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Neuroethical implications of focused ultrasound for neuropsychiatric illness

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ABSTRACT

Background: MR-guided focused ultrasound is a promising intervention for treatment-resistant mental illness, and merits contextualized ethical exploration in relation to more extensive ethical literature regarding other psychosurgical and neuromodulation treatment options for this patient population. To our knowledge, this topic has not yet been explored in the published literature.
Objective: The purpose of this paper is to review and discuss in detail the neuroethical implications of MR-guided focused ultrasound for neuropsychiatric illness as an emerging treatment modality.
Methods: Due to the lack of published literature on the topic, the approach involved a detailed survey and review of technical and medical literature relevant to focused ultrasound and established ethical issues related to alternative treatment options for patients with treatment-resistant, severe and persistent mental illness. The manuscript is structured according to thematic and topical findings.
Results: This technology has potential benefits for patients suffering with severe mental illness, compared with established alternatives. The balance of technical, neuroscientific and clinical considerations should inform ethical deliberations. The nascent literature base, nuances in legal classification and permissibility depending upon jurisdiction, influences of past ethical issues associated with alternative treatments, tone and framing in media articles, and complexity of clinical trials all influence ethical assessment and evaluations of multiple stakeholders. Recommendations for future research are provided based on these factors.
Conclusion: Salient ethical inquiry should be further explored by researchers, clinicians, and ethicists in a nuanced manner methodologically, one which is informed by past and present ethical issues related to alternative treatment options, broader psychiatric treatment frameworks, pragmatic implementation challenges, intercultural considerations, and patients' ethical concerns.

1. Introduction

Emerging neurotechnologies for neuropsychiatric illness are transforming care for common and devastating disorders that have lacked mechanism-based treatments. Focused ultrasound for the brain is a promising, emerging technology that combines the benefits of non-invasiveness and deep brain spatial precision. Low intensity focused ultrasound (LIFU) neuromodulation, high intensity focused ultrasound (HIFU) psychosurgical ablation, direct CNS drug delivery, gene therapy [1] and editing [1UG3NS115598-01], and optogenetics delivery via blood-brain-barrier disruption using microbubbles [2] (FUS BBB-opening) are promising preclinical tools and treatments for neuropsychiatric illness which traverse an extensive and complex ethical landscape. To our knowledge, manuscripts on the ethics of focused ultrasound for neuropsychiatric illness have not yet been published in the literature.

However, entities within the FUS community are exploring neuroethics. The Focused Ultrasound Foundation (FUF) sponsored a panel discussion on neuroethics of emerging neurotechnologies in 2021 [3]. The associated white paper is not explicitly centered upon focused ultrasound, but merits mention as the FUF is a significant player in the FUS neuropsychiatric landscape. The FUF sponsored one of the largest HIFU trials for OCD, designated Yonsei University (from which the first published HIFU study and subsequent longest follow-up was published) as a center of excellence (in addition to the home institution of three of this manuscript's authors), and sponsored one of the FUS-BBB pilot studies

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for Alzheimer's [4]. Common themes discussed in the white paper and this manuscript are complexities of psychosurgical law in different jurisdictions, including indigenous and other marginalized communities in collaborative research design, accessibility, cost, and challenges of establishing registries.

Importantly, ethical concerns regarding broader categorical treatment applications of FUS (e.g., ablative psychosurgery, neuromodulation, gene therapies) have been discussed extensively elsewhere [5–9]. While new technologies do not necessarily correspond to entirely new neuroethical issues, comparatively situating focused ultrasound relative to other treatments available to similar patient populations is ethically valuable for stakeholders, particularly in clinical decision-making context. These groups include (but are not limited to) patients and their social networks, researchers (scientists, clinicians, ethicists and others), payers, clinicians, professionals across many disciplines, governments, regulatory bodies, and the public.

We will provide a brief overview of clinical/technical literature and then perform an ethico-legal analysis including clinical risk/benefit and applicable themes as articulated in a 2022 review of multiple well-established neuroethics frameworks [10]. Please see this manuscript, particularly tables 1–3, for reference. Discourse is aimed primarily at an audience of clinicians, researchers, and ethicists. Analysis will be organized first by treatment modality (HIFU, LIFU, FUS BBB-opening), with an emphasis on HIFU given its relatively more established (albeit still nascent) application in psychiatric patients. The discussion will then transition to examining issues of diversity and inclusion in larger treatment context.

Our intent is to provide an anticipatory intellectual foundation for collaborative dialogue and research amongst stakeholders with diverse interests, one which is responsive to wider critiques regarding implementation and inclusivity in the neuroethics literature. For clinicians and neuroscience researchers who do not specialize in neuroethics or FUS, meaningful involvement and engaging the moral imagination is possible even in the context of time, accessibility, and funding constraints. For some clinician-researchers, this may mostly involve introducing oneself to the field (see Refs. [11–16] as examples). For others, this may involve smaller scale approaches within or outside of research context (with examples provided in this manuscript), including brief exploratory conversations with patients regarding some of the issues discussed herein.

Finally, as the insufficient integration of ethical and scientific inquiry is an active area of concern, leveraging specific skill sets of experts in diverse fields is discussed. Examples in the setting of transdisciplinary research are explored to address this (including work with data scientists using publicly available online data). Neuroscientists and clinicians can contribute by providing brief technical/clinical overviews related to specific studies and developments, while ethicists can comment on their specific areas of expertise. Small contributions related to their respective areas of expertise is far less time intensive, can improve efficiency in terms of keeping pace with frontiers of the other's knowledge, and does not necessarily depend on large trials (or any funding for smaller commentaries). If leveraged collectively, these approaches can improve the integrative architecture of the larger neuroethics-neuroscience academic enterprise. To improve accessibility and approachability, ethicists can frame the field as a point of engagement within these specialists' methodological techniques, expertise, and interests [17].

2. Overview of FUS applications and clinical literature

Intracranial therapeutic applications of focused ultrasound for neuropsychiatric illness (OCD, as a lobotomy alternative) began in the 1950s [18] and have accelerated recently. In vitro studies combining a multi-element phased-array system to focus the ultrasound combined with MRI allowed for MR-guided FUS [19], and pretreatment CT scans were utilized for phase-correction methods to minimize skull attenuation, improve spatial resolution, and increase energy delivery [20]. MR-guided FUS has numerous technical advantages including ability to target deep brain structures [21] non-invasively and without general anesthesia [22]. Real-time anatomical and thermometric monitoring facilitate safe, submillimeter spatial resolution for ablative lesioning and intraprocedural assessment of adverse effects and improvement in motor symptoms [22]. Multifocal capability may allow for investigation of distributed neural network disturbances characterized by psychiatric pathophysiology [23]. For a clinically contextualized and detailed overview of the biophysical effects of focused ultrasound, see Darrow (2019) [23].

These factors have contributed to the use of FUS in treatment of movement disorders such as treatment-refractory essential tremor and tremor-predominant Parkinson's disease (both of which are FDA-approved [24]). Preliminary evidence is encouraging in the small number of published trials for chronic pain, OCD, and MDD [1]. While these factors may be advantageous, limitations of FUS include contraindication to high field MRI [25], inaccessibility of more peripheral anatomical sites [21], poor efficiency with low skull-density ratios which increases risk of off-target heating [22], lack of standardized treatment parameters [21], on and off-target sonication adverse effects [26], and a nascent evidence base. HIFU to treat primary neuropsychiatric disorders was first published in 2015 as a small case series for treatment-resistant OCD [22,27]. Results of two larger studies since this time are encouraging in terms of percentage of responding participants for OCD (4/6 patients in OCD and 2/6 in MDD [28], and 7/11 in OCD [29]). There have been minimal to no adverse effects as well as rapid resolution of symptoms (within days to weeks [30]) and persistence of such improvements at 12 months [31]. However, the total number of cases in the published literature is very small and long-term follow-up data is even more limited. In the largest trial 16 patients were treated but 4 patients were unable to receive treatment due to limitations of inefficient sonication due to skull-based factors [32].

The neuromodulatory effects of LIFU are less well understood than the thermoablative mechanism of HIFU. Multiple theories have been proposed for mechanism of action, many of which are nonthermal mechanical [23]. In the clinical domain, a 2022 review of LIFU included 35 studies, although very few in primary psychiatric patient populations [33]. Three studies related to mood (two in healthy participants), with the largest cited having a sample size of 24 with improved worry and positive mood scores after five treatment sessions in mild to moderately depressed patients [34]. LIFU has also been used in multiple studies with Alzheimer's patients, mostly without adverse effects (occasionally transient) [33], and with 63% demonstrating cognitive improvement at 8 weeks in one study [35]. Interest in LIFU research is rapidly increasing [33], with multiple NIH-funded clinical trials ongoing for a variety of psychiatric disorders including PTSD, anxiety disorders, bipolar disorder, depressive disorders, OUD, OCD, schizophrenia, and ADHD [NCT04405791, NCT04775875, NCT04197921, NCT04497363, NCT04250441, NCT04620460, NCT03782194, NCT05147142, NCT05259306, NCT05228964]. Transcranial pulsed ultrasound (transcranial pulsed stimulation, TPS) is likewise being used in Europe with preliminary evidence for improving cognitive and affective (depressive) symptoms in Alzheimer's disease [36].

Regarding comparative evidence between FUS ablation/neuromodulation and treatment alternatives, Kinfe et al. summarize the issue well: "The insufficient number of in-human studies comparing the impact of MRgFUS (HIFU/LIFU) for the treatment of psychiatric disorders versus other brain stimulation/neuromodulation currently limits the comparative interpretation of the safety, ease of tolerability, and efficacy of MRgFUS versus noninvasive (GKRS, TMS, tDCS, tACS, ECT) and invasive brain modulation (RFA … DBS, MCS)" [21]. One would be comparing review and meta-analysis level evidence [37,38] with large effect size and percentage of responding OCD participants for ablation and DBS (56 and 57%, comparatively, in a recent 2021 meta-analysis including 38 studies [37]), to that of a much fewer number of small sample size HIFU and LIFU trials as described above. Gamma knife could

be a particularly relevant future comparator for HIFU given its non-invasiveness and ablative modality; one relevant disadvantage of the former being rare, late-onset radionecrotic cysts (albeit increasingly less common with radiation dosage changes) [39]. To the authors' knowledge, there are currently no published comparative efficacy trials between HIFU/LIFU and other treatment alternatives in these populations, and LIFU studies thus far have mostly involved patients with lower illness severity to those involved in DBS, HIFU, and other ablative procedures.

FUS BBB-opening has been shown to focally and reversibly open the blood-brain-barrier with minimal adverse events in preliminary studies with Alzheimer's patients (microhemorrhages shown to resolve within 24 h in two patients) [40]. A more extensive review of preclinical and clinical FUS BBB-opening for drug delivery noted mostly transient effects in patients, but significant limitations in type of safety assessment amongst studies (predominantly structural at gross and microscopic levels) and lack of sham or control groups [41]. Preclinical studies have also shown evidence for reduction of AB plaques through facilitating entry of endogenous antibodies into the brain [42]. Acoustically-targeted chemogenetics and optogenetics have been used with FUS preclinically for neuromodulation with combined "spatial, temporal, and cell-type specificity" [43], and work is ongoing using CRISPR to study neurodegenerative disease in mouse models [1UG3NS115598-01].

3. Legal considerations in FUS treatment applications

From a legal perspective in the United States, focused ultrasound devices with neurological applications in the brain are class III, meaning that use of the device for this indication must occur in clinical trial context [44]. As of 2021, the only country with federal approval for FUS treatment in primary psychiatric illness is South Korea [24], and transcranial pulsed ultrasound (transcranial pulse stimulation, TPS) for Alzheimer's disease has clinical approval in the EU [36] and research approval in the United States (FDA IDE approval). In addition to the complexity and likelihood of multiple intersecting regulatory guidelines as would be the case with a CNS device delivering gene therapy or CRISPR [10,45,46], it is not clear in which jurisdictions HIFU would be legally classified as psychosurgery. This is due to significant variation in overall permissibility, quantity and clarity of psychosurgery definitions internationally and across state lines in the US [47,48]. Definitions are often vague or circular and some explicitly include destruction of tissue (which would apply to HIFU) while others do not [48].

Psychosurgical legal classification impacts not only regulation but accessibility to HIFU, given that psychosurgery is prohibited in certain jurisdictions [47]. Given evidence for the public's more negative comments on media articles towards ablation vs. deep brain stimulation (DBS) in light of psychosurgery's ethically controversial history [49], patient attitudes, perception of risk relative to treatment alternatives, and medical decision-making may be influenced by this classification. On the other hand, the non-invasiveness of the procedure may be attractive and distract from focus on ablation and irreversible lesioning. The beneficial contrast to DBS, where neurosurgery is performed, and an electrode and battery remain in place, should be noted. One Canadian treatment center observed increases in self-referrals for FUS for movement disorders in the setting of increasing numbers of FUS media articles [50]. Most of these patients had not heard of and perceived DBS as more experimental, despite its equally if not more well-established evidence base [50].

In the case of psychosurgery, however, positive bias and sparse discussion of ethical issues in DBS media articles rather than efficacy differences may play an additional role in differential perception of modern ablative procedures [51]. For FUS and other neurotechnologies, proactive efforts by ethicists at studying balance in article tone, facilitating journalists' access to scientific articles, and fostering dialogue on ethical concerns between the media, scientists, and the public [52] is warranted. Industry-related COIs can also impact framing of FUS research results, patient trust of treatment, and pose legal ramifications.

Collaboration with computational sociologists and information scientists could facilitate data-driven action, as these disciplines have modeled the spread of hype and disinformation in large data samples [53] as well as sentiment analysis of public ethical concerns on emerging medical technology using online commentary [54]. Such studies use publicly available online data and can be done entirely outside of the context of clinical trials. These transdisciplinary approaches, particularly using various big data methodologies, are increasingly explored in convergence science funding structures [55], inquiry for global mental health challenges [56], and in bioethics. A very recent review of bioethical studies (October 2022) included work emerging within the past two years specifically utilizing such methods (e.g., NLP in digital humanities, online sentiment analysis, and others) [57].

4. Neuroethical considerations for HIFU in context: patient population considerations and psychosurgical treatment alternatives

For HIFU, one could reference many elements of soft law guidelines for psychosurgery such as those written by Muller (which are inclusive of HIFU) [5] and the consensus statement by Nuttin et al. on stereotactic neurosurgery for psychiatric disorders [58]. While not an exhaustive summary, these guidelines emphasize the necessity of multidisciplinary treatment teams (including ethicists), establishment of treatment refractoriness (including all evidence-based, less intrusive interventions, such as other neuromodulation therapies (TMS, ECT)), and improvement in comparative evidence across modalities as previously discussed. Important differences exist in extent and kind of post-procedural support between these procedures, and there is even interinstitutional variability in the very same ablative procedure which confound comparison in comparative effectiveness trials. Registries and open science could theoretically improve evidence-base quality and are often encouraged, but these issues and the ability to perform some psychiatric neurosurgery outside of trial context (i.e., DBS humanitarian device exemption for OCD) complicates the process of aggregating and interpreting such data. Data interpretation without contextual annotation can be quite difficult and academic climates often incentivize against such sharing [59], although consortia studies with larger N's and data sharing are becoming more common. These factors, combined with high cost and time-intensive requirements [59], present implementation barriers which would preclude participation for some institutions. Preliminary efforts to address these challenges could include specification of a limited dataset across a small number of structurally compatible departments with assistance from implementation scientists. They can also include advanced analytics that can address inter-site and inter-patient variability issues.

Additionally, there is significant phenotypic heterogeneity amongst OCD patients and multiple different interventional sites in DBS and ablation [27]. In addition to its titratability and the possibility for surgical lead revision in the setting of complication, adverse effects or decreased efficacy [60], DBS has utilized multiple strategies and modalities for personalization of treatment. These include continuous analysis of pathological biomarkers with closed loop models (for which varying data privacy, autonomy, and additional ethical concerns have been discussed [61]) and advances in DBS electrode mapping integrated with structural and functional brain connectomics for individual response prediction [62]. Intraoperative behavioral verification [63] and enhanced understanding of effects of varying patterned stimulation [64] are additional advancements. Although in much earlier stages of development, some precision methods have been applied to focused ultrasound including target optimization for HIFU in OCD [65] as well as preclinical closed loop [66], neuromodulatory multifocal models [67], and advances in array systems for improved anatomical customization [23]. LIFU is less well understood mechanistically and has a vast and

complex parameter space where treatment protocols are in relatively early stages of exploration.

The presence of more well-established precision approaches in DBS (as an example) is particularly important to consider from an ethical point of view, given prolonged histories of suffering for many treatment-resistant patients with SPMI. Opportunities for personalized treatment, limitations in assessing FUS' efficacy and safety relative to other treatments, varying opinion on treatment efficacy, limited availability of FUS for neuropsychiatric illness, and specific neurosurgeon expertise could lead a surgeon (or any clinician) to frame and weigh certain alternatives differently. In addition to presenting all available and appropriate psychosurgical alternatives, maintaining vigilance regarding the risk of therapeutic misconception [68] when presenting treatments conducted in research (such as FUS) vs. clinical context (DBS in some cases) is important. During the informed consent process for FUS, the six categories of risk proposed by Hendriks et al. [69] in neural device trials should be discussed: surgical, hardware-related, stimulation-related, incremental risks, emerging/unanticipated risk, privacy/security, and financial risk. However, further research into the "on the ground" realities of informed consent procedures in psychosurgery should be conducted by ethicists to better inform guideline implementation. Time constraints, emotional state, trust in the patient-physician relationship and factors related to culture, history, and power in the medical system more broadly, and treatment search fatigue [70] can impact patient perception of treatment alternatives.

Beyond safety factors and other side effects related to comparison of treatment alternatives, concerns have been expressed regarding both DBS [71] and modern ablative procedures and associated personality changes in some patients [5,72]. As an ablative procedure used to treat psychiatric disorders, the small body of literature associated with HIFU has not yet amassed sufficient evidence to demonstrate lack of similar long-term effects. In DBS, certain authors have emphasized the importance of such issues while others have argued for empirical exaggeration or inflation of specificity, prevalence, salience, and mistaken attribution of such effects to stimulation itself [71].

Etiologic misattribution of PIAAAS directly to stimulation could certainly skew perceptions of prevalence of such phenomena in the literature [71]. Residual or altered psychopathology may influence the way in which the patient perceives the procedure and its consequences [73]. Psychosocial adaptation to the rapid changes in symptoms demonstrated in some FUS studies could pose a disconcerting 'burden of normality' (as discussed in the DBS literature) for patients [74], while others may view significant changes in mood and behavior positively. Indeed, positive direction of identity change may increase likelihood that an individual is perceived as 'the same' person [75], which could merit consideration in FUS studies.

In considering assessment and study of issues in focused ultrasound related to psychopathology, personality, identity, authenticity, autonomy, and self-related issues (PIAAAS) [71], maintaining awareness of the complexities, limitations and evolution of neuroethical debates regarding these themes in psychosurgery is critical. Given the complexity, ambiguity, and differences in meaning of these constructs across cultures (and even between individuals), definition and measurement is very challenging [71]. In FUS, studies of these phenomenon by multidisciplinary teams from diverse perspectives (e.g., patient, caregivers, physicians, ethicists), may provide contextually nuanced and empirically rigorous investigative approaches [76]. If ethicist-researchers are not available, clinicians could start by administering personality psychometrics (see Kubu et al. [76] for examples) at baseline and following treatment modification within or outside of FUS research context. Notably, preliminary evidence from online comment analysis has indicated less concerns regarding identity and autonomy by patients in comparison to providers [77], and perceived changes in selfhood and identity can also occur in the setting of other treatment modalities [78].

Importantly, in many cases the changes following DBS may not be enduring and can be addressed by titrating stimulation parameters or modifying approaches to other contributing dynamics [76]. This could likely be the case with LIFU as well given its reversibility. If personality changes were attributed to the ablative aspects of HIFU, they may indeed be more enduring and difficult to modify. This is one of many reasons why the imbalance between extensive proliferation of ethics papers on DBS and relative paucity on modern psychosurgical ablation in recent years is concerning [5]. One must consider as well whether the common modality and benign perception associated with noninvasive ultrasound will conflate perception of both risk-related and ethical differences between LIFU and HIFU amongst patients and the public.

As challenging as it may be to ethically compare FUS to these modalities, there are many difficulties inherent to the operational pragmatics of DBS which simply do not apply to HIFU. In comparison to DBS, HIFU does not have medical risks associated with invasive surgery (including bleeding, infection and neural disruption, treatment changes), lead migration and disconnection, battery depletion, frequent need for adjustment of programming parameters and associated psychological factors, and neuropsychiatric and physical side effects during this process [79]. There are no post-trial responsibilities in terms of (potentially perpetual) device upkeep and associated costs, which has been debated extensively in the neuroethics literature [8,69], issues of forced explanation, concerns regarding poor access to DBS programming [79], or ethical complexities which have arisen in the setting of fluctuating decision-making capacity in on vs. off stimulation settings [80]. As there is no device implanted, concerns regarding decision-making autonomy (regardless of one's position on the nature or extent of such issues) could be less likely. While all of the above is shared with gamma knife (and partially with radiofrequency ablation), FUS allows better control of lesion size and location during the procedure and does not have radiation-related side effects [27], but is much less well-established.

For all of the above reasons (and more), selecting deep brain stimulation due to the advantages of reversibility and/or evidence base over HIFU or contemporary ablation is not necessarily a straightforward decision from a physician, patient or an ethicist's perspective, and should (as with any treatment) be customized to the needs of the individual patient. Valuation of invasiveness or non-invasiveness for any given patient may likewise be less simple than anticipated, as there is evidence for ascribed meaning to other categorical interpretations of the term (emotional, physical, lifestyle) and a variety of factors which mediate its salience in psychiatric treatment [81,82]. Issues of cost and access are often significant, and a 2019 cost-effectiveness threshold analysis on HIFU vs radiofrequency capsulotomy favored HIFU in terms of a range of costs and possible complication rates [83]. While much more data would be required, one could argue regardless that a one-time ablative treatment more effectively addresses this (vs maintenance requirements in DBS). However, this does not address equity issues associated with racial, socioeconomic, and rural disparities in access to emerging neurotechnology [84,85], which are often compounded by preapproval and later denial of coverage (particularly of off-label DBS) by payers [86].

5. Neuroethical considerations for LIFU in context: patient population considerations and treatment alternatives

While neuroethical discussion of HIFU is warranted given its presence in the literature, investigation in LIFU is growing rapidly. If LIFU does develop an established evidence base for efficacy in treatment-resistant psychiatric disease, its non-invasiveness and precision relative to other neuromodulation therapies (DBS and TMS/ECT, respectively) and reversibility relative to other FUS applications could appeal to a broader range of groups. While LIFU could raise dual use concerns for similar reasons (such as by the public or military for enhancement), we will defer extensive speculation about this. The relevance of many of these issues is dependent on changes in portability and design,

establishment of safety, efficacy for enhancement, social acceptance, and widespread prevalence and attrition rate [87] of use [88]. All of these factors are either entirely inapplicable or unknown at this time for LIFU.

The potential benefits of effective treatment if supported by an adequate evidence base are clearer for patients with severe, refractory psychiatric illness that causes enormous disability and suffering. While predicated on establishing a much stronger evidence base, this merits brief anticipatory discussion. A noninvasive and titratable neuromodulation modality with high spatial precision, lower cost, and a favorable safety profile thus far (mostly transient, mild/moderate adverse effects noted in 3.4% of patients in a 2022 review [33]) could transform the clinical decision-making pathway between psychopharmacologic and other neuromodulatory treatments (ie. TMS, ECT) and psychiatric neurosurgery. This could potentially influence assessment of treatment alternatives and differential risk profiles between FUS therapies, such as FUS-BBB opening vs LIFU in Alzheimer's disease or LIFU vs HIFU in treatment-refractory psychiatric illness.

These very qualities may be appealing to patients particularly vulnerable on the basis of desperation [89] and treatment search fatigue [70], as well as medical complexity, advanced age, younger age (pediatric) or other factors impacting DBS candidacy [25]. Clinicians have expressed concerns regarding the uncertainty of the impact of DBS for OCD on the brain and personality in developing children, as well as obtaining adequate patient assent, and the challenge of determining treatment-refractoriness [90], all of which would merit analogous ethical study in focused ultrasound if pediatric clinical trials were to occur. Some have argued for the ethical imperative of DBS over ablation procedures in anorexia nervosa due to advantages of reversibility in a disorder in which control is central [91], while others have noted the importance of respecting patients' autonomy to choose irreversible lesioning [92]. Ethical considerations with differential salience in certain disorders would be important to consider in future empirical FUS ethics research if conducted.

As in any field, clinicians and researchers with significant career investment in established vs emerging neurotechnologies may struggle to view comparative evidence objectively even in the absence of overt conflict of interest. The Focused Ultrasound Foundation, which is explicitly dedicated to "overcoming technological, economic, regulatory, and reimbursement obstacles," funds FUS neuropsychiatric research, has an Advocacy and Government affairs program [93], and provides consultation to device manufacturers regarding regulation and reimbursement, intellectual property, and financial capital. DBS, modern ablation, and many emerging neurotechnology communities would likewise leverage resources for similar aims. The complexity of these interwoven interests poses challenges for navigating COIs amongst these actors. Inherent tension exists between the ethical imperative of improving access through decreasing regulatory barriers and using regulation to adequately address safety concerns, both of which can be coopted as tools to optimize profits and constrain the landscape of "competing" treatments. Even if unconscious, optimism, familiarity, incentive, probability insensitivity and other cognitive biases can all impact clinician-researchers' evaluation of psychiatric clinical trial data [94].

LIFU application to patients with relatively less severe mental illness and healthy participants would be important to consider as well (25/35 studies in the 2022 review referenced above [33] were in healthy populations). Altruistic motivations are commonly provided in healthy patients as reasons for participations in research [72]. Briefly exploring this in individual conversation with patients could enhance providers' understanding of participant motivations. If a participant expresses communitarian values and a commitment to altruism as a central driver to research participation, would it be sufficient to provide individually focused information accompanied by a brief statement regarding the scientific benefit of the research? Making neuroethical information regarding emerging technologies available to the public has been suggested more broadly [10]. Perhaps providing patients with the option of comparative ethical analysis of their treatment during informed consent would be more respectful of their specific values and autonomy as well. Among the many complications associated with both are who and what perspectives would be appropriate to privilege in such an analysis for any given patient. If the process of informed consent is likewise viewed as an on-the-ground opportunity for stakeholder engagement, ethicists' efforts to collect data from patients prospectively about their own ethical concerns regarding the delivery technology and treatment modality could strategically serve to give patients the voice they deserve in such discussions and characterize decision-making in these complex trials. Patients with cognitive impairment, severe depression, psychosis and/or lack of insight raise issues in any such considerations in terms of capacity to provide consent.

6. Future possibilities: neuroethical considerations for FUS BBB-opening in psychiatry

Both LIFU and HIFU have published studies and ongoing trials in psychiatric illness. While FUS BBB-opening for delivery of experimental therapeutics has been trialed in neurodegenerative disease, scientific and technical barriers remain to first-in-human trials in psychiatric patients. The likelihood of imminent application of gene editing therapies in primary psychiatric illness is complicated by the polygenic nature of such disorders, risks such as off-target effects, and immunogenicity of vectors among other issues [95]. However, maintaining awareness that the availability of non-invasive and temporary BBB opening may accelerate and increase the feasibility of delivering other experimental therapeutics to these patients is justified. In considering this FUS treatment application, it is important to not conflate ethical issues of the technology itself with the extensive neuroethical literature associated with the specific treatments it may deliver, which is beyond the scope of this paper. Certainly, issues associated with cellular, molecular, and other agents affecting the brain-mind have their own additional considerations. Despite the logic inherent in these arguments, whether IRBs, patients, and other stakeholders will maintain this cognitive separation in real-world decision-making and whether informed consent discussions will (or could in some cases) include all available treatment alternatives is another matter. Inclusion of decision scientists can help refine guidelines contextualized by evidence-based models for ethical decision-making and moral deliberation more broadly [96] to facilitate implementation.

Among ethics committees in particular, aversion to ambiguity uncertainty can bias attention and ethical recommendations more heavily towards novel treatments at the expense of more "mundane" but equally significant adverse effects such as surgically-related neurologic complications or infections [97]. In extremis, the combination of neuroscientific hype inflating potential therapeutic benefits with reactionary ethics hype invoking overly harm-centric responses [98] may lead to public mistrust in science [99,100]. Complex translational clinical trials combining multiple emerging neurotechnologies and neurotherapeutics such as FUS BBB-opening may be particularly vulnerable to hype and attentional ambiguity aversion bias, which can interfere with systematic, nonarbitrary risk/benefit analysis [97].

7. Issues of diversity, representation, and international inclusivity

As of 2021, there were no FUS clinical trials in South America, Africa, New Zealand, Russia, and multiple Asian countries [24]. Emerging neuromodulation treatments are often quite restricted in availability [84], being costly and dependent often on large, specialized interdisciplinary teams and driven initially by establishment of safety and efficacy in symptom reduction. This lack of diversity, in combination with primarily symptom-based outcomes measures, limited information on sociodemographic factors [31], and lack of details on informed consent

processes or inclusion of individuals without consent (although not uncommon in clinical trials) increases the risk of bias and unfair distribution of risks and benefits in research [16,101]. While access issues for marginalized group to neuromodulation and psychiatric neurosurgery cannot be ignored in publications and practice, the explicit inclusion of racial, ethnic, and ancestry categories is a space with some degree of consensus (e.g., regarding transparency with how and why certain categories are used), but significant residual conflict [102]. A 2022 review of 121 guidelines (predominantly American) noted as such, particularly with respect to differences in views on appropriate definitions of population categories and contexts for use [102]. The American predominance of high output neuroethics researchers [103] can impact research goals and questions, participant/data set selection, as well as information dissemination, assessment, and feedback [104]. Creating structure for integration of diverse neuroethicists and neuroscientists together is a means to address this [16], but gauging the level of familiarity and interest amongst the public in any location for FUS treatment is challenging at this time.

Community Based Participatory Research (CBPR) and collaborative learning/research initiatives with culture-specific expertise [105] (such as neuroethics research models in the Emory-Tibet Initiative and Te Kotahi Research institute) can shape research questions that are important to specific communities. Te Kotahi is an initiative with neuroethical expertise led by Maori academics which includes community members' voices from project design to completion. In preliminary conversations with Maori sound healers regarding LIFU, many found the technology appealing due to its common use of sound as a treatment modality, but concerning regarding power dynamics (who would have control over treatment) and potential impact on the self. Nuances regarding reporting of race or ancestry are certainly relevant for Maori populations, given that some individuals may be considered Maori by ancestry and others by certain tribal marital customs. While open science guided by interculturally-focused neuroethics guidelines [11] and international data governance frameworks are relevant for the optimization of data size, impact, and quality [106], such nuances would be difficult to adequately address in that setting. We also note that deliberative constraint in research rather than open science and rapid expansion of neurotechnology access may be more useful initially for certain populations. This is particularly significant with respect to cultivating trust through awareness of indigenous data governance frameworks [107] and conducting smaller scale mixed methods studies or forums to gauge specific community interest in FUS.

Combining the complex, multimodal datasets in FUS on a large scale poses difficulties for data usage from jurisdictions with different ethical frameworks and increases the risk of de-identification [16] and maligned access [104]. This is significant for any patient but perhaps particularly so in South Korea, given federal-level approval and high cultural value placed on privacy [108]. Likewise, stigma associated with individual mental health diagnosis and genetic data may be more likely to extend to family and wider community [11]. Raising awareness of "neurorights" frameworks to mental privacy, liberty, and integrity, creating defaults that require opt-in for sharing brain data, encryption from recording site to output device, and significant restrictions on commercial sharing of data [104] can all be applied to the FUS research and clinical community. Inclusion of global mental health, intercultural communication scholars and translators could add nuance to the highly valuable and often more culturally essentialist international neuroethics articles aimed at broader audiences.

8. From international context to diverse treatment frameworks for FUS patients: neuroethical tensions

Ethical concerns of diverse stakeholders evolve within complex relational and sociocultural ecosystems. Evaluation of emerging neurotechnologies is often tied directly to symptoms-based outcomes measures, yet a participant population with treatment-refractory, severe and persistent mental illness (SPMI) can prioritize outcomes differently than their clinicians and caregivers [109]. Although representation in costly neurointerventional trials could be limited, some SPMI participants may be involved in community mental health programs, recovery frameworks, open dialogue, or palliative psychiatric frameworks [110]. Many such programs deemphasize the centrality of pharmacologic treatment or symptomatic change as a measure of success [109,110]. Palliative psychiatric care programs (adapted from similar models in medicine for patients with SPMI) do not exclude concurrent disease-modifying interventions, however, and have argued for the establishment of clinical trial pipelines for such patients [110].

Positioning treatments with explicit curative or disease-modifying goals in dialogue with palliative psychiatric frameworks for SPMI may engender conflict, yet improve balance between highly subjective and relativistic outcomes or narrowly defined symptoms-based criteria as defining of success. While establishing such clinical trial pipelines would be demanding logistically and not without ethical controversy given patient population vulnerability, doing so is particularly important for the small but significant population of treatment-resistant SPMI patients for whom medically-assisted dying (MAID) is a consideration. The morbidity and mortality associated with severe mental illness should not be underestimated, and psychiatric patients deserve access to the same level of sophisticated care as those with medical illness. Irremediable suffering can be difficult to determine in psychiatry and we will not expand on the ethical implications of MAID for psychiatric patients here. However, if such patients are not made aware of the range of psychiatric neurosurgical approaches, can or should we establish refractoriness of suffering [111]? For some individuals, the proper channels to and opportunity for the range of such treatments (including FUS) could make a life-and-death difference.

9. Conclusion

Focused ultrasound for neuropsychiatric illness is a highly versatile technology with much promise in treating neuropsychiatric illness. This technology is part of a rapidly emerging group of brain-based, mechanism-based interventions that are transforming the field of psychiatry, which has lacked such offerings for patients. In terms of ethical analysis, the current distribution of trials and literature does tell us whose voices are more likely to be heard, and whose are likely to be left out. Facilitating dialogue with patients and the public is crucial, and learning scientists (specialists with expertise in innovative educational design), public communication experts, or artistic program designers could be engaged to do so. In assessing FUS ethically, knowledge of scope and limitations for existing applicable frameworks and their evolution in the literature is necessary. More broadly, care must be taken to not repeat the realities for which the field of neuroethics has been criticized, such as failing to address pragmatics of design for specific audiences, inadequate attention to racial injustice [112], limited diversity and inclusivity, excess speculation, hype, and inadequate attention to issues of implementation [105]. In addition to embedding neuroethicists alongside neuroscientists, clinicians, and industry, collaboration with disciplines traditionally considered 'outside' of neuroethics (e.g., implementation science, computational sociology, intercultural communication) could assist in bridging this gap. Conceptual and empirically-driven neuroethical analysis should compare FUS to treatment alternatives for similar patient populations such that the uniqueness and salience of various points can be appropriately contextualized.

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CRediT authorship contribution statement

Rachel Asher: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Insoo Hyun:** Writing – review & editing. **Mitchell Head:** Conceptualization, Supervision. **G. Rees**

Cosgrove: Conceptualization, Supervision. **David Silbersweig:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Declaration of Interest: Drs. Silbersweig and Cosgrove are participating in a study that the Focused Ultrasound Foundation will fund in part. Dr. Cosgrove is a consultant for the Focused Ultrasound Foundation.

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