CHAPTER

15

"Strangers" in Neuroscientific Research*

B. Bringedal[1,5], *M. Christen*[2], *N. Biller-Andorno*[2], *H. Matsuzaki*[3] *and A. Rábano*[4]

[1]LEFO - Institute for Studies of the Medical Profession, Oslo, Norway [2]University of Zürich, Zürich, Switzerland [3]University of Oldenburg, Oldenburg, Germany [4]Carlos III Health Institute, Madrid, Spain [5]Columbia University, New York, United States

INTRODUCTION

New technological opportunities drive new types of research. The developments in digital technology have made it possible to collect, store, and analyze huge amounts of data, with significant impacts on science and society. "Big science" is the common term for such large-scale research, and the associated digitalization of research has simplified scientists' collaboration in many ways. It allows the creation of new types of research infrastructures—durable institutions, technical tools and platforms, and/or services that are put in place for supporting and enhancing research. Such infrastructures are increasingly set up as virtual research environments (VREs): web portals that provide services to users that are connected to underlying databases and repositories of various kinds. The technological developments promote collaboration among

*The title is inspired by David Rothman's book *Strangers at the Bedside* (Rothman, 1991). It also implies advantages of being an "external insider" who can discover new perspectives that the internal insider hardly becomes aware of. It does not imply that the members of the former Ethics, Legal and Social Aspects Committee and the current Ethics Advisory Board of the Human Brain Project are nonexperts in neuroscience—actually 8 out of 11 members of the current EAB have a primary background (PhD) in neuroscience or technology.

The Human Sciences after the Decade of the Brain.
DOI: http://dx.doi.org/10.1016/B978-0-12-804205-2.00015-X

many research institutions, research groups, and individuals, which facilitates the sharing of knowledge and contributes to more effective knowledge accumulation. The technological opportunities also involve new practical and ethical challenges tied to the size of the project, e.g., related to the collection, storage, analysis, and application of large amounts of data (usually referred to as "big data").

The European Commission's Human Brain Project (HBP) is an example of research that aims to create various VREs involving big data. The HBP is one of the world's largest initiatives in brain research and neuroscience, comprising more than 110 partners and, with matched partner funding for research, a 10-year budget of €1.2 billion.

Early on, there was an awareness of the need to pay attention to the inherent ethical, social, legal, and philosophical implications of the research.[a] Two ethics committees were established, later merged to one, as well as The Ethics and Society subproject assigned to explore social and normative issues emanating from the HBP research and to contribute to fostering responsible research and innovation by raising ethical awareness among the project participants.

The former Ethics, Legal and Social Aspects Committee (ELSA) and the Ethics and Society subproject complement ethics and ethically justified research. While the ethics committee was intended to provide independent views on ethical issues raised during the progress of the HBP, the research subproject identifies ethical issues qua the actual research.[b] In September 2015, ELSA was merged with the second committee that advised the HBP executive management: the Research Ethics Committee (REC). The two bodies were merged during the course of various organizational changes in the ramp-up phase of the HBP (see additional explanations in the text). All authors of the current chapter were members of the previous ELSA, while Christen, Rábano, and Bringedal are also members of the current EAB. The views expressed in the chapter are the views of the five authors only, and are not intended to reflect either the view of the (former or current) committee as a whole or the views of the leaders of the HBP.

In this chapter, we report our experiences of being involved in the ethical oversight of such a large-scale project and discuss some of the challenges from the perspective of experts that currently are mainly

[a]In fact, the importance of paying proper attention to ethics in this research was underscored as early as in 2010 by Dudai and Changeux (personal communication) in a meeting with the EC.

[b]An example is the "foresight lab," which "will be responsible for monitoring HBP research and exploring its social and ethical implications for European citizens, European industry, the European economy and European society." (See https://www.humanbrainproject.eu/ethics-and-society.)

active in ethics/sociological research.[c] We intend to highlight a few selected issues to promote an open discussion of how crucial ethical, social, and legal questions can be addressed and dealt with in such a large-scale project. Although many of the issues pertain to research promoting VREs and big data in general, our discussion is limited to the HBP.

We begin with a brief presentation of the HBP and the newly formed EAB, followed by a description of features (of the organization) of the research that pose particular ethical challenges. (For readability, we use "ethical aspects" as short for "ethical, legal, social, and philosophical" aspects.) Based on this description, we discuss how the issues could be dealt with. We suggest three overarching normative principles as guidance for all activity in the HBP in general and the work of the EAB in particular, and conclude the chapter by suggesting recommendations.

THE HUMAN BRAIN PROJECT

General Description

The HBP is a large-scale, long-term research project that includes 112 partners in 24 countries with a budget of €1.2 billion over 10 years. The project's central aim is "to build a world-class experimental facility to study the structure and functions of the human brain. This new information and communications technology (ICT) infrastructure will integrate neuroscience data and will be used to design brain-computer models to understand and simulate the human brain" (European Commission, 2014). This will "accelerate our understanding of the human brain, make advances in defining and diagnosing brain disorders, and develop new brain-like technologies" (the official HBP website: https://www.humanbrainproject.eu).

The HBP is one of the two winning projects of the European Commission's flagship initiative.[d] This initiative was formulated under the 7th Research Framework Program of the European Union in the field of Future and Emerging Technologies (FET). The intent was for FET flagship projects to be large-scale, ambitious research projects with a visionary goal in ICT. A total of 26 consortiums submitted projects. In 2011, six candidates were nominated to prepare a detailed

[c] The disciplinary background of the authors is as follows: BB: sociology; MC: empirical ethics/neuroinformatics; NBA: biomedical ethics/medicine; HM: sociology/science and technology studies; AR: neuroscience/neuropathology.

[d] The other is the Graphene flagship project; see: http://graphene-flagship.eu/.

proposal. In January 2013, the European Commission announced the two selected projects.

These FET flagship projects are big science projects with a strong focus on ICT, but the projects' activities are expected to extend beyond research, addressing aspects such as coordination, strategy development, mobility programs, international cooperation, road-mapping activity, training and education, outreach, communication, and PR activities (http://cordis.europa.eu/fp7/ict/programme/fet/flagship/doc/flagshipflyer-july2013_en.pdf).

The HBP structures its research along three major topics: First, *Future Neuroscience*, i.e., the aim to achieve a unified, multilevel understanding of the human brain that integrates data and knowledge about the healthy and diseased brain across all levels of biological organization, from genes to behavior. This also includes establishing in silico experimentation as a foundational methodology for understanding the brain. Second, *Future Computing*, i.e., the aim to develop novel neuromorphic and neuro-robotic technologies based on the brain's circuitry and computing principles. This includes the build-up of supercomputing technologies for brain simulation, robots and autonomous systems control, and other data-intensive applications. Third, *Future Medicine*, i.e., the aim to create an objective, biologically grounded, map of neurological and psychiatric diseases based on multilevel clinical data. This map should then be used to classify and diagnose brain diseases and to configure models of these diseases. It finally should lead to personalized medicine for neurology and psychiatry.

The HBP flagship project is coordinated by the Swiss Ecole Polytechnique Federale de Lausanne. Other important members include the German Ruprecht-Karls-Universität Heidelberg and the Forschungszentrum Juelich, the French Centre National de la Recerche Scientifique, the Swedish Karolinska Institutet, and the Spanish Universidad Politecnicade Madrid.

Controversy in the Neuroscientific Community—The Open Letter

In 2014, a debate emerged in reaction to developments within the HBP. The debate was initiated by a change of plans in the project, in particular when cognitive and systems neuroscience (cognitive architecture) allegedly was given diminished significance in the project. Within a few months, an open letter to the European Commission was signed by more than 800 scientists, who were not part of the HBP (see http://www.neurofuture.eu). The letter included a critique regarding the scientific approach ("overly narrow approach") as well as the

governance structure ("lack of flexibility and openness of the consortium"). For a similar critique, see Frégnac and Laurent (2014).

The critique led to a mediation process, which focused on conflicts in the management.[e] "The open letter influenced the first review process that began with a screening but led to a full review due to the complexity and size of the project. It was no surprise to anyone that a full hearing would take place," says Kevin Grimes, research coordinator for the Human Brain Project Ethics Governance and Regulation (personal communication). The European Commission's response to the open letter included an independent review and a mediation process.

As a result of the external review and the mediation, cognitive architecture became part of the project again (including a new call for proposals), and significant changes were made in the governance structure. We return to the question of organization and governance later. One of the changes, however, concerned the role and structure of the ethics committees directly.

The Ethics Advisory Board

Ethical, social, legal, and philosophical aspects of the research were part of the project from the beginning. One of the subprojects, Ethics and Society, focused on research regarding these aspects. In addition, two external advisory committees were established; one was dedicated to research ethics (REC) while the second was intended to take a broader long-term perspective on ethical, legal, and social aspects (ELSA). One and a half years after the external ethical review of the HBP and the mediation report initiated by the open letter, the Board of Directors decided that the two committees should be merged into one Ethics Advisory Board (EAB).[f] The rationale for the decision was the recognition of overlap between the responsibilities of the two committees, that the REC could not and should not provide a formal evaluation of the projects, and the need to adapt ethical advice to a new governing structure. The members of the two committees considered the change an improvement and suggested they merge as soon as possible. The leadership of the ELSA and the REC, as well as the coordinators of the two committees, led the progress toward the merger.

[e]See the official HBP response to the open letter (https://www.humanbrainproject.eu/documents/10180/17646/HBP-Statement.090614.pdf).

[f]The idea of merging the two committees had come up earlier, independent of the open letter. One of the reasons was that the sharing of responsibilities between the Ethics and Society research project and the ELSA was unclear.

The current board was established in September 2015.[g] The majority of the members of the two previous committees were reappointed. The selection of members was primarily based on the assessment of core competencies needed in the group, while geographic distribution, balanced gender representation, and availability to attend meetings were also considered. The required expertise was assessed by the four chairs and cochairs of the ELSA and the REC in collaboration with administrative support in the HBP and based on the contents of the 12 HBP subprojects. Eight out of eleven members of the current EAB have a primary background (PhD) in neuroscience or technology.

The responsibilities of the EAB are similar to those of the former ELSA and REC. In both cases, the description of responsibility is described in general terms. The EAB, to a large extent, decides its specific tasks by itself—thus far based on deliberation in the committee of how the general mandate should be interpreted and operationalized. A standard operating procedure was recently agreed on.[h]

The EAB currently consists of 11 members with diverse disciplinary and professional backgrounds. The members are appointed for 3 years and may be reappointed for a second period. The general mandate of the EAB is to advise the direction of the HBP on specific ethical, regulatory, social, and philosophical issues raised by the HBP research. In this respect, the principle of subsidiarity will be upheld; i.e., the responsibility for ensuring compliance with ethical and legal principles and regulations (local, national, and European Union (EU) level) will lie with the research organizations and research groups who are actually undertaking the research. Thus the EAB will not duplicate the work of those organizations and procedures for vetting and approving research activities. However, the EAB is expected to advise on matters regarding the ethical review of research where conformity with relevant legislation and Horizon 2020[i] rules is not guaranteed by existing bodies and procedures.

This includes in particular issues related to data-sharing and research procedures, e.g., research involving the use of data, samples, or resources generated outside the HBP or carried out in non-EU countries (e.g., China and the United States).

[g]See https://www.humanbrainproject.eu/ethics-advisory-board?inheritRedirect = true.

[h]A standard operating procedure can be found at https://www.humanbrainproject.eu/documents/10180/1139903/EABSOP_2015-10-06-2.pdf/0132960f-77cb-4782-ba5d-946eca9c0e25.

[i]Horizon 2020 is the EU's new program for research and innovation that runs from 2014 to 2020 with a ~€70 billion budget. The research program is managed by the European Commission.

CHALLENGES

Before we identify and discuss some of the characteristics of the HBP that pose potential ethical challenges, the general tendency toward optimism bias (Kahneman, 2011) in many technological and scientific undertakings should be examined. Researchers, policymakers, and funding bodies frequently are disproportionally optimistic about what the research can accomplish. "Innovation in basic science is often a cause for wonder and excitement," says Jonathan Wolff (2014, p. 27), and "(t)hose associated with a new development are quick to point out the anticipated benefit: a cure for cancer or dementia, an end to unsafe water and hunger."

The optimism bias phenomenon is more likely to be pronounced in a big science project, since so much is at stake, in terms of resources, political expectations, more or less explicit promises, and academic expectations. This phenomenon is obviously not restricted to innovation and research; public policy frequently shares the same bias (see, e.g., Irwin & Wynne, 1996).

Disproportional or exaggerated focus on the positive achievements expected from research involves the risk of downplaying the potential negative effects (which, of course, may include the lack of effects). The selection process of the flagship project itself could also be seen to promote this tendency, as an attempt and/or prerequisite to win the competition. Several of the finalists had similar broad expectations. "Overselling" of, or overoptimistic expectations for, the research can have significant ethical implications, since adverse effects almost always are inherent and unavoidable, as are errors and negative results. To reduce the problem of optimism bias, explicit attention to "what can go wrong?" is required. We will elaborate on this in subsequent parts of the chapter.

Specific Challenges in the HBP[j]

The following description of features of the HBP research that may pose particular ethical challenges is not intended to be exhaustive; the description is limited and based on the experiences we as authors have encountered thus far as members of the advisory committees. Further, the categories are not mutually exclusive; characteristics can obviously belong to more than one category.

[j]The description builds on Christen, Biller-Andorno, Bringedal, Grimes, and Savulescu (2016); Christen, Domingo-Ferrer, Draganski, Spranger, and Walter (2016).

Big Data—Big Neuroscience

A salient feature of the HBP is its size. Several hundred researchers are involved, as well as huge amounts of data. This poses particular challenges for communication, coordination, and accountability. The HBP involves substantial geographic (research institutions in different countries and cities), economic (half of the funds for research are expected to come from local sponsors, while the other half is provided by the EU[k]), multidisciplinary and multicultural (including different cultures in different disciplines), and multinational collaboration. The last involves not only different cultures and values but also different legislation.

Some of the specific issues raised by the project's size are as follows: (1) "too big to fail," (2) unclear responsibilities, (3) important issues are lost in the structural complexity, (4) the relationship between massive public investments and the potential for private gain, and (5) implications of the public/private partnerships. When so much money has been invested in a project, the expectation of getting a substantial return on investment may bias progress evaluations. Any decision to terminate a flagship project early might also embarrass those who had given a greenlight for the funding so it can be assumed efforts will be made to stabilize the project in a way that smaller and less visible projects could not expect.

The larger a project, the more complex its management will become. As scientists are not usually trained as administrators and communicators, this task may be underestimated. However, good governance is paramount for the success of a project.

Another issue regards the interface of public and private interests. Projects such as the HBP receive significant public funding. Although public/private partnerships are quite fashionable today, a number of issues remain unresolved regarding fair distribution of investment and gain.

Further, big data projects require advanced ICT. The technology itself contributes to structuring the scientific research, as well as the communication between different researchers, subprojects, and stakeholders.

Big data also means big money. In this case, the European Commission's financial support is particularly generous since the project is one of the two FET flagship projects. In addition to the funding from the EU, there is also a substantial amount of local cofunding. The concentration of funds was one of the primary concerns of the critics (cf. the open letter). Clearly, the HBP takes up a substantial

[k]For research funding, 50% comes from EU FET and 50% from partners; for management activities, 100% comes from the EU.

amount of resources at the expense of other projects. Seen from the critics' perspective, the concentration of funding poses a threat to securing diverse approaches; however, the concentration of resources can be essential in order to realize the ambitious goals that are set for the research—not least, the goal of developing models and simulation tools to reach a unified understanding of the human brain.

Big money on the funding side is just one part of the ethical challenge. Big money in terms of the potential commercial use of research findings also involves ethical challenges. Where prospects of big profit are involved, there is always the risk of ignoring, or, at least, a lack of attention to, the potential unfavorable effects of the enterprise—be it in pharmaceutical research, technological innovation, or neuroscience. Recent years have seen a growing awareness of this issue in pharmaceutical research (Goldacre, 2012; Healy, 2012). There is, however, no reason to believe that this phenomenon is limited to pharmaceutical research only.

Not only profit motives can lead to (or, diminish proper attention to) misuse of data or findings. Social acknowledgment, scientific standing, and power—there are a number of motives why some individuals are willing to use data or scientific knowledge for unethical or illegal purposes. Pioneering research in an area, which characterizes the HBP, may in particular involve such risks, since it involves the prospects of gaining high academic and social status as well as significant commercial gains.

Organization and Information Flow

The project's size represents particular organizational and governance challenges. Essential information can be "lost in complexity" or responsibilities unclear. Good coordination and communication require unambiguous and well-known responsibility, decision, and information lines. Clear systems are essential—in each subproject as well as in the HBP as a whole.

Further, many scientists are involved in formal modes of collaboration that create a tradeoff between organizational coordination and individual freedom. In particular, the interests of individual members can be overridden in the pursuit of the collective goal (Shrum, Genuth, & Chompalov, 2007), which requires governing structures to manage such conflicts. In contrast to other types of formal collaboration in science (e.g., universities, faculties, institutes), big science projects usually lack a long "collaboration history" among members and are confronted with a fixed termination date, which generates management challenges, in addition to a requirement to communicate regularly with the funding organizations and the public. This means that much "nonscientific" expertise is needed, which was not present during the generation of the

proposal, when the scientific goals dominate. Integrating management and communication structures among consortium members thus is a process largely performed after the project starts—and has to be done in parallel to the scientific work. This may lead to conflict regarding resources for securing such "nonscientific" activities.

Expectations Regarding the Aims of the Projects

The ambitions of the project are high. It aims at collecting a huge amount of data, both research published in scientific journals as well as clinical data from hospital records. The intention is to bring all these data together into several ICT platforms to make all the data available to the researchers and to simulate the human brain (brain-related processes). If this goal is reached, the next step is to use the model to study brain diseases and analyze how different therapeutic interventions affect the brain.

There is a risk that some researchers and other stakeholders will be tempted to exaggerate the potential achievements of the research. This may be due to the competition for funding, but there is also a driving force created by communication with the public and other stakeholders. It is much easier to communicate, and gain enthusiasm, for research that promises to solve some of the big challenges of our time, than to promote a new technology that—in principle perhaps—can provide the possibility of simulating a human brain on selected dimensions. The specific contents of the research are currently vague. At some point in the evolution of the project, more specific objectives regarding what can really be modeled and simulated will have to be established.

To what extent some of these goals are achieved is also an ethical question. It contains at least three aspects. First, economically: Since the project takes such a large part of the research budget,[1] it supersedes other projects. In principle, alternative uses of the research funds could provide more valuable knowledge. In economic terms, the question is whether the opportunity costs of this allocation of research resources are lower compared to alternative uses of the resources.

The second ethical element is epistemological: Is it feasible to integrate knowledge from such diverse disciplines and scientific studies into one and the same model? (Rose, 2014). In both cases, economically and epistemologically, it can be hard to assess the probability of success ex ante (which, of course, is an inherent problem in many scientific enterprises). There are, however, strategies, insights, and

[1]The HBP takes up a substantial part of not only EU research funds but also from other sources since half of the money should be provided by the partners. Thus HBP projects must compete with other neuroscience research groups for available European public and private research funds.

perspectives that might help to identify flaws and weaknesses in the scientific approaches. We will discuss these strategies in the following sections.

The third ethical element concerns data origin, quality, and storage (Christen, Domingo-Ferrer, et al., 2016). One of the main objectives of the HBP is to develop models that can identify clusters of data that serve as specific signatures of human neurological and psychiatric diseases. Such models require the use of huge numbers of multilevel data from patients originally obtained for clinical care. Accordingly, the Medical Informatics Platform of the HBP has to deal with the substantial challenge of optimizing the scientific quality and use of the patients' sociodemographic and clinical data while respecting the ethical-legal context in which these data were obtained (original informed consent) and/or anonymizing personal data at the highest standards recommended by the EU (Opinion 05/2014 on Anonymization Techniques). These issues are particularly relevant now, since within the next 2 years the EU is expected to adopt a new General Data Protection Regulation that poses explicit limitations to the use of personal data for biomedical research. Protection of personal data and responsibility, transparency, and provenance in the use of data related to human beings will undoubtedly be a key factor in the perception of the HBP by patients, relatives, and charities, and for their active and enthusiastic involvement in the project.

Finally, the expectations for the project may involve an element of competition between the three largest economies of the world, Europe, the United States, and China. Currently, similar neuroscience research initiatives being conducted in all three economies[m] and it would be naïve to ignore that government funding on this scale most likely involves an element of competition for an economic head start.

Specific Challenges for the EAB

Determining the Expectations for the EAB

The expectations for the previous REC and ELSA were formulated in the work package description: "The ELSA committee will support HBP management on issues of policy and strategy. The REC will support local research sites on regulatory issues and compliance, maintain an ethics data registry, and the responsibility for communicating the

[m]In the United States, the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) initiative (see http://braininitiative.nih.gov/) is comparable. In China, the Chinese Brain Project was recently announced to be funded from 2016 to 2030 (http://en.people.cn/n/2015/0630/c98649-8913112.html).

official project position on specific issues in research ethics" (Work package description December 12, 2013). The subsequent description of the responsibilities of the ELSA gave a detailed description of its composition, number of meetings, and other administrative requirements but very little about its mandate. In addition to supporting the management on policy and strategy, "strategic oversight of ethical, legal and social issues" is stated. The open mandate led to a period of deliberation in the committee in order to determine specific tasks, which were continued in the new EAB.

The expectations for the REC were more specific and broader: "A separate Research Ethics Committee (REC), independent of the ELSA, will help the partners ensure that HBP research meets the highest possible ethical standards and that it complies with all relevant European, national and regional, law, as well as with the deontological standards imposed by relevant professional bodies (...) The work (...) will include preparing and revising guidelines, responding to researcher queries, and mandatory reviewing HBP local research ethics applications prior to their submission to local Independent Review Boards" (Work package description December 12, 2013).

This statement is not clear on the distinction between an IRB function of research proposals and a monitoring, higher-level role. The members of REC agreed that the research institutions themselves should be responsible for the ethical reviews, while the REC's role should be to advise, monitor, and promote research ethics, especially for data collection and protection. The REC made the following clarification: "The HBP REC is an advisory committee which will endeavor to assist with inquiries in regard to ethics, as is our remit. ... The REC does not receive or proactively collect all the ethics material for all studies associated with the HBP. We see our role as giving advice and helping resolve any queries in regard to ethics which are brought to us by ELSA or Sub-Projects of the HBP or in issues identified by REC members" (Office of Management of Work Package 12.5).

The task description of the EAB is as general as that for the ELSA and the REC. The EAB is expected to advise the Board of Directors of the HBP on "specific ethical, regulatory, social and philosophical issues raised by research that is being undertaken or planned under the auspices of the Human Brain Project" (SOP, EAB, 2015). A vague broad mandate clearly involves the possibility of defining the EAB's specific responsibilities independently. A vaguely stated mandate also involves the possibility of developing and changing the tasks during the project. The strength is flexibility and involvement by the members, but the weakness is that too much time is spent on deliberation and clarification, in contrast to implementation.

Independence and the Composition of Members

The independence of the previous ELSA and REC and the current EAB has been a manifest value since its start-up. Financial independence, meaning that no member receives an honorarium for his or her work, promotes such independence. The voluntary commitment implies, of course, that the members of the committee work under a significant time restriction. This involves a tension between expectations and what the EAB can accomplish in practice.

In principle, financial dependence can be a hindrance for an objective and/or sufficiently distant perspective. However, it seems unlikely that an honorarium for ethics consultants should compromise independence, unless the honorarium is unrealistically high. From a more cynical perspective, the volunteer contributions of ethicists signal how ethics is valued in the project or, more pragmatically, as a way to save money.

More important, in order to promote independence, EAB members must not hold a financial interest in the research itself, either as researchers or as funders. A slightly more subtle version of interest is the following: Since most members are in the same research fields, in broad terms, there can be a tradeoff between the need for well-informed experts as members on the one hand, and influence from individual academic interests, or intellectual bias toward certain scientific perspectives, on the other. Such potential influences on the EAB's work can, and should, be reduced through a diverse representation of members.

Generally, ethics committee should be aware of their members' potential conflicts of interest. The members, and/or their employers, may have academic or financial interests in certain parts of the research. Although the members of ELSA, REC, and EAB were selected on the basis of their personal capacities, there is reason to pay attention to their positions outside the ethics committee as well—since such roles implicitly or explicitly influence their judgments.

Clearly, influences from the different roles that an individual holds are unavoidable. In order to be aware of any unjustified influence, however, explicit attention to this fact is crucial. It should be noted that professional positions and experiences not only pose potential conflicts of interest; they can also be beneficial for the work of and ethics committee, since systems and tools from other contexts can improve the work of the committee.

In conclusion: the diversity of professional backgrounds represents a challenge with respect to identifying potential conflicts of interest and unjustified influence on judgments, while, at the same time, representing a strength due to the transferability of systems to improve research ethics.

In addition to the members of the ethics committee, REC, ELSA, and the current EAB are supported by people who are employed in the project. The ethics manager, who is part of the Ethics and Society subproject, plays an important role in terms of contributing to the preparation of cases, the agenda, and the minutes, as well as serving as the connection between the EAB and the Board of Directors (BoD) as a nonvoting member of the BoD. The experiences thus far are that the ethics manager has significantly promoted information flow and communication compared to the first year when the committees lacked this function. However, there is the potential for unjustified or too much influence on the work of the EAB by the ethics manager, due to the power generated by the information privileges as well as the double, if not triple, roles he or she holds in the EAB, in the BoD, and as part of a research subproject. The perspectives of the BoD and the EAB in many cases differ and could turn out to be antagonistic. There is a need to be aware of the potential conflict of interest if such a situation arises (Box 15.1).

Further, there are four "ex officio members" of the EAB, three of whom are on the HBP payroll. Similar to the ethics manager, these

BOX 15.1

FEATURES THAT POSE POTENTIAL ETHICAL CHALLENGES IN THE HBP

- Size
- Organization
- Distribution of responsibility
- Optimism bias
- Exaggerated expectations
- Concentration of funding
- Too big to fail
- Data origin
- Data storage
- Informed consent procedures
- Information flow
- Role of EAB
- Role of ethics management
- Communication between EAB and the scientists
- Communication between EAB and the management

members are nonvoting, but they contribute to the discussions that in principle and in practice influence the work in the EAB.

ADDRESSING THE CHALLENGES

Ethics work can be characterized as an oscillation between practical, empirical challenges and principled thinking. In the following, we suggest three basic principles on which the strategies to meet the specific challenges should or may build on. Those principles reflect the opinion of the authors; they do not represent an ethical framework to which all EAB members have formally agreed on. Our intention is to propose a general account, in order to promote a principled approach to the challenges in this kind of research. Clearly, the proposal is open to suggestions and amendments. As most of the work in ethics (committees), the perspectives and strategies must continuously develop in close connection to the challenges as such become evident. At the same time, general principles can prevent unjustified ad hoc solutions, as well as contribute to stronger awareness of inherent challenges (Box 15.2).

Principles

Primum Non Nocere—*First Do No Harm*

The golden rule of medicine can guide more than medical treatment. The positive intentions of research—producing new knowledge for the benefit of humans—cannot come without the downside of potential negative or harmful effects. The assessment of the balance between positive and negative implications tends to be in favor of the positive, due to optimism bias. To counteract this tendency, explicit attention to

BOX 15.2

GUIDING PRINCIPLES

- *Primum non nocere*—a precautionary attitude
- Weighing benefit and harm ("first do no *net* harm")
- Transparency

"what can go wrong?" is helpful. Such a precautionary attitude[n] is important in order to pursue a careful and cautious approach and to promote guards against hubris caused by optimism bias.

A precautionary attitude involves a necessary epistemological correction, since it challenges scientists—and others involved—to be concerned with observations that count against what one is eager to prove. Karl Popper's principle of falsification goes well with a precautionary attitude. Originally, Popper distinguished between a scientific and nonscientific statement according to whether the statement is, in principle, possible to falsify through empirical testing (Popper, 1959/1999). It is not the task of scientific inquiry to prove that a particular empirical statement is correct, but rather to search for evidence to its rejection. We are not concerned with demarcation between science and nonscience in this context, but the epistemological attitude it expresses. The difference between searching for verification versus falsification reflects a fundamental difference in attitudes to knowledge. Further, the falsification attitude can be a safeguard against optimism bias.

It is almost impossible to predict the total effects of research and innovations, especially the longer-term effects. For this reason, the precautionary principle is advocated. On a global level, the principle is included in virtually every policy document on environmental protection, sustainable development, and public health (Andorno & Biller-Andorno, 2015).

In European law, the principle is operationalized as follows: "The precautionary principle in public decision making concerns situations where following an assessment of the available scientific information, there are reasonable grounds for concern for the possibility of adverse effects on the environment or human health, but scientific uncertainty persists. In such cases provisional risk management measures may be adopted, without having to wait until the reality and seriousness of those adverse effects become fully apparent" (Von Schomberg, 2012, p. 147).

In public health, the principle is formulated as follows: "(W)here there are significant risks of damage to public health, we should be prepared to take action to diminish those risks, even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it!" (Horton, 1998, p. 252).

To be willing to take action despite insufficient evidence is less straightforward than it might seem at first sight, as the debate on

[n]Although we discuss *primum non nocere* as a variant of the precautionary principle, they are not equivalents. One important difference is that the precautionary principle generally concerns groups of people, while *primum non nocere* regards the individual patient.

precautionary principles readily demonstrates. Precautionary principles are accused of being antiscientific, conservative, and outright irrational—as potential benefits of scientific and technological advances are sacrificed on its altar (Harris & Holm, 2002).

Since the potential negative implications of research and innovation can be seen as arguments against innovation altogether, a principle of precautions seems too absolute. A precautionary attitude, however, is in place. The challenge is to strike a balance between benefit and harm; the duty to avoid harm is not the same as the duty to abstain from carrying out research (or any action) altogether—clearly also because no action can involve more harm than the action itself. This introduces a second general principle we build on, namely, the need to weigh the benefits and the drawbacks.

Weighing Benefits and Harm

Jonathan Wolff argues in favor of the precautionary attitude not least because it involves a more pragmatic attitude to risk, compared to the precautionary principle (Wolff, 2006). Any action involves risk; thus, the task is not to avoid risk altogether but to weigh the potential positive implications against the negative ones. This requires an explicit assessment of the potential beneficial as well as potential harmful implications.

Risk is a product of hazard and probability. There is a substantial difference between severe, perhaps fatal, outcomes of low probability and minor problems of high probability. As a guiding principle, identifying high-risk areas—those that should be marked with red lights—is useful.

When weighing benefits against harm, it is important to address the question, "Whose benefit, whose harm?" Whether the decision maker and those affected by the decision are one and the same or not is important since one person's benefit can be another person's harm (Luhmann, 2005). The same holds true for harm and risk. In a risk situation, the one who runs a risk, for example, in order to obtain a preferred state in the future, need not be the same one who bears the costs. One HBP-related example would be the differences regarding risk-taking in controversial areas such as neuroenhancement to improve individual performances of healthy subjects, or neuroeconomics research that could inform neuromarketing (Voarino, 2014).[o] Those who

[o]Neuro-marketing is a new discipline that uses expertise in medical neuro-technology to study brain responses to marketing stimuli and to attain specific business goals. Although its applications are still preliminary, it seems likely that research in this area will provide subtle means of brain manipulation to provoke desired behaviors without consumers being aware that they are being manipulated (Breiter et al., 2015).

exploit commercial opportunities and laypeople tend to have different views, especially when it comes to potential long-term threats emerging from the uncontrolled application of neuroscientific findings. This makes it difficult to reach a consensus because someone's risk is often another's danger, and perspectives differ according to the respective position. Thus the evaluation of risk associated with the outcomes of scientific research in the HBP, and the willingness to accept risk decisions, are most of all social problems.

As a starting point, scientific knowledge never comes free from social interests or implications. Disregard of public concern and laypeople's perspective in the scientific enterprise entails a normative problem; as such disregard undermines the possibility of establishing a democratic knowledge society (European Commission, 2007). It is also important to acknowledge laypeople's specific knowledge, based on their everyday lives, and needed for assessing long-term ethical/social implications (Myskja, 2007) in terms of benefits and harms. The inclusion of lay expertise is thus crucial to establish empirically well-informed ethical governance of science and technology.

The combination of the "first do no harm" principle and the weighing of harms and benefits can be combined into a principle of "first do no *net* harm." Since all action potentially involves negative and positive outcomes, the task is to choose the ones where the harm is as little as possible, while the benefit is maximized.

Transparency

Transparency not only has the advantage of enhancing quality of research but also increases our attention to what can go wrong. When the research content is shared within a wider community, epistemological and ethical implications are laid open to broader scrutiny. Transparency has the potential benefit of involving diverse individuals and approaches, which can be particularly helpful in large collaborations such as HBP, since it is impossible for the few to maintain oversight over, or possess insight into, all dimensions of all subprojects.

Clearly, transparency is not always justified; in some situations, it can involve a breach in fundamental ethical principles, such as when information includes confidential medical records. The principle of transparency means that nondisclosure is explicitly qualified (e.g., by reference to the rules of confidentiality) in contrast to a requirement to qualify openness explicitly.

Why Principles—And Why These Three?[P]

Advice to researchers and management in the HBP concerns a wide range of issues. They include short- and long-term consequences; implications for individuals, smaller groups, or for societies; and consequences in terms of ethical, legal, or social aspects (or a combination of the three). To prevent inconsistent choices of the issues that are selected for discussion or inconsistent advise to the researchers and other stakeholders, the determination of fundamental principles is crucial. This way, the EAB itself, as well as the researchers, the managers, and the public, will be aware of what basic principles we build on when actions are taken, or advice is given.

The three principles we suggest in this chapter are chosen for three reasons. First, it is necessary that the principles are on a level of generality that make them relevant for a wide number of issues that can come up. This way, only a small number of principles are required.

Second, it is necessary that the principles at least are internally consistent. Ideally they should support each other mutually, such as when the principle of transparency can serve as a hinder for unwarranted exaggeration of potential gain from the research. In this case, the principle of transparency enforces the principle of balancing harm and gain.

The third reason for the choice of the particular principles is that they should reflect common values in the European research community as well as in the general public. First, do no harm is the essential ethical principle in medicine, hence clearly also a core value in this context. Since the extent of unforeseen consequences is very high in the HBP, a guiding principle should concern how to relate to uncertainty. Combining the recognition of great uncertainty with the human tendency to optimism bias, we should be concerned with precaution as well the need to weigh negative and positive effects (harms and benefits). Finally, the choice of the principle of transparency is supported by its being a widely shared value in our culture. Transparency is also an essential principle because of its strength as one of the most effective safeguards against misconduct or other unjustified or illegitimate actions.

Finally, the determination of basic principles also helps to identify specific measures required in order to do our work. If, for example, transparency is a principle, measures to secure openness are required. In the next section we describe the measures we have developed so far.

[P]Clearly, the choice of principles is not cut in stone. They are suggestions, and as such considered to be open for substitution and/or completion.

Measures

The choice of measures is based on two elements. First, it is crucial that the guiding, normative principles are clear (they were stated in the previous section). Second, the measures should be based on a description of the challenges identified in the research (provided in the first part of the chapter). Let us underscore that this description is preliminary; thus it is important that new measures are included in accordance with how the research develops. It is also crucial that measures are determined as a result of the experiences along the way. Thus what we propose here is what we think is needed and/or useful at this stage.

To avoid harm, risk assessment systems are necessary—in all research projects and for general governance. Risk assessments are already part of the governance activity; however, the explicit weighing of benefit and harm is a necessary prerequisite to avoid an unjustified over- or underestimation of benefits and risks. Further, the explicit attention to optimism bias is required.

The work of the EAB includes concrete systems to register and follow up on concerns among the scientists or other stakeholders. An online submission application, called Point Of Registry (PORE), can be used to contact the ethics committee, while a system with "ethical rapporteurs" is established to promote contact between the committee and the scientists. The appointment of an ombudsperson is also discussed. All three systems are described in detail in a forthcoming paper.

To promote collaboration, information sharing, and ethical values in general, transparency and explicit and public reason-giving are necessary. The members of the ethics committee publish scientific papers and discussions on different aspects of their work, of which the current chapter is an example.[q] These publications are a way to facilitate public participation and to open up a wider discussion of values and measures, while it also serves as reason-giving for, or qualification of, the EAB's decisions. Encouragement of transparency and public debate should be part of the HBP generally, and systems to support this should be developed.

External ethical reviews are also a way of promoting awareness, transparency, and information sharing. As part of the review carried out after the first year, the external committee met with all principal investigators to discuss specific ethical challenges in all subprojects. Representatives of the ELSA and REC committees were invited to these

[q]Such publication needs to follow a certain etiquette. In addition to the Vancouver system for scientific publications, specific attention to the relation between the contents of the chapter and the views of the committee as a whole is required. A description of this etiquette is currently in progress.

BOX 15.3

MEASURES FOR REDUCING INHERENT CHALLENGES

- Identify high-risk areas (where are the red lights?)
- Risk assessments that include weighing of benefit and harm
- Streamlined information and decision routes
- Clear responsibility
- Must be well-known to all stakeholders (Internet sites)
- Regular external ethical reviews (EAB members present in the discussions with PIs)
- Data origin always declared
- Declaration of conflict of interest as routine for all scientists and decision-makers and other stakeholders (including EAB members)
- Data protection systems
- Ethical rapporteurs
- Other systems for communication between the EAB and scientists (PORE)
- Ombudsperson
- Transparency measures: All is public unless there are important reasons; public and explicit reason-giving

discussions, which was a valuable information source for the committees. If not exactly the same model, a similar way of identifying ethical challenges in each subproject should be carried out yearly (Box 15.3).

Finally, attention to the social implications of HBP research requires specific measures. The tradition in research ethics is to focus on data protection and informed consent (data origin, storage, and protection). While recognizing the importance of these issues, there is also a need to pay specific attention to social implications. The issue should be part of the risk assessments (who bears the risk, who gains?), and the EAB should have a specific responsibility in identifying social aspects of the research.

CONCLUSION

So, how can an ethics committee contribute to the goal of promoting strong research that will ultimately have some public benefit? The first

message is that there is a need to translate general mandates into concrete measures, such as the ethical rapporteur system that promotes information flow and collaboration between the committee and the researchers.

The vague goals of the ELSA/REC and the subsequent EAB involved a slow start-up; a clearer goal could have sped up the work. However, the opportunity to define the specific goals and measures by the committees themselves promoted a wider discussion of their role and tasks. This opened up the discussion of the fundamental question of how ethics can contribute. The answer to this question needs to evolve from practical activities of the ethical committee and the sharing of these experiences. This requires vivid exchange and collaboration between the EAB and the researchers, as well as an open discussion and publication of experiences.

Further, "strangers" in a research community can provide fresh perspectives on the research, precisely because of their outsider position. However, there is a fine line between being ignorant and providing a fresh outsider approach. Striking a balance requires continuous collaboration and candid information-sharing between the EAB and the researchers.

Another issue to negotiate is the balance of a close and trusting relationship with researchers and critical distance to see potential flaws. If researchers cannot trust their ethical advisors, important information might be withheld. However, if the ethicists feel obliged to be loyal to "their researchers," the ethicists might misinterpret this as trying not to stand in the way and being disruptive. It is important to reach a common understanding that the role of the members of the EAB is to look for potential problems and bring up criticism, albeit in a constructive and respectful way. This can be an important contribution to avoiding pitfalls and, at worst, scandals that can jeopardize the success of a project.

Finally, if the EAB is to have any real impact, structural systems must be established to support the board's role. Without such systems, the ethics discussions and recommendations can easily serve as the frosting on the cake—as an ethical alibi without any practical significance. An interesting thought experiment might be the following: How could we tell in a few years if the EAB has worked well or has had "real impact"?

In this chapter, we identified the EAB's role as consisting of three parts: (1) to identify the inherent ethical challenges, (2) to provide a normative framework for EAB contribution, and (3) to suggest measures including structural systems that support the goals. Examples of supporting structures include the presence of EABs at external ethical reviews, regular meetings with the BoD, a system with ethical

rapporteurs and their contact persons in the EAB, and the promotion of transparency through publications.

Acknowledgments

Thanks to Karin Blumer, Jean-Pierre Changeux, Kathinka Evers, Kevin Grimes, Abdul Mohammed, and Henrik Walter for valuable comments.

References

Andorno, R., & Biller-Andorno, N. (2015). The risks of nanomedicine and the precautionary principle. In B. Gordijn, & A. M. Cutter (Eds.), *In pursuit of nanoethics*. New York: Springer.

Breiter, H. C., Block, M., Blood, A. J., Calder, B., Chamberlain, L., Lee, N., et al. (2015). Redefining neuromarketing as an integrated science of influence. *Frontiers in Human Neuroscience*, *8*, 1073. Available from http://dx.doi.org/10.3389/fnhum.2014.01073.

Christen, M., Biller-Andorno, N., Bringedal, B., Grimes, K., & Savulescu, J. (2016). The ethical challenges in simulation-driven "big neuroscience." *American Journal of Bioethics Neuroscience*, *7*(1), 1–13.

Christen, M., Domingo-Ferrer, J., Draganski, B., Spranger, T., & Walter, H. (2016). On the compatibility of big data driven research and informed consent based on traditional disease categories—the example of the Human Brain Project. In L. Floridi & B. Mittelstadt (Eds.), *Ethics of biomedical big data*. Law, Governance and Technology Series, vol 29, pp. 199-218. Springer International; Switzerland.

European Commission (2007). *Taking European knowledge society seriously: Report of the Expert Group on Science and Governance to the Science, Economy and Society Directorate, Directorate-General for Research*. Luxembourg: European Commission.

European Commission. (2014, July 18). *No single roadmap for understanding the human brain*. Retrieved from <https://ec.europa.eu/digital-agenda/en/blog/no-single-roadmap-understanding-human-brain>.

Frégnac, Y., & Laurent, G. (2014). Where is the brain in the Human Brain Project? *Nature*, *513*, 27–29.

Goldacre, B. (2012). *Bad pharma: How drug companies mislead doctors and harm patients*. London: Fourth Estate.

Harris, J., & Holm, S. (2002). Extending human lifespan and the precautionary paradox. *Journal of Medicine and Philosophy*, *27*(3), 355–368.

Healy, D. (2012). *Pharmageddon*. Berkeley, CA: University of California Press.

Horton, R. (1998). The *new* new public health of risk and radical engagement. *The Lancet*, *352*, 251–252.

Irwin, A., & Wynne, B. (Eds.), (1996). *Misunderstanding science?* Cambridge: Cambridge University Press.

Kahneman, D. (2011). *Thinking, fast and slow*. New York: Macmillan.

Luhmann, N. (2005). *Risk: A sociological theory*. New Brunswick, NJ: Aldine.

Myskja, B. K. (2007). Lay expertise: Why involve the public in biobank governance? *Genomics, Society and Policy*, *3*, 1–16.

Popper, K. (1999). The logic of scientific discovery. London: Routledge (Original work published 1959).

Rose, N. (2014). The Human Brain Project: Social and ethical challenges. *Neuron*, *82*, 1212–1215.

Rothman, D. (1991). *Strangers at the bedside: A history of how law and bioethics transformed medicine*. New York: Basic Books.

Shrum, W., Genuth, J., & Chompalov, I. (2007). *Structures of scientific collaboration*. Cambridge, MA: MIT Press.

SOP, EAB. (2015). *Human Brain Project*. Retrieved from <https://www.humanbrainproject.eu/documents/10180/1139903/EABSOP_2015-10-06-2.pdf/0132960f-77cb-4782-ba5d-946eca9c0e25>.

Voarino, N. (2014). Reconsidering the concept of "dual-use" in the context of neuroscience research. *Bioéthique Online*, *3*/16, 409–427.

Von Schomberg, R. (2012). The precautionary principle: Its use within hard and soft law. *Symposium on the European Parliament's Role in Risk Governance. European Journal of Risk Regulation*, *2*, 147–156.

Wolff, J. (2006). Risk, fear, blame, shame and the regulation of public safety. *Economics and Philosophy*, *22*, 409–427.

Wolff, J. (2014). Precautionary attitude. Special report: Synthetic future: Can we create what we want out of synthetic biology? *Hastings Center Report*, *44*, S27–S28.