IMAGEN STUDY

AIM

Identify and learn more about biological and environmental factors that might have an influence on mental health in teenagers. This knowledge will then help develop better prevention strategies and therapies in the future.

METHOD

multi-centre study conducted in the UK, Germany, France and Ireland on a total of 2000 fourteen year olds and their parents.

assessing:

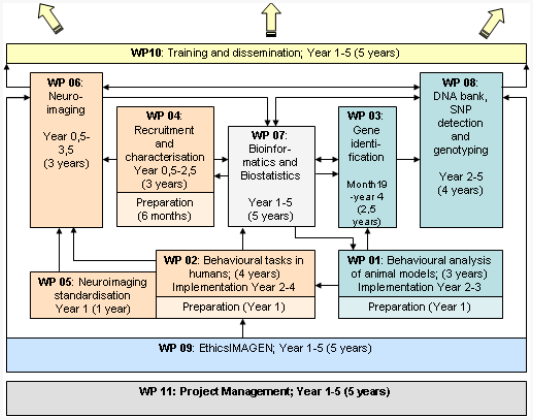
-psychopathology

-neuropsychology

-neuroimaging

-genetics

-environment



EthicsIMAGEN-
The Ethics Sub-Project

Lead Participants:

Central Institute of Mental Health, Mannheim, University of Heidelberg
German Reference Centre for Bioethics, Bonn, University of Bonn

Marcella Rietschel

Psychiatrist
Psychotherapist
Medical Geneticist

Christine Braeman

Psychiatrist
Psychotherapist

Dirk Lanzerath

Philosopher
Biologist

Bert Heinrichs

Philosopher
Mathematician

Tade Spranger

Lawyer

ETHICAL CHALLENGE

Identification of the genetic basis of behavioural traits, psychological disturbances and personality is an extremely sensitive area of research as it involves research on core issues as the origin of the "self", "self-determination" and "free will."

A specific problem, from an ethical perspective, arises when children are the subjects of research since they are not legally able to give informed consent.

This issue remains critical from an ethical standpoint, even though the child and the parents or legally entitled representatives have a right to permit active informed participation as well as withdrawal from the study.

EthicsIMAGEN

"…..The project is not a project concerning some harmless condition or disease, it is a project regarding mental disorders, genetic analyses and dealing with difficult issues like substance abuse, domestic violence etc. The project includes minors who are generally classified as "vulnerable" subjects, as they are legally incompetent and thus have to be protected….."

EthicsIMAGEN

Issues related to conduct of IMAGEN

- Informed consent, privacy of adolescents, rights and responsibilities of parents
- Data and DNA storage, data protection, and their ownership in the future
- Concept of “minimal harm“, potential benefit of research – no justification for „harm“
- Communication of relevant and irrelevant, expected and unexpected information

EthicsIMAGEN

Objectives

- Offer researchers strategies for solving, in an appropriate manner, ethically sensitive problems which may arise within this project
- Elaborate strategies and models for decision making processes regarding the relevant ethical problems emerging in the project context
- Disseminate these result in form of publications and teaching materials

EthicsIMAGEN

“Models for decision making processes” – Schematic Overview

1. IMAGEN partner encounters an issue that s/he considers to be normatively (ethically or legally) relevant

2. Partner reports issue to WP9 (EthicsIMAGEN)

3. Initial analysis of the issue by WP9

   Is the issue really normatively relevant?

   No → Answer to partner: Not a normatively relevant issue
   Yes→ Are all relevant aspects known?
   No → Request to partner to provide missing information, re-entry
   Yes → Is the issue of ethical or legal nature?

EthicsIMAGEN

“Models for decision making processes” – Schematic Overview

4. Ethical or Legal Issue

Does it directly affect the progress of the project?

Yes → Assessment by WP9 and detailed information about the state of the art with respect of discussions/ considerations of this problem. Suggestions to partner how to approach/solve the problem.

Existing assessments are collected in the document “IMAGEN / WP9 Record of Questions and Answers” and “Thematic folders” which are available through the IMAGEN Website.

The final decision concerning ethical decisions rests with the responsible ethics committee. Potential changes to the research protocol must be reported to the relevant ethics committee. Ethical/legal liability cannot be taken by WP9 but rests with the PI

EthicsIMAGEN

“Models for decision making processes” – Schematic Overview

4. Ethical or Legal Issue

Does it directly affect the progress of the project?

No → Detailed investigation by WP9; report in form of publication on IMAGEN Website (and potentially external publication).

The final decision concerning ethical decisions rests with the responsible ethics committee. Potential changes to the research protocol must be reported to the relevant ethics committee. Ethical/legal liability cannot be taken by WP9 but rests with the PI

EthicsIMAGEN

IMAGEN Webside and Forum

- The IMAGEN online library for ethical and legal documents includes a wide variety of texts relevant to the project such as laws and regulations from the participating countries and the EU, national and international guidelines as well as some statements from other relevant bodies.

- The Ethic-Forum: any ethical or legal question related to the IMAGEN project can be posted it in the ethics forum (http://www.imagen-europe.com/members/forum/).

EthicsIMAGEN

Workshop - Ethical Issues
Combined IMAGEN/EUREC Workshop
Paris Hospital Rothschild, January 26th, 2009
.

- Research on minors
- Informed consent
- Incidental findings
- The right to obtain information
- Outlook: Bridging research and health care
- Data and DNA storage and data protection

EthicsIMAGEN

Workshop - Ethical Issues
Combined IMAGEN/EUREC Workshop
Paris Hospital Rothschild, January 26th, 2009
.

- **Research on minors**
- **Informed consent**
- Incidental findings
- The right to obtain information
- Outlook: Bridging research and health care
- Data and DNA storage and data protection

Obtaining Informed Consent in Minors

With respect to the concept of minimal risk minimal burden
it was felt that the adolescents are old enough to assess their subjective burden and choose whether or not to participate (7 hours of testing)

Originally IMAGEN investigators proposed that a parent may consent on behalf of the other parent and states that s/he has informed the other parent, who is aware of and agrees to the study.

This proposal was rejected by EUREC.

Informed Consent

Absolutely no inducement financial or other pressures are allowed to be placed on the investigators, children or their parents/guardians to persuade children to participate in research

We would like to introduce a **Prize Draw** for the adolescents in order to **increase their motivation** to complete the home assessment. They would **gain** an entry for the draw upon successful and quick online assessment completion.
The IMAGEN 2-year Follow-up procedure consists of a home-based online assessment. Currently, both parent and adolescent are given £20 each as compensation for their effort and time. To join the Prize Draw, the adolescent should fully complete the questionnaires within a period of 2-3 weeks from the date they have received their log-in details. We are planning to hold one Prize Draw every three months (waves of assessment) and the **prizes will be 1 Apple iPad for each draw.** Draw date would be advertised in our website.

EthicsIMAGEN

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Informed Consent in the Genomics Era

Deborah Mascalzoni, Andrew Hicks, Peter Pramstaller, Matthias Wjst*

Since the Nuremberg trials, informed consent (IC) has been recognized as a basic ethical requirement for research involving human participants [1] (Table 1). Such consent encompasses two distinct elements: (1) researchers communicate detailed information about study procedures, outcomes, risks, and benefits for the participating individual or community, and (2) after understanding and careful consideration, the participants consent to take part under these conditions. However, the suitability of IC for genomic studies has been recently challenged [2,3]. Because the research protocol for such studies may evolve over time, the condition in IC of providing detailed information for a *well-defined* protocol is not easily satisfied.

Large amounts of data stored as electronic records allow multiple post-hoc analyses, which in many cases were not foreseen at the beginning of a study. The potential for analysis is constantly growing and recently has increased dramatically with the development of high-throughput

Summary Points

- Genetic cohort studies storing biological materials hold great promise for medical research, but also present new problems that are profoundly different from the classical clinical trial for which informed consent was developed.
- The classical risk/benefit analysis of physical harm doesn't take into account new threats to the individual such as uninsurability, unemployability, genetic discrimination, or disruption of family relationships.
- Traditional informed consent may therefore no longer be appropriate when dealing with long-term studies using biological materials.
- Informed consent should be seen as an ongoing process between researcher and participant and not just as a once-and-for-all decision.
- Research following the initial storage of samples needs to be likewise explained and may be announced using new communication methods.

has the right to know who owns the data, who guarantees proper handling, who will have further access to the data, and what security measures are in place. And all these concerns arise against a background in which the research questions themselves may rapidly change with the advancement of technical knowledge [10]. Any further genetic analysis may in fact severely compromise individual interests and autonomous choice, particularly if the individual is not fully aware of the very nature of the generated data and the implications of its use (or potential abuse). A stepwise informed consent should therefore be considered in accordance with the Council for International Organizations of Medical Sciences guidelines, one of the first to define IC not as a finite time step, but as an ongoing process [11] (Figure 1). Also, UNESCO's International Declaration on Human Genetic Data states that "clear, balanced, adequate and appropriate information shall be provided to the person whose prior,

Funding: The authors' research is funded by the European Academy Bolzano. MW is further funded by Helmholtz Zentrum München grant number FE

EthicsIMAGEN

Workshop - Ethical Issues
Combined IMAGEN/EUREC Workshop
Paris Hospital Rothschild, January 26th, 2009
.

- Research on minors
- Informed consent
- **Incidental findings**
- The right to obtain information
- Outlook: Bridging research and health care
- Data and DNA storage and data protection

Incidental Findings

and the right to know and not to know

Incidental findings:

Possible discovery of unexpected, but clinically relevant, incidental findings

- **Irregularities in imaging which require clarification**
- **Irregularities in psychological assessment which require clarification, treatment or intervention, e.g. depression, suicidality, history of either being a victim or having carried out acts of aggression.**

Incidental Findings

in neuroimaging:

The incidence of clinically relevant incidental findings in normal individuals undergoing neuroimaging studies for research purposes has been reported to range from 1% to 15%.

The prinicples of autonomy and non-maleficence:

- **The right of subjects to know their own findings if desired**
- **The right of subjects not to know their own findings if desired**
- **The freedom of subjects to act upon any clinically relevant findings in whatever way they wish, e.g. to ignore them.**
- **The researchers duty not to expose subjects to disproportionately high risk or discomfort through research activities.**

The problem of how best to deal with incidental findings is often a matter of the conflicting demands of the principles of autonomy and non-maleficence especially when it involves minors

Incidental Findings

Practical recommendations

- **Explanation of the researcher-subject relationship:**
  It is not the purpose of the study to search deliberately for abnormalities in the brain -
  Clinically relevant findings may not be discovered.

- **Explanation of incidental findings:**
  He or she must be told about the possiblity that deviations from the normal state, or clinically relevant pathology in the brain, might be discovered in the course of the study.

- **Minimal harm:**
  Immediate clarification of the relevance of the finding through the researcher (No time-delay)

- **Inclusion criteria for participation in the study**
  The subject has to consent to the communication of any clinically relevant findings that may be suspected, as well as to the recommendation of further clinical diagnostic testing…..but there is also the right „not to know“ when participating in a study

Incidental Findings

Study Center	Incidental findings	Clinical significance	Artefact	Cases	Percent
Nottingham	4	2	1	263	1.52
Mannheim	7	7	0	175	4.00
Hamburg	5	3	0	224	2.23
Dublin	0	0	0	202	0
Berlin	5	3	1	199	2.51
Dresden	1	1	0	131	0.76
overall	**22**	**16**	**2**	**1194**	**1.84**

Incidental Findings

…no sufficient ressources are available to have all brain images scanned by an expert---

----- is this a problem?

MEDICINE

ORIGINAL ARTICLE

Incidental Findings in Neuroimaging: Ethical Problems and Solutions

Thomas Heinemann, Christian Hoppe, Susanne Listl, Andreas Spickhoff, Christian E. Elger

SUMMARY

Introduction: Brain research in humans relies increasingly on neuroimaging. However, controversy surrounds the question of how to deal in an ethically and medicolegally with incidental structural or functional findings. Methods: Based on an a between researcher and study subject, and of the widely accepted ethic and non-maleficence, current practice is criticized and criteria are dev Discussion: No patient-physician-relationship is established in a resea recording and analysis of data is solely based on scientific criteria and individual clinical diagnosis. The study subject must be informed abou ethical and legal conflicts, the subject must give consent in advance to r about incidental findings. Although incidentally detected abnormalities researcher, the researcher has the obligation not to inflict any further h respect of their communication. Dtsch Arztet

Key words: brain research, neurological sciences, ethics, incidental fin

ORIGINALARBEIT

Zufallsbefunde bei bildgebenden Verfahren in der Hirnforschung

Ethische Überlegungen und Lösungsvorschläge

Thomas Heinemann, Christian Hoppe, Susanne Listl, Andreas Spickhoff, Christian E. Elger

ZUSAMMENFASSUNG

Einleitung: Die Hirnforschung stützt sich zunehmend auf bildgebende Verfahren. Kontrovers diskutiert wird, wie mit dem Risiko struktureller und funktioneller Zufallsbefunde ethisch und rechtlich angemessen umzugehen ist. Methoden: Basierend auf einer Analyse des Legitimations- und Pflichtenverhältnisses zwischen Forscher und Proband sowie der anerkannten ethischen Prinzipien der Autonomie und des Nichtschädigens werden gegenwärtig praktizierte Verfahrensweisen beurteilt und – unter anderem – folgende Grundsätze für konkrete Handlungsempfehlungen entwickelt. Ergebnisse und Diskussion: Durch die Teilnahme an einer Studie wird zwischen Forscher und Proband kein Arzt-Patient-Verhältnis etabliert. Die Datenerhebung und -analyse folgen daher ausschließlich wissenschaftlichen

SUMMARY

INCIDENTAL FINDINGS IN NEUROIMAGING – ETHICAL PROBLEMS AND SOLUTIONS

Introduction: Brain research in humans relies increasingly on neuroimaging. However, controversy surrounds the question of how to deal in an ethically and medicolegally appropriate manner with incidental structural or functional findings. Methods: Based on an analysis of the relationship between researcher and study subject, and of the widely accepted ethical principles of autonomy and non-maleficence, current practice is criticized and criteria are developed. Results and Discussion: No patient-physician-relationship is established in a research study. Therefore, the recording and analysis of data is solely based on scientific criteria and does not aim at an individual clinical diagno-

MEDIZIN

DISKUSSION

zu dem Beitrag

Zufallsbefunde bei bildgebenden Verfahren in der Hirnforschung. Ethische Überlegungen und Lösungsvorschläge

von Prof. Dr. med. Dr. phil. Thomas Heinemann, Dr. rer. nat. Christian Hoppe DTh DPs, Susanne Listl, Prof. Dr. jur. Andreas Spickhoff, Prof. Dr. med. Christian E. Elger, in Heft 27/2007

2. Kreuzer A: Die unterlassene ärztliche Hilfeleistung in der Rechtsprechung; NJW 1967, 278.
3. Urteil des Bundesverfassungsgerichts vom 18. 11. 2004 Az.: 1 BvR 2315/04.

Wolf-Ekkehard Klix
Rechtsanwalt
Münchener Straße 18
82362 Weilheim bei München
E-Mail: rechtsanwalt@klix.de

Interessenkonflikt
Der Autor erklärt, dass kein Interessenkonflikt im Sinne der Richtlinien des International Committee of Medical Journal Editors besteht.

Zentrales juristisches Problem nicht verstanden

Mit Interesse haben wir den Artikel von Heinemann et al. gelesen, zumal wir bereits in 2006 eine Arbeit zu den juristischen Aspekten des Themas veröffentlicht haben (1).

Juristisch interessant ist die enorme Erweiterung des Schadensbegriffs im Artikel. Das Gesetz geht in erster Linie von einem materiellen Schadensbegriff aus.

Beim Spezialisten rückversichern

Im Rahmen der IMAGEN Studie (www.imagen-europe.com/) werden bei 2 000 14-jährigen Jugendlichen bildgebende, neuropsychologische und geneti-

Rietschel and Büchel 2007

EthicsIMAGEN

Workshop - Ethical Issues
Combined IMAGEN/EUREC Workshop
Paris Hospital Rothschild, January 26th, 2009
.

- Research on minors
- Informed consent
- Incidental findings
- **The right to obtain information**
- **Outlook: Bridging research and health care**
- Data and DNA storage and data protection

The Right to Obtain Information

Confidentiality

Possible conflict between the principle of parental fiduciary duty and the principle of autonomy of the child.

- Medical professionals have a duty of confidentiality to all patients including children. Legally competent children are entitled to expect that information about themselves will not be provided to a third party, including their parent/guardian, without their consent.

- It is important that wherever possible the parents/guardians are informed, and young people should be encouraged to involve them unless it is not in their best interests to do so. However, if competent children do not wish to involve their parents/guardians this should be respected.

The Right to Obtain Information

In the era of „direct-to-consumer genetic testing“

Participants ??? Physicians ???

Knowledge of basis information may later become important (Methylation status, fMRI findings, psychopathology etc)

To whom participants may return after termination of the study

EthicsIMAGEN

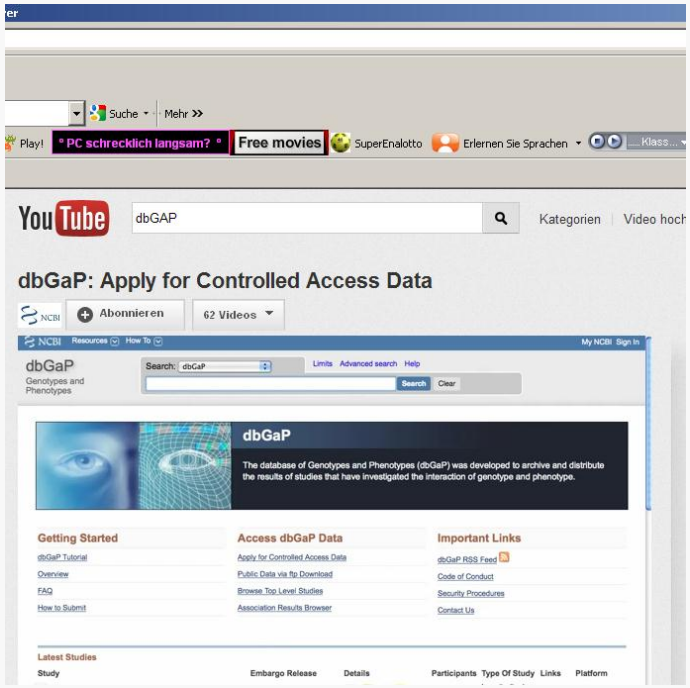
Workshop - Ethical Issues
Combined IMAGEN/EUREC Workshop
Paris Hospital Rothschild, January 26th, 2009
.

- Research on minors
- Informed consent
- Incidental findings
- The right to obtain information
- Outlook: Bridging research and health care
- **Data and DNA storage and data protection**

Data Storage and Data Protection

(Semi)-publicly available data bases

Database of Genotypes and Phenotypes (dbGAP).



This public database was established by the National Institutes of Health in the USA in order to archive and distribute data from genome wide association studies, and thus provide a central resource for international researchers.

Data Storage and Data Protection

The IMAGEN team approached WP9 for advice concerning the inclusion of IMAGEN data in the Database of Genotypes and Phenotypes (dbGAP).

In particular, the IMAGEN teams required clarification as to how this issue should be addressed in the informed consent documentation.

After consent of the ethic committee, data protection authority and lawyer, we included the following passage in the informed consent:

In addition we want to include your data in a pseudonomyzied way in international data banks
Access to these data banks is regulated, i.e. that data will only be made available for a limited time to selected researchers who have to apply for them. The transmission of data will be controlled by specific task groups.

Is this precise enough?

Personal Conclusions

In general researchers showed limited interest in ethical and legal questions.

With respect to legal questions they were grateful to relay on somebody offering competent guidance and/or solving problems.

With respect to ethical questions they were not pleased if problems were brought up which had the potential to hamper or delay their main research goals.

Personally it was an interesting experiment to screen all steps for legal and ethical pitfalls - and I believe that the continuous discussions about those issues helped to integrate this line of thinking in the mind of researchers and into this project.

However, the value of those ethic-workpackages is debatable

Thank you