RESEARCH ETHICS

Review of a mock research protocol in functional neuroimaging by Canadian research ethics boards

J de Champlain, J Patenaude

See end of article for
authors' affiliations

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Correspondence to:
J Patenaude, Department
of Surgery, Faculty of
Medicine, Université de
Sherbrooke, 3001 Twelfth
Avenue North,
Sherbrooke, QC, Canada
J1H 5N4;
johane.patenaude@
usherbrooke.ca

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Objective: To examine how research ethics boards (REBs) review research projects in emerging disciplines such as functional neuroimaging.

Design: To compare the criteria applied and the decisions reached by REBs that reviewed the same mock research protocol in functional neuroimaging.

Participants: 44 Canadian biomedical REBs, mostly working in public university or hospital settings.

Main measurements: The mock research protocol "The Neurobiology of Social Behavior" included several ethical issues operating at all three levels: personal, institutional and social. Data consisting of responses to closed questions were analysed quantitatively. Qualitative analysis of open-question responses used mixed classification.

Results: Similar criteria were used by most participating REBs. Yet the project was unconditionally approved by 3 REBs, approved conditionally by 10 and rejected by 30.

Conclusions: The results point to the difficulty for REBs of reviewing all kinds of research projects, regardless of field, by relying on international and national norms framed in general terms and a possible variation between REBs in the interpretation of their mandate for the protection of research subjects.

Ethical guidance for research on humans exists in the form of a vast corpus of international and national norms.¹⁻³ Some of these norms, which take the form of various instruments and documents, are applied generally in any discipline of research, whereas others apply only to a specific discipline.

These norms, which underlie decisions made by research ethics boards (REBs), present regulations that are for the most part framed in general terms. How then are they interpreted and applied by REBs specifically? How are they applied by REBs taken as a group? What relevance is given to these norms during the process of decision making about the ethical acceptability of a research project? More specifically, how are they applied when REBs are faced with an emerging discipline of research, such as functional neuroimaging?

Considerable divergence is believed to occur in the way REBs interpret and apply these norms. It goes without saying that if this proves to be true, the potential exists for marked variation in decision-making criteria, which, in the context of the review of a given research project, would play out as differing decisions and justifications.

To examine the possibility of the existence of variability among the decision-making criteria used by REBs, a pan-Canadian in vivo action-research study was conducted with 71 biomedical REBs operating in Canada. Participating REBs were requested to review mock research protocols that presented a range of ethical issues.

The goal of this study was to determine whether Canadian biomedical REBs proceed homogeneously in conducting ethical reviews when dealing with an emerging discipline of research such as functional neuroimaging or whether divergences exist and, if they do exist, whether they are noteworthy. In this article, we present our main findings.

METHODS

As part of a pan-Canadian survey on the review of the risks and benefits of biomedical research on humans, 71 biomedical REBs in Canada were requested to review a mock protocol for a research project, in the field of functional

neuroimaging, entitled "The Neurobiology of Social Behavior".

The goal of this pan-Canadian action-research project was to bring to light the decision-making criteria used by each of the participating biomedical REBs in dealing with the ethical review of a single mock research protocol.

The biomedical REBs that were approached were informed from the outset of the fictional nature of the protocol submitted to them for ethical review. They were explicitly asked to handle this protocol just like any other that might normally come to their attention in the course of their work, and to give it no special treatment. A further requirement was that the ethical review handed down should represent the review of the REB as a whole and not that of an individual member.

The mock protocol was accompanied by a brief questionnaire consisting of open questions intended to guide the ethical review of the project and not to direct the REBs' approach to or processing of it.

The mock protocol related to a functional neuroimaging research project whose goal was to obtain scientific understanding of the psychological, social, anthropological and neurobiological bases of social behaviour. The protocol provided, without going into detail, for access to the medical records of research subjects and for the building of a database.

Under the mock protocol, two of the most powerful functional brain-imaging technologies, a 3-T functional magnetic resonance imaging scanner and a quantitative electroencephalograph (QEEG), were to be used, for the first time, to identify the various neurobiological correlates (neuroelectrical and functional neuroanatomical) of disturbed social behaviour.

The mock protocol provided for the participation of 60 subjects, distributed in four groups as follows: one group of men and women aged between 18 and 25 years, with a

Abbreviations: QEEG, quantitative electroencephalograph; REB, research ethics board

Table 1 Institutional distribution of the 44 participating Canadian biomedical research ethics boards

University	Hospital	Hospital and university	CLSC	Other	Total
4	24	8	1	7	44
9.1%	54.5%	18.2%	2.3%	15.9%	100%

CLSC, Community Health and Social Services Center.

history of social behaviour problems; one group of women and men in the same age range, with no history of social behaviour problems; one group of men and women aged between 40 and 50 years, with a history of social behaviour problems; and one group of women and men in the same age range, with no history of social behaviour problems.

Research subjects needed to be healthy and have no history of neurological or psychiatric illness requiring medical monitoring at the time of the experiment.

The mock protocol specified that subjects would be scanned by functional magnetic resonance imaging and QEEG during three experimental states: an ordinary state, a meditation state and a violent state. In the ordinary state, subjects would be asked to voluntarily think about everyday things such as grocery lists or the range of shapes and colours they were familiar with. In the meditation state, subjects would be asked to remain “within” and introspect. In the violent state, subjects would be asked to view a series of photographs showing extreme violence.

On completion of the QEEG, research subjects would be asked to leave the premises. The mock protocol provided for the eventuality of the need for psychological help, in which case subjects would be given a referral. This information was not included in the consent form accompanying the protocol.

To compile our findings, we first devised analytical grids for confidentiality, free and informed consent, presentation of the form, the study procedure, risks, the mock protocol, and level of risks and benefits to the subjects. These grids effectively covered all the broad areas of ethical review. Next, we compiled the response of the different REBs with these grids. Lastly, we applied the triangulation method (inter-judge) to the compilation of responses and grids.

It should be noted that participant REBs in this survey are not representative of the whole community of biomedical REBs in Canada. The findings we present here make no claims to predictive value or statistical validity. Their purpose is first and foremost to offer the most faithful possible reflection of the decisions and decision-making criteria used by the participating REBs in reviewing a single research protocol.

The pan-Canadian action-research study project was approved by the REB of the Sherbrooke University Hospital Center (Centre hospitalier universitaire de Sherbrooke), in Sherbrooke, Quebec, Canada.

FINDINGS

Forty four Canadian biomedical REBs agreed to review a mock research protocol. Table 1 presents the distribution of their institutional provenance, table 2 presents the results of their review of the mock protocol and table 3 presents the distribution of the REBs that approved the protocol.

Of the 3 (6.8%) REBs that approved the project unconditionally, two provided reasons for their decisions, saying that they “liked the idea and the scope of the research and that the concept was good and valuable”. They believed that the “study would produce interesting and valuable knowledge which will be of future value, especially for social science and psychology”. Two REBs said that research subjects would incur little risk by participating in the study. Among these

Table 2 Distribution of decisions made by participating research ethics boards

Unconditional approval	Conditional approval	Rejection	No answer	Total
3	10	30	1	44
6.8%	22.7%	68.2%	2.3%	100%

three REBs, one considered it important to note that, even though it had reviewed and approved the protocol, the project was not of the kind it usually reviews.

Of the 10 (22.7%) REBs that approved the project conditionally, 5 (50%) considered the question of the photographs containing images showing extreme violence. Of these five, one REB asked for more details about the nature of the photographs and raised the question of the risks associated with their use, and another called for explicit inclusion in the consent form of information regarding the extreme violence shown in these photographs. Yet another REB reflected on the appropriateness or inappropriateness of informing research subjects of this point. It wrote as follows:

We note that the consent does not explain that the subject will be exposed to violent photographs—we had a lot of discussion on the balance between deception and the need to not fully inform for fear of influencing responses or detracting from the responses in the previous 2 phases of the study. We would like to better understand the Researchers’ perception of the balance between deception and the risks to the study of being fully informed.

One REB made the following suggestion on the subject of the photographs with extremely violent content, providing a reference:

The consent form should mention the violent nature of the photographs used for the third task, since these could be disturbing to the patient. Our REB also suggests using photographs that have already been analyzed with respect to the level of their violence.

Of the 10 REBs that conditionally approved the project, 3 (30%) reflected on follow-up to be provided to research subjects after the photographs were projected; 2 (20%) raised questions about the project’s scientific validity; 6 (60%) raised a whole range of questions about the recruitment process; and 3 (30%) wondered about the appropriateness of the researchers’ having access to the medical records of subjects.

Finally, 2 (20%) of the REBs asked for clarification of the meaning of the expression “social behaviour problems”. One of these REBs wrote as follows:

We were uncomfortable with the way the purpose of the study was explained in the proposal—“It is conceivable that in the near future we will have enough neurobiological knowledge to be able to piece together the human brain to obtain a clearer idea of the direction in which we wish to see society develop”. In the consent, the purpose is more acceptable—“You are requested to participate in a research project that aims to identify and understand the brain processes associated with social behavior”. This statement does not suggest or imply manipulation or predetermination of societal traits.

Table 3 Institutional distribution of the 13 research ethics boards that approved the protocol

	University	Hospital	Hospital and university	CLSC	Other	Total
Unconditional approval		3				3
Conditional approval		7	3			10
Percentage		22.7%	6.8%			29.5%

CLSC, Community Health and Social Services Center.

Of the 44 participating REBs, 30 (62.8%) rejected the project. These rejections could be grouped into two categories: unqualified and qualified. Rejections of the second kind left room for the researchers to add specifics and correctives of greater or lesser magnitude to the protocol. Table 4 presents the distribution of rejections.

Of the 30 REBs that rejected the project, 21 (70%) dealt with the matter of the photographs with extremely violent content. Of these 21, 10 emphasised that the consent forms did not mention this component of the study; 7 called for inclusion of information about the nature of the extreme violence on the consent form; 4 reflected on the risks associated with the use of this kind of photograph in the study; 3 asked to see the photographs to be able to evaluate them; and 2 raised ethical concerns about the use of a vulnerable population for this purpose. Finally, one REB questioned the fundamentally ethical nature of such a study. It wrote,

Secondly, for lack of disclosure/clarity in the "consent process", a deception is created: subjects who have been ... pre-screened for their violence (although not told so) are then subjected to violence without their prior awareness, and their reactions measured. This is exploitation.

Of the 30 REBs rejecting the project, 10 (33%) raised points about the follow-up to be provided to research subjects after projection of the photographs. Of these 10, 8 said that information on this subject was lacking, 1 said that the consent form was not clear on the matter, and 1 said that all research subjects must be debriefed and those requiring psychological follow-up after debriefing must receive it. Finally, two REBs expressed concerns about the risk to the research subjects and the population in general of allowing the subjects to leave the study premises without ensuring effective follow-up.

In all, 10 (33%) of the 30 REBs rejecting the project raised concerns about the use of magnetic resonance imaging. Of these 10, 7 raised questions about the risks associated with this technology and 5 questioned the use of such a costly device for this kind of study.

Of the 30 REBs rejecting the project, 23 (77%) questioned the scientific validity of the study, 8 (27%) criticised the absence of a definition for the expression "disturbed social behaviour"; 2 (6.7%) expressed grave doubts about the appropriateness of this research; and 6 (20%) expressed

concern about the objective of the study—namely, social change. On social change, we quote the comments of two REBs. One wrote:

It is also alarming to confront the statement "Once we have identified the correlates, it is conceivable that in the near future we will have enough neurobiological knowledge to be able to piece together the human brain to obtain a clearer idea of the direction in which we wish to see society develop". This reminds one of the atrocious eugenics movement in the late 19th century. It is difficult to believe that a knowledgeable, compassionate professional authored this protocol!

Another wrote:

How, in any case, do we define "social behavior problems"? There seems to be much room for social control—as contrary to a free society where individuals could enjoy personal rights and freedoms. It was felt that the extensive risks involved this reductionistic approach in favor of determinism, without allowing for cognitive/rational screening and censorship prior to manifest behavior, contribute to rendering the study unacceptable in its current form.

Of the 30 REBs rejecting the project, 11 (37%) expressed concerns about access to the medical records of research subjects; 9 (30%) questioned the building of a database and the lack of transparency about this; and 11 (37%) raised a range of questions about recruitment.

Finally, 10 (33%) of these 30 REBs said that this kind of study did not fall under their mandate or area of expertise.

Taking the first aspect into account, table 5 presents the distribution of the decisions made by the 44 participating REBs.

ANALYSIS

The ethics of research on human subjects is embodied in a vast corpus of international and national norms, which brings forth regulations of a general nature.¹⁻³

REBs are aware of the existence of these norms: they are published and easy to access, and are the subject of

Table 4 Distribution of rejections by 30 research ethics boards

Unqualified rejection	7	23%
Qualified rejection	23	77%
Total	30	100%

Table 5 Distribution of the decisions of the 44 REBs, including the distribution of rejections

Unconditional approval	Conditional approval	Unqualified rejection	Qualified rejection	No answer	Total
3 7%	10 22.7%	23 52%	7 16%	1 2.3%	44 100%

numerous publications.⁴ They enjoy endorsement by all the major funding bodies; indeed, familiarity with them is required under any accreditation process.

How do REBs operationalise these norms when faced with a given protocol and, more specifically, a protocol in an emerging discipline of research from which the REB has not so far had study protocols to analyse? This is the question at the heart of our study, which sought to identify the norms that are currently invoked by REBs in handing down their decisions, whether negative or positive.

A salient point emerging from analysis of the findings is the large number of participating REBs that rejected the project. This factor led us to examine more closely the justifications made by all the rejecting REBs and to carry out an analysis of the rejections. Surprisingly, we observed that the concerns raised by 23 of the 30 rejecting REBs resembled, overall, the concerns mentioned by the 10 REBs that handed down conditional approvals. Thus, certain REBs shared a set of concerns; yet, some approved the project and others rejected it.

Another interesting factor is that some REBs reviewed the protocol but specified that it fell into a category that did not correspond to their usual mandate or subject of expertise. This may partly account for the large number of concerns raised about the project's scientific validity and its appropriateness; the risks associated with the use of magnetic resonance imaging; the appropriateness of accessing the medical records of subjects and of building a database; and the recruitment process.

In our opinion, the above two factors constitute eloquent examples of a problem inherent in the functioning of REBs—namely, the capability of reviewing any type of research project, regardless of the discipline it falls into, while relying on national and international norms framed in general terms. Would the solution to this problem lie in creating thematic REBs specialising in a single subject or perhaps a central REB to review multicentre studies?^{5 6}

Multicentre studies account for an increasingly large proportion of the work of REBs. Unfortunately, the current instruments used for the ethical review of studies are ill-suited to this reality. This situation has given rise to numerous criticisms, in particular from researchers, relating essentially to the efficiency of ethical review procedures.

Researchers argue that the current mechanisms of ethical review and monitoring display a lack of consistency that complicates and increases their work unduly. Some say that current mechanisms result in an increase in the time and resources assigned to ethical concerns, without necessarily enhancing protection of the research subjects. Moreover, it exposes researchers to variability in the requirements stipulated by different REBs and this needlessly complicates the way studies unfold.

REBs for their part state that they are subject to pressures that limit their power and leeway in the exercise of their responsibility in the review and follow-up of multicentre studies.

Could the solution lie in creating a multicentre REB? Certainly, made-to-measure REBs of this kind offer certain advantages. But would this mean creating tailored REBs for every new technology? In terms of efficiency, centralising the whole process of ethical review in a single authority offers many advantages: it would result in simplification of the process and a definite savings in time and money for researchers. Further, it would ensure consistency in reviews and decisions. Lastly, it would result in bringing together the most competent ethical reviewers and people with the greatest scientific expertise.^{5 6}

Centralisation, however, raises numerous concerns—for instance, regarding judicial feasibility, accountability of the various partners, costs associated with implementation,

financial effects and the dilution of ethical expertise in different settings. Some therefore argue that centralisation would result in a homogenised and impoverished ethical vision that would fail to reflect the richness of thought encountered in various settings.^{5 6}

Several REBs said that, in a true ethical review, they would have insisted on meeting with the researchers to ask questions necessary for a better understanding of the project and thus to hand down a more satisfactory review. The net benefit of this approach is that it allows each party to better understand the concerns and issues preoccupying the other and to engage in a discussion of these. REBs thus develop the necessary expertise for reviewing the projects.

Several REBs considered the matter of photographs containing extremely violent images to be their primary concern. This widely shared concern raises the question of the limits of acceptability. How far can we go in exposing research subjects to the performance of certain tasks in a functional neuroimaging research project? And in so doing, what kind of supervision, protection and follow-up must researchers provide? These questions, more than any others, engage the sensitivities of an REB and its ability to review short, medium and long-term risks in the light of expected benefits.

These questions also raise the matter of the existence of variations in the perceptions of REBs about the limits of their mandate. Thus, for some REBs, it is up to the person invited to participate in a study to assess the acceptability of the risk to which the study will expose him or her. Other REBs consider this assessment to constitute one element of their own mandate and responsibilities. The debate over the effective mandate of the REBs and its limits inevitably transpires in the decisions of REBs and accounts for some degree of variability.

The mandate of the REBs is to oversee the safety and well-being of research subjects and to respect their rights.

In fulfilling this mandate, REBs must conduct a scientific review of a study; ensure that the scientific components of the study are ethically acceptable; ensure that the study is relevant; examine the consequences to research subjects; examine the ethical appropriateness of the subject selection criteria; ensure that subject recruitment methods are acceptable; review provisions for obtaining consent from subjects; examine the suitability of provisions with regard to respect for private life and the protection of confidentiality; ensure that researchers and their team are competent; ensure that ethical obligations related to scientific and professional integrity are respected (in particular by determining whether a real, apparent or potential conflict of interest exists or could arise); and examine provisions for disseminating findings.⁴

During ethical review, REBs must also determine whether the risk–benefit ratio is favourable to research subjects: assessment of the risks and benefits is at the heart of the mandate of REBs.^{7–9}

As regards risk assessment in the determination of risks and benefits, the minimum risk threshold is applied. This consists of comparing the probability and significance of the potential risks and the inconvenience associated with the study with those that subjects would encounter in those aspects of daily life found in the study. Benefit assessment requires determining whether subjects can look to health benefits or, where appropriate, whether findings could benefit people with the same age, disease or handicap characteristics as those of the subjects in the experiment.

The risk–benefit component is the most difficult for REBs to assess, more so when the study relates to an emerging discipline. REBs have little guidance to turn to in risk–benefit assessment. That they are thus effectively left to find their own way may partly account for the variability of decisions in our study.

This absence of guidance in analysing risks and benefits explains, in our opinion, the comment made by several REBs to the effect that they would have asked for a meeting with the researcher to ask questions that would enable them to pinpoint the issues at stake.

Other concerns raised by REBs in this study had to do with the objectives of the mock research project—that is, these concerns related to the question of social behaviour problems and the improvement of social behaviour.^{10–12} Clearly, these factors in themselves raise important ethical questions and, inevitably, the question of the normal versus the abnormal. As with any practice that is not governed by guidelines, the odds of going off the rails are high.

CONCLUSION

In a pan-Canadian study, 44 Canadian biomedical REBs conducted ethical reviews of a mock research protocol in functional neuroimaging. One finding of the study is that few REBs reached unqualified decisions in favour of the research project or against it: most REBs preferred to put questions to the researchers.

Another interesting aspect of the reviews of the acceptability of mock protocol was that decision-making criteria clustered around some ethical issues, whereas other issues entailed by the protocol either went unmentioned or received very little attention.

Does this pattern reflect the cautiousness of REBs when faced with an emerging discipline of research? However that may be, it could expose researchers to variations in requirements by different REBs reviewing their projects.

The appropriateness of setting up tailored, thematic REBs is under consideration. Despite its evident limitations, this solution may be envisaged as a way of enabling REBs to conduct more adequate reviews of research projects in emerging disciplines such as functional neuroimaging.^{5,6}

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Authors' affiliations

J de Champlain, Centre de recherche clinique, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Quebec, Canada

J Patenaude, Department of Surgery, Faculty of Medicine, Université de Sherbrooke, Sherbrooke

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