EUROPÄISCHE AKADEMIE
zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen
Bad Neuenahr-Ahrweiler GmbH
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NEWSLETTER
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EDITORIAL

■ Awareness of the ambivalence of scientific and technological developments has grown considerably over the last few decades. Problems associated with scientific and technological advancement and their possible but sometimes uncertain consequences are accordingly the subject of political and public debate. The "International Journal of Ethics of Science and Technology Assessment *Poiesis & Praxis*" is therefore conceived as an inter-disciplinary forum for reflections on the scientific and technological future of our civilisation. It aims at interested researchers from philosophy, natural, social and legal sciences, as well as from medical disciplines. Moreover, it addresses decision-makers in political institutions and in business and industry.

The contributions collected within this journal are devoted to: (1) Research into the societal consequences of scientific, technological and bio-medical advancement; (2) corresponding reflections in the sense of technology assessment and/or ethics of science; (3) discussion of the ideas and procedures of ethics of science and technology assessment; (4) the analysis of the relation between these reflective efforts and society.

The most recent issues of *Poiesis & Praxis* focused on problems of modern "IT and Society" and on prospects and perils of "Innovations in Neuroscience". New authors and readers are highly welcome to enrich this forum of interdisciplinary reflection. Interested parties may visit the corresponding pages of the academy's site at www.europaeische-akademie-aw.de. SL

FOCUS

Deep Brain Stimulation

Neuromodulation Therapies for Psychiatric Disorder and their Ethical Implications

Thomas E. Schläpfer

Depression refers to a set of prevalent, extremely debilitating disorders that can be characterized by a triad of symptoms: extreme anhedonia (complete loss of pleasure from previously pleasurable activities), depressed mood, and low energy. Other cognitive symptoms (e.g. pessimistic thoughts, feelings of guilt, low self-esteem and suicidal ideations) and somatic symptoms (e.g. sleep and psychomotor disturbances, food-intake and body-weight dysregulation) are also present quite often. Unipolar major depression is the leading cause of disability worldwide and is associated with a high mortality due to suicide and increases in mortality in comorbid somatic disorders such as cardiovascular disorders or cancer. Modern medication treatments, in conjunction with certain methods of psychotherapy, are effective at alleviating depressive symptomatology in most patients. However, these treatments do not work for all affected subjects. A sizable minority of patients does not respond. Indeed, 17–21% of patients suffering from major depression have a poor outcome after two years, and 8–13% have a poor outcome even after five years of treatment. Since these patients do not respond to any known treatment combination including electroconvulsive therapy, they are referred to as "treatment resistant". This underserved population has had little hope of recovering from this disease.

Early Promise of Neuromodulatory Treatments

■ Psychotropic drugs work by altering neurochemistry in widespread regions of the brain, many of which may be unrelated to depression. It might be that more focused, targeted treatment approaches that modulate specific networks in the brain will prove a more effective approach to help treatment-resistant patients. In other words, whereas existing depression treatments approach this disease as a general brain dysfunction, a more complete and appropriate treatment will arise from thinking of depression as a dysfunction of specific brain networks that mediate mood and reward signals. This conceptualization leads to novel ideas about targeted neuromodulatory treatments.

Indeed, a first approach for intervening in very treatment resistant patients by neurosurgical means dates back to the origins of neurosurgery itself. Targeted *irreversible* destruction of brain tissue – more or less guided by hypotheses on the neurophysiology of the disorders to be treated – was used to modulate networks and behaviors. The new neuromodulatory technique of deep brain stimulation (DBS) has none of the shortcomings of the traditional methods. It refers to the delivery of electrical currents with adjustable frequency, polarity, amplitude and pulse-width by a system consisting of electrodes connected to an

implanted neurostimulator. The intended neuromodulation is *adjustable* and fully *reversible;* the preoperative situation can be restored if needed.

At present, DBS is a common treatment for movement-related symptoms of Parkinson's disease (specifically tremor), and essential tremor, and is currently also under investigation for use in other indications such as dystonia, cluster headache, and treatment refractory obsessive-compulsive disorder. Recently, the results of DBS close to the subgenual cingulate region in six patients with refractory depression were reported by Mayberg et al. (cf. *Neuron* (2005) 45:651–660). The authors chose this target based on their previous findings that this region is involved in acute stimulus-induced sadness, is metabolically overactive in treatment-resistant depression, and that clinical improvement after pharmacotherapy and psychotherapy is correlated with decreases in its metabolic activity. After two months of stimulation five patients responded, four maintained response after six months.

Ethical Issues in this Patient Group

Although these published and other not yet published results are very promising, even the use of reversible neuromodulatory techniques for the putative treatment of depression raises several concerns not or less associated with other treatments being researched. *Firstly,* the need for this new therapeutic option is questioned since there is a broad range of available treatments for chronic and severe depression and since clinical experience shows that some patients even with severe and chronic forms of the disorder may finally respond after months or years of creative treatment. *Secondly,* DBS is associated with severe risks occurring rarely such as bleeding into the brain, infection related to the implants, or hemiparesis. *Thirdly*, the use of neurosurgery for psychiatric disorders has a long but somewhat tainted history. Therefore, surgery on the brain – even when fully reversible and adjustable, and even if only applied in extremely desperate patients suffering from a potentially deadly mental disorder – requires special ethical consideration. These reasons necessitate a careful multidisciplinary and systematic assessment of treatment refractoriness in the consideration of patient eligibility. The strict adherence to the inclusion criteria approved by an ethical board should be confirmed for each patient by a review board independent from the research group or at least by an independent psychiatrist. Early on, consensus guidelines have to be established cooperatively by psychiatrists, neurosurgeons and ethicists, continuously weighing potential risks and benefits of the procedure as new data become available.

Patients with chronic pain, depression and obsessive-compulsive disorder are vulnerable groups and therefore require particularly careful scrutiny because the long-term safety of neuromodulatory therapies is unknown. Furthermore, the clinical use of DBS in patients with dystonia and Parkinson disease occurs in a situation in which no other treatment is available and the prognosis for continued worsening is almost universal. This is not the case for treatment resistant major depression or obsessive-compulsive disorder since spontaneous improvements and even recovery are possible and since new therapeutic agents are continually being developed that do benefit some individuals who have not responded to prior treatments. This is not true of many patients with psychiatric disorders or chronic pain; we therefore believe that extra scrutiny in patient selection is required.

Depression is the most burdensome disorder both for society and the affected individual. Depressed patients have an extremely reduced quality of life and total hopelessness is a key diagnostic factor of the disorder. It is understandable that these patients, certainly after a long and treatment resistant course would do anything to improve their condition. While patients with depression are generally considered to be able to give informed consent, decisions about inclusion in a DBS protocol have to include in the consenting process extra steps in information of the patients' social network and independent physicians.

Outlook

There is certainly no consensus as of yet about the exact mechanisms of action of how the neuromodulatory technique DBS might induce antidepressant effects. However, this is also the case for many (most) other antidepressant treatments. There are many variables of DBS application and a large parameter space has therefore to be explored in order to find out the most efficacious treatment. This process will most likely be slow, because there is much less public and industry funding than for pharmaceutical studies. Nevertheless, DBS has clearly effects on behavior, which is certainly remarkable. From the viewpoint of the neuroscientist, DBS is a methodology with great potential as a research tool. This technique, by itself and combined with other methods, for instance from neurophysiology and neuroimaging, may be useful to test functional connectivity, neuroplasticity, information processing, indirect and direct motor control, as well as aspects of mood control. It affords testing of either general hypotheses of the brain's functioning at different levels or hypotheses of the underlying pathology of neuropsychiatric disorders and thereby contributes to the conceptualization of even more efficacious treatments.

The clinical significance of these results remains to be determined. But regardless of the outcome of this process, this research might well shed light on some factors essential to antidepressant response. We are physicians in addition to being researchers; in this chosen role we are committed to help patients afflicted with a deadly disease. How could we possibly disregard data probably contributing to the knowledge on the neurobiology of this very disease? This knowledge might most certainly contribute to the development of more focused treatments. In the double role as physicians and researchers we should balance the goals of establishing more effective treatments while simultaneously searching for ways to improve the quality of life for patients in our care. These goals are certainly not mutually exclusive, as some might perceive it. Rather to the contrary, the concern for the suffering of patients is the most important driving factor leading, complemented by rigorous and critical science, to even better treatments in the future.

Although the elegant work by Mayberg et al. can certainly be seen as a proof of the principle that reducing depression associated hyperactivity in a certain brain region (cg25) is associated with symptomatic improvement, we are far from embracing DBS as a new clinical opportunity. Further studies should use controlled designs, explore different stimulation sites and parameters within known neural depression networks and should follow up patients

for longer time periods to determine the necessary length of treatment and possible cessation effects. Following this path, we might not only find new treatment modalities for very severe, chronic and treatment-refractory forms of depression, but in addition learn more about the underlying neurobiology of one of the most disabling psychiatric disorders; knowledge which might ultimately lead to the development of treatment modalities with an even more favorable risk-benefit-profile. In the meantime, DBS in the treatment of depression will take place within the constraints of carefully planned clinical trials with the highest ethical standards possible. Historically, neurosurgical interventions for psychiatric disorders were radically destructive crude interventions, indiscriminately applied, often undertaken with the aim to better control difficult patients, neither guided by sound hypotheses nor having assessed its effects systematically. The refinement of neurosurgical methods, the results from translational research on the pathways implicated in depression, the standard of clinical research in psychiatry and probably most importantly the application of ethical research guidelines have changed this perspective completely. Neurosurgery might have the potential to help those patients with the severest forms of major depression.

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WORKING GROUPS

Practical Philosophy

■ The scientific staff of the Europäische Akademie regularly meets up to work on special normative questions that derive from discussions in the academy's project groups or in the context of other research activities as e.g. the doctorate or habilitation programme. Due to the composition of the academy's staff the work within this study group is genuine interdisciplinary research and at the same time for each participant an internal further training across the limits of disciplines.

In the first half of 2006 the study group discussed a thesis on "autonomy" and "consent" by Dr. med. Felix Thiele, M.Sc., as worked out in his philosophical habilitation, that will be completed soon. Further topics will be the plurality of the concepts of risk and the limits and power of contractarian ethics.

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For more information please see
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NEWS

Bundesverdienstkreuz

■ Professor Dr. phil. Dr. phil. h.c. Carl Friedrich Gethmann wurde vom Bundespräsidenten das Bundesverdienstkreuz am Bande des Verdienstordens der Bundesrepublik Deutschland verliehen und vom Ministerpräsidenten des Landes Nordrhein-Westfalen am 5.9.2006 im Schloss Berge (Gelsenkirchen-Buer) persönlich überreicht.

For more information please see
www.europaeische-akademie-aw.de

Berufung

■ Professor Dr. phil. Dr. phil. h.c. Carl Friedrich Gethmann wurde in den Wissenschaftlichen Beirat des *Philosophischen Jahrbuchs* (Verlag Karl Alber Freiburg i.Br./München) berufen.

European Platform

■ Dr. phil. Thorsten Galert has been invited to participate in the "European Platform for Life Sciences, Mind Sciences, and the Humanities". The aim of this initiative which is sponsored by the Volkswagen-Foundation is to establish an interdisciplinary network of young European scholars who are carrying out research in topics related to the growing academic and societal influence of neuroscience and neurotechnologies. The first activity of this platform will be a workshop of 59 selected applicants scheduled to take place from 11th to 13th October 2006.

New Staff Members

■ The academy welcomes its new staff members, Dipl.-Kff. Margret Heyen and Dr.-Ing. Bert Droste-Franke, Dipl.-Phys. Heyen will be responsible for all matters of administration and finance. She will also be the contact person for all business and legal matters concerning the corporation, especially for the shareholders and sponsors of the Europäische Akademie.

Droste-Franke will coordinate the project "Fuel cells and virtual power plants as elements for a sustainable development. Innovation barriers and implementation strategies", running from July 2006 to December 2008.

For more information please see
www.europaeische-akademie-aw.de

Potentials and Risks of Psychopharmaceutical Enhancement

■ The newly established project group met for the first time on July 24th/25th 2006 in Bad Neuenahr Ahrweiler. The project picks up a topic which has already been dealt with in the now concluded project "Intervening in the Psyche. Novel Possibilities as Social Challenges". This project explored various new methods of intervening in the brain and, among other legal and ethical issues, tackled questions related to the possibility of such interventions being used for non-therapeutic purposes. In doing so, the project group became increasingly aware of the diversity and dazzling complexity of the issues raised by an emerging social trend toward utilizing medical means for the enhancement of emotional wellbeing and cognitive performance beyond what is considered "normal" or "natural" in healthy individuals. The clearest indication of this kind of development is given by the well-established fact that a growing number of people are ready to consume psychopharmaceutical drugs to achieve mood or cognitive enhancement. The two most cited examples for this trend are, first, regarding mood enhancement the Selective Serotonin Reuptake Inhibitors (most notably "Prozac"), antidepressants allegedly permitting people without depression to feel "better than well", and second, as regards cognitive enhancement Methylphenidate ("Ritalin") which seems not only fit for restraining hyperactive children but apparently also gives a competitive edge to everyone else who feels in need of some extra attentive capacity. (For a recent account of selected ethical questions concerning cognitive enhancement see the contribution of Cambridge psychologists Professor Barbara Sahakian and Dr. Danielle Turner to the latest issue of *Poiesis & Praxis* (2006) 4/2:81–94.)

The new joint project is funded by the German Federal Ministry of Education and Research (BMBF) as part of an initiative for "Research into Ethical, Legal and Social Aspects of Biomedicine". For seamless continuation of the former project group's work its chairman, Professor Dr. jur. Reinhard Merkel (Universität Hamburg), and its coordinator, Dr. phil. Thorsten Galert, also participate in the new project. Next to them, Professor Dr. med. Isabella Heuser, director of the University Hospital for Psychiatry and Psychotherapy (Charité, Berlin), accepted to contribute her medical expertise to the project group. Finally, Professor Dr. med. Bettina Schöne-Seifert, director of the Institute for Ethics, History and Theory of Medicine at the Universität Münster and member of the former German National Ethics Council, will devote herself to issues of medical ethics pertaining to psychopharmaceutical enhancement. The particular scope of the German Ministry's initiative affords each of the three partners of the Europäische Akademie to employ a junior scientist to assist them in their research for the project. The first meeting was primarily devoted to set the agenda for the two-and-a-half years of the project's course (scheduled end: December 2008). Furthermore, Professor Merkel, whose main contribution to the concluded project "Intervening in the Psyche" regards issues of mental enhancement, presented the results of the old project group. Hopefully in October, when the project group meets again in Hamburg, it will be completed by the three junior scientists yet to be employed.

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PUBLICATIONS

Margret Engelhard/Friedrich Breyer

■ „Organspende – Krankenhäuser brauchen Unterstützung, keine Bestrafung", in: Verband der Leitenden Krankenhausärzte Deutschlands e.V. *Arzt und Krankenhaus. Fachzeitschrift für die Krankenhausärzte und das Krankenhaus.* 79 (8), Lübeck, 2006, 235–238

Carl Friedrich Gethmann

■ *Manifest Gesundheitssystem*, Berlin-Brandenburgische Akademie der Wissenschaften, Berlin, 2006 (mit W. Gerok, H. Helmchen, K.-D. Henke, J. Mittelstraß, E. Schmidt-Aßmann, G. Stock, J. Taupitz, F. Thiele)

Felix Thiele

■ "Predictive medicine and the role of the physician's power of judgment", in: A. de Bouvet, P. Boitte, G. Aiguier (eds.), *Questions éthiques en médicine prédictive.* Paris, 2006, 19–27

LECTURES

Carl Friedrich Gethmann
15.9.06

■ „Dadurch, daß oder Indem? Handlungstheoretische Überlegungen zur sogenannten Willensfreiheit"
Interdisziplinäre Arbeitsgruppe *Humanprojekt* der Berlin-Brandenburgischen Akademie der Wissenschaften, Berlin

19.9.06

■ „Gerechtigkeit im Gesundheitswesen"
Vorstellung des *Manifest Gesundheitswesen,* Berlin-Brandenburgischen Akademie der Wissenschaften, Berlin

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PERSONALITIES

Angelika Schnieke, born in Oberhausen, North-Rhine Westfalia, holds the chair of Livestock Biotechnology at the Technische Universität München. She gained a diploma in bioengineering at the Fachhochschule Hamburg and a Ph.D. from the University of Edinburgh, UK. From 1978 to 1987 she worked with Professor Dr. med. Rudolf Jaenisch at the Heinrich-Pette Institut, Hamburg, and subsequently at the Massachusetts Institute of Technology, Massachusetts, USA. Here she carried out early development work on retroviral vectors for insertional mutagenesis and gene therapy, gene targeting and the production of transgenic models of human genetic disease. Subsequently she joined Colorado State University, Colorado, USA, where her research extended to the production of transgenic livestock. From 1992–2003 she worked with the biotechnology company PPL Therapeutics in Edinburgh, UK, becoming Assistant Director of Research in 2001. Her research at PPL focused on production of pharmaceutical proteins in the milk of transgenic large animals and generation of xenotransplantation donors. She has developed key technologies for the production of transgenic livestock, most notably somatic cell nuclear transfer – achieved with the birth of Dolly the sheep – and the first gene targeted livestock. Her current research focuses on animal stem cells and genome engineering in livestock species for bio-medical applications and functional genomics.

***Professor D.Phil. Angelika Schnieke** holds a chair for Livestock Biotechnology at the Technische Universität München. She is a member of the academy´s project group "Pharming. Genetically Modified Plants and Animals as Future Production Site of Pharmaceuticals?".*