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HERRENHAUSEN CONFERENCE

HERRENHAUSEN PALACE, HANOVER, GERMANY



## CONFERENCE SUMMARY MENTAL HEALTH THROUGHOUT LIFE

by Alison Abbott

The meeting aimed to discuss research priorities in the area of mental health and outline scientific priorities for the future. The 140 participants included 14 speakers, presenters of the 44 posters as well as a few representatives of funding agencies. Presentations were structured around the different times of life in which people are vulnerable to mental illness: from the womb to early infancy, in adolescence and in adulthood. There was extensive time for general discussions whose themes ranged from the challenge of acquiring interpretable information from the brains of individuals, to the inequity of access to care in poorer countries.

Most particularly, the meeting noted how powerful gene-environment interaction can be in increasing risk of psychiatric disease – and the importance of adopting imaginative interdisciplinary approaches to studying the interaction.

### THE BURDEN OF MENTAL ILLNESSES

The statistics speak for themselves. More than half of the European Union population can expect to suffer from a mental disorder, as defined by DSM-IV diagnostic criteria, in their lifetime. Top among them is depression, but psychotic disorders like schizophrenia also represent a major burden. Statistics show that each year, 38% of the European Union population suffer from a mental disorder, at least for some time. But individual risk depends on disposition and circumstance; the challenge for science is to unpick these risk components.

Young people are particularly at risk, as are women of all ages; among adults, those with a partner, and those with a higher income, are less vulnerable. The risk for developing a psychiatric disorder is significantly higher among those brought up or living in a city, compared to those brought up or living in the countryside.

Statistics in other high-income countries tell a similar story. On the positive side, there is no epidemiological indication that incidence is increasing. However, this stability of incidence also implies that psychiatric disorders will be at least as prevalent in low-income countries – where data are not routinely collected because mental illness is not considered a high health priority.

The economic impact is high. In 2010, the estimated costs in Europe, in terms of treatment, support and lost productivity was 674 billion EUR – a huge price that reflects the very many years of disability imposed by psychiatric diseases because they tend to have early onset and are often poorly treated.

Research over the last couple of decades has revealed the extent to which these disorders result from complex interactions between genes and environment. A prominent example is the long-lasting neurobiological and psychological effects of child abuse and neglect on both the susceptibility to psychiatric disorders and their response to therapy. The consequences of this interaction become biologically embedded in the brain, often at very young ages: robust changes in the neural circuitry that process stress, including the hypothalamus-pituitary axis (HPA) have been observed in different psychiatric disorders, for example, as have changes in the epigenetic states of genes.

All academic titles have been omitted.



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## GAPS

The understanding of the biological underpinnings of psychiatric disorders is very much at its beginnings though, and much more research is required at the molecular, cellular, and neural-circuitry levels to identify where best therapeutic interventions might be targeted, and how diagnostic tools might be developed. More research is also needed into the environmental influences on mental health – and how malign influences could be avoided in real-world situations and positive influences exploited.

Even the poorly understood mechanisms behind brain plasticity could present a future target. Such brain plasticity is most evident during adolescence when individuals begin to explore the world beyond their families, in which they will have to find their place as adults. Extensive plasticity at this time allows appropriate adaptation to new situations – but it can also allow inappropriate adaptation, and consequent vulnerability to mental disorder. Important plasticity also exists in the adult brain which can reorganise itself according to functional demands, as evidenced by studies in professional musicians and taxi-drivers.

New targets will emerge when pathological mechanisms are better understood. Neurodevelopmental psychiatric disorders have their roots in early development. Neural circuitry and neuroanatomy can be subtly altered by physical events like oxygen deprivation during birth, and other early-life stressors like maternal neglect or other types of parental cruelty. These alterations increase the risk of a psychiatric disorder like schizophrenia emerging in adolescence or young adulthood. Particular genes influence this risk. Environmental stressors – including extreme physical and psychosocial stressors like drugs or physical abuse – in adolescence may then propel the vulnerable into a psychosis; such stressors in childhood can lead to severe behavioural disorders or depression later in life. The biological consequences of these pathogenic interactions remain to be worked out in detail. In adulthood, severe trauma can precipitate post-traumatic shock disorder (PTSD) in some – but not all – people. The biological basis of this individual mental resilience similarly remains to be worked out.

Understanding biological details will help generate biomarkers which are urgently needed to help diagnose mental disorders, and begin to treat them much earlier. There is an average gap of nine years in the United States – and 6.8 years in the European Union – between emergence of first symptoms and start of treatment of a mental disorder. Uncertainties in diagnosis account for much of the delay. This is regrettable, particularly because untreated disorders lead to co-morbidities – early-life anxiety leads to depression for example – which further confounds diagnosis.

Early research hints that epigenetic marks may provide a potential source of biomarkers to aid diagnosis and perhaps also predict response to different treatments. But epigenetic data need to be collected at the -omics level, and ideally together with transcriptome data, to take this forward. The meeting suggested that the International Human Epigenome Consortium (<http://www.ihec-epigenomes.org>) could be approached to include a programme for psychiatric diseases.

Functional brain imaging may also eventually be used to support diagnosis, for example by analysing stress processing in the brain which differs subtly in psychiatric disorders.

Given the different vulnerabilities to psychiatric disease at different times of life, the meeting noted that longitudinal studies are necessary to understand normal baselines and to identify the environmental impacts that are most relevant to mental health. But they are fraught with problems. A study at the National Institute of Mental Health has over the last two decades been following the development of brain structures in around 3000 subjects, hoping to map the different trajectories in health and disease. The study aims (ideally) to image brain structures of participants every two years from babyhood. So far the study has accumulated 9000 or so images, but has



also revealed challenges for such studies. It has proven hard to get the subjects to return regularly, for example. Unexpectedly large individual differences in brain anatomical structures, even sometimes between twins, make interpretation difficult and demonstrate the need for even larger studies.

An unanticipated challenge to interpretation of such longitudinal data has been the advent of the digital revolution. 'Screen-time' represents an important environmental element for developing brains. Its impact is poorly understood but expected to be high. When the NIMH study began, screen-time was quantified as the number of hours of watching TV, but this is no longer very relevant in the new era of computer games – and the baseline shifts year by year as computer games increase in sophistication. This confounds attempts to normalise environmental impact across participants recruited in different years.

Cutting edge technologies are being used to investigate the interaction of risk genes and neural circuitry in psychiatric disease. The European Union's Innovative Medicines Initiative (IMI), for example, is supporting a large ongoing Iceland-based study combining gene sequencing and functional brain imaging of around 700 participants. The other half of the gene-environment equation has until now been difficult to quantify experimentally. But new digital tools are now becoming available to measure different aspects of the physical and psychosocial environment. The meeting stressed the importance of social scientists adopting these tools and working more closely with biologists.

Some social scientists have already started using the technologies. Peer influences can impact mental health – for example by encouraging drug taking – but social scientists have never before been able to gather quantitative data in the field in a way that could allow the influences to be related to biological states. Mark Pachucki reported his ongoing Boston-based study which quantifies social contacts between peers among high-school students during lunch breaks. Each student wears a smart tag on his or her chest which records the number and duration of interactions between different individuals.

The meeting noted the impact such methodology could have on mental health research if social scientists and biologists worked together. Andreas Meyer-Lindenberg reported a further example of the application of social tracking technologies. His new collaboration will try to unpick the elements of a city which may be responsible for increasing risk of mental disorder. It will combine data from mobile tracking devices that participants will carry around Mannheim and Heidelberg – and which will also provide them with cognitive tests to be carried out online at particular city locations – with functional imaging data.

It is difficult for research funders to support research with such extreme interdisciplinarity – 'neurobiology meets city planning meets ICT' for example – because reviewing procedures tend to be discipline-based. Several agencies and foundations at the meeting agreed that reviewing processes may need to be structured such that such important new research approaches are not excluded from funding.

In a similar vein, Thomas Schlaepfer reported the 'near impossibility' of getting independent funding for clinical studies on deep brain stimulation (DBS) in the treatment of psychiatric disease. Only industries manufacturing DBS electrodes are keen to support these difficult, highly invasive studies which hold out promise for severely depressed patients resistant to other therapies, for example, but may also help clarify the neurobiological basis of psychiatric disease.

## THE TRANSLATION GAP

The technologies now available to image the functioning brain, to gather large-scale molecular data, including full gene sequencing, relatively cheaply and to monitor individuals in their social environments will all allow better understanding of where future therapies or preventative measures should be targeted. But it will take very many years to arrive at this point.

In the meantime, most major pharmaceutical companies have abandoned the area of psychiatric disorders, defeated by the magnitude of our ignorance of how the brain works. And funding agencies also invest too little in the area.

However the meeting stressed the importance of translation of the knowledge we do have into the clinic in the short-term – knowledge that is not necessarily based on new biology. Current treatment of the psychiatrically ill can be improved simply by changing normal clinical practice to allow current, imperfect, drugs to be used more efficiently; for example, patients will stay on therapies longer if they have more support from medical and social workers. A Johnson & Johnson research project in Lower Saxony, Germany, is testing whether such additional services to patients has quantifiable effects on their quality of life.

Psychotherapy could similarly be used to greater effect if new research which is starting to generate evidence for which types of psychotherapy are useful in which particular conditions were to trickle down into clinical practice. Such research needs to be extended to identify methods that impact recurrence of disease, not just its onset, noted the meeting. Psychotherapeutic approaches are particularly important given the failure of biological studies to yield effective new drugs for mental illnesses.

Outside of the clinic, social-science research has shown how those with a mental illness can be offered a better quality of life and can be integrated better into society. In terms of employment for example it has been shown that ‘first place then train’ works better than ‘first train then place’ – and that employers can take relatively simple steps to reduce stress levels in the workplace, which can precipitate mental disorders.

Most employers don’t engage with this work though – and part of this translation failure comes down to the stigma that continues to be associated with psychiatric disease, and frequently leads to ostracization.

This stigma still needs to be addressed. It has a wider influence – psychiatric disease often fails to be integrated into broad health-research policies. For example a new series of national health institutes in Germany excludes psychiatric disorders, despite their acknowledged burden. But one of the largest remaining challenges is to translate the level of care and treatment accorded to the mentally ill in high-income countries, inadequate as it is, to low-income countries which spend barely a tenth of what the US spends of mental health treatments. Expanding the new Global Mental Health programme would without doubt have the most impact in terms of helping the largest number of effected people. The final conclusion of the meeting was that policy-makers at all levels must be on board just as much as scientists.

Environmental influences on mental health are well known but little researched. Future research needs to pay more attention to both physical and psychosocial influences at all stages of life – prenatal and well as postnatal. It needs to address how experiences are processed from babyhood on and why individuals have different responses or resilience – to the same environments. It needs to test the causal environmental influences in psychiatric disease and investigate the neurobiological basis of brain plasticity in the face of new environments using epidemiological and longitudinal strategies in combination with basic biology approaches. Psychotherapy needs to be optimised as a better clinical instrument; and psychiatric disease needs to be destigmatized.



## SPEAKERS

**Thomas Becker** University of Ulm  
**Mathias Berger** University Hospital Freiburg  
**Pamela Y. Collins** National Institute of Mental Health  
**Jay N. Giedd** National Institute of Mental Health  
**Lydia Krabbendam** VU University Amsterdam  
**Husseini K. Manji** Janssen Research & Development, LLC  
**Michael J. Meaney** McGill University  
**Sir Robin M. Murray** King's College, London  
**Charles B. Nemeroff** University of Miami  
**Mark C. Pachucki** Massachusetts General Hospital /  
Harvard Medical School  
**Sir Michael Rutter** King's College, London  
**Thomas E. Schläpfer** University Hospital Bonn  
**Bernd Weber** University of Bonn  
**Hans-Ulrich Wittchen** Technical University Dresden

## CHAIRS

**Philip Campbell** nature  
**Peter Falkai** University of Munich  
**Helge Frieeling** Hannover Medical School  
**Andreas Meyer-Lindenberg** Central Institute of  
Mental Health, Mannheim  
**Aribert Rothenberger** University of Göttingen

## MORE INFORMATION

For Pictures and Audios:

<http://www.volkswagenstiftung.de/index.php?id=2475>

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