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CONSENSUS CONFERENCE

Immunological research in clinical psychiatry: report on the consensus debate during the 7th expert meeting on psychiatry and immunology

V Arolt[1], M Rothermundt[1], M Peters[1] and B Leonard[2]

[1]*Department of Psychiatry, University of Muenster, Germany;* [2]*Department of Pharmacology, University of Galway, Ireland*

There is convincing evidence that cytokines are involved in the physiology and pathophysiology of brain function and interact with different neurotransmitter and neuroendocrine pathways. The possible involvement of the immune system in the neurobiological mechanisms that underlie psychiatric disorders has attracted increasing attention in recent years. Thus in the last decade, numerous clinical studies have demonstrated dysregulated immune functions in patients with psychiatric disorders. Such findings formed the basis of the 7th Expert Meeting on Psychiatry and Immunology in Muenster, Germany, where a consensus symposium was held to consider the strengths and weaknesses of current research in psychoneuroimmunology. Following a general overview of the field, the following topics were discussed: (1) methodological problems in laboratory procedures and recruitment of clinical samples; (2) the importance of pre-clinical research and animal models in psychiatric research; (3) the problem of statistical *vs* biological relevance. It was concluded that, despite a fruitful proliferation of research activities throughout the last decade, the continuous elaboration of methodological standards including the implementation of hypothesis-driven research represents a task that is likely to prove crucial for the future development of immunology research in clinical psychiatry.
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Introduction

The complex biological background of psychiatric disorders such as major depression or schizophrenia reflects dysfunctions in various biological systems that are closely interlinked such as gene functions, cellular neurochemical pathways, neurotransmitter systems, endocrine regulatory mechanisms, and immune functions. We are only now beginning to understand the functions and dysfunctions of the highly sophisticated networks through which these different biological levels are integrated. Nevertheless, the possible involvement of some aspects of the immune system in the neurobiological mechanisms that underlie psychiatric disorders has attracted increasing research attention. It appears that as the immune system is an integral part of the biological network, it should be included in the research into the biology of psychiatric disorders. In support of this view, there is now convincing evidence that cytokines are involved in the physiology and pathophysiology of brain function and that they interact with different pathways of neurotransmission.

In the last decade, numerous studies have demonstrated that patients with schizophrenia and major depression for example show a dysregulation in their immune function. Other studies have also shown that there are abnormalities in immune function following acute and chronic psychosocial stress. Such studies are helping to yield a better insight into the links between the immune system and the neurobiological aspects of different psychiatric disorders. Against this background, the organizers of the consensus meeting brought together a group of international researchers in the field of psychoneuroimmunology to critically consider the validity of the research findings, particularly in the area of schizophrenia and major depression, and to discuss possible future developments. Arising from the meeting, it was felt that more attention should be given to hypothesis-driven studies; promising goals for future research were also considered. It was generally felt that although the conclusions of the consensus meeting cannot fully be achieved at the present time, it was important to initiate an ongoing debate on this subject. The main conclusions of the meeting form the basis of this report.

Correspondence: V Arolt, MD, Department of Psychiatry, University of Muenster, Albert-Schweitzer-Strasse 11, D-48129 Muenster, Germany. E-mail: arolt@uni-muenster.de
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The 1990s—research in progress

Mind–body relationships and the involvement of the immune system have been the subject of systematic research since the 1930s, inspired not only by the rise of the psychoanalytically based psychosomatic medicine but also by the empirical work of Hans Selye on stress and the endocrine system. Since then, a large body of research has been accumulated. This includes basic research on the interfaces between the endocrine and immune systems, increasingly regarding neurotransmitter function, but also clinical and preclinical research into the effects of stress and distress. The pioneering work of George Solomon and Robert Ader in the United States and Robert Dantzer in France has led to an integration of psychoneuroimmunology into the field of neuroscience.

With respect to psychiatric disorders, it was as early as 1937 that the German neuropsychiatrist Lehmann-Facius[1] suggested the possible role of autoimmunity in the pathophysiology of schizophrenia. However, in contrast to other areas of psychoneuroimmunological research, psychiatric research has often been hindered by methodological shortcomings which resulted in findings that were often conflicting and difficult to interpret. This situation is reflected in the critical reviews of Stein *et al*[2] for major depression and Kirch[3] for schizophrenia. The widespread scientific doubts that confront researchers in the interface between psychiatry and immunology can, at least in part, be attributed to these problems.

However, this situation has substantially changed since the beginning of the 1990s. The access to novel immunological techniques, the increased awareness for possible confounders such as age, gender and medication status, and the choice of more homogeneous clinical samples not only led to findings that were evidently replicable, but also allowed new insights into the disordered mechanisms of immunological subsystems. Such dysfunctions may not only be epiphenomena of psychiatric disorders, but may also represent relevant factors in the pathogenesis not only of Alzheimer's disease, but also of major depression and schizophrenia. Immunological processes play a putatively relevant role in stress and adaptive disorders, as well as anxiety disorders. Research into the field of immunology and psychiatry has also been stimulated by the observations of side effects from novel cytokine therapies for certain somatic disorders.[4,5]

In schizophrenia research, there is now substantial evidence that there are abnormalities in the productions of proinflammatory cytokines of the TH1/TH2 system in the blood[6–9] of patients with acute schizophrenia. Findings from the CSF are few and not yet consistent,[10,11] but IL-2 in the CSF has been reported to be a marker for psychotic relapse.[12] There are also replicated findings of indicators of immune activation[13–15] and the increase of adhesion molecules, together with disturbances of the brain–blood barrier.[16] For the benefit of research, putative confounding factors have also been reported.[17,18] The recent delineation for a role of human endogenous retroviruses in the schizophrenic disease process might open an important research perspective.[19] The majority of findings point towards the possibility of subtle inflammatory/autoimmune processes in the brains of at least a subgroup of schizophrenic patients.

In depression research, results from a number of studies indicate an activation of the first-line immunological response in acute major depressive disorder.[20] Yet there is another line of evidence from numerous but often replicated findings of older studies that show reduced NK-cell numbers and biological activity and also reduced lymphocyte numbers and proliferation. It is not yet clear how the gap between these two groups of findings (activation *vs* deactivation) can be bridged. One possibility for understanding this potential contradiction is the observation that different clinical subtypes of major depression are involved. Nevertheless, the early activation of inflammatory cytokines not only seems to be correlated with the symptoms of major depression, but might also interact with serotoninergic transmission within the brain and thereby initiate these symptoms. Such findings may have therapeutic implications for the future.[21–23]

The 7th expert meeting at Muenster/Germany

As such new developments emerged, a first German meeting of experts working in the field of immunology of severe psychiatric disorders was initiated by the psychoimmunology research group of the University of Lübeck/Germany in 1995. In the following years, researchers from other countries joined and meetings were held in Austria and Germany every year. In the meantime, a large funding project was implemented by the Volkswagen Foundation ('Neuroimmunology—Signs, Symptoms and Behaviour'), and provided substantial support for mainly basic research but also some clinical studies. Through this funding activity, research interest in the immunology of different aspects of psychiatric disorders also grew stronger in Germany and today seems to be more intense than it is in many other countries. After the 6th meeting was held in Bethesda (USA) together with the Stanley Foundation, the 7th meeting took place in Muenster, Germany, bringing together 39 experts from seven countries (Austria, Germany, Greece, Ireland, Israel, Sweden, USA). Sessions on new research results covering the topics of schizophrenia, major depression, sleep and immune conditioning were chaired by Volker Arolt (Muenster, Germany); Julio Licinio (Los Angeles, USA), Mark Rapoport (San Diego, USA), and Pinkhas Sirotha (Bat Yam, Israel). One major task of the meeting was to initiate a consensus debate, in which the different theoretical backgrounds and practical experiences of the attending researchers could be brought together to tackle problems arising as the research field continues to develop.

Results of the consensus conference on clinical immunology in psychiatry

The consensus debate was held under the title 'Serendipity *vs* Hypothesis-Driven Research' and was chaired by Brian Leonard (Galway, Ireland). After a general discussion that was centered around the question of hypothesis-driven research, the following topics were focused upon: (1) methodological problems in laboratory procedures and clinical sample recruitment; (2) pre-clinical research and animal models; and (3) the question of biological *vs* statistical relevance. The results of the discussions were transcribed independently by two raporteurs. The minutes were compared and drafted for a manuscript by the authors which was then sent out for review to the participants of the conference. After this review process, the manuscript was revised by the authors, following the suggestions of the participants.

General discussion

The current research situation can be described as a coexistence and, in some cases, collaboration of groups with different research interests and a variety of technological backgrounds. This heterogeneity is complemented by a general methodological level of research which can be characterized mainly by explorative study designs. In this context, immunological techniques have been used as screening instruments in order to detect immunological abnormalities in patient samples with certain psychiatric disorders *vs* control samples. Although progress is apparent, conclusive results are still rare in the interface between immunology and psychiatry. This situation offers strengths but also weaknesses that have to be overcome.

On the one hand, the activities of different research groups led to observations such as dysregulation of cytokine functions in the peripheral blood and CSF of patients with psychiatric diseases, of which some could be reliably replicated; also, the influence of putatively confounding variables, such as age, gender and medication, could be estimated. These efforts have yielded increasingly coherent conclusions about the immunological dysfunctions in major psychiatric disorders. On the other hand, the biological mechanisms underlying these findings, as well as their biological meaning for the individuals affected have yet to be explored.

Although theoretical considerations were integrated into initial hypotheses, hypothesis-driven experimental studies are still rare. Such designs, based on sound neurobiological theoretical work, will be needed for future progress and will replace a decade of research that can be characterized by 'serendipity'. In the field of immunology and psychiatry, hypotheses should be developed that not only center on dysfunctional immunological mechanisms, but also link such considerations with more established abnormalities in other biological systems, eg the serotonergic transmission deficits in major depression. Such efforts should be supplemented by rigorous reviews whereby the findings should be classified with respect to their empirical evidence. In clinically-based research projects, hypothesis-driven experimental designs should be applied on homogeneous patients and matched with control samples, wherever possible. Regarding laboratory procedures, it is necessary to reach high immunological standards and a maximum comparability between the technical procedures. If research groups follow these proposals, helpful tools such as in-depth reviews and meaningful meta-analyses can be reliably employed.

(1) Methodological problems in laboratory procedures and clinical sample recruitment

Laboratory procedures The comparability of findings, and the evaluation of their validity, is hindered by the wide variety of laboratory procedures that have been applied by different research groups. In such a situation, it seems reasonable to establish a set of standardized techniques (eg one assay from one manufacturer from one country). Efforts towards a common level of quality and a consequent increase of reliability and validity of laboratory results would be facilitated by an open and critical exchange of researchers between laboratories. Furthermore, as in clinical chemistry, specimen samples could be comparatively processed by different laboratories. However, shipping of eg blood samples represents a problem that will be difficult to solve. Comparability or even standardization of laboratory procedures should also be achieved with respect to the fact that the reported differences between probands and controls in certain immune functions are only subtle and hence can easily be subject to aberrations in technical procedures. On the other hand, it can be argued that the reproducibility of the findings through the use of different techniques and technical suppliers can be interpreted as an argument for positive empirical evidence.

Recruitment of patients and controls Clinical researchers from many fields of biological psychiatry have recognized an 'endless story' of problems in patient recruitment. In a number of studies, lack of homogeneity of the patient samples makes it impossible to draw firm conclusions regarding the pathophysiology of a psychiatric disorder. For instance, in depression research, it is obvious that the category of major depressive disorders is fragmented by numerous variables together with yet unknown neurobiological causes. Such variables are gender, age, polarity of the disorder, family history, depressive subtype, duration of disorder, treatment history, response to medication and the duration of the depressive episode at the time of recruitment.

For the purposes of immunological studies in clinical psychiatry, the following points should be focused upon: (1) It is necessary that the question of statistical power be critically considered in the study design. (2) In the recruitment of patient and control samples,

reasonable homogeneity must be achieved regarding disease characteristics, gender and age. The respective information must be given in detail. (3) It is crucial for case-control designs that adequate controls be recruited; these should be matched with respect to age and gender. (4) As is commonly practised in psychopharmacological studies, therapeutic response and dropouts from the study should always be reported. (5) A family history of disorders should be taken from every proband and control subject.

In addition, the issue of gender differences should be explicitly focused upon in psychoimmunological studies, since there are well established differences between the immune functions of women and men. Thus, for example, the rhythm of the menstrual cycle, as well as the menopausal status, represent topics of interest that so far have received insufficient attention. This implies that not only should the hypothalamic-pituitary-adrenal axis be monitored in such studies, but also the regulatory role of the sex hormones should be considered.

(2) Pre-clinical research and animal models

The advantages of animal models for neurobiological research are impressive. It is obvious that animal models lead to a better understanding of biological mechanisms at the interface between behavior and cellular function. Nevertheless, the relevance of such models must be verified by appropriate clinical studies. A continuous and substantial exchange between animal-based and clinical research is crucially important in psychoneuroimmunology, in order to obtain an understanding of neurobiological mechanisms in man. As in other research fields, it must be emphasized that the main problem of transferring results from one species to another, and particularly to man, is not an easy task. Although there seem to be parallel mechanisms that have been derived from psychoimmunological research (for example, studies on the effects of different types of stress), there are also fundamental discrepancies in immune function between species. For example, most experimental studies are conducted on rodents and it is uncertain whether the functional activity of the rodent and human immune systems is similar. Thus it is doubtful if extrapolations made from immune functions in animal models are necessarily relevant regarding an understanding of immune functions in man. This is particularly relevant to schizophrenia where there are no reliable animal models; this may also apply to a lesser extent to major depression.

(3) Statistical vs biological relevance

In the field of immunology and psychiatry, as in other research areas, the results of studies are mostly reported as statistically significant differences between the arithmetic means of samples. In this, but also in more complex, forms of statistical analysis it is often difficult to decide whether the statistical relevance of respective results is also biologically relevant. Although some putatively important statistical differences between patients and controls could be reliably replicated, the biological validity of these findings is largely unclear. It might be the case that observations from individuals with psychiatric disorders represent subtle biological variations that lack any biological or clinical relevance. Thus there is always the danger in assuming that a statistically significant correlation implies a causal association. As an example, numerous studies have shown significant immunological 'abnormalities' in patients with major depression, yet there is as yet no convincing evidence from epidemiological studies that individuals with major depression show any consistent clinical effects, for example, increased incidences of severe infections or cancer (except perhaps breast cancer in women). Also, in the context of major depression, the possible influence of immunological dysfunction on the development of coronary heart disease is as yet inconclusive. It might also be the case that the findings in psychiatric patients represent changes that exert a relevant biological influence that is so subtle that it can not be assessed at the present time. In this situation, one strategy might be to determine whether the sample differences in individuals with psychiatric disorders resemble those of subjects with certain somatic disorders, eg autoimmune diseases. Another promising strategy is to concentrate on the biological links of such findings to other, better established abnormalities with other biological systems, for example, neurotransmitter functions.

Limitations of the consensus debate

Although the consensus debate covered some of the most important topics in the field of immunology in clinical psychiatric research, a number of limitations could not be overlooked. First, the debate could not be based on a systematic selection of researchers from all branches of research. The majority of participants came from clinical psychiatry and fewer originated from basic (particularly immunological) and other clinical research areas. Secondly, due to the eclectic nature of the debate, it is doubtful whether the consensus reflects opinions that are fully representative for all of researchers in the field. Thirdly, due to limits on time and preparation, some problems could not be discussed in the desired detail. However, despite these obvious shortcomings, it was felt by the participants that an attempt had been made to address the main issues. Nevertheless, despite these limitations, those attending the meeting represented some of the most active groups in the clinical branches of psychiatry and immunology.

Conclusions and recommendations

The following conclusions can be drawn from the consensus debate. (1) There is widespread agreement that a better comparability of study designs should be achieved. (2) Although efforts for a definitive standardization of laboratory techniques may prove means-consuming, collaborative efforts should be actively supported in order to reach a better homogeneity not

only with respect to immunological techniques, but also with regard to the recruitment of clinical material. (3) In future, such activities will provide a basis for data pools that can be used not only to achieve greater statistical power, but also to compare relevant clinical subgroups. Such goals can be achieved by modern information technology. (4) It should also be noted that, as is apparent in the field of psychogenetics, the question of comparability and reproducibility should not obscure the search for meaningful biological interactions and appropriate working hypotheses.

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