Author's response to reviews

Title: Ethics of neuroimaging after serious brain injury

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Author's response to reviews: see over
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My co-authors and I are grateful for the helpful comments on our study protocol, "Ethics of neuroimaging after serious brain injury". Below I provide a detailed response to each of the suggestions. A revised version of the study protocol is appended. (I have retained a track-changes version of the protocol, and would be pleased to forward this document as well.)

I hope you will agree that the study protocol is now suitable for publication.

Sincerely,

Charles Weijer.

Detailed response

-Please could you kindly include a section on ethical considerations in your methods section, specifying the ethics committee which has approved your studies and details on informed consent.

We have added an ethics section at the end of the Methods/Design section of the paper, as follows:

"Subproject 1b (Demonstrating the feasibility of decision making capacity assessment using neuroimaging) and project 3 (The impact of neuroimaging on families of patients with serious brain injury) involve research on human participants. Both studies have been reviewed and approved by the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (#100070 and #104684). Informed consent will be obtained from all study participants."

- Please could you remove your funding documents and ethics approval documents from your additional files.

We have removed these documents from the additional files.

-Please clearly state the aims of your study in both the background section of your abstract and the background section of your main document rather than in your methods section.

We have added a statement of study objectives in the background section of the abstract and study protocol. The study objectives in the background section of the protocol reads as follows:

"The overarching goal of this project is to investigate ethical issues in the use of neuroimaging in behaviorally nonresponsive patients who have suffered serious brain injury. We will build a lasting collaboration between philosophers, physicians, and neuroscientists that draws upon the strengths of each discipline, and produces significant contributions to the scholarly literature, advances ethical practice in
neuroimaging, and ultimately improves the care of patients with serious brain injuries. Specific objectives are to:
1. Create a conceptual framework for capacity assessment in behaviorally nonresponsive patients using neuroimaging and demonstrate its feasibility in healthy controls;
2. Develop an ethics of welfare framework to guide the use of neuroimaging in behaviorally nonresponsive patients and apply it to considerations of quality of life;
3. Explore the impact of neuroimaging on the families of behaviorally nonresponsive patients; and,
4. Provide the first sustained ethical analysis of the use of neuroimaging to detect residual cognitive function in comatose patients.

Detailed aims and questions are found within each of the project descriptions. The detailed aims and questions are a key part of the project descriptions and we feel that moving them to the background section of the paper would make the descriptions less clear. We no longer refer to the detailed aims and questions as 'objectives'.

-Please could you improve the clarity of your methods section, please clearly state and provide more specific details on how you will conduct each project. It would be useful for readers if you could provide inclusion and exclusion criteria for participants.

The Methods/Design section contains descriptions of eight projects and subprojects. Five of the eight projects involve ethical analyses (Projects/subprojects 1a, 2a, 2b, 3, 4a and 4b). The methodology for these projects is covered by the description at the beginning of the Methods/Design section. We say:

"Ethical analysis in bioethics is not amenable to the degree of a priori methodological specification that is expected of empirical research. Statistical rigor and reproducibility are indispensable features of science, necessitating the clear and up-front statement of hypotheses and experimental methods. High-quality ethical analysis, on the other hand, relies neither on statistical rigor nor on reproducibility. Rather, it begins with the articulation of clear and important questions and is realized in the construction of sound arguments in peer-reviewed publications and policy reports. For each question, an extensive review of the scholarly literature will document and critically analyze arguments proffered for and against particular positions. Where gaps exist, we will develop our own ethical arguments. The ethical analysis will then seek to synthesize foundational documents, regulations, and existing and novel arguments into a coherent position. Where disagreement among the various sources cannot be resolved by ethical analysis, the details of the dispute will be documented."

Project 2c seeks to undertake the preliminary development of quality of life (QoL) instruments for use in behaviorally nonresponsive patients after serious brain injury. For reasons we outline in the subproject description, standard approaches to the development of quality of life instruments do not apply. We say:
"Recognizing that these limitations undermine standard methods for QoL instrument development, we will convene an interdisciplinary group of experts (including QoL methodologists, philosophers, neuroscientists, health care workers, and family members of patients who have suffered a serious brain injury) in a two day workshop to address the problem. The purpose of the meeting is (1) to develop an approach to assess overall QoL in behaviorally nonresponsive patients, (2) to develop an approach to assess the health-related QoL in these patients, and (3) to develop strategies to validate these instruments."

This project is only meant to address the very difficult conceptual challenges in the development of QoL measures in this patient population. We do not include plans to empirically validate or otherwise study prospective QoL instruments.

Project 1b (Demonstrating the feasibility of decision making capacity assessment using neuroimaging) is an fMRI study involving health volunteers. As requested we have added details on how the study will be conducted, including details on participant eligibility, fMRI methodology, and the use of the scenario and questions. Regarding study eligibility, we say:

"Following previous work on single subject fMRI techniques in healthy participants [21,22], our study will recruit 20 healthy volunteers. Volunteers will be native English speakers between the ages of 18 and 60, have no history of neurologic or psychiatric illness and normal hearing."

Project 3 (The impact of neuroimaging on families of patients with serious brain injury) uses grounded theory interviews to explore the experiences of families with neuroimaging. As requested, we have added details regarding eligibility criteria, recruitment, interviews, and data analysis. Regarding study eligibility, we say:

"English speaking family members who are acting as the surrogate decision maker for patients participating in our neuroimaging research program on serious brain injury at Western University are eligible for this study. Patients must have a diagnosis of vegetative or minimally conscious state and be at least 1 year post-injury."

-It would also be useful if you could provide a section on Data Analysis.

Only two of the projects/subprojects involve any data analysis (subproject 1b and project 3). As the methods for the two studies are very different, we have added further details on data analysis in the individual project descriptions.

-Please provide a section on Sample Size especially for project one, in which you have specified the quantity of healthy volunteers you will require. Please include a power calculation and details on statistical significance.

As requested, we have added details on sample size and power:

"Scores of greater than or equal to 9 correct answers will be considered a "success". Decoding accuracy at the group level will be determined with a binomial test. With a sample size of 20 participants, statistical significance (p<0.05) will be achieved if 14 or
more participants succeed. If the true probability of success is 80% [22], 20 participants provide a power of 80%. " 