organization. The projects were multi-centered in such a way that vertical and horizontal networking was indispensable or at least encouraged for their implementation. They were carried out in cooperation of 19 psychiatric university hospitals, 14 regional and district hospitals as well as six local networks of psychiatric specialist practices from all over Germany (see list in[1]). The university hospitals of Bonn, Düsseldorf, Cologne, Munich and Tübingen as well as the Central Institute of Mental Health Mannheim formed a kind of "backbone" due to their participation in most principal projects. The authors of this paper served as the executive board of the GRNS with authors WG as the chairman and HJM as the vice chairman.

Regarding content, the main objective was to improve the course and the treatment outcomes in schizophrenia patients, and to improve their quality of life. The research was focused in particular on the following aspects:

- strategies for early detection and treatment in high risk and prodromal stages of psychosis,
- possibilities for optimizing the acute and long-term treatment of first-episode patients and the rehabilitation of patients with residual symptoms,
- the quality of care in clinics and practices, including the implementation of treatment guidelines
- structural and functional imaging and genetic characterization to find predictors and risk factors of first onset, relapses and individual treatment effects.

Further projects on fighting stigma and discrimination, on health economics and on public relations completed the project spectrum. In the following chapter some essential projects and their respective results are presented as examples.

Selected Research Projects and Their Results

Early detection and treatment of psychoses

Retrospective studies show that the first treatment contact of schizophrenia patients is delayed for years since the onset of the first psychotic symptom ("duration of untreated psychosis") or the first non-specific symptoms ("duration of untreated illness")[2,3]. Delayed treatment, however, is accompanied by higher relapse rates, a delayed recovery and reduced social functioning in the further course of the disorder[3]. Therefore, the GRNS aimed to improve methods of early detection and to evaluate new strategies for early treatment. First, four new early detection and intervention centers were established in 1999, supported by respective awareness programs. In the meantime, about 26 centers have been established in Germany[4]. In parallel, a two-stage early detection inventory (ERIraos) consisting of a short checklist for risk screening and a symptom list for risk prediction was developed and prospectively validated in two early detection and early intervention studies[5].One of these studies focussed on early at risk stages (defined by the presence of cognitive "basic symptoms"[6] or an affected first-degree relative in combination with marked reduction of functioning) and showed, that multimodal cognitive-behavioral therapy adapted to the target group was superior to supportive intervention with respect to transitions from early at risk stages to later stages or to manifest psychosis within two years[7]. The second early intervention study addressed individuals in late at risk stages (defined by the presence of attenuated or brief limited intermittent psychotic symptoms); it could be shown that an atypical antipsychotic (amisulpride) as a supplement to needs-based supportive treatment was significantly superior to needs-based supportive treatment alone with regard to the reduction of already existing symptoms and the prevention of transitions into psychotic stages[8]. Clinical, neuropsychological and neurobiological predictors of the transition to psychosis were subsequently validated in an EU-funded multicenter study under the leadership of the Early Detection Center in Cologne (EPOS study)[9]. Positive symptoms, bizarre thinking, sleep disorders, a schizotypal disorder, level of functioning in the last year, and education were identified as significant predictors. In addition, the above-mentioned treatments (pharmacological or cognitive-behavioral therapy) were compared with each other and against a placebo treatment in a further study, which has recently been finished only (PREVENT study)[10]; results are to be awaited.

Acute and long-term treatment of first schizophrenia patients

At the time of planning the studies of the GRNS there was evidence for a certain superiority of atypical versus conventional antipsychotics[11,12] in the treatment of first-episode patients (FEP), but it was unclear whether these results were biases by high dosing of conventional antipsychotics. Uncertainties also existed with regard to the necessary duration of treatment after first episodes, though respective guidelines recommended at least one year of continued medication for relapse prevention[13,14]. In order to contribute to the open questions of the optimum choice and duration of drug treatment in FEP and to

identify clinical, neuropsychological and neurobiological outcome predictors, a comprehensive clinical treatment study with several supplementary predictor projects was performed in 13 university hospitals. In a randomized, controlled, double-blind trial, an atypical was compared to a conventional antipsychotic drug (risperidone vs. haloperidole) in acute and long-term low dose treatment over 2 years. Overall, both antipsychotics proved to be clinically efficacious without significant drug differences in relapse prevention, symptom reduction and improvement in quality of life. However, haloperidol was associated with higher extrapyramidal motor side effects than risperidone even in the low dose range[15]. This lack of clinical advantage of atypical antipsychotics together with similar results from other parallel studies has led to a reformulation of the recommendations in the treatment guidelines. Also results of the second year of treatment casts doubt on previous guideline recommendation: in the GRNS study, drug discontinuation was associated with an increased risk of relapse even in previously sufficiently stabilized patients and despite prodrome-triggered early intervention[16]. Surprisingly, complete and stable remission was even one of the significant predictors of clinical deterioration after discontinuation of medication[17]. These findings underscore the need to critically balance reasons on treatment strategies in order to be able to adapt them to individual needs. Very high dropout rates in this study and other comparable studies have generally shown that FEP require a specially designed treatment framework. Based on corresponding international developments, these experiences are currently being used in the conception and establishment of special treatment centers for FEP[18].

Genetic factors related to therapy response and disease progression

In particular, primary negative symptoms are difficult to treat in many schizophrenia patients[19]. At the same time, negative symptoms are associated with poor social and occupational functioning and thus improvement of negative symptoms is essential for a good treatment outcome[20]. In addition to the development of new therapeutic approaches, the study of prognostic and moderating factors of the treatment response is of substantial importance. Regarding drug treatment, atypical antipsychotics are considered to be a promising option, due to their high affinity for serotonin receptors: serotonin receptors are altered in schizophrenia and were discussed as potentially relevant for negative symptoms[21,22]. Previous evidence indicated that patients with a C allele (CC, CG) in the promoter region of the serotonin receptor gene showed a better response to atypical antipsychotics in negative symptoms than patients with a GG genotype[23]. These results were verified in the FEP of the comprehensive drug trial mentioned in the previous paragraph. As expected - and as replicated in a second random sample of the University of Bonn - a moderating effect of this polymorphism could be obtained specifically for the treatment effect of the atypical antipsychotic: patients with the C allele showed larger reductions in negative symptoms than patients with the GG genotype[24]. In addition, the early detection and early intervention studies (see above) were used to examine whether transitions from the risk or prodromal stage of a psychosis into a manifest disorder were increased in the presence of certain gene variations, which were discussed as susceptibility genes at the time of study. In one of the first studies worldwide it could be shown that among persons at risk who developed a manifest psychosis within 24 months, carriers of certain gene variants of the D-amino acid oxidase activator DAOA / G72 were significantly more frequent than carriers of other gene variants[25].

Quality management in the routine care of schizophrenia patients

In recent decades, treatment guidelines have been developed for schizophrenia in many countries, including Germany with a leading participation of the GRNS[14]. However, it is estimated that only about half of the patients are treated according to these guidelines[26]. Thus, several GRNS projects aimed at a systematic development, implementation and evaluation of specific quality management measures. One study included 54 psychiatric practices in order to improve the quality of outpatient care by either implementing the guidelines as part of a new digital “decision support system” integrated into the documentation system, or by conventional measures of internal (documentation systems, monitoring) and external quality management (benchmarking). The study showed better treatment results by either using the guideline-based digital decision support system or by participating in quality circles compared to practices only documenting treatment without any decision support[27].

A second study compared the effects of benchmarking and quality circles in four experimental hospitals with four control clinics without these measures. The results based on approximately 1200 patients impressively showed that lower compliance to guidelines was associated with poorer clinical outcome. Benchmarking proved to be a good measure to promote such compliance and to improve the quality of treatment[28]. In order to disseminate these successful measures to a broader range of care and to evaluate them in everyday practice, routine benchmarking was implemented afterwards in nine psychiatric specialist clinics within a succession project funded by the Federal Ministry of Health. At the same time, appropriate quality indicators were developed in close cooperation with the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN)[29]. Funded by various

health insurance companies, it was also investigated whether a multi-professional, guideline-based and individual aftercare program can improve quality of life of schizophrenia patients with multiple inpatient previous visits[30].

Fighting stigmatization of schizophrenia patients

Stigmatization due to mental illness and the frequently related discrimination are often perceived as a kind of additional illness due to the associated burdens. In order to reduce stigma and discrimination against people with schizophrenia, the World Psychiatric Association initiated the global campaign "Fighting Stigma and Discrimination Because of Schizophrenia - Open The Doors" in 1999[31]. In Germany, seven centers were involved, partly within the scope and with the financial support of the GRNS[32]. In this context, GRNS members, the DGPPN, and the association "Open the Doors e.V.", in 2004 also established the "German Alliance for Mental Health - a National Program for the Destigmatization of Mental Illness", for which the respective Federal Minister of Health acted as the patron.

As an essential component of the GRNS's anti-stigma work, a population-based survey on the attitudes towards patients with mental illness was conducted in 7246 people in six German cities[33]. The survey was repeated three years later after interim interventions in four of the cities, which showed improvements in attitudes specifically in the cities with targeted educational measures. In a further step, it was attempted to address stigmatization directly in psychiatric and psychosocial institutions; because of their frequent and intensive contact with the mentally ill, employees of such institutions play a central role in stigmatization: on the one hand they may stigmatize patients by their own attitudes and behavior, on the other hand they can act as multipliers in fighting stigmatization, and not the least they are often also targets of stigmatization. Especially for these employees, a workshop "Antistigma competence" was designed, explicitly including "service users" in its development and implementation. The aim was to initiate a dialogue between professionals and "service users" on stigmatization and to acquire skills in dealing with stigmatization in daily work and thus contribute to fighting the stigma of mental illnesses[34].

Critical Evaluation and Perspectives

More than 250 papers have been published up to now on the issues, methodological approaches and study results of the GRNS – the majority of them as papers authored by multiple researchers from different institutions. Moreover, in addition to funding provided by the BMBF, additional funds were successfully raised to finance further collaboration between GRNS centers (and newly added centers) through new projects, although not all of these projects are formally tied to or formally initiated by the GRNS. In this context, two research networks funded by the BMBF are to be especially mentioned, i.e. the POSITIVE-network ("psychotherapy of psychotic symptoms" led by Stefan Klingberg (Tübingen)[35] with a total of nine projects and the ESPRIT-network ("improvement of prevention and recovery in schizophrenia") led by Andreas Meyer-Lindenberg (Mannheim) with a total of seven projects[36]. Both networks were or are primarily run by institutions which formed the GRNS-"backbone" before.

Such results without any doubt show that the BMBF-funding of the GRNS has structurally led to a significantly intensified horizontal networking in the field of schizophrenia research. For the first time in German schizophrenia research the funding of the GRNS has made it possible to conduct major industry-independent treatment trials; in particular, low-prevalence populations (e.g. at risk individuals, FEP) could be recruited for clinical trials in sufficient number and time through multicentre recruitment. The first specialized early detection and early treatment centers were also set up at a number of German universities.

In addition to these structural contributions, substantive contributions were made to highly relevant issues that have led and will continue to lead to an improvement in the care of the mentally ill. German schizophrenia research seems to be much more visible nationally and internationally than the years before. The European Conference on Schizophrenia Research (ECSR) initiated by the GRNS in 2007 and since then organized every two years contributes to this effect, just as the foundation of the "European Scientific Association on Schizophrenia and other Psychoses" (ESAS) in 2011. Both are intended to create platforms for scientific exchange and the promotion of young researchers and to serve as a horizontal link across national borders.

In the long term, further scientific work of such networks will only be sustained via third-party funding; BMBF funding for the GRNS has expired at the end of 2011. Subsequent national funding programs mostly focus on clinical treatment studies, whereas funding for other areas, e.g. more basic research from pathophysiology to innovative treatment strategies is scarce. Nevertheless, the large number of funds raised from public funding agencies in the meantime is an appropriate way to maintain such networked research in schizophrenia - even though not all applications are made on behalf of the GRNS and not all follow-up projects were formally committed to the GRNS. Priority is given to the further promotion of intra- and interdisciplinary cooperation in larger networks, which appears to be the appropriate strategy to respond to the most urgent, yet unresolved questions on schizophrenia - given the complexity of mental disorders and the specialization of research (especially in complex biological methods). The GRNS was a novel model for disorder-

specific networking across Germany by then; together with comparable networks on depression and dementia, the GRNS in that sense was a kind of trailblazer for psychiatric network research in Germany.

Research in such networks in the meantime has also been established elsewhere on national and international levels. To the best of our knowledge none of these networks is comparable with the GRNS in broadness of topics and approaches spanning from basic research to clinical and health care studies, and public relations activities including destigmatization. At least in Europe, preference is given to focus funding on selected topics (e.g. EU-GEI: European Network of National Schizophrenia Networks Studying Gene-Environment Interactions - www.eu-gei.eu/; OPTIMISE: OPtimization of Treatment and Management of Schizophrenia in Europe - www.optimisetrial.eu/) or methods (e.g. PRONIA: Personalised Prognostic Tools for Early Psychosis Management - www.pronia.eu/; TRIMAGE: A dedicated trimodality [PET/MR/EEG] imaging tool for schizophrenia - cordis.europa.eu/result/rcn/197890_en.html) rather than trying to cover the whole field of schizophrenia research. A combination of both approaches probably would serve best the needs in schizophrenia research and care in the future.

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