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Picturing neuroscience research through a human rights lens: Imaging first-episode schizophrenic treatment-naive individuals

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ABSTRACT

In this paper we examine imaging research involving first-episode schizophrenic treatment-naive individuals (FESTNIs) through a legal human rights lens; in particular, the lens of the Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research. We identify a number of ethical and legal hot spots highlighted by the Protocol, and offer a series of recommendations designed to ensure the human rights compatibility of this research. Subsequently, we argue that the lack of reporting on design elements related to ethical concerns frustrates commitments at the heart of the human rights approach, namely, transparency and openness to international scrutiny. To redress this problem, we introduce two norms for the first time: *ethical transparency*, and *ethical reproducibility*. When concluding, we offer a set of reporting guidelines designed to operationalize these norms in the context of imaging research involving FESTNIs. Though we will not make this case here, we believe that parallel reporting guidelines should be incorporated into other areas of research involving human subjects.

1. Introduction

Imaging is a key research tool in neuroscience, and studies of brain anatomy and brain function have provided valuable insights into the structural and functional underpinnings of psychiatric illness overall, and schizophrenia in particular. Of specific and increasing interest for imaging research are studies involving first-episode schizophrenic treatment-naive individuals (FESTNIs).[1] In these studies, FESTNIs are scanned prior to the administration of medication in order to control for the confounding effects of treatment. Imagers hope that these studies will enable both accurate cross-sectional understandings of the anatomic and functional neuro-anomalies characteristic of schizophrenia and provide a reliable baseline for longitudinal work.

In this paper we examine imaging research involving FESTNIs through a legal human rights lens; in particular, the lens of the Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research (hereafter 'the Protocol'). We identify a number of ethical and legal hot spots highlighted by the Protocol, and offer a series of recommendations designed to ensure the human rights compatibility of this research. We acknowledge the likelihood that researchers are already taking steps along the lines recommended, but note the almost total absence of transparency in this regard; discussion of these issues is virtually non-existent in the peer-reviewed literature. Subsequently, we argue that the lack of reporting on design elements related to ethical concerns frustrates commitments at the heart of the human rights approach, namely, transparency and openness to international scrutiny (Faunce, 2005). These commitments are implicit in the Protocol (they feature only in the Preamble, not in the Articles) and in the human rights approach more generally. In order to make these commitments explicit, we introduce two norms for the first time: *ethical transparency*, and *ethical reproducibility*. In closing, we offer a set of reporting guidelines designed to operationalize these norms in the context of imaging research involving FESTNIs. Though we will not make this case here, we believe that parallel reporting guidelines should be incorporated into other areas of research involving human subjects.

2. The human rights approach and the Additional Protocol concerning biomedical research

Recent years have witnessed growing interest in the development of legal human rights based approaches to medical ethics and biomedical research involving human subjects (Ashcroft, 2010; Kim, Ubel, & De Vries, 2009). Interest in this approach has been driven by a number of factors including the increasingly international character of biomedical research. A global research context requires a transparent, consistent, credible, and enforceable regulatory framework (Faunce, 2005). Human rights based approaches are endorsed precisely because they promise to facilitate these goals. For instance, due to their universal

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[1] We are sensitive to the reductive and essentializing connotations of the term 'schizophrenic'. We use the term for economy of expression, and not because we endorse reductive or essentialist views of schizophrenia or persons living with schizophrenia.

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nature, human rights based frameworks cut across national and institutional jurisdictions, harmonize protections, and foster consistency (Ashcroft, 2010). Second, because human rights are independent of governmental and institutional recognition (Ashcroft, 2010), they provide an external standard for the evaluation of local policy (Plomer, 2005) and encourage transparency and openness to international scrutiny (Faunce, 2005). Third, because human rights based frameworks naturally articulate with domestic and international legal systems, implementation and enforcement are simplified (Ashcroft, 2010). Finally, because human rights based instruments provide a *lingua franca* that is comprehensible to parties living in disparate locations with different practices and assumptions, these instruments enable cogent discussion of bioethical issues across laboratories, disciplines, and nations (Ashcroft, 2010).

The Additional Protocol is the most direct, specified and legally enforceable human rights instrument for biomedicine and medical research. The Protocol entered into force in 2007. The Protocol binds States who have signed and ratified it and its mother Convention, the Convention on Human Rights and Biomedicine (hereafter 'the Convention').[2] As of the date of writing (January 20, 2012), only 15 of the 47 member States (of the Council of Europe) have signed the Protocol, and only 7 of these 15 have ratified it (Council of Europe, Treaty Office).[3] Its regime, thus, is still expanding. The Protocol is designed to protect the human rights of research participants by specifying the more general provisions found in the Convention, the European Convention on Human Rights (ECHR) and the Universal Declaration of Human Rights (UDHR) in the contexts of biomedicine and biomedical research respectively.[4] As its preamble makes clear, facilitating trans-disciplinary and trans-national cooperation are central goals of the document.

3. Imaging first episode schizophrenic treatment-naive individuals (FESTNIs)

Imaging has been used to study schizophrenia ever since the technology was available to do so. Early work aimed to identify structural and functional abnormalities in cross-sectional studies of populations with chronic schizophrenia (Shapiro, 1993). One of the first consistent discoveries for schizophrenia was enlargement of the lateral and third ventricles in affected people (Linden & Fallgatter, 2009). Over time, however, investigators discovered substantial variation in other brain features depending on factors such as age of onset, illness duration, and treatment history (Harrison & Roberts, 2000).

To control for these confounds, imagers began to study FESTNIs (Schimanzi & Lieberman, 1995). FESTNIs are persons, typically in their late teens or early twenties (Frangou, 2000), who are experiencing the symptoms of schizophrenia for the first time and are still treatment-naive (Harrison, 1999; Leung, Cheung, Yu, Yip, Sham, et al., 2010). By definition, FESTNIs are a homogenous study population because they have no treatment history. Depending on how the first-episode is defined, furthermore, variability in illness duration and age of onset are substantially reduced, if not eliminated.[5] Imagers hope that studies involving FESTNIs will provide a more accurate cross-sectional understanding of the anatomic and functional neuroanomalies characteristic of schizophrenia. Imagers also hope that studies involving FESTNIs will provide an accurate baseline for longitudinal studies designed to elucidate the effects of these factors (i.e., age of onset, illness duration, and treatment history) on the structure and function of the brain over time (Brown & Eyler, 2006).

Before moving on to our analysis, a few brief comments about schizophrenia will help to clarify the clinical, ethical and legal complexity of imaging research involving FESTNIs. Schizophrenia is a mental health condition involving a range of symptoms. These symptoms include delusions, paranoia and hallucinations, low affect and social withdrawal (Kay, Fiszbein, & Opfer, 1987). Prognosis for this mental health condition is often dire due to the lack of effective treatment and social support, and high levels of stigmatization (Landeen, Seeman, Goering, & Streiner, 2007). Persons diagnosed with schizophrenia frequently acquire co-morbid disorders such as addictions and iatrogenic disorders (Batel, 2000) and almost invariably suffer significant employment and interpersonal difficulties. For the purposes of this paper it is important to note that FESTNIs are identified when they arrive in the emergency department or psychiatric ward of their local hospital where they are examined and diagnosed with schizophrenia for the first time. It is at this point that they are approached concerning participation in imaging research.

4. Imaging research involving FESTNIs under the protocol: Raising red flags

Imaging research involving FESTNIs raises a number of red flags when examined through the lens of the Protocol. After a brief description of the relevant Articles from the Protocol below, we will identify these areas of concern. It is important to be clear that our intention is not to impute wrongdoing on any researcher's behalf; rather, our aim is to identify hotspots that demand additional attention on the part of researchers and reviewers from an ethical and legal human rights point of view.

4.1. Risk, benefit, and burden

The first red flags can be identified under the Articles concerning risks, burdens, and benefits. Articles 6, and 21 provide the relevant general guidance (see Box I). Articles 15 and 17 stipulate additional requirements for research participants who cannot consent to research (see Box II).

Paragraph 1 of Article 6 mandates that the risks and burdens of trial participation, overall, be proportionate to the potential benefits. The second paragraph pertains to research that does not offer participants the prospect of direct benefit. It restricts research of this type to studies that entail no more than 'acceptable risk and acceptable burden'. The second paragraph also refers to Article 15, which details additional restrictions for research involving persons not able to consent to research, including: (1) the provision that the goals of the research need to be connected to improved understanding of the condition in the population being researched; and (2) the provision that such research must not involve more than minimal risk and minimal burden. According to Article 17, research is minimally risky if, with "regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned". Research is minimally burdensome if "it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned". Finally, Article 21 requires that all reasonable measures be taken to minimize the risk and burden of research participation.

Imaging research involving FESTNIs raises at least four red flags under these provisions. First, though imaging research that does not

[2] The Convention is an international legal treaty and binds the Member States of the Council of Europe, as well as Non-Member States in so far as they have signed and ratified the document, and the document has entered into force. As of January 20, 2012 35 Member States have signed on to the Convention and 29 have ratified it.

[3] Turkey ratified the Protocol in September 2011, where it entered into force on January 1st, 2012. Treaty office: http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=195&CM=&DF=&CL=ENG.

[4] These human rights documents have full legal status and contrast with the international medical ethics regimes. Ethics regimes, overall, tend to bind if, with "regard to the professional members and organizations morally rather than legally. Some of these ethics regimes may have become 'customary law', and have acquired a legal status. They can be invoked in front of Courts. The Helsinki Declaration is such an example. Still, these documents do not have the same legal status as the Convention and will not provide the same protective regime.

[5] What a first episode is, or what (Council of Europe (Treaty Office), 2011) timeline a first episode covers is not unequivocally defined.

Box I
General guidance concerning risk, burdens, and benefits.

Article 6 Risks and benefits

1. Research shall not involve risks and burdens to the human being disproportionate to its potential benefits.
2. In addition, where the research does not have the potential to produce results of direct benefit to the health of the research participant, such research may only be undertaken if the research entails no more than acceptable risk and acceptable burden for the research participant. This shall be without prejudice to the provision contained in Article 15 paragraph 2, sub-paragraph ii for the protection of persons not able to consent to research.

Article 21 Minimisation of risk and burden

1. All reasonable measures shall be taken to ensure safety and to minimise risk and burden for the research participants.
2. Research may only be carried out under the supervision of a clinical professional who possesses the necessary qualifications and experience.

Box II
Additional requirements for research involving persons not able to consent to research.

Article 15 Protection of persons not able to consent to research

1. Research on a person without the capacity to consent to research may be undertaken only if all the following specific conditions are met…
2. Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, sub-paragraphs ii, iii, iv, and v above, and to the following additional conditions:
   i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition
   ii. the research entails only minimal risk and minimal burden for the individual concerned; and any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden.

Article 17 Research with minimal risk and minimal burden

1. For the purposes of this Protocol it is deemed that the research bears a minimal risk if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned.
2. It is deemed that it bears a minimal burden if it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned. In assessing the burden for an individual, a person enjoying the special confidence of the person concerned shall assess the burden where appropriate.

use a contrast agent or sedation is typically considered to involve minimal risk (Pinxten, Nys, & Dierickx, 2009; Racine, Northoff, Menon, Kimmelman, & Illes, 2011; Rose, 2011), research involving vulnerable participants clearly deserves additional attention.[6] In the case of FESTNIs, it is an open question whether the risks and burdens of research participation are "very slight and temporary." The noise and claustrophobic environment associated with the scanner, and the scanner itself, may be particularly traumatic. FESTNIs suffering from paranoid delusions may be more prone to false beliefs concerning mind reading, or come to believe that researchers are directing their thoughts and behaviors using the scanner (Lennox, 2009).

Second, the tasks involved in these studies may also pose a threat to FESTNIs. Take, for example, lip reading tasks or the judging of facial expressions (Gur, McGrath, Chan, Schroeder, Turner, et al., 2002; Reske, 2008; Surguladze, Calvert, Brammer, Campbell, Bullmore, et al., 2001). While these tasks may not seem risky or burdensome to healthy individuals, the risks and burdens posed by lip-reading tasks for individuals who believe they are hearing voices, or the showing of angry faces to individuals who are experiencing paranoid delusions for the first time, may be more than minimal.

Third, imaging studies involving FESTNIs are not to our knowledge designed to offer participants the prospect of direct preventive, diagnostic, or therapeutic benefits. In any case, clinical applications of imaging for the prevention, diagnosis, and treatment of schizophrenia have yet to be developed (Schleim & Roiser, 2009). It is always possible, of course, that researchers will find something clinically relevant that may prompt further clinical investigation or treatment, but incidental findings of this kind cannot be used to justify claims concerning the direct benefits of study participation (Racine, Northoff, Menon, Kimmelman, & Illes, 2011). The potential benefits of these studies, thus, are entirely downstream in nature, turning on the value of the knowledge they produce. Given the concerns about the scientific quality discussed in the next section, this requirement also raises another red flag.

Finally, there is the question of capacity. We recognize that this is a complex issue and that it would be a mistake to assume that persons with schizophrenia necessarily lack capacity.[7] But, given that imaging studies involving FESTNIs often enroll participants who are actively experiencing the symptoms of schizophrenia (e.g., negative symptoms, disorganization, Schneiderian delusions and hallucinations, and suspicion or hostility (Gur, Petty, Turetsky, & Gur, 1996)), there are *prima facie* grounds for questioning whether participants are in a position to consent to research participation.[8] Concerns about capacity are increased by the fact that potential participants are going through the experience of schizophrenia for the first time and have never received treatment. Though first-episode is treated rather loosely in the literature, some first-episode studies seem to include patients who have already been ill for a number of years (Pantelis, Yucel, Wood, Velakoulis, Sun, et al.,

[6] See paragraph 100 of the explanatory report (Marshall, Martin, Downie, & Malisza, 2007).

[7] For detailed discussions of this issue see: Kaup, Dunn, Saks, Jeste, and Palmer (2011), Jeste, Depp, and Palmer (2006) and Carpenter, Gold, Lahti, Queern, Conley, et al. (2000).

[8] Gur et al. (1996).

Box III

Article 8 Scientific quality

Any research must be scientifically justified, meet generally accepted criteria of scientific quality and be carried out in accordance with relevant professional obligations and standards under the supervision of an appropriately qualified researcher.

Box IV

Article 23 Non-interference with necessary clinical interventions

1. Research shall not delay nor deprive participants of medically necessary preventive, diagnostic or therapeutic procedures.
2. In research associated with prevention, diagnosis or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment.
3. The use of placebo is permissible where there are no methods of proven effectiveness, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden.

2005), persons in this category are less likely than persons with chronic schizophrenia to have developed the coping skills required to support autonomous decision-making, in spite of symptoms. This entails a major red flag: Article 15 states that research involving persons who are not able to consent and does not offer the prospect of direct benefit, must not involve more than minimal risk and burden. But, as we have discussed above, whether imaging research involving FESTNIs is minimally risky or burdensome is an open question. Thus, the question of capacity has significant implications for risk assessment under the Protocol.

4.2. Scientific quality and imaging

Article 8 provides guidance concerning scientific quality. Article 8 is listed in Box III.

Research that fails to satisfy Article 8 is impermissible under the Protocol. According to the explanatory report, which sets out what scientific quality entails, this criterion is defined through peer review and sample size.[9] In general, studies must be designed using the smallest number of participants required to obtain valid results.[10]

From an ethical/legal point of view, scientific quality is relevant because quality is tightly related to the potential knowledge-value of research and, thus, to the evaluation of risk-benefit proportionality (Article 6). An invalid study is ethically problematic because it puts research subjects at risk and consumes scarce resources, while not producing knowledge. Imaging research involving FESTNIs raises another red flag under Article 8 because the scientific quality of imaging studies of schizophrenia is variable. These concerns are well documented in the review literature (Agarwal, Port, Bazzocchi, & Renshaw, 2010; Brown & Eyler, 2006; Carter, Heckers, Nichols, Spine, & Strother, 2008; Davis, Jeste, & Eyler, 2005; Fusar-Poli, Allen, & McGuire, 2008; Kindermann, Karimi, Symonds, Brown, & Jeste, 1997; Nakamura, McCarley, Kubicki, Niznikiewicz, Voglmaier, et al., 2005).

A major locus of criticism in the review literature relates to the uncontrolled character of many studies in this area. Of course, as we noted above, imagers began studying FESTNIs in order to control for the confounding effects of age of onset, illness duration, and treatment history. But there are many other threats to internal validity in this context, and the degree to which studies are designed to control for these factors varies across the literature. Confounds of particular concern are the type and level of the symptoms experienced by participants. Though this problem has been noted in the review literature (Agarwal et al., 2010; Brown & Eyler, 2006; Carter et al., 2008; Davis et al., 2005; Fusar-Poli et al., 2008; Nakamura et al., 2005), it is still common to see imaging studies involving individuals with different types and levels of schizophrenic symptoms. Since it has been shown that factors such as subtype (Buchsbaum, 1990) and clinical symptoms (Franck, O'Leary, Flaum, Hichwa, & Andreasen, 2002) are related to brain functioning among patients with schizophrenia, uncontrolled variation in the type and intensity of symptoms may well compromise the internal validity of studies.

Another threat to internal validity arises in relation to the tasks employed. Tasks designed to target functional deficits particular to schizophrenia may in fact target other capacities that may or may not be related to the disease, confounding valid inference (Brown & Eyler, 2006; Snitz, MacDonald, Cohen, Cho, Becker, et al., 2005). There are also concerns about confounds related to anxiety and fear. Anxiety stressors have already been shown to have an impact on data in unaffected individuals (Prevost, Rodier, Lionnet, Brodeur, King, et al., 2011; Racine & Illes, 2007), and persons with schizophrenia may be particularly subject to anxiety or heightened emotional responses to stressful or fearful tasks. Stress responses may directly confound results, or inhibit capacities that are otherwise normal (Prévost et al., 2011; Brown & Eyler, 2006).

4.3. Safety and delay in imaging research

Article 23 provides guidance concerning non-interference with necessary clinical interventions. Article 23 is listed in Box IV.

Article 23 stipulates that "research shall not delay nor deprive participants of medically necessary preventive, diagnostic, or therapeutic procedures." The explanatory report, for Article 23, states that delay should be understood as "any delay that would be detrimental to the medical care of a patient."[11]

Imaging research involving FESTNIs necessarily involves the postponement of medically necessary therapeutic procedures. This follows from the nature of the research. Participants are recruited after they are diagnosed with schizophrenia for the first time. However, since investigators are interested in imaging schizophrenia before the brain is affected by treatment, intervention must be delayed until scanning is completed. Though a standard research scan may only take 45 min, additional delays may occur because scan time can be a scarce commodity.[12] In most jurisdictions, scanners are subject to tight scheduling constraints.[13] This is particularly true in countries with comparatively low ratios of scanners/population. In such contexts, it seems unlikely that a scanner will be available as soon as a FESTNI is diagnosed. Even if these studies are piggy-backed on imaging protocols undertaken for clinical reasons, e.g., to rule out structural neuro-anatomical abnormalities, delays are minimized but not

[9] The explanatory report, as the title suggests, discusses the Protocol's provisions in more detail. It defines some of the terms used in the protocol and attempts to clarify ambiguities. Paragraph 37 of the explanatory report deals with scientific quality.

[10] See paragraph 37 of the explanatory report.

[11] See explanatory report paragraph 119.

[12] In Europe, on average, there are about 10 scanners per million individuals (OECD, 2011), and Canada had 6.1 scanners available per million individuals in 2008 (CIHI, 2007).

[13] CIHI, 2008.

eliminated. To our knowledge, research tasks used in these studies are not part of any standard clinical diagnostic workup.

The additional question, then, is whether the delays involved in imaging research with FESTNIs are detrimental to the medical care of participants, as per Article 23. Given that FESTNIs are suffering from symptoms, have sought out medical treatment for these symptoms, and are approached for research participation immediately after they are diagnosed, treatment delays in this context warrant additional scrutiny. Absent additional information, however, it is impossible to determine if the delays involved are detrimental. Insofar as participation in imaging research involving FESTNIs necessitates detrimental treatment delays, then, this research raises a red flag under Article 23 of the Protocol.

5. Recommendations: Some green flags

Here we offer a range of recommendations – we call them 'green flags' – designed to help investigators assess and ensure the human rights compatibility of their work. These recommendations are summarized in Box V.

Our first set of recommendations pertains to risk and burdens. We highlight five steps of particular relevance in this research context. First, we recommend that all imaging studies involving FESTNIs be designed to ensure that the risks and burdens presented by participation are minimal. If this is impossible, enrolment should be restricted to participants who possess the capacity to consent to research participation, as per the results of an independent capacity assessment. Second, we recommend consideration of the prospective exclusion of FESTNIs who score above a chosen threshold on a reliable severity (such as the Brief Psychiatric Rating Scale of the Positive and Negative Syndrome Scale) (Kay, Fiszbein, & Opler, 2004), as well as those FESTNIs who are particularly prone to psychological risks. Third, researchers should choose tasks that are minimally risky and burdensome for FESTNIs when they design their studies. Tasks that provoke anxiety, paranoia, delusions, or hallucinations, should be avoided. Fourth, whenever possible, research procedures should be piggy-backed on procedures undertaken as part of standard clinical practice in so far as this reduces the risks, burdens, or potential treatment delays (see below). Finally, debriefing and follow-up should be a routine feature of study design in this area.

Our second set of recommendations pertains to issues of consent and capacity. These issues have not been a central focus of this paper, but questions of consent and capacity are entangled with risk assessment under the Protocol. For this reason, we offer two recommendations concerning capacity assessment. We recommend that, given the often acute nature of potential participants' symptoms, all imaging studies involving FESTNIs be designed so to assess the capacity and consent of potential participants on an individual and task-specific basis. We hasten to add, however, that capacity assessments should be based on cognitive ability (Carpenter & Conley, 1999); a diagnosis of schizophrenia does not entail a lack of capacity.

Our third set of recommendations concerns the delay of therapeutic procedures. Given that FESTNIs are suffering from the symptoms of schizophrenia, have sought out medical treatment for these symptoms, and are approached for research participation immediately after they are diagnosed for the first time, treatment delays are particularly problematic. With respect to delays in therapeutic procedures we recommend that: steps be taken to minimize the delay required by participation; protocols specify maximum tolerable delays of treatment; and that participants be closely monitored during the period of treatment delay.

Our fourth, and final, set of recommendations concerns scientific quality. Given concern in the review literature about the scientific quality of imaging studies of schizophrenia, and the fact that these studies do not offer participants the prospect of direct benefits, we recommend that steps be taken to augment the scientific quality of research in this area. We cannot provide an exhaustive list of such steps here, but we highlight a few that are particularly relevant: tighter controls related to the type and level of participants' symptoms; and, tighter inclusion/exclusion criteria with respect to symptoms.

Box V

Recommendations

1) Recommendations concerning risk and burden minimization:
   - 1.1 All imaging studies involving FESTNIs should be designed so as to ensure that the risks and burdens presented by participation are minimal. If this is impossible, enrolment should be restricted to participants who possess the capacity to consent to research participation, as per the results of an independent capacity assessment (see below).
   - 1.2 Consideration should be given to the prospective exclusion of FESTNIs who score above a chosen threshold on a reliable severity scale (such as the Brief Psychiatric Rating Scale of the Positive and Negative Syndrome Scale) (Kay et al., 2004) and to FESTNIs whose individual symptom-set make them particularly vulnerable to psychological risks or burdens that are more than minimal (even if their global severity score is not above the threshold noted above).
   - 1.3 Consistent with sound study design, tasks that are minimally risky and burdensome for FESTNIs should be chosen as starting points for the research.
   - 1.4 Whenever possible, research procedures should piggy-back on to procedures undertaken as part of standard clinical practice (e.g., imaging undertaken to rule out gross structural anomalies) in so far as this reduces the delays, risks and burdens.
   - 1.5 FESTNIs should be debriefed and follow up should be ensured where necessary.
2) Recommendations concerning consent and capacity:
   - 2.1 FESTNIs should be systematically and individually assessed for capacity levels that include task-related concerns.
   - 2.2 To consent to research participation should be based on their cognitive capacity (Carpenter & Conley, 1999). A diagnosis of schizophrenia does not entail a lack of capacity.
3) Recommendations concerning delays:
   - 3.1 Steps should be taken to minimize the delay of treatment required by participation.
   - 3.2 Protocols should specify maximum tolerable delays of treatment.
   - 3.3 Participants should be assessed individually to determine the maximum delay that would be held tolerable.
4) Recommendations concerning scientific quality:
   - 4.1 Tighter controls related to the type and level of participants' symptoms.
   - 4.2 Tighter inclusion/exclusion criteria with respect to symptoms.

6. *Ethical transparency* and *ethical reproducibility*

The recommendations we offer are designed to help investigators assess and ensure the human rights compatibility of their work. Again, it is important to note that our intention is not to impute wrongdoing;

indeed, we acknowledge that investigators are already taking steps along the lines of, if not identical to, those recommended. Insofar as informed consent, risk-minimization, risk-benefit proportionality, and scientific quality are generic components of ethics review (and they are), it is difficult to understand how investigators could avoid doing so. From this perspective, our recommendations may strike some readers as obvious.

The problem from our perspective, however, is that it is not at all obvious from reading the literature whether researchers actually have recognized the red flag issues identified above, or what steps if any they have taken to deal with these issues. Aside from cursory references to ethics approval, discussion of these issues is virtually nonexistent in published work in this area (Garnett, Whiteley, Piwowar, et al., 2011). There is a near total absence of transparency concerning the ethical design elements of these studies. This lack of transparency makes it impossible to know how significant ethical concerns are approached and resolved. Readers are left wondering how investigators and research ethics committees dealt with these issues. Short of contacting investigators personally and asking them, readers are left in the dark.

We find this situation troubling. We are concerned about the missed opportunity for learning and critical engagement. Scientists have been committed to transparent reporting of their research methods for hundreds of years precisely because reporting fosters critical engagement across the global scientific community (Poldrack et al., 2007) and, in due course, scientific progress. Since transparent reporting of ethics methods, i.e., design elements related to ethical concerns, would also foster critical engagement and ethical progress, we are struck by its absence.

We are concerned, furthermore, that the lack of reporting on design elements related to ethical concerns frustrates commitments at the heart of the human rights approach: namely, transparency and openness to international scrutiny (Faunce, 2005). As we noted above, human rights based approaches are endorsed precisely because they promise to facilitate these goals. Lack of reporting on the ethical dimensions of research in this area hinders international scrutiny and the growth of ethics knowledge across the global scientific community. For detailed information concerning the ethical dimensions of particular studies, interested parties currently have no recourse but to contact the investigator personally. This approach seems extraordinarily inefficient and ineffective. Furthermore, by failing to report on the ethical dimensions of their work, the care and concern scientists bring to these issues is hidden from view. The consequence of this opacity is the impression that scientists, as well as the editors of journals, are inattentive to and unconcerned with these issues.

For these reasons, we believe the lack of reporting on ethics methods runs counter to the human rights approach in general, and the rationale of the Protocol in particular. We refer to the rationale of the Protocol because commitments to transparency and openness to international scrutiny are not actually articulated in the Articles of the Protocol. They are found, instead, in the preamble, and in the rhetoric surrounding the human rights approach more generally. In order to make these commitments explicit, we now propose two novel norms: *ethical transparency,* and *ethical reproducibility*. These norms are designed to foster transparency and open scrutiny across labs, disciplines, and nations concerning both the ethics hotspots arising in a particular research domain, and the measures taken to deal with them.

Ethical transparency mandates transparent reporting concerning the ethics methods, i.e., design elements related to ethics concerns undertaken in a study. *Ethical reproducibility*, by contrast, mandates critical engagement with, and learning from, the ethics practices of other investigators. The primary goals of both norms are the growth of ethics knowledge and the improvement of ethics practices that foster respect for the human rights of participants in biomedical research. Secondary goals include accountability, credibility, and enforcement. In sum, the norms of ethical transparency and ethical reproducibility render explicit commitments at the heart of the human rights approach to biomedical research: transparency, consistency, accountability, credibility, and international cooperation.

7. Reporting guidelines

In closing, we now offer a set of reporting guidelines designed to operationalize the norms of ethical transparency and ethical reproducibility in the context of imaging research involving FESTNIs. Though we will not make this case here, we believe that parallel reporting guidelines should be incorporated into existing reporting guidelines in other areas of research involving human subjects.

1. Documentation of risk and burden minimization strategies, including the measures taken to deal with specific types and levels of symptoms, assurance of individualized, task-specific assessment, and details concerning debriefing strategies.
2. Documentation of the methodological steps taken to ensure scientific validity including, in particular, the measures taken to mitigate the confounding effects of symptom variation both across and within patient participants.
3 Documentation of the safety measures taken in the research, including safeguards surrounding possible delays, reports on the maximum acceptable delay that treatment may be postponed, and how delay is connected to the level and nature of symptoms of the participant.
4 We acknowledge that researchers may see these requirements as yet more red tape among processes already viewed as burdensome (Illes, Tairyan, Federico, Tabet, & Glover, 2010). But this is not our intention. Indeed, one of the chief advantages of the approach endorsed here is that it fosters the internalization of ethical and legal norms by imagers. By building these elements into standard reporting practice, consideration of ethical and legal concerns becomes part and parcel of good scientific reporting. And good reporting is quite literally the *lingua franca* of science.

8. Conclusion

We conclude that the unique partnership between imaging researchers and FESTNIs would be greatly enhanced if imagers explicitly undertook a commitment to the norms of ethical transparency and ethical reproducibility. In practice, this means imagers should explicitly report the steps they took to minimize the ethical and legal concerns posed by their research. By so doing they can facilitate the ethical assessment of their work by peers and the dissemination of best ethics practices within the broader imaging community. Overall, commitment to these norms, and to the reporting guidelines provided, will help to assure the human rights compatibility of imaging research involving FESTNIs.

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References

Agarwal, N., Port, J. D., Bazzocchi, M., & Renshaw, P. F. (2010). Update on the use of MR for assessment and diagnosis of psychiatric diseases. *Radiology*, *255*(1), 23–41.
Ashcroft, R. E. (2010). Could human rights supersede bioethics? *Human Rights Law Review*, *10*(4), 639–660.
Batel, P. (2000). Addiction and schizophrenia. *European Psychiatry*, *15*(2), 115–122.

Brown, G. G., & Eyler, L. T. (2006). Methodological and conceptual issues in functional magnetic resonance imaging: Applications to schizophrenia research. *Annual Review of Clinical Psychology*, *2*, 51–81.
Buchsbaum, M. S. (1990). The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophrenia Bulletin*, *16*, 379–389.
Canadian Institute for Health Information (CIHI) (2007). *Medical imaging in Canada.* Ottawa: CIHI (2007/8).
Carpenter, W. T., & Conley, R. R. (1999). Sense and nonsense: An essay on schizophrenia research ethics. *Schizophrenia Research*, *35*, 219–225.
Carpenter, W. T., Gold, J. M., Lahti, A. C., Queern, C. A., Conley, R. R., Bartko, J. J., et al. (2000). Decisional capacity for informed consent in schizophrenia research. *Archives of General Psychiatry*, *57*, 533–538.
Carter, C. S., Heckers, S., Nichols, T., Spine, D. S., & Strother, S. (2008). Optimizing the design and analysis of clinical functional magnetic resonance imaging research studies. *Biological Psychiatry*, *64*, 842–849.
Council of Europe (Treaty Office) (2011). CETS No. :195'. http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=195&CM=8&DF=21/01/2012&CL=ENG (accessed November 3, 2011)
Davis, C. E., Jeste, D. V., & Eyler, L. T. (2005). Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophrenia Research*, *78*, 45–60.
Faunce, T. (2005). Will international human rights subsume medical ethics? Intersections in the UNESCO Universal Bioethics Declaration. *Journal of Medical Ethics*, *31*, 173–178.
Franck, N., O'Leary, D. S., Flaum, M., Hichwa, R. D., & Andreasen, N. C. (2002). Cerebral blood flow changes associated with Schneiderian first-rank symptoms in schizophrenia. *Journal of Neuropsychiatry and Clinical Neuroscience*, *14*, 277–282.
Frangou, S. (2000). How to manage the first episode of schizophrenia. *British Medical Journal*, *327*(7260), 522–523.
Fusar-Poli, P., Allen, P., & McGuire, P. (2008). Neuroimaging studies of the early stages of psychosis: A critical review. *European Psychiatry*, *23*, 237–244.
Garnett, A., Whiteley, L., Piwowar, H., et al. (2011). Neuroethics and fMRI: Mapping a fledgling relationship. *PLoS One*, *6*(4), 1–7.
Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., et al. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *American Journal of Psychiatry*, *159*, 1992–1999.
Gur, R. E., Petty, R. G., Turetsky, B. I., & Gur, R. C. (1996). Schizophrenia throughout life: Sex differences in severity and profile of symptoms. *Schizophrenia Research*, *21*(1), 1–12.
Harrison, P. J. (1999). The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain*, *122*, 593–624.
Harrison, P. J., & Roberts, G. W. (2000). *The neuropathology of schizophrenia: Progress and interpretation.* Oxford, New York: Oxford University Press.
Illes, J., Tairyan, K., Federico, C. A., Tabet, A., & Glover, G. H. (2010). Reducing barriers to ethics in neuroscience. *Frontiers in Human Neuroscience*, *4*(167), 1–5.
Jeste, D. V., Depp, C. A., & Palmer, B. W. (2006). Magnitude of impairment in decisional capacity in people with schizophrenia compared to normal subjects: An overview. *Schizophrenia Bulletin*, *32*(1), 121–128.
Kaup, A. R., Dunn, L. B., Saks, E. R., Jeste, D. V., & Palmer, B. W. (2011). Decisional capacity and consent for schizophrenia research. *IRB: Ethics & Human Research*, *33*(4), 1–9.
Kay, S. R., Fiszbein, A., & Opfer, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.
Kay, S. R., Fiszbein, A., & Opler, L. A. (2004). *Positive and Negative Symptoms Scale (PANSS).* Switzerland: Psychiatric University Hospital Zurich.
Kim, S., Ubel, P., & De Vries, R. (2009). Pruning the regulatory tree. *Nature*, *457*(7229), 534–535.
Kindermann, S. S., Karimi, A., Symonds, L., Brown, G. G., & Jeste, D. V. (1997). Review of functional magnetic resonance imaging in schizophrenia. *Schizophrenia Research*, *27*, 143–156.
Landeen, J. L., Seeman, M. V., Goering, P., & Streiner, D. (2007). Schizophrenia: Effect of perceived stigma on two dimensions of recovery. *Clinical Schizophrenia & Related Psychoses*, *1*(1), 64–68.
Lennox, B. R. (2009). The clinical experience and potential of brain imaging in patients with mental illness. *Frontiers in Human Neuroscience*, *3*, 46.
Leung, M., Cheung, C., Yu, K., Yip, B., Sham, P., Li, Q., et al. (2010). Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. *Schizophrenia Bulletin*, *37*(1), 199–211.
Linden, D. E. J., & Fallgatter, A. J. (2009). Neuroimaging in psychiatry: From bench to bedside. *Frontiers in Human Neuroscience*, *3*, 49.
Marshall, J., Martin, T., Downie, J., & Malisza, K. (2007). A comprehensive analysis of MRI research risks. *Canadian Journal of Neurological Sciences*, *34*, 1–7.
Nakamura, M., McCarley, R. W., Kubicki, M., Niznikiewicz, M. A., Voglmaier, M. M., Seidman, L. J., et al. (2005). Fronto-temporal disconnectivity in schizotypal personality disorder: A diffusion tensor imaging study. *Biological Psychiatry*, *58*(6), 468–478.
Organization for economic cooperation and development (OECD) (2011). OECD Health Data 2011—Frequently Requested Data. http://www.oecd.org/document/16/0,3343,en_2649_34631_2085200_1_1_1_1,00.html (accessed 3 November 2011)
Pantelis, C., Yucel, M., Wood, S. J., Velakoulis, D., Sun, D., Berger, G., et al. (2005). Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophrenia Bulletin*, *31*(3), 672–696.
Pinxten, W., Nys, H., & Dierickx, K. (2009). Ethical and regulatory issues in pediatric research supporting the non-clinical application of fMR imaging. *The American Journal of Bioethics*, *9*(1), 21–23.
Plomer, A. (2005). *The law and ethics of medical research: International bioethics and human rights.* London, Sydney, Portland: Cavendish Publishing.
Poldrack, A. R., Fletcher, P. C., Henson, R. N., Worsley, K. J., Brett, M., & Nichols, T. E. (2007). Guidelines for reporting an fMRI study. *NeuroImage*, *40*, 409–414.
Prévost, M., Rodier, M., Lionnet, C., Brodeur, M., King, S., & Debruille, J. B. (2011). Paranoid induction reduces N400s of healthy subjects with delusional-like ideation. *Psychophysiology*, *48*(7), 937–949.
Racine, E., & Illes, J. (2007). Emerging ethical challenges in neuroimaging research: Review, recommendations and research agenda. *Journal of Empirical Research on Human Research Ethics*, *2*(1), 1–10.
Racine, E., Northoff, G., Menon, R. S., Kimmelman, J., & Illes, J. (2011). A Canadian perspective on ethics review and neuroimaging: Tensions and solutions. *Canadian Journal of Neurological Sciences*, *38*(4), 1–9.
Reske, M. (2008). Differential brain activation during facial emotion discrimination in first-episode schizophrenia. *Journal of Psychiatric Research*, *43*(6), 592–599.
Rose, S. (2011). *Risks (Chapter 3.2). Brain waves module 1: Neuroscience, society and policy.* The Royal Society 69–76.
Schimanzi, S., & Lieberman, J. A. (1995). Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *The American Journal of Psychiatry*, *125*, 698–703.
Schleim, S., & Roiser, J. P. (2009). FMRI in translation: The challenges facing real-world applications. *Frontiers in Human Neuroscience*, *3*, 63.
Shapiro, R. (1993). Regional neuropathology in schizophrenia: Where are we? Where are we going? *Schizophrenia Research*, *10*(3), 187–239.
Snitz, B. E., MacDonald, A., Cohen, J. D., Cho, R. Y., Becker, T., & Carter, C. S. (2005). Lateral and medial hypofrontality in first-episode schizophrenia: Functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. *American Journal of Psychiatry*, *162*, 2322–2329.
Surguladze, S. A., Calvert, G. A., Brammer, M. J., Campbell, R., Bullmore, E. T., Giampietro, V., et al. (2001). Audio-visual speech perception in schizophrenia: An fMRI study. *Psychiatry Research*, *106*(1), 1–14.