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A New Challenge for Research Ethics: Incidental Findings in Neuroimaging

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Abstract It has become evident that neuroimaging raises new normative questions that cannot be addressed adequately within the (in this regard unspecific) frameworks of existing research ethics. Questions that are especially troubling are, among others, provoked by incidental findings. Two questions are particularly intricate in view of incidental findings: (1) How can the research subject's right not to know be guaranteed? And (2) should a diagnostic check of scans by a neuroradiologist become an obligatory part of neuroscientific research protocols? The present paper examines these questions against the background of two recent recommendations. The differentiation between "difference position" and "similarity position" serves as an analytic tool to further investigate the issue and to develop a distinct proposal for answering the questions.

Keywords Incidental findings · Neuroimaging · Right to know/not to know · Diagnostic misconception · Similarity/difference position · Neuroethics

Introduction

Since the late 19th century, biomedical research involving humans has been the subject of intense ethical and legal debate. This has led to a number of regulatory frameworks, the most prominent being the Nuremberg Code (Nuremberg Military Tribunal 1950), the Declaration of Helsinki by the World Medical Association (World Medical Association 2008), the Council of Europe's Additional Protocol concerning Biomedical Research (Council of Europe 2005) and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002). Additionally, most countries have enacted laws that regulate at least some forms of biomedical research involving humans, although comprehensive legal regulations specifically addressing biomedical research are not existent in many industrialized countries. In the 1980s, some authors were convinced that almost all normative issues in the context of biomedical research were solved and that the issue had been settled (Howard-Jones 1982). However, new challenges such as the HIV/AIDS pandemic, as well as ongoing advances in biotechnology and numerous other scientific findings, have raised many new normative problems in the past three decades.

As a result, it became clear that existing frameworks need to be continuously adapted and advanced in order to ensure ethically and legally sound research. This is being reflected *inter alia* in the latest revisions of the World Medical Association's Declaration of Helsinki (1996; 2000; 2008) and in the Council for International Organizations of Medical Sciences' International ethical guidelines for biomedical research involving human subjects (2002) as well as in the ongoing comprehensive debate in research ethics. Experience shows that the process of continuous adaptation needs an interdisciplinary effort: ethics cannot apprehend new normative challenges on its own—only practice reveals them—nor can medicine and the

sciences advance ethical and legal frameworks on their own—genuine normative expertise is necessary for this task.

A case in point is brain research and, more particularly, the method of neuroimaging. In recent years, an increasing number of research projects have included this method. In practice it has become evident that neuroimaging raises new normative questions that cannot be addressed adequately within the (in this regard unspecific) frameworks of existing research ethics (Illes et al. 2006). Questions that are especially troubling are, among others, provoked by incidental findings. Wolf et al. have suggested a helpful definition according to which: “An IF [i.e. incidental finding] is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study” (Wolf et al. 2008, 219). The occurrence of incidental findings is not limited to brain research that involves methods of neuroimaging. They can also occur in the context of genetic research and imaging research focusing on other parts of the human body. Examples of incidental findings in brain research include unexpected aneurysms and tumors visualized in the course of structural magnetic resonance imaging (MRI) of the brain.

In their analysis and recommendations, Heinemann et al. cite empirical data suggesting that incidental findings occur in approximately 1 to 8% of the brain scans performed (Heinemann et al. 2007). Wolf et al. refer to literature reporting an incidental finding in 13 to 84% of brain fMRI or MRI scans (Wolf et al. 2008, 221). However, only 1.2% were in need of immediate referral, 0.4 to 14% urgent referral, 1.8 to 43% routine referral, and 13 to 40.4% no referral at all. It seems obvious that more research is needed on the prevalence and significance of IF in brain imaging research (Wolf et al. 2008, 224), especially since a recent meta-analysis study suggests that incidental findings on brain MRI

are more common (Morris et al. 2009).

In large-scale research projects such as the current EC-funded IMAGEN project, which strives for recruiting 2,000 research subjects, one must be prepared to encounter a significant number of cases in which pathological aberrations will be found.¹ Experience from this project shows that standard procedures for the handling of incidental findings are missing. This corresponds to empirical findings of a study undertaken by Illes and colleagues (Illes et al. 2004) who conclude that “Guidelines for minimum and optimum standards for detecting and communicating incidental findings on brain MRI research are needed” (Illes et al. 2004, 743). How such regulations should look is, nonetheless, subject of an intense debate and, at present, highly controversial. In line with this, Susan Wolf observes: “The truth is that no-one knows how to handle these difficult questions. There is no consensus as yet on how to handle incidental findings in human subject research” (Wolf 2008, 216).

Two questions are especially intricate in view of incidental findings: (1) How can the research subject’s right not to know be guaranteed? And (2) should a diagnostic check of scans by a neuroradiologist become an obligatory part of neuroscientific research protocols? At least two sets of recommendations have been published lately that, among others, address these questions (Wolf et al. 2008; Heinemann et al. 2007). The present paper examines the question against the background of these recommendations in turn. The differentiation between “difference position” and “similarity position” introduced by Miller and Brody (2003) serves as an analytic tool to further investigate the issue and to develop a distinct proposal for answering the questions. Finally, an outlook will be given as to what changes in the organization of research seem crucial from an ethical point of view in light of the new challenges posed by incidental findings.

¹ IMAGEN—a European research project on risk-taking behaviour in teenagers. URL <http://www.imagen-europe.com/en/project-summary-imagen-europe.php> [29.06.2010].

Incidental Findings and the Right Not to Know

The right not to know is a well-established element in modern medical ethics and medical law. There is a widely shared consensus that it is a fundamental right of patients to decide whether they want to know about diagnostic findings or not. This is, for example, documented in the Council of Europe's Convention on Human Rights and Biomedicine, which states: "Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed" (Council of Europe 1997, Art. 10.2). Even if a therapy exists and, from a medical point of view, it may thus seem irrational to limit one's options by not knowing about one's health condition, the decision whether to obtain information about diagnostic findings or not rests with the individual patient alone—only in exceptional cases may restrictions be placed by law in the interests of the patient (Council of Europe 1997, Art. 10.3). As a fundamental right, the right not to know applies, in general, not only to patients but also to research subjects. In Article 27 of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (2005) the Council of Europe states clearly: "If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a framework of health care or counselling. *In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of a participant not to receive such information*" (Emphasis added).

In the context of brain research and neuroimaging the right not to know can, however, become highly problematic. While Miller, Mellon and Joffe simply state: "if a subject has explicitly indicated that she does not want to receive incidental findings, this preference

surely should be honoured” (Miller et al. 2008, 277), it is doubtful whether a strict adherence to the right not to know is always feasible. Heinemann et al. have shown that in certain situations the principle of self-determination and the principle of nonmaleficence can come into conflict (Heinemann et al. 2007, A1984– A1986). The situation can become particularly troubling if the researcher has reason to believe that the state of the research subject is life-threatening and could also become dangerous for other persons (e.g. because the research subject is unfit to drive). Then, the conflict between the principle of (informational) self-determination and the principle of nonmaleficence (or the principle of justice, if one prefers to conceptualize the conflict in question as a conflict between the principle of self-determination and the principle of justice) is evident. The question is, then, whether it is possible to avoid the described conflict of principles by specific regulations altogether or, if this is not the case in brain research, how the conflict should be solved.

Heinemann et al. have suggested defining an initial insistence on the right not to know by potential research subjects as an exclusion criterion. This does not, however, solve the problem: such an exclusion criterion could only avoid getting into the described problematic situations if research subjects were strictly bound to their decision. Yet, the decision not to exercise one’s right not to know, but rather to accept any information about incidental findings is part of the consent to take part in the research project. One may argue that in practice this will not happen too often, so the “exclusion criterion” solution proposed by Heinemann and colleagues could be seen, at least, as an acceptable workaround. Still, it is conceptually flawed since it rests on the idea that the right not to know can be permanently waived. What is more, this approach might have the problematic consequence that research subjects do not grasp their right to informational

self-determination as well as their right to withdraw consent at any time. This would undermine key elements of research ethics. Taking the right not to know as an exclusion criterion might raise another problem: generally, only scientific parameters relevant to the experiment can serve as exclusion criteria in research projects. To draw on other facts can be seen as a form of discrimination. In particular, to request a specific attitude towards medical information could be seen as illegitimate. Therefore, it seems preferable to look for a different approach.

Wolf et al. in principal acknowledge the right not to know (Wolf et al. 2008, 233). In their view, researchers shall either elicit in the consent procedure whether a research participant wishes to be informed about an incidental finding (that is likely to offer strong net benefit or possible benefit) or researchers can tell participants in the course of the consent procedure which information they intend to disclose or withhold. In the latter case participants may, nevertheless, assert a right not to be informed about certain kinds of incidental findings. In cases where an incidental finding reveals a life-threatening or grave condition Wolf et al. advise, however, always to double-check an initial consent “without revealing the information itself”. It is hard to imagine how that should work in practice. Research participants will, obviously, realize that the renewed request signifies a grave condition. The right not to know would instantaneously be infringed, even if the information itself is not being revealed.

What could an alternative approach look like? Is there really a way to avoid the described conflict between the principle of self-determination and the principle of nonmaleficence in connection with incidental findings? I don't think so. Because of this, the most appropriate approach seems to be straight- forward: In the course of the consent procedure, the possibility of conflicts of principles must be made explicit. Potential research subjects should

be informed that they have a right not to know and that researchers will respect this right unless concealing an incidental finding could be immediately life-threatening or comparably dangerous for the research subject or third persons. Research subjects should be fully aware that in such cases their right to informational self-determination might be outweighed by the right to psychophysical integrity (theirs and others'). On this basis they should freely decide whether they want to participate in a research project or not. At the same time, a procedure should be implemented for dealing with such situations. This should include that an ethics board be nominated or specifically installed within research projects including neuroimaging that advises the team of researchers on how to balance the two conflicting principles in cases of conflict. This approach does not, of course, avoid ethically problematic situations. In contrast, it allows for the fact that ethical principles can come into conflict and makes such conflicts explicit, whereas the "exclusion criterion" approach pretends to circumvent problematic situations. In contrast to the solution proposed by Wolf et al. it clearly determines conditions under which the right not to know will be suspended. By doing so, it avoids the irresolvable task of getting back to participants in order to ask them whether they adhere to their initial decision without revealing to them that there is something that could be revealed.

Diagnostic Obligation and Diagnostic Misconception

A second vital question in the context of brain research and neuroimaging is the following: should a diagnostic check of the scans by a neuroradiologist become an obligatory part of research protocols? This would clearly be appropriate if, by accepting a research subject, the researcher takes over something like a "therapeutic" or "diagnostic obligation." In fact, many have argued that researchers do have such an obligation. Especially in the context of

clinical trials and in relation to the problem of equipoise the “therapeutic obligation” of researchers has been stressed. Wolf et al. recognize the obligation within research projects to “take steps to validate an incidental finding and conform its health or reproductive importance before communicating the finding to a research participant” (Wolf et al. 2008, 237). Furthermore, they state that the “cost of compensating the consultant for IF verification and evaluation should be built into the research budget” (Wolf et al. 2008, 237). They consider such costs to be either direct costs of the project or an infrastructure cost. In contrast to this, Heinemann et al. acknowledge the duty of the researcher to communicate—in an appropriate manner—incidental findings, but object to the view that costs associated with this should be considered part of the research budget (Heinemann et al. 2007, A1985). The fundamental question here is whether researchers have “therapeutic” (or “diagnostic”) obligations towards research participants.

Miller and Brody have argued that acting on the assumption of a “therapeutic obligation” in the strict sense is reasonable if and only if one adopts a “similarity position.” They have introduced this expression to denote a position that views medical research and medical practice as essentially similar fields of action. By contrast, a “difference position” holds that medical research and medical practice are characterized by significant dissimilarities. Miller and Brody convincingly argue that the “difference position” is the appropriate one: “Clinical medicine aims at providing optimal medical care for individual patients. [...] Clinical research, in contrast, is not a therapeutic activity devoted to the personal care of patients. It is designed for answering a scientific question, with the aim of producing ‘generalizable knowledge’” (Miller and Brody 2003, 21). Since the nature of an activity shapes the ethical standards that ought to apply to that activity, the similarity position and the difference position come to quite different views on which obligations researchers have towards

research subjects (cf. Miller and Brody 2003, 22). In particular, on the basis of the “difference position,” a “therapeutic” or “diagnostic” obligation by researchers towards research subjects does not exist. Consequently, a comprehensive diagnostic check-up of scans in brain research is, in general, not required. However, the fact that research protocols are not intended to promote the welfare of individual research subjects must be made unmistakably clear to the participants. This should be warranted anyway since the research subjects’ consent does otherwise not meet the essential condition of being “informed”. However, empirical evidence suggests that research subjects often do not fully appreciate that they are taking part in research projects in which their individual wellbeing is not the primary objective. Appelbaum et al. have coined the term “therapeutic misconception” for this phenomenon (Appelbaum et al. 1987; Lidz et al. 2004).

Analogously, one could speak of a “diagnostic misconception” in the context of brain research and neuroimaging. It seems reasonable to assume that the probability for this form of misunderstanding is especially high with neuroimaging. The fact that certain methods of brain scanning are not appropriate for making specific diagnostic checks is difficult to understand for lay people. Therefore, every effort must be undertaken to make clear to research subjects that in the course of a research project pathological aberrations may not be discovered. Ethics committees must be especially sensitive to this issue when they review information material used for informed consent procedures.

It is important to observe, however, that the “difference position” does not deny every kind of obligation on the side of the researcher towards the research participants. Obligations of general beneficence, for example, hold for researchers. Such obligations are, arguably, strong enough to justify a (limited) duty to promote research subjects’ autonomy and wellbeing (cf. Miller et al. 2008, 273–79). In particular, researchers have the obligation to

minimize risks and burdens for participants. This means that if incidental findings occur, it must be guaranteed that research subjects have quick and easy access to specialists who offer a comprehensive diagnosis and, if necessary, therapeutic measures. In view of incidental findings, Miller, Mello, and Joffe apparently come to the same conclusion: “Considerations of general beneficence, along with the normative structure of professional relationships jointly ground a duty of investigators to respond to incidental findings that emerge in the course of clinical research. This obligation to respond to incidental findings does not, however, entail an obligation to actively seek out incidental findings through routine clinical review of research data or to provide follow-up clinical care” (Miller et al. 2008, 279).

What is, nevertheless, crucial at this point is what is meant by “respond.” In general, researchers do not have the expertise to carry out comprehensive diagnostic check-ups. Therefore, the services of a specialized medical doctor need to be available throughout the course of the research project. If easy access to such a specialist offering a comprehensive diagnosis is not warranted, the time of uncertainty between being informed about an incidental finding and receiving a detailed diagnostic check-up is clearly associated with severe psychological anxiety and must count as harm directly induced by the research project. Hence, not providing the possibility of immediate diagnostic check-up would be a violation of the beneficence (or the nonmaleficence) principle. Almost certainly, the described guarantee cannot be given if no resources are specifically allocated for diagnostic specialists within the research project budget; “pro bono” arrangements that are currently common will, at least in large-scale projects, not be sufficient. Wolf et al. realize the described problem in their set of recommendations. They clearly state: “Handling IFs responsibly is a research obligation” (Wolf et al. 2008, 237). Heinemann et al. highlight the difference between the physician–patient relationship on the one side and the investigator–

participant relationship on the other side (Heinemann et al. 2007, A1985). They also acknowledge certain duties of the researcher. They reject, however, that an appropriate financial coverage should be mandatory within this kind of research project. Without further justification, they consider it only to be “preferable” (Heinemann et al. 2007, A1987). Finally, Miller, Mello, and Joffe concede: “The ethical tightrope that researchers and ethicists walk in defining the scope and limits of investigators’ obligations with respect to incidental findings—a task we have left unfinished—is to fulfill obligations of beneficence, as it is understood in the research context, while not going so far as to contribute to the therapeutic misconception” (Miller et al. 2008, 279). Perhaps they would accept the duty to provide easy access to comprehensive diagnosis as grounded in the researcher’s obligation of beneficence.

Conclusion

In view of brain research and neuroimaging, a number of new normative questions arise, especially in connection with incidental findings. I have argued above that existing standards of research ethics need to be adapted and advanced in order to ensure ethically and legally sound research in this field. Potential conflicts between the principle of self-determination and other principles, especially the principles of nonmaleficence, beneficence and justice should be made explicit in the course of the consent procedure. Research subjects must be fully aware that their right not to know might be overruled in certain situations. Furthermore, every effort must be made to avoid a “diagnostic misconception.” In turn, it has been argued that no general “diagnostic obligation” exists on the side of the research team. However, if incidental findings occur research participants must have easy access to comprehensive diagnosis. In order to ensure this, dedicated

financial resources should be a mandatory part of research projects that include neuroimaging.

With the problem of incidental findings the strained double role of physician-investigators once more comes to the fore of research ethics. Both the question of how to handle the right not to know, and the question of whether diagnostic check-ups must be covered within a research project can only be adequately addressed against the background of a clear understanding of the rights and duties of investigators. In particular, it should be clear that investigators and physicians act on different justifying grounds with different rights and duties towards participants and patients respectively. With their differentiation of “difference position” and “similarity position” Miller and Brody have laid the conceptual ground for such a clear understanding. In practice, however, implications of this differentiation must be further elaborated. Moreover, caution must be exercised that the difference position is not being used to reject specific duties of investigators.

A final remark: It is interesting to observe that physician-investigators in practice tend to stress their specific duties as physicians towards research subjects in view of the first problem discussed above. They argue that they have to disclose incidental findings with considerable clinical importance if they occur because, as physicians, they are committed to the wellbeing of their patients. It is, as already mentioned, doubtful, whether this argument is really convincing. What is more, the same physician-investigators tend to reject the obligation to provide diagnostic check-ups for participants with incidental findings within research projects, claiming that no supporting obligation exists within research projects. This discrepancy points to the inherent problems of the role of the physician-investigator. With their call for adhering to the “difference position,” Miller and Brody have tried to open up a way for managing these problems more comprehensively.

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