Invasive experimental brain surgery for dementia: Ethical shifts in clinical research practices?

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Abstract

The increasing dementia prevalence worldwide is driving the testing of novel therapeutic approaches, such as invasive brain technologies, despite limited clinical evidence and the risk of accelerating cognitive decline. Our manuscript 1) reviews the NIH ClinicalTrials.gov database for deep brain stimulation, stem cell implantation, and gene therapy trials on people with dementia; 2) discusses issues on beneficence, non-maleficence, and autonomy associated with these trials; and 3) proposes nine recommendations that build on elements from the Declaration of Helsinki. We found 49 preregistered high-risk trials from nine countries planning to or involving 11,801 people with Alzheimer's or Lewy body dementia or dementia secondary to Parkinson's or Huntington's disease. Most of the people with Alzheimer's who are in these trials are from North America and East Asia. There is substantial heterogeneity in the enrolment criteria, even for trials recruiting only those with Alzheimer's disease. Although most trials enrol people in mild to moderate stages of Alzheimer's disease, trials in China enrol people who have severe Alzheimer's. Our findings highlight a pressing need to review and refine the enrolment criteria for invasive neural trials in people with dementia, considering risks, potential benefits, and capacity for informed consent. As a multidisciplinary team from Australia, USA, Canada, and Germany with expertise in neurology, neuroscience, and ethics, we examine how it is essential to balance the risks of invasive neural research in a vulnerable population with limited capacity to provide informed consent to help advance the body of knowledge regarding a disease with limited therapeutic options.

Keywords:

Alzheimer's disease, Deep brain stimulation, Dementia, Ethics, Experimental trial, Gene therapy, Informed consent, Invasive brain surgery, Stem cell implantation

Introduction

Dementia is a pressing global health concern, affecting around 50 million people worldwide (1). Developed countries are facing an unprecedented increase in dementia cases, mostly due to Alzheimer's disease (AD) that affects at least 28 million people in the world (2,3) and for which there is still no cure (4). In addition to its impact on affected individuals, dementia places a significant financial burden on society, with total estimated worldwide costs of up to $1 trillion USD (5). Currently, increasing rates of dementia are outpacing the success of research trials (6). Between 1990 and 2014, 99.6% of all pharmacological clinical trials on AD failed at phase III (7). Consequently, some industrial drivers of innovation such as Pfizer Inc. have shifted away from research on AD (8,9). With the failure of multiple pharmaceutical approaches and with established pharmaceutical companies exiting the field, novel invasive neurosurgery protocols and interventions are now being tested on persons with dementia.

The movement from pharmaceuticals towards high-risk invasive neurotechnological interventions for dementia creates a need to examine ethical and regulatory implications. Aside from questions relating to the decisional capacity of people with significant cognitive impairment for enrolling in trials, there are three main reasons why special protections for people with AD must be considered. First, interventions that require neurosurgery involve a known risk of harm that substantially outweighs the foreseeable potential benefits to participants. Even though deep brain stimulation, stem cell therapy, and gene therapy have different putative therapeutic modes of action and also have varying regulatory approvals for certain conditions, their degree of invasiveness, irreversibility, and associated risks similarly outweigh those of other forms of dementia research, such as observational studies, behavioural interventions, or some pharmacologic trials (10). This suggests that such trials more appropriately belong within the

category of non-therapeutic high-risk research, where safety and effectiveness have not been fully demonstrated and more-than-minimal risks are evident. In addition to surgical risks, such interventions may aggravate rather than ameliorate the neurodegenerative trajectory of the disease (11), worsen cognitive deficits in people with AD, and exacerbate emotional and physical burden on caregivers (12). Second, disappointment about failure of recent pharmaceutical trials may lead to a greater tolerance for risk in the field of dementia research, thereby undermining traditional norms of protection for vulnerable research participants with AD. Third, early clinical trials of unproven invasive neurotechnologies may lead to increased experimentation with risky interventions despite little support from pre-clinical studies (13).We have formed a multidisciplinary team from Australia, USA, Canada, and Germany, with members who have expertise in neurology, neuroscience, and ethics, to explore the aforementioned issues and other relevant ethical concerns raised by invasive neurotechnological trials in people with dementia. We first examine our findings by focusing on the notion of minimal risk in the context of dementia trials involving highly invasive procedures per countries, and then, we examine more broadly the ethical considerations arising from this line of research in light of current protections for research participants. We conclude with a proposal for ethical recommendations to ensure protection of participants who might have impaired decisional capacity.

Methods

To evaluate the ethical issues raised by the increasing use of invasive interventional trials in people with dementia, we examined the U.S. National Institutes of Health Clinical Trials database (clinicaltrials.gov) to determine the number of registered studies using invasive interventions involving people with existing or eventual dementia symptoms between January

2003 and December 2020.[1] The term "dementia" was indicated in the "condition or disease" field, and the terms "deep brain stimulation" (DBS), "stem cell", or "gene therapy" were used as entries for the "other terms" field. These terms capture the three most common neurosurgical procedures that are performed in people with dementia. Author JNMV identified relevant protocols and analyzed the studies. Author FG cross-checked the validity of the analytic process at various intervals on a random 50% of the data. Author IS updated the collected data through the manuscript review process in 2020. Studies that did not enroll participants with a confirmed dementia diagnosis or with a condition that may eventually lead to dementia and those that did not introduce an electrode, stem cells, or a foreign gene into a living human being were excluded. For each year included in the analysis, we accounted for the number of newly launched trials and newly recruited or expected participants to illustrate the trend of invasive dementia trials. Participants in follow-up studies involving the same group of participants from an earlier study were not included in the 'total participant' count (see Figure 1). Similarly, when multiple studies were listed under the same institution(s), primary investigator, and country, the number of participants was counted only once to mitigate the risk of double counting (e.g., Clinicaltrials.gov Identifiers: NCT00888056 and NCT00947934). In addition, studies that have different Clinicaltrials.gov identifiers (NCT numbers) but pertain to the same part and phase of one study were only counted once (see Figure 2).We then focused on studies that recruited people with AD for a subsequent in-depth analysis. Studies that only recruited people with AD were tabulated in Excel by Clinicaltrials.gov identifier and the following details: target brain region/s, country, age (years), Mini-Mental State Examination (MMSE – a general assessment of cognitive impairment

[1] We planned to include findings between 1/2000 and 12/2020. The earliest official starting date for a trial matching the study criteria was 1/2003.

level from 0 – 30 with higher numbers indicating intact cognitive faculties (14)), medical history, consent, context (living and caregiving situation), and information about institutional ethics approval (IRB/REB). We also examined the geographic distribution of people with Alzheimer's disease who have been or will be recruited in these trials.

Results

The search yielded 49 clinical trials (Figure 1) involving a total of 11,801 participants with existing or eventual dementia (Figure 2) being performed in the USA, Canada, China, France, Germany, Spain, South Korea, and Sweden (Figure 3). Search results included: implantable intraventricular reservoirs for stem cells, DBS electrodes implanted in different brain regions, and viruses directly injected into the brain of people with dementia. The trials generated by the search included those recruiting people with dementia due to AD, Parkinson's disease, or Lewy bodies and those that also recruited people who may eventually develop dementia due to Huntington's disease. For the six-year period from January 2014 to December 2020, results show an estimate of 11,490 people with dementia enrolled in 29 new trials. This is in contrast with the period before 2014 (January 2003 to December 2013) when only an estimated total of 311 people with dementia were involved across 15 experimental trials. The number of people with dementia recruited in the past six years corresponds to a greater than 36-fold increase from the period preceding it.

There was substantial heterogeneity across protocols, even for studies involving only people with AD (Tables 1 to 3). In 12 studies, the informed consent process involved the subject exclusively, whereas others required involvement of the subject and/or a caregiver/family member (n=8) or consent of the subject and/or a legal delegate (n=6). Eight trials recruited people up to 85 years, one trial recruited people until 86 years old, and seven trials did not specify an upper age limit. Fourteen out of the 15 trials allowing recruitment of advanced ages (85 and above) were

from Asian and American countries. Two trials registered in China enrolled participants with an MMSE score as low as 3 (Clinicaltrials.gov Identifiers: NCT01547689 and NCT02672306) and one study allowed recruitment of participants with an MMSE score as low as 0 (Clinicaltrials.gov Identifier: NCT03115814). No study indicated whether or not an ethics approval from an IRB or REB was already obtained or whether such approval would be sought.

The majority of the trials included people with a confirmed dementia diagnosis, such as only those with Alzheimer's disease (n=31/50 or 62%), whereas others also recruited people with Parkinson's dementia or Lewy body dementia, or people who might eventually develop dementia due to Huntington's disease. We noted that Huntington's trials, such as trials NCT03297177, NCT02728115, NCT04120493, and NCT02263430, do not explicitly accommodate for potential loss of subject autonomy with the progression of dementia by requiring an advance directive pre-enrolment. However, it should be noted that neither do AD-focused research trials. Given the nature of Huntington's and the potentially of having subjects shifting from a state of independence to one of dependence, it may be crucial having standardised documentation regarding the subjects' future care preferences.

Discussion

Minimal risks and harms

From the analysis of invasive neurotechnology trials for dementia, we observe a substantial increase in the number of participants when comparing two key time intervals from 2014 to 2020 and 2003 to 2013. This trend spans several countries and continents and their respective legal regulatory systems. The populations involved in these trials comprise people experiencing a wide range of diverse neurodegenerative disorders that can cause dementia.

We found substantial heterogeneity across protocols, even when the search was narrowed to trials in people with AD. Approaches to diagnosis were widely variable, suggesting substantial differences in how enrolment is conducted across countries. Trials in China that recruit people with MMSE scores as low as 0 or 3 are particularly troublesome (Clinicaltrial.gov Identifiers: NCT03115814, NCT01547689, and NCT02672306) as these scores equate to a late and final clinical stage of the disease and associate severe neurodegeneration (15).

This heterogeneity is evidence of a lack of international consistency in enrolment criteria and trial design. In the absence of an explanation for heterogeneity, enrolment criteria may be dictated by scientific interests only, rather than by both scientific interests and ethical principles. Although enrolment criteria must be adjusted depending on the intervention, proper justification for these parameters should be provided. For instance, drug development regulation requires that the safety of an intervention must first be demonstrated in at least two animal studies in two different mammalian species, which have a condition resembling or predictive of the situation in humans (16). These studies should be of high quality (17) and should be adequate to inform which parameters are safe, which parameters show no effect, and which parameters tend to be toxic (18). The lack of uniformity in the trials, even among trials testing the same type of intervention, emphasizes the need for an international consensus about which subgroups of people with AD will most likely benefit from and be least harmed by these invasive interventions. We note that none of the trials found within the trial registry specified the status of ethics approval. Since clinicaltrials.gov registration of studies that are already recruiting participants necessitates human subjects review board approval (19), it can be assumed that a number of the listed trials have obtained ethics approval, especially some of those with a recruiting status (e.g., NCT03959124, NCT04040348, NCT04133454, NCT03622905, NCT02833792, and NCT03172117). Similarly,

those with a "not yet recruiting" status or an "unknown" status also do not imply that ethics approval has been ascertained or being sought. Particularly for research involving vulnerable populations, information in trial registries including whether a protocol has a planned, pending, or approved ethics status, at which level, the name of the granting IRB/REB, the IRB organisation (IORG) or identification number, and the contact persons is essential. Trial registries may be the earliest contact point for patients and caregivers who are exploring research opportunities. It is reasonable and ethically responsible that they have access to the status of ethics approval.

Establishing ethical research protocols for different forms of dementia is a challenging task, especially for clinical trials that test novel approaches (20). A responsible approach considers not just the different capacities of participants, depending on the degree of dementia, but also the different degrees of risk and burden involved in the research protocol. By their very nature, clinical trials involve some level of uncertainty as to the safety and effectiveness of a new intervention in humans. Thus, for novel neurosurgical interventions, it is not possible to guard participants against all related or iatrogenic harms. In response to this challenge, the minimal risk standard has been established to protect vulnerable persons in non-therapeutic research. This standard states that either participants are legally competent and have mental capacity to provide valid personal informed consent by themselves or – among other things – it is guaranteed that "the research entails only minimal risk and minimal burden" (21). In this context, the term minimal risk is legally operationalized as risk that such persons would also encounter in their normal life, including standard medical care. The ordinary meaning of the phrase minimal risk does not intuitively or reasonably extend to procedures such as brain surgery, particularly in conditions where it is not part of regular diagnostic, monitoring, and management practice (22). For instance, even if brain surgery is part of FDA-approved and CE-marked deep brain stimulation therapy for people with

Parkinson's disease (23), current medical treatment for the non-refractory symptoms of AD does not require any procedure that involves stereotactic surgery. Given the imperative to promote AD research, there have been attempts to expand the minimal risk condition to allow for minor increase to minimal risk and burdens. However, there is a need to determine whether the additional risks from invasive procedures such as neurosurgery can be considered only as a minor increase in the burdens already experienced by people with AD in their daily lives and as part of routine medical care.

Mapping the international standard of minimal risk in nontherapeutic research with people cognitive impairment

The minimal risk condition is deeply anchored in legal systems across the world. In pharmacological research within the European Union, research must either produce a direct benefit or impose only minimal risk and burdens (Article 31, Regulation EU No 536/2014, (24)) For clinical investigations of medical devices, the respective norm demands that "there are scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit to the incapacitated subject outweighing the risks and burdens involved" (Article 64, Regulation EU No 2017/745, (25). Also, the European industry standard demands that the Declaration of Helsinki must be understood, observed, and applied in all research phases (EN ISO-14155:2003, 5.1 Declaration of Helsinki). In the USA, Canada, and Australia, protection of incapacitated persons from non-therapeutic research is achieved by the minor increase formulation of the minimal risk condition (e.g., US Code of Federal Regulations 21 CRF 50 §50.52 to 50.53, (26)). For instance, the Canadian Tri-Council Policy Statement (27) emphasises that if the research entails more than minimal risk, then "it should have appropriate justification aimed at generating

knowledge of sufficient importance to addressing the participants' disorder, condition, interest or situation. Such research should have the prospect of direct benefits for the participants themselves commensurate with the level of foreseeable risk to participant" (27). The Australian Therapeutic Goods Administration, Health Canada, and the US Food and Drug Administration also require research to adhere with the ICH Good Clinical Practice (GCP) guidelines (e.g., TGA Clinical Trial Exemption or Notification schemes), which demands only minimal risks and burdens. Moreover, the minor increase formulation is also codified in the guidelines of the International Society for Stem Cell Research: "Where individuals lack [adequate decision-making] capacity [to exercise valid informed consent], surrogate consent should be obtained and human subjects should be stringently protected from nontherapeutic procedures that involve greater than minor increase over minimal risk" (28).

Chinese Clinical Drug Trial Guidelines require clinical trials to comply with the Council for International Organizations of Medical Sciences (CIOMS) Guidelines, the Declaration of Helsinki, and Good Clinical Practice (GCP). These necessitate that ethics committees give special protections to vulnerable persons, including children and persons suffering from cognitive impairment (29). Article 20 of the Measures on Ethical Review over Biomedical Research Involving Human Subjects, promulgated by the Ministry of Health in 2007, also emphasises that Institutional Review Boards should examine whether the extent of the risk suffered by research subjects is appropriate with their expected benefits from the research, and whether protective measures are taken against the harms that may be suffered. Furthermore, the Ministry of Health has classified stem cell treatment, gene treatment technology, and certain operations requiring stereotactic surgery as Class III medical technologies involving significant ethical requirements to

ensure safety and validity, which need further demonstration by standard clinical tests and studies (30,31).

In South Korea, clinical trials should conform to the Korean Good Clinical Practice (GCP) regulations, which are in line with the ICH guidelines and are rooted in the Declaration of Helsinki, under the Pharmaceutical Affairs Law (32,33). Given its compliance with the 1996 International Conference on Harmonisation's Guideline for Good Clinical Practice, it is expected that the Korean GCP advocates that a legally acceptable representative can only provide consent for a subject in a non-therapeutic trial if the foreseeable risks to the subjects are low and if the negative impact on the subject's well-being is minimised and low (16,34). Moreover, research involving human subjects is covered by the 2012 Bioethics and Safety Act, which underscores the importance of minimising risks posed by the research to human participants (Article 3). Article 16 also mentions that for people who are incapable of or incompetent for giving consent, an appointed legal representative can provide consent. The consent of the representative must not be contrary to the intention of the human subject of research (34).

In sum, the standard of minimal risk in nontherapeutic research with people who lack mental capacity is commonly implemented in biomedical science and is firmly anchored in research regulations from protocol planning to publication (21). All the countries where DBS for people with AD is being conducted have a formulation for the magnitude of risk that people with limited capacity to consent can be exposed to in a clinical trial. However, considering the great variability among countries in the MMSE scores of people with AD for invasive neurotechnological trials, experimental protocols and guidelines need to be harmonised, specified, and stratified for the level of risk to the participant (e.g., FDA and EMA risk class I, II, and III), level of decisional capacity impairment, and finally, level of resulting caregiver burden from the

procedure and follow-up. Firmly established ethical protection of people with dementia from greater-than-minimal-risk clinical trials is vital, as well the need for the therapeutic efficacy of the trial being no lower than existing therapies (30). In addition, compliance of study protocols with the Declaration of Helsinki and their complete registration, including measures to protect vulnerable persons, ethics approval, and informed consent information, are important for successful publication and in the self-interest of clinical investigators from academia.

Paradigm Shift

The idea that society must not stigmatise people with AD as individuals with physical and cognitive vulnerabilities, and consequently include them in research is an important landmark for ethics. However, shifting the research focus to increase the number of people with AD within experimental trials may lead to novel risks for participants. This shift is characterised by two core ethical issues: elevation of the standards of nonmaleficence and clinical trials being pursued in advance of data from animal studies.

Elevation of the standards of nonmaleficence: By ~~their very~~virtue of their intrusive and irreversible nature, invasive brain surgeries targeting dementia induce ~~novel degrees of~~ vulnerabilities~~, particularly those~~ linked to irrevocable harms. The possibility of such consequences calls for the review, and potentially revision of aspects of the experimental protocol.~~The present of inextricable consequences linked to the intervention itself indicates the nonmaleficence principle requires revisions of some aspects of the protocol. Obviously, the potential irreversible harms are not intentionality administrated, however, their presence clearly demonstrate that most aspects linked to potential therapeutic beneficence are likely to be excluded from the experimental protocol. In~~

~~other terms, because the endpoints of these experimental trials are to test safety and not therapeutic outcomes, little benefit should be expected from patients and clinicians, hence the burden of carrying intervention involving the likelihood of irreversible harms.~~ The ethical novelty results ~~then presents~~ from ~~the amalgam of these subjects~~both the defining characteristic of dementia (i.e., continuously increasing degree of cognitive impairment that progressively impacts ~~their~~ a peron's competence to make decisions) and neurosurgical interventions (i.e., non-therapeutic high-risk research ~~with little to no rewards~~). ~~as their characteristics are typically not seen elsewhere unlike to other lower risk interventions like non-invasive transcranial magnetic stimulation~~ (32). ~~Influencing this migration towards~~The greater-than-minimal-risk for people with dementia ~~trials~~ requires extra attention to~~may the goal of research itself. This may increase incidences of prioritizing the object of the trial – brains of people with AD – instead of~~ valuing them as ~~and protecting the~~ participants of the trials, and protecting them from harm ~~– people with AD~~ (35,36).

Acceleration of experimental neurosurgery prior to the availability of evidence from animal models: Incidences of accelerated invasive experimental testing have already occurred in Phase I and Phase II clinical trials of DBS for AD. For example, one trial on fornix DBS in six people with AD was based on a serendipitous discovery of memory improvement in one patient with obesity (37), rather than on pre-clinical studies using relevant animal models of AD (13). The results of the first animal study on fornix DBS were published in 2012 (38), whereas the first Phase 1 trial of fornix DBS for people with AD was conducted in 2010 (39) (Figure 4). Most preliminary animal studies on fornix DBS also utilised pharmacological approaches to produce memory impairments, rather than mouse lines with mutations linked to familial AD, and they provided stimulation that does not adequately capture the length that DBS is provided to humans in clinical and research

settings (13). This non-linearity may be justifiable from a technical point of view, but it undermines the gradual up titration of risk and benefit analysis assumed in research ethics for in-human trials. This may introduce the risk of accelerating experimental neurosurgery unnecessarily. A balance must be struck between the shift to include people with AD in a variety of clinical trials and the race to include them in invasive experimental brain trials. As we have argued, the latter is accompanied by ethical issues that require new and distinct ethical instruments.

Key Ethical Concerns

Within the ethical shifts in clinical AD research practices, we highlight five ethical concerns.

1) Vulnerability and informed consent: In AD-type dementia, affected individuals demonstrate irreversible impairments in memory, reasoning and executive function, visuospatial abilities, language functions, and/or personality. As such, self-determination and decision-making capacity with regards to participation in research trials can become severely compromised and continue to deteriorate as the disease progresses (40). This leads to a profound concern on how to ethically ensure ongoing voluntariness of participation from participants. Standard informed consent to start and finish a high-risk trial may be ethically inappropriate as it is counterintuitive to ask a participant suffering from moderate or advanced AD to consent to risks that he or she may not fully understand. Obtaining consent for additional procedures or for continued trial participation

may even become more challenging as the clinical trial and disease progress and also places increased responsibility and burden on the family/surrogate. Ideally, having ethicists present during informed consent procedures throughout this process may help mitigate the concerns on participant vulnerability, however this continuous inclusion could be unrealistic in practices (41–43). Moreover, advance research directives can be obtained from participants, especially those in earlier stages of the disease. These can provide some guidance on whether the participant wishes enrolled or continued intervention (44).

2) Recruitment: Novel trials involving invasive procedures are now enrolling populations traditionally excluded from research participation because of their limited capacity to consent (13,44). Yet, the opportunity to advance potentially beneficial therapies by enrolling people with AD in trials cannot be rejected outright (45,46). Furthermore, the requirements for capacity may be lower when direct medical benefits from research can be reasonably expected (9,47). Cognitive capacities that facilitate understanding and decision-making also progressively deteriorate with disease progression. Thus, deeper collaboration between researchers and caregivers through the progression of the disease, or even through a period of therapeutic improvement, would reveal where each participant falls on this spectrum.

3) Mitigating procedural risks: Even if Phase I and II trials establish that a nascent intervention is sufficiently safe to advance to Phase III, uncertainty regarding severe risks remain (48). Occurrence of serious adverse events, even in phase III research, suggests the need for adopting the precautionary principle: when an intervention may lead to severe or irreversible harm without any foreseeable benefits, precautionary measures shall be taken to prevent such harms. Each

invasive intervention possesses unique risks and, in some cases, severe irreversible harms (Table 4). In addition, there is the challenge of properly communicating to and ensuring the understanding of participants and their co-decision maker on established and hypothetical risks from an invasive neurotechnological intervention (47). Obtaining this understanding with the subject and their caregiving individual or team may minimize stressors on the caregiver and mitigate risks of potential caregiver burnout (49).

4) Balancing expectations while honoring autonomy: Family members or surrogates may have to undertake the responsibility of guiding people with AD through decisions before, during, and after the trial (50). However, they may hold inflated expectations of the effectiveness of a neurotechnological intervention and may expect unrealistic improvements in independence and autonomy for the person with AD (49). This could affect their judgement, and steps must be undertaken to ensure that their choices honour and acknowledge the participant's preferences and promote his or her welfare. While advance directives might exist for medical decision-making (51,52), they should not be used to enroll people incapable of giving consent for greater than minimal risk non-therapeutic research unless explicitly specified.

5) Advancing science: Altruism is a driving force in research, but non-maleficence must supersede altruism, and even beneficence, in some cases (53). In Germany and the EU, the *status quo* favors the non-maleficence of research participants unable to provide informed consent if the trial poses more than minimal risk and burden, does not provide direct medical benefit to participants, and only has possible downstream research benefits for the sake of others affected by the same conditions (24,51,54,55).

Ethical Recommendation for Invasive Trials for Dementia

We provide a set of nine recommendations for invasive medical research involving human subjects with dementia (Table 5). These recommendations are based on principles in the Declaration of Helsinki, and target areas where ethical protections are missing today.

1) Developing clear policy guidance (Table 5; Recommendation 4, 5, 6, 7, 8 and 9): Even if people with AD are legally capable of giving consent, some concerns remain, mostly due to uncertainty about the evidence supporting the protocol on which the informed consent must be given. Without clear policy guidance, it is uncertain whether persons with AD with decreased cognitive capacities and their families will be adequately positioned to balance harms and benefits of a clinical trial, especially as the disease progresses. Given the variation among countries in acceptable enrolment criteria, such as MMSE score and age, there needs to be sound policy on the specific populations that can be enrolled for different types of high-risk trials. This policy should account for both the cognitive capacity of the participants and the risk that they are subjected to from various study-related procedures, such as stereotactic injection and general anaesthesia. The development of clear guidelines even becomes more pressing as multi-country studies start to be conducted and as later clinical trial phases begin to recruit more people with AD, including those at moderate to severe stages of the disease.

2) Minimizing and communicating risks of harm (Table 5; Recommendation 1, 2, 3, 7, 8): The degree of potential benefit to participants and society should be directly correlated with the degree of experimental invasiveness (54,55). The higher the level of invasiveness, the higher should be the bar concerning the evidence for benefit to patients, compared with existing

treatments, caregiving or disease management practices (56,57). Trials should ensure that the participants will experience the least possible amount of harm from the procedure, that proper measures are undertaken to minimize this potential harm, and that participants are properly and adequately informed of expected and hypothetical harms (24,56). Knowing the extent of harms that may result from various invasive neurotechnological procedures necessitates complete and unbiased reporting of the outcomes for every single participant. The establishment of an anonymised database might help invasive neurotechnological trial groups around the world share results more readily, harmonise selection criteria and study design, and refine the information presented in the informed consent form, especially about the risks of participating in a trial as soon as an adverse event is observed. Finally, non-medical risks of invasive neurotechnological interventions, such as feelings of self-estrangement and difficulties in social adjustment, should be given importance, presented to the participants during the informed consent procedure, and reported in the literature (49).

3) Easing withdrawal (Table 5 Recommendation 1, 5, 8, and 9): Considering that invasive neurotechnological trials are likely a last resort for participants makes study withdrawal particularly difficult. Participants are in a vulnerable situation when in a high-risk invasive brain trial because they are approaching an irreversible life-altering situation (to some extent, a life-threating situation in late disease stages). Even if the experimental trial maintains the person with AD in a stable condition, it does not mean that substituting a current trial for a later superior treatment will be easily possible due to technical and biological challenges such as safety or adverse interaction effects. Not having access to a treatment due to the potential harms and irreversibility of the treatment is only one dimension of the problem. People with AD may also

lose the chance to access a better treatment in the future because of their involvement in an earlier experimental invasive trial, such as inability to obtain magnetic resonance imaging studies following deep brain stimulation device placement (58,59). The potential irreversibility of an invasive neurotechnological procedure (10) and the fact that participation in one trial might prevent them from participating in other clinical trials need to be communicated to participants and their co-decision makers during the informed consent procedure.

Limitations

Research protocols on clinicaltrials.gov are not exhaustive and incomplete registration occurs. Therefore, registration data may lack certain relevant details to the present study. The search terms we utilized might not have fully captured all invasive neurosurgical trials enrolling people with dementia or have included all conditions in which dementia-related symptoms arise. Nonetheless, the three technologies in focus here combined with the keyword "dementia" provide a reasonable sampling of the current research terrain, enabling reflection on salient ethical issues and the formulation of recommendations to address them. It is important to note that 10,000 subjects of the total 11,801 are only for two stem cell trials (NCT03899298 and NCT04684602). These studies plan to investigate stem cell therapies for a broad range of neurologic, cardiovascular, pulmonary, and urology disorders, among other conditions. Thus, the actual number of patients with dementia or AD to be enrolled in these studies may be low, but current available information on clinicaltrial.gov does not allow us to exactly determine the exact proportion of people with dementia enrolled. Thus, while off the present data, participation in research trials suggests an increase of ~36-fold when comparing 2003 – 2014 and 2015 – 2020

timelines; however, this may be inflated due to limited information made available on clinicaltrials.gov.

Separate from the quantitative observations of this study, our ethical recommendations presented in Table 5 provide specifics about articles from the Declaration of Helsinki, which may be interpreted as general advice for clinical investigators. Some readers may prefer to see practical examples of research protocols. While valid, the goal of this article is largely to provide an empirical base to justify further assessment. The ethical recommendations presented are proportionate with available information on ClinicalTrials.gov. A systematic analysis of research protocols is the next major step in developing even more concrete and intervention-specific ethical recommendations for clinical investigators.

Conclusion

Considering the global burden of dementia, new interventions must be explored to expand the therapeutic repertoire. Currently, invasive neurotechnologies such as deep brain stimulation, gene therapy, and stem cell therapy are those being investigated. As these forms of neurotechnology are invasive, results from past trials and protocols for ongoing and forthcoming trials must be thoroughly reviewed, and ethical issues arising from recruitment criteria and design must be identified and addressed.

Ethicists play an important role in appraising this information and engaging in a dialogue with clinicians and researchers in the neurological sciences to ensure maximal protection of people who are not just impaired by cognitive decline but are also subject to adverse effects related to invasive neurotechnological interventions (60–67). Overall, there is strong justification for a shift in research practices away from ‘absence of safety and efficacy evidence’ to ‘evidence of safety

and efficacy' in preclinical trials (68,69). Ethics serves a prudent and important function in making the clinical neuroscience landscape safe and reflective.

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Table 1. Stem cell trials for AD. LAR*: Legally acceptable representative; N/A: Not available; PET: Positron Emission Tomography; MRI: magnetic resonance imaging; ADAS-Cog: Alzheimer's Disease Assessment Scale-cognitive Subscale. Source: clinicaltrials.gov 2020.

Country	CT Number	Route	Age (years)	MMSE	Neurological data	Consent	Ethics Approval	Context (Living and caregiving situation)
USA	NCT02833792	Intravenous	55 - 80	12 - 24	PET (Aβ)	N/A	N/A	N/A
USA	NCT03117738	Intravenous	≥ 50	16 - 26	N/A	Subject	N/A	Adult caregiver who understands the language at the study site, lives with subject or sees subject frequently, and agrees to accompany the subject to each study visit.
USA	NCT02600130	Intra-venous	50 - 80	18 - 24	PET (Aβ)	Subject and caregiver	N/A	As above for caregiver, plus ability to provide consent; participant lives in the community or assisted living facility, but not in a long-term care nursing facility.
USA	NCT04228666	Intravenous	50 - 85	N/A	PET (Aβ)	Subject	N/A	N/A
USA	NCT04482413	Intravenous	≥ 50	20 - 24	ADAS-Cog	Subject (or assent)	N/A	Patients with one (or more) adult caregiver who is able to read, understand, and speak the language of the study site, who either lives with the subject or sees the subject ≥ 2 hours/day ≥4 days/week, and who agrees to accompany the subject to each study visit.
Korea	NCT01297218	Intracerebral	50 - 75	10 - 24	PET (Aβ)	Subject	N/A	N/A
Korea	NCT02899091	Intravenous	≥ 50	10 - 26	PET (Aβ, glucose); MRI	Subject or LAR*	N/A	Adult caregiver who can provide information on the subject's condition.
Korea	NCT02054208	Intra-ventricular	50 - 85	18 - 26	PET (Aβ); MRI	Subject or LAR*	N/A	N/A
Korea	NCT01696591	Intracerebral	50 - 75	N/A	PET (Aβ)	Subject	N/A	Enrolled and completed the Phase I clinical trial (NCT01297218).
Korea	NCT03172117	Intra-ventricular	50 - 86	N/A	N/A	Subject or LAR*	N/A	Enrolled and completed Phase 1/2a clinical trial of NEUROSTEM® (NCT03172117).
China	NCT01547689	Intravenous	50 - 85	3 - 20	N/A	Subject	N/A	N/A

China	NCT02672306	Intravenous	50 - 85	3 - 20	N/A	Subject	N/A	Home monitoring available.

Table 2. DBS for AD. N/A: Not available; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; CDR: Clinical Dementia Rating; ADAS-Cog: Alzheimer's Disease Assessment Scale-cognitive Subscale. Source: clinicaltrials.gov 2020.

Country	CT Number	Brain Region	Age (years)	MMSE	Neurological data	Consent	Ethics Approval	Context (Living and caregiving situation)
USA, Canada, and Germany	NCT03622905	Fornix	≥ 65	N/A; CDR global of 0.5 - 1.0; ADAS-Cog 11 of 10 - 24	CSF (Tau and Aβ)	Subject and caregiver	N/A	Has an available caregiver or other appropriate knowledgeable informant who can reliably report on daily activities and function and signs the informed consent for participation
USA	NCT01559220	N/A	45 - 85	N/A	N/A	N/A	N/A	N/A
USA and Canada	NCT01608061	Fornix	45 - 85	N/A	N/A	N/A	N/A	Caregiver who is willing to participate; participant living at home and likely to remain at home for the study duration.
Canada	NCT00658125	Fornix	40 - 80	20 - 28	N/A	N/A	N/A	N/A
China	NCT03115814	Fornix	40 - 80	0 - 10	N/A	Signed informed consent (no specific details)	N/A	N/A
China	NCT03352739	Fornix or nucleus basalis of Meynert	45 - 75	N/A; CDR of 1.0 - 2.0	PET (Aβ)	Subject	N/A	N/A
China	NCT02253043	N/A	40 - 80	20 - 28	N/A	N/A	N/A	N/A
Germany	NCT01094145	Nucleus basalis of Meynert	60 - 80	> 18, < 26	N/A	Subject and at least two family members	N/A	N/A
France	NCT00947934	Fornix	50 - 70	20 - 24	N/A	Subject	N/A	Participants covered by social security.

France	NCT00888056	Hypothalamus/fornix	50 - 65	20 - 24	MRI and PET	Subject	N/A	Affiliated to the French national health and pensions organization
Spain	NCT03290274	Fornix or nucleus basalis of Meynert	50 - 80	N/A; CDR of 1	CSF (Tau, p-tau or Aβ) or PET (Aβ)	Subject and caregiver or legal representative	N/A	N/A

Table 3. Gene therapy for AD (nerve growth factor). N/A: Not available. Source: clinicaltrials.gov 2020.

Country	CT Number	Delivery Mode	Age (years)	MMSE	Neurological data	Consent	Ethics Approval	Context (Living and caregiving situation)
USA	NCT00017940	Intracerebral via fibroblasts	≥ 50	N/A	N/A	Subject	N/A	Available for many visits in CA in the first year.
USA	NCT00087789	Intracerebral - AAV-mediated delivery	50 - 80	16 - 28	N/A	Subject and surrogate/legally authorized power of attorney/family member.	N/A	N/A
USA	NCT00876863	Intracerebral - AAV-mediated delivery	55 - 80	N/A	N/A	N/A	N/A	Study partner who can attend all study visits.
USA	NCT03634007	Intracisternal	≥ 50	N/A	N/A	Subject or LAR	N/A	N/A

Sweden	NCT01163825	Intracerebral – encapsulated cell biodelivery	50 - 80	15 - 24	N/A	Subject and caregiver	Informed consent must be obtained from the subject together with a close caregiver, in accordance with the requirements of the ethics committee.	Caregiver who can assist in trial protocol compliance and is willing to provide the information required at assessment interviews.

Table 4. Properties of different invasive neurotechnologies being tested for dementia. The trials provided in this table are illustrative only.

	Deep brain stimulation	**Stem cell therapy**	**Gene therapy**
Possible risks	Intraoperative events such as vasovagal response, hypotension, seizure, asymptomatic intracerebral haemorrhage, asymptomatic intraventricular haemorrhage and ischemic infarction associated with hemiparesis, and/or decreased consciousness (65)	Teratoma formation, immunological reactions, unpredictable cell migration, and long-term health effects yet unknown (66)	*In vivo* gene therapy: Immune response to viral particles; genotoxicity through random integration of vector genomes to host DNA (67)
Reversibility	Partially reversible	Irreversible when cells are directly introduced.	Irreversible
Re-introduction of AD-linked mutations or polymorphisms	Not applicable	Yes, for autologous cells, unless they are in a reservoir and not directly in contact with other cells.	Yes, for delivery via autologous cells (*ex vivo* gene therapy), unless the mutations were corrected in the re-introduced cells.
Illustrative trials			
Clinical trial number	NCT01608061 (11,68)	NCT01297218, NCT01696591 (69)	NCT00087789 (70)
Phase	II (pivotal)	I (pilot)	I (pilot)
Number of participants	42	9	10

MMSE	No range mentioned	10 - 24	16 - 28
ADAS-Cog	12 - 24	15 - 21	No range mentioned
Stimulation parameters/ Cell source/ Delivery method	3.0 - 3.5 V, 130 Hz, 90 µs	Umbilical cord mesenchymal stem cells	Nerve growth factor-gene carrying adeno-associated virus
Region of injection/ implantation	Fornix (bilateral)	Hippocampus (bilateral), precuneus (unilateral)	Nucleus basalis of Meynert (bilateral)
Safety outcome	First 12 months: Four acute device or procedure-related safety events in three participants and three long-term serious therapy-related event in one participant who did not receive stimulation; 13 to 24 months: 24 SAEs were reported by eight participants.	No severe acute or long-term side effects	No unusual surgical complication except for hygroma; few adverse events unrelated to intervention; one participant died due to failure to thrive.
Efficacy outcome	Possible benefit for older participants (<65 yrs); however, potential initial deleterious effect in younger people with AD (<65 yrs)	Faster rate of decline compared to the standard rate in people with AD (potentially due to recruitment of participants with early onset AD)	Recipients of the highest viral dose demonstrated the least amount of cognitive decline.

Table 5. Recommendations for ethics guidance.

		Mental incapacity, compromised, or fluctuating mental capacity	Mental capacity, foreseeable progression to incapacity to make research decisions during trial participation	Mental capacity to give valid, voluntary, and informed consent to participate in all phases of trial	Articles from the Declaration of Helsinki
1	Risk minimization	Risk must be minimized. Trials should not be explored in humans unless strong empirical evidence promises superior or expected benefits to the standard of care and non-inferiority in terms of the likely harms and burdens compared to standard therapy or alternative research.	Risks ought to be mitigated or removed. Any research decision potentially needed to be taken under foreseeable incapacity should only be about options involving minimal harm. The informed consent should prospectively inform about any kind of research decisions that may eventually become necessary in a state of incapacity. All options of those decisions need to be discussed with patients in great detail and in advance before consenting to the research.	Risks ought to be mitigated or removed.	Art. 16, 17, and 18
2	Direct benefit and non-minimal risk	Either direct benefits need to be empirically demonstrated, or only interventions posing minimal risk or minor increase in minimal risk are to be investigated.	Risks ought to be mitigated or removed. Any research decision potentially needed to be taken under foreseeable incapacity should only be about options involving minimal harm. The informed consent should prospectively inform about any kind of research decisions that may eventually become necessary in a state of incapacity. All options of those decisions need to be discussed with patients in great detail and in advance before consenting to the research.	Participants are free to decide to take as much risk in altruistic research as they wish. Underrepresented groups should gain access to research.	Art. 13 and 28
3	Group benefits and minimal risk	Interventions with no direct medical benefit (non-therapeutic) can be tested for group benefits only if these are clinically meaningful and the research poses minimal risk or minor increase.	Risks ought to be mitigated or removed.	Participants are free to decide to take as much risk in altruistic research as they wish. Underrepresented groups should gain access to research.	Art. 28
4	Research rationale validity	The rationale is justified by empirical data and an exhaustive and specific literature assessment explicitly unveiling any potential	The rationale is justified by empirical data and an exhaustive and specific literature assessment explicitly unveiling any potential inconsistencies and knowledge gaps (Systematic Review).	If the research rationale is not based on a systematic review of the literature or if it is plainly exploratory, this needs to	Art. 21 and 22

		inconsistencies and knowledge gaps (Systematic Review).		be communicated in the informed consent.	
5	Exhausted research alternatives	The examination of less risky alternatives should be offered and receive research priority.	The examination of less risky alternatives should be offered and receive research priority.	The examination of less risky alternatives should be offered and receive research priority.	Art. 21
6	Necessity of the research and non-replaceability	If the full or parts of research question can be answered by performing research enrolling a different cohort of patients (e.g., people with AD with less cognitive decline), then such cohort should be enrolled instead.	If the full or parts of research question can be answered by performing research enrolling cohorts without foreseeable progression to incapacity, then such cohort should be enrolled instead.	Human subjects to be enrolled should be informed why the research they are about to participating in is necessary for answering the research question at hand.	Art. 20
7	Research load minimization	Non-therapeutic parts of a research protocol yielding no direct benefit should be minimized.	Non-therapeutic parts of a research protocol yielding no direct benefit should be minimized as soon as enrolled patients lack the capacity to consent.	If transparently communicated in the informed consent, patients can participate in as much additional research parts and testing as they may wish.	Art. 16, 17, and 18
8	Co-consent (supported decision making)	Without co-decision maker, no participation in invasive neurotechnological trials should be allowed unless there is strong evidence for a direct therapeutic benefit or only minimal risk.	No participation without co-decision maker unless firm evidence establishes the tested intervention's safety and efficacy.	Not applicable	Art. 30
9	Continued assent and continuous respect for dissent	The right of research subjects to discontinue participation must be always respected.	The right of research subjects to discontinue participation must be always respected.	The right of participants to discontinue participation must be always be respected s.	Art. 29

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Figure Legends

Figure 1: Number of studies assessing the use of invasive brain technologies in people with dementia through December 31, 2020 (n = 49). Search limited to deep brain stimulation (DBS), stem cell therapy, and gene therapy. Source: clinicaltrials.gov.

Figure 2: Estimated number of past/present/future participants in studies assessing the use of invasive brain technologies (deep brain stimulation [DBS], stem cell therapy, and gene therapy) in people with dementia until December 31, 2020 (n = 11,801). Source: clinicaltrials.gov.

Figure 3. Geographic distribution of the number of past/current/future people with AD enrolled in clinical trials involving invasive neurotechnological interventions. Source: clinicaltrials.gov (December 31, 2020)

Figure 4. Timeline of initial clinical trials and animal studies on fornix deep brain stimulation

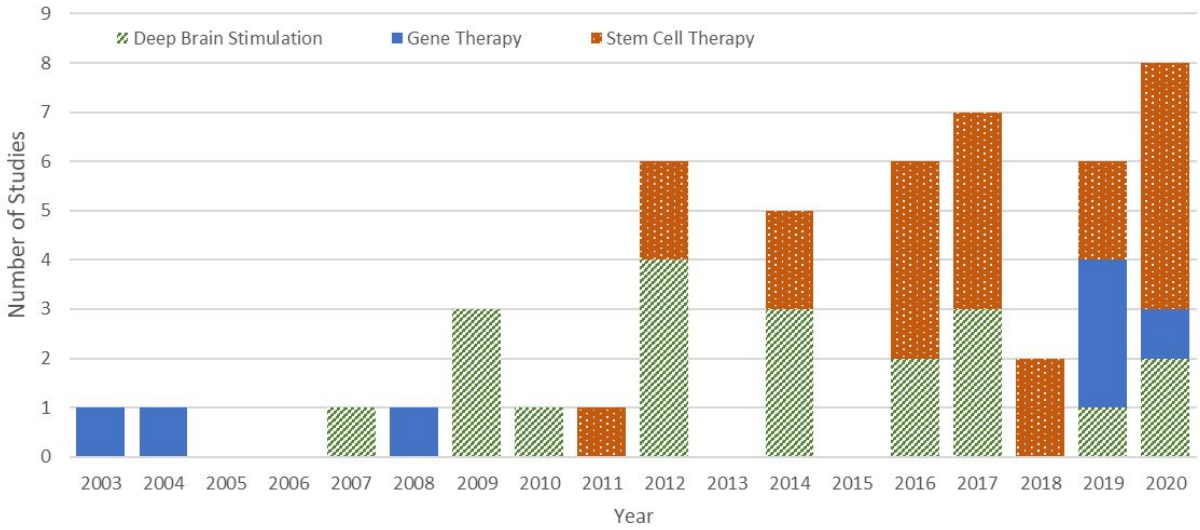


Figure 1: Number of studies using invasive brain technologies in people with dementia through December 31, 2020 (n = 49). Search limited to deep brain stimulation (DBS), stem cell therapy, and gene therapy. Source: clinicaltrials.gov.

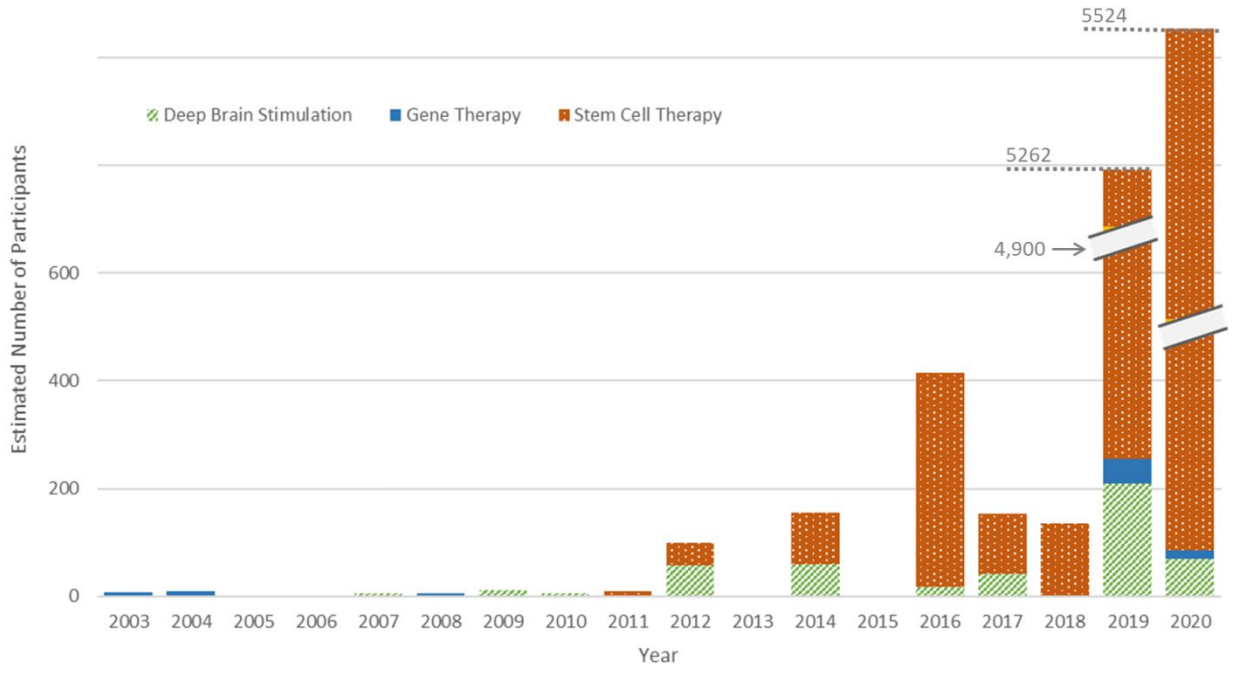
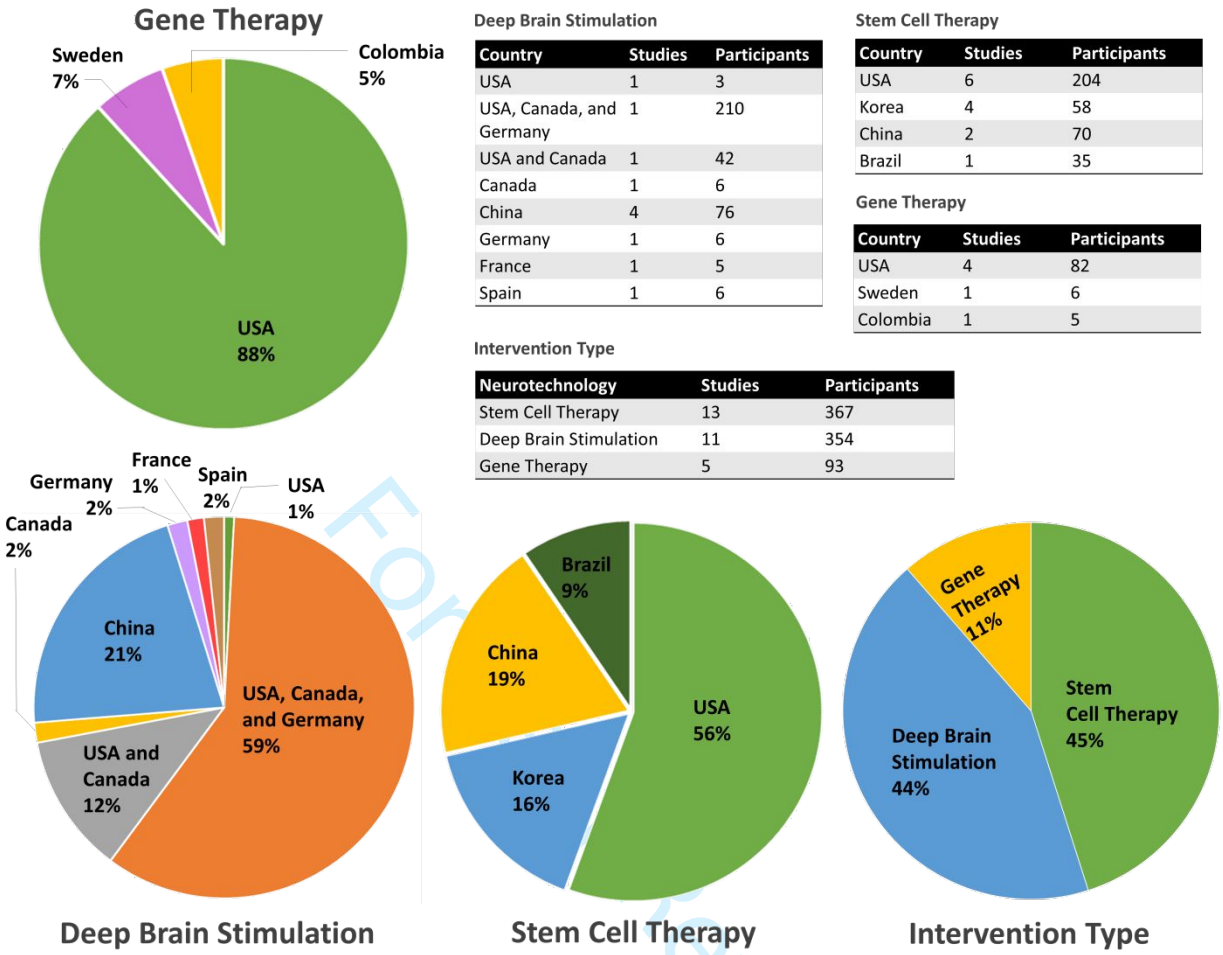


Figure 2: Estimated number of past/present/future participants in studies using invasive brain technologies (deep brain stimulation [DBS], stem cell therapy, and gene therapy) in people with dementia through December 31, 2020 (n = 11,801). Source: clinicaltrials.gov.



Deep Brain Stimulation

Country	Studies	Participants
USA	1	3
USA, Canada, and Germany	1	210
USA and Canada	1	42
Canada	1	6
China	4	76
Germany	1	6
France	1	5
Spain	1	6

Stem Cell Therapy

Country	Studies	Participants
USA	6	204
Korea	4	58
China	2	70
Brazil	1	35

Gene Therapy

Country	Studies	Participants
USA	4	82
Sweden	1	6
Colombia	1	5

Intervention Type

Neurotechnology	Studies	Participants
Stem Cell Therapy	13	367
Deep Brain Stimulation	11	354
Gene Therapy	5	93

Figure 3. Geographic distribution of the number of past/current/future people with Alzheimer's disease enrolled in clinical trials involving invasive neurotechnological interventions through (December 31, 2020. Source: clinicaltrials.gov

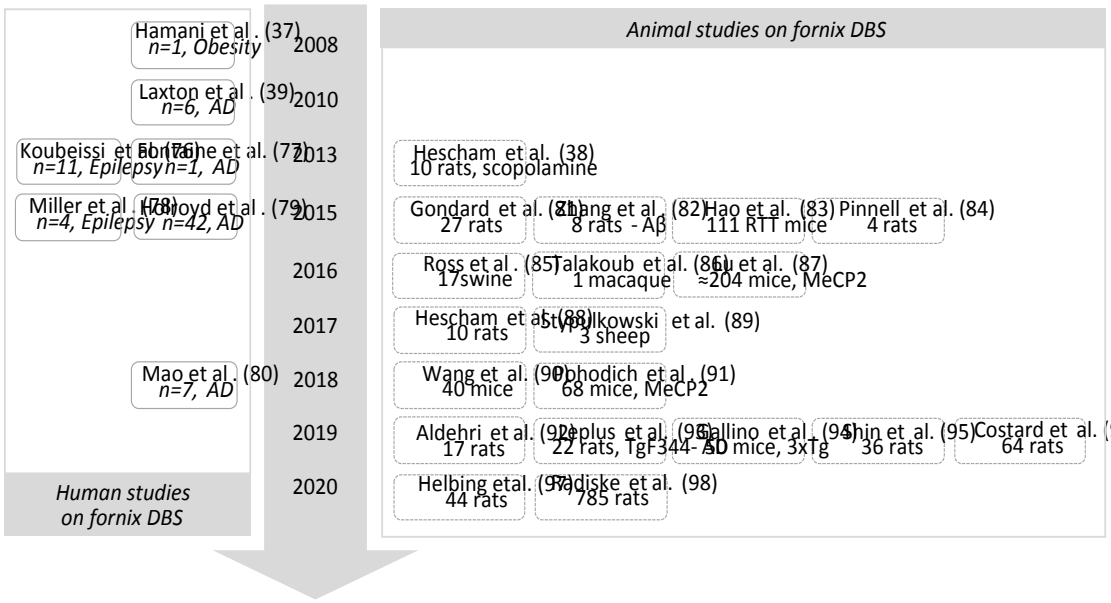


Figure 4. Timeline of PubMed-indexed initial clinical trials and animal studies on fornix deep brain stimulation. The search was conducted on June 17, 2021, and only articles that performed DBS of the fornix were included. For in-human trials, only the first publications per population were included in the graph, and follow-up or retrospective studies were excluded.