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Stakeholders' Perspectives regarding Participation in Neuromodulation-Based Dementia Intervention Research

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Abstract

This study evaluated stakeholders' perspectives regarding participation in two hypothetical neuromodulation trials focused on individuals with Alzheimer's disease and related disorders (ADRDs). Stakeholders (i.e., individuals at risk for ADRDs [n=56], individuals with experience as a caregiver for someone with a cognitive disorder [n=60], and comparison respondents [n=124] were recruited via MTurk. Primary outcomes were willingness to enroll (or enroll one's loved one), feeling lucky to have the opportunity to enroll, and feeling obligated to enroll in two protocols (transcranial magnetic stimulation, TMS; deep brain stimulation, DBS). Relative to the Comparison group, the At Risk group endorsed higher levels of "feeling lucky" regarding both research protocols, and higher willingness to participate in the TMS protocol. These findings provide tentative reassurance regarding the nature of decision making regarding neurotechnology-based research on ADRDs. Further work is needed to evaluate the full range of potential influences on research participation.

Keywords

cognitive disorders; dementia; Alzheimer's disease; caregivers; decision making; research participation; clinical trials; neuromodulation

INTRODUCTION

Alzheimer's disease (AD) and related neurocognitive disorders (ADRDs) represent one of the leading sources of global disease burden ("2020 Alzheimer's Disease Facts and Figures," 2020). Despite massive investments by both public agencies and private companies in clinical trials of pharmacologic agents, no substantially effective intervention strategies to prevent, halt, or reduce the cognitive or behavioral impact of ADRDs have been found to

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date (Cummings et al., 2020; Lyketsos, 2020). New models and paradigms that go beyond targeting general neurotransmitter systems, or those intended to impede the accumulation of amyloid plaques, are needed for hope of making genuine breakthroughs.

One emerging domain of clinical trials research for ADRDs is that of non-pharmacologic neurotechnology-based neuromodulatory interventions. Based on observations of effects of neuromodulation on memory (Arendash, 2016; Laxton et al., 2010), investigators have begun to evaluate various forms of neuromodulation—including transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS)—for potential efficacy in disorders affecting cognition (Arendash et al., 2019; Deeb et al., 2019; Laxton et al., 2010). Although such studies remain less common than pharmacologic clinical trials for ADRDs, the march toward precision medicine and targeted therapies, which include such neurotechnological approaches, is likely to continue and intensify.

Ethical concerns regarding the application of DBS to the treatment of psychiatric disorders have been noted and discussed for over a decade (Dunn et al., 2011; Park et al., 2017; Rabins et al., 2009). For example, Park et al (2017) provide a cogent framework for identifying and weighing ethical concerns related to the use of DBS for anorexia. Much of this frame has direct and obvious relevance to those with ADRDs too. The one salient difference with research on DBS for ADRDs is the absence of effective alternatives for long-term treatment of ADRDs. This may engender higher desperation and a misplaced sense of “lucky opportunity” for those at risk ADRDs and their caregivers when offered opportunity to participate in a novel treatment approach. At the same time, DBS involves invasive brain surgery in patients already experiencing deterioration in brain structure and function. The effects of the surgery itself, including surgical anesthesia, may thus bring elevated risk in this population. It is thus essential to have research on the factors influencing risk perception and therapeutic misconception among such persons.

Due to the relatively recent nature of efforts to apply TMS and DBS in the context of research on ADRDs, the various domains of influence on research decision-making for such studies have not been examined. For example, the invasive nature of neuromodulatory strategies—particularly DBS—might serve to dissuade some individuals from enrolling. Or, due to the unrelenting and progressive nature of these disorders, as well as the absence of effective treatments, some individuals or families might experience a sense of desperation for any potentially helpful intervention (Dunn et al., 2011; Roberts, 2002). Measuring a sense of desperation, however, has remained elusive.

Intriguingly, we found in preliminary, qualitative interviews with a range of stakeholders (including clinical researchers, patients, and family members) that some individuals expressed a sense of feeling lucky or fortunate to have the opportunity participate in the proffered research [Roberts et al., forthcoming]. To our knowledge, this sense of “feeling lucky” remains unexplored in the context of research on ADRDs. In a qualitative study of 16 cancer patients who had recently been offered enrollment in clinical trials, Murphy and colleagues (2020) noted a thematic subcategory, “Feel lucky,” under the core theme of “Trusting Relationship,” providing an example of a patient being told they would be “treated

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like a VIP." This framing of "feeling lucky" centers on an increased level of attention and personalized care.

Another possibility is that "feeling lucky" to have the opportunity to participate in research could represent a form of desperation among patients or their family members, when the patient has exhausted other treatment options, or when there are few, if any, available treatments. The idea of desperation appears as a theme in qualitative studies of reasons for research participation among volunteers for AD clinical trials (Bardach et al., 2020), and desperation has also been described as a factor in research decision making in the context of other serious illnesses, such as cancer (Murphy et al., 2020). For instance, Murphy and colleagues identified a core theme of "Nothing to Lose" (along with its subthemes, labeled "Just want to live" and "Maintaining hope"), which was noted in interviews of both patients with cancer and their oncologists.

Another potential factor in research decision making, and one that has not been studied in the setting of ADRD research, is a sense of obligation (e.g., to the research team, to one's offspring, or to society more broadly) (Bardach et al., 2020). As with the idea of feeling lucky, a sense of "obligation" remains underexplored in empirical ethics work. These ideas of feeling fortunate or obligated to participate in research differ from the therapeutic misconception, which is the notion that study volunteers believe that they will receive benefit from a clinical trial and do not understand the primary objective of clinical research as answering a key scientific questions (Appelbaum & Lidz, 2008).

Evaluating these potential influences on research decision making is critical to the development and implementation of appropriate safeguards for studies seeking to enroll individuals with or at risk for ADRDs. Moreover, there is an immense need to increase the representativeness of volunteers for research on neurodegenerative disorders (Gilmore-Bykovskyi et al., 2019); understanding factors that may motivate or impede research participation would assist these efforts. At the same time, it is important that concerns about influences on research participation—particularly those that are non-evidence-based—should not lead to excessive constraints on the very research that is aimed at advancing care for individuals with the disorders in question. Thus, there is a critical need for empirical information to delineate the scope of these problems, and factors that may unduly influence decisions to enroll on the part of patients themselves or those authorized to make consent decisions for them (Benson et al., 2020).

The present report is the first in a series of articles describing findings from a broader study of the factors that influence perceptions of and willingness to enroll in novel, neurotechnology-based clinical neuroscience research for ADRDs. The purpose of this first report is to examine whether the type of decision maker role affects willingness to enroll, feelings of being lucky to have the opportunity to enroll, and feeling obligated to enroll in either of two types of neurotechnology-based clinical trials for ADRDs. Decision maker types include individuals at risk for ADRDs (based on being a first-degree relative of an individual with a cognitive disorder); individuals with experience as a caregiver for someone with a cognitive disorder; and non-at risk/non-caregiver comparison respondents. We analyzed survey responses to two hypothetical research vignettes, which were designed

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to be realistic and which differed in terms of invasiveness of the experimental intervention (i.e., a TMS study or DBS study focusing on individuals with ADRDs). Given the current absence of substantially effective treatments, we hypothesized that at-risk individuals would be more willing to participate, and endorse feeling luckier to participate, in each of the clinical trials, relative to their comparison group.

Furthermore, we hypothesized that caregivers would differ from their comparison group in all three outcomes. We explored but had no *a priori* hypotheses regarding feelings of obligation to enroll in research.

METHODS

Participants:

Data for the current report were collected as part of a larger online survey study focused on ethical issues related to innovative, clinical research focused on individuals with ADRDs. Participants were recruited using the Amazon Mechanical Turk (MTurk) online crowdsourcing platform (Gillan & Daw, 2016). MTurk workers who reported living in the United States, being at least 18 years of age, and who had an MTurk approval rating of 95% or greater were eligible to participate in a brief screening survey. The screening survey was open from February 11th to 14th, 2020, and respondents were paid $0.30 for completing the screening assessment. In total, 918 Mturk workers completed the screening survey.

Based on the screening assessment, we ascertained the study inclusion criteria, i.e. self-reporting as either: (a) reported having a blood-related first or second degree relative (i.e., parent, child, grandparent, grandchild, aunt, uncle, niece, nephew) with a memory disorder or a form of cognitive impairment (*"At Risk" group*); (b*)* who reported having been or being a spouse, long-term partner, or primary caregiver of an individual with a memory disorder or a form of cognitive impairment (*"Caregiver" group*); or c) met neither of the inclusion criteria above (i.e., NOT an individual with a memory disorder or a form of a cognitive impairment; NOT blood-related to an individual with a memory disorder or a form of cognitive impairment; and NOT the spouse, long term partner or primary caregiver of an individual with a memory disorder or a form of cognitive impairment) (*"Comparison" group).* At Risk participants who also endorsed being a spouse, long-term partner, or primary caregiver of an individual with a memory disorder or cognitive impairment were excluded from the study. While we considered including an additional respondent group who met eligibility criteria for both caregiver and at-risk, we ultimately decided, because each additional respondent group adds further interpretative complexity, that we would focus this study on comparisons among the more discrete groups (i.e., at risk, caregiver, and their respective comparison groups.

An advertisement for the full survey was posted for two months in Spring, 2020 and was visible to the 888 MTurk workers who met the eligibility criteria for any of the above-described groups. After excluding respondents who provided discrepant self-reported eligibility information, our final sample consisted of 56 At Risk, 60 Caregivers, and 124 Comparison group participants (total n=240).

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Three attention check questions were included, and no participants failed the attention check questions. Eligible MTurk workers who chose to take the full survey were given a short description and a web link to the survey, hosted on Stanford RedCap. Before taking the survey, respondents were required to read and agree to an electronic consent. Respondents who consented were led to a 290–315 question survey, which took an average of 36.3 minutes to complete. Research participants were paid $8.00 for completing the survey.

This study was reviewed and approved by the Stanford University IRB.

Measures and procedures:

Sociodemographic characteristics: included self-reported age, gender, ethnicity, race, education, employment status, marital status, household income, and insurance status).

Research vignettes.—The primary outcomes (willingness, feeling lucky to participate, and feelings of obligation to enroll, described below) were responses related to each of the following two hypothetical research projects:

(a)TMS project: The transcranial magnetic stimulation (TMS) project describes Mary, a 75-year-old woman with a diagnosis of Alzheimer's disease, who lives with her spouse, upon whom she is dependent for many of her day-to-day activities. Mary's doctor informs her of a research study involving a 30-minute session of transcranial magnetic stimulation, 5 days a week, for 2 weeks (10 days total), with a monthly follow-up for the 6 months after the initial treatment. If she decided to participate, she would be compensated $500 for her time and effort. The researchers believe there is a chance her symptoms may improve.

(b)DBS project: The deep brain stimulation (DBS) project describes Joe, a 78-year-old man with a diagnosis of Alzheimer's disease, who lives with his daughter, upon whom he is dependent for his day-to-day activities. Joe's doctor informs him of a research study, in which the goal is to understand the changes in the brains of people who receive a procedure called deep brain stimulation. If he decided to participate, he would undergo surgery to have the electrodes and stimulation device implanted. For six months following the procedures, he would have monthly check-ups, and would be compensated $500 for his time and effort. The researchers believe there is a chance his symptoms may improve, but do not know with certainty how DBS will affect Joe personally.

In terms of the use of hypothetical research vignettes, Schoenberg and Ravdal (2000) note two key benefits of using vignettes in social research: first, the 'flexibility that allows the researcher to design an instrument uniquely responsive to specific topical foci' as well as "depersonalization that encourages an informant to think beyond his or her own circumstances, an important feature for sensitive topics or for illuminating future use patterns of services.

Willingness to participate, feeling lucky, and feeling obligated to participate:

All of the *At Risk group* respondents (n=56) were asked to answer survey items from the perspective of an at-risk individual. In addition, approximately half (selected randomly) of the *Comparison group* respondents (n=64, "Comp-AR") were asked to answer from the

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perspective of an individual at risk for cognitive impairment (in order to compare their responses to those of the At Risk group). Thus, these two sets of respondents were asked the following questions: “How willing would you be to sign up if you were in Mary’s/Joe’s shoes?” (1 = “not at all willing” to 7 = “very willing”); “If I were in Mary’s/Joe’s shoes, I would feel lucky that I was offered the opportunity to participate in this study” (1 = “strongly disagree” to 7 = “strongly agree”); and “If I were in Mary’s/Joes shoes, I would feel obligated to participate in this study” (1 = “strongly disagree” to 7 = “strongly agree”).

All of the *Caregiver group* respondents (n=60), and approximately half of the *Comparison group* (selected randomly; n=60, “Comp-CG”) were asked to answer from the perspective of a caregiver for an individual with cognitive impairment. Thus, these two sets of respondents were asked the following questions: “How willing would you be to sign up Mary/Joe to participate in this study if you were in Casey’s/Pat’s shoes?” (1 = “not at all willing” to 7 = “very willing”); “If I were in Casey’s/Pat’s shoes, I would feel lucky that Mary/Joe was offered the opportunity to participate this study” (1 = “strongly disagree” to 7 = “strongly agree”); and “If I were in Casey’s/Pat’s shoes, I would feel obligated to sign Mary/Joe up for this study” (1 = “strongly disagree” to 7 = “strongly agree”).

Data analysis.

Data were analyzed with SPSS (Version 27) and R (Version 4). Descriptive statistics were generated for continuous and categorical variables. Distributions of variables were checked for violation of assumptions for parametric testing, and non-parametric methods were substituted were appropriate. Differences between groups were analyzed using Chi-square tests, one-way analysis of variance (ANOVA) or Kruskal-Wallis, or *t*-tests or Mann-Whitney U tests as appropriate.

The group comparisons of willingness to participate, feeling lucky to participate, and feeling obligated to participate were conducted within each protocol type (TMS or DBS) group, and involved bi-group comparisons (i.e., from the perspective of an “at risk” individual: At Risk group vs. parallel-instructed Comparison group; and from the perspective of a caregiver: Caregiver group vs. parallel-instructed Comparison group). Willingness and feelings of luck or obligation were not directly compared between At Risk and Caregiver groups. Statistical significance was defined as $p < .05$ (two-tailed).

RESULTS

Sociodemographic characteristics:

As shown in Table 1, sociodemographic characteristics of the three groups were generally similar, although there were significant global differences in mean age ($F(2,237) = 3.41$; $p = .035$) and proportion of women ($X^2(2, n = 239) = 6.78$; $p = .034$), proportion of Hispanic participants ($X^2(2, n = 239) = 6.31$; $p = .043$), and marital status ($X^2(4, n = 240) = 21.76$; $p < .001$). Follow-up comparisons indicated a higher proportion of the comparison group was male (61.3%) compared to the At Risk (51.8%) and Caregiver (41.7%) groups, status; a higher proportion of the Comparison group (50%) were never married, compared to the At Risk (35.7%) and Caregiver (23.3%) groups.

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Willingness to participate, feeling lucky, and feeling obligated to participate:

As shown in Tables 2a and 2b, relative to their Comparison group, the At Risk group endorsed significantly higher mean levels of "feeling lucky" regarding both the TMS ($F(1,115) = 9.836$, p = .002) and DBS protocols ($F(1,118) = 11.540$, p = .001), as well as significantly higher willingness to participate in the TMS study ($F(1,118) = 8.157$, p = .005). While not compared directly, inspection of the mean scores in Table 2a (TMS) versus 2b (DBS) suggested lower interest in the DBS relative to TMS protocols in both groups.

In contrast, as shown in Tables 2c and 2d, the Caregiver group did not differ from their Comparison group on willingness, feeling lucky, or feeling obligated to participate with regard to either the TMS or DBS protocols. Similar to the comparison of willingness ratings for the At Risk group vs. their Comparison group, inspection of Tables 2c and 2d suggested lower interest in the DBS relative to the TMS protocol among both groups.

DISCUSSION

Alzheimer's disease and related dementias (ADRDs) are the source of immense suffering and disease burden, and the impact continues to grow with the aging of the world's population. This study sought to extend the available literature on decision making in the context of hypothetical research scenarios related to ADRDs, with a specific focus on innovative neuroscience interventions (TMS and DBS).

This study was designed to evaluate the effects of decision-maker type on the willingness to enroll (or enroll one's loved one), feeling lucky to have the opportunity to enroll, and feeling obligated to enroll in two hypothetical, non-pharmacologic, neuromodulatory trials for ADRDs (TMS and DBS). The three groups (At Risk, Caregiver, or Comparison) were generally similar in terms of sociodemographic variables, although there were some specific group differences in mean age, gender, ethnicity, and marital status. In particular, the Caregiver group was slightly older, and had slightly more women and Hispanic participants relative to the other groups.

In comparing the Caregiver group to their Comparison group, we found no significant differences in any of the three outcome variables (willingness to participate, feeling lucky to participate, or feeling obligated to sign up), for either of the two research vignettes. As the TMS protocol was described as requiring numerous visits (10 daily visits over the first 14 days), and given the general high prevalence of stress and burden among caregivers, one might have expected this protocol to be less attractive to caregivers than to the non-caregivers. Although this study was not powered as an equivalence design study, it is possible that factors such as stress and burden are more predictive of within-group differences in these outcomes. Thus, future reports of data from the larger study will included multivariable analyses for more fine-grained examination of the person-level characteristics associated with willingness, feelings of luck or obligation to enroll.

It was noteworthy that caregivers did not feel significantly more "obligated" to participate in these novel, neurotechnologically-focused clinical ADRD trials, when compared to respondents without caregiver experience. Feelings of obligation have been minimally

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explored in the context of research on ADRDs. While one recent study of individuals who had participated in multiple AD-related trials found that some participants (including study partners of people with AD) described a sense of "moral obligation" to help others (Bardach et al., 2020), our findings provide reassurance that caregivers do not feel a greater sense of obligation compared to non-caregivers.

In contrast to the lack of differences in key outcomes between the Caregiver group and their Comparison group, we found that, compared to their Comparison group, the At Risk group endorsed higher levels of willingness to participate in the TMS protocol, as well as feeling lucky to have the opportunity to participate in both the TMS and the DBS scenario. As the present analysis did not examine potential factors that influenced these differences, such factors will be further explored in within-group multivariable analyses in future reports. For instance, given the inclusion criteria for the At Risk group (i.e., having a first-degree relative with ADRD or cognitive impairment), it is possible that, for this group, the importance of research on effective treatments for ADRDs is felt more keenly, or is more salient. Such saliency would be consistent with findings from prior studies that have examined the motivations of individuals *without* current cognitive impairment, but who have a family history of AD, to participate in ADRD-focused research (Bardach et al., 2020).

One of the primary ethical concerns surrounding individuals with cognitive disorders—whether through the provision of their own consent, or the consent of a surrogate decision maker—is that the progressive and largely untreatable nature of neurodegenerative disorders could influence people to participate in research that they might otherwise not, including research posing significant risks but few or no potential benefits (Wilkins & Forester, 2020). Although the present study utilized only two hypothetical research vignettes, the present findings nevertheless provide some solace in terms of the general lack of strong differences in willingness to participate, or in feeling lucky or obligated to participate, among both the At Risk and Caregiver groups relative to their respective Comparison groups. Moreover, the general tendency toward lower ratings for the more invasive DBS vignette, relative to the cumbersome but less invasive TMS vignette, suggests that the relevant decision maker groups are in fact sensitive to the risk and invasiveness, and not just short-term burden, associated with different forms of non-pharmacologic neuromodulation studies.

Several interpretative limitations of the present study should be acknowledged. MTurk and similar platforms permit recruitment of large samples from across the United States, rather than reliance on local samples of convenience. However, there is a potential tradeoff in regard to potential reduction in validity of group assignment and data collected due to the unsupervised, self-administration format. In order to address this concern, and consistent with evidence regarding attentional performance among MTurk participants (Hauser & Schwarz, 2016), we applied attention checks embedded within the survey to ensure that participants were carefully reading and responding to the survey questions.

Another important limitation of this study is that the sample does not fully represent the diversity of the U.S. in terms of several dimensions that could theoretically affect trust or candor in responding to survey items, as well as trust and risk/benefit perception of medical research. Although consistent with typical MTurk samples (Levay et al., 2016) the sample

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was predominantly non-Latino Caucasian. Such demographic characteristics could impact research-related ratings (i.e., of perceived risk, benefit, and feeling lucky to participate) in ways that the present data are unable to address. The limitations of MTurk samples have been described previously (Chandler et al., 2019); other methods of sampling that result in more diverse and broadly representative samples would be useful in future studies of research-related attitudes.

Several disadvantages to use of hypothetical scenarios must be acknowledged. Foremost, the contextual aspects of real-life decisions are not presented in a simulated situation. Feelings of hope and desperation are likely less intense. Also, in clinical trials there is often a pre-existing relationship—sometimes brief, but often of longer duration—between the potential participant and the person offering enrollment (i.e., the investigator). Such relational characteristics are not replicable in an anonymous survey of hypothetical choices. On the other hand, when linked to a specific clinical trial (which will generally have a relatively small n at any particular site), it is more difficult to study a large number of people and thereby get a sense of diversity of choices and factors that may influences those choices. Therefore, the use of hypothetical protocols permits greater control over the content, allowing inclusion of realistic procedures that may be on the horizon but not yet present in any particular large-scale trial. To help mitigate, to the extent possible, the limitations of hypothetical scenarios, we intentionally provided content with ecological validity with regard to the types of decisions that people at risk for ADRDs and caregivers may encounter in the coming years. Finally, given the limitations of using hypothetical research scenarios, and the pragmatic challenges of linking empirical ethics research to ongoing clinical trials, we view the two types of studies as providing complementary information, rather than either approach being the ideal one.

However, use of hypothetical scenarios enabled us to tailor the protocols, representing cutting-edge and emerging interventions for which minimal empirical ethics data currently exist, in order to evaluate factors relevant to research participation decision making. In addition, numerous studies from our group (Dunn et al., 2009, 2013; Roberts et al., 2002, 2006; Tsungmey et al., 2020) and others (Bentley & Thacker, 2004; Cotter et al., 2019; Nuño et al., 2017) have demonstrated the feasibility of using hypothetical scenarios to examine informed consent and enrollment choices. The use of these vignettes also allowed us to compare perspectives across respondent groups with different experiences related to ADRDs.

Despite the above limitations, the present study is important as the first to comprehensively compare people at risk for developing ADRDs, caregivers (i.e., the individuals who are most likely to make enrollment decisions when the person with an ADRD lacks decisional capacity), and non-at risk/non-caregiver respondents within the context of non-pharmacologic, neuromodulatory clinical trials for ADRDs. The overall pattern of findings suggests that, in general, both the At Risk and Caregiver respondent groups discerned appropriate differences between the protocols. Although respondents in the At Risk group were more likely to endorse being willing to participate or feeling lucky to have the opportunity to participate, when compared to their Comparison group, they did not manifest higher feelings of obligation to do so. Moreover, they showed lower levels of interest in

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participation in the DBS vs. TMS protocol, which appears appropriately sensitive to the relatively greater risks and/or invasiveness of the DBS protocol (further data examining the influence of perceptions of risk and invasiveness will be described in a separate manuscript). The above speaks to differences in group means, yet there is also much to be learned from factors influencing within group differences. The potential factors for the latter are multiple, and may interact in a complexity of ways. These questions will be the focus of analyses for forthcoming reports from this dataset.

Best Practices

Our finding that the At Risk and Caregiver respondent groups were more likely to endorse willingness to participate/enroll their loved one, as well as feelings of good fortune to have the opportunity to participate, in the clinical trials exemplifies the importance of being clear within the consent process and discussion about the distinction between the goals and expectations of clinical trials versus clinical care. In particular, it may be helpful to explicitly acknowledge, in lay terms, what is referred to as the "therapeutic misconception" (Appelbaum et al., 1982, 2004; Henderson et al., 2007)—and explore ways in which this may manifest among people considering the trial at hand, especially in the context of novel neuroscience-based clinical research. On the other hand, the finding that neither group felt an elevated sense of obligation to enroll offers some tentative reassurance that the primary issue that researchers should be attuned to relates to appropriate information and dialogue, rather than feelings of subtle coercion. It is also comforting that participants were appropriately sensitive to the level of invasiveness of the experimental interventions. Of course, the above discussion is of necessity speculative, given the nature of the present sample and the simulated process used, which is distinct from patients and caregivers invited to actual participation within a typical academic research center. Therefore, explicit awareness of, and care to avoid, any potential for undue influence, must also be retained.

Research Agenda

The present study contributes to a growing body of empirical research on factors affecting the risk:benefit perceptions and willingness of patients and surrogate consent providers to enroll in clinical trials research. Further, this study extends this body of work beyond standard clinical drug trials and toward novel, neuromodulatory trials, which are emerging as part of a broader agenda of dementia interventions research. A next step for this line of research is to consider the possible interactive factors that may moderate relationships between willingness to participate in research and participant perspectives, such as caregiver burden and cultural expectations. Multivariable analyses would enable higher-resolution examination of person-level characteristics associated with willingness, and feeling fortunate or obligated to enroll. Other key steps in this line of research include moving beyond surveys and into novel trials involving actual patients at risk of, or diagnosed with, MCI or ADRDs, to be certain that the patterns seen with simulated scenarios generalize when the decision is salient, real, and pressing. Nevertheless, the initial use of surveys and simulated scenarios is critical to identifying the relevant universe of factors and questions before embedding and adding further non-clinical assessment time to actual trials; the latter will be essential to developing more specific policy recommendations and improving

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safeguards while maintaining respect for autonomy of individuals and protection of those with diminished autonomy.

Educational implications:

This line of research can help inform efforts to educate investigators and their research staff regarding ethical recruitment and enrollment into neuromodulatory dementia research trials. In particular, investigators may want to consider and explore how potential research participants feel about the opportunity to participate. As discussed in the broader literature on informed consent, ethical recruitment and consent practices depend upon an open exchange of information, including clarifying the perspectives, hopes, and expectations of potential participants.

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Authors' Biographical Sketches:

Laura B. Dunn is a Professor in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. Her research focuses on the ethical dimensions of research involving patients with psychiatric illnesses and neurocognitive disorders. Dr. Dunn helped design the study, participated in data analysis, and directed the overall manuscript development, including drafting, revision, and approval of the manuscript.

Jane Paik Kim is a Clinical Assistant Professor in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. She is interested in statistical application to areas of ethics and public mental health. Dr. Kim directed and executed the statistical analysis for this work and assisted in drafting and revising the manuscript.

Maryam Rostami is a Social Science Research Professional in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. Dr. Rostami assisted in data collection, undertook the statistical analyses for this manuscript, and assisted in manuscript development, including helping to draft the manuscript.

Sangeeta Mondal was a Research Data Analyst in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine, at the time this research was conducted. Ms. Mondal assisted in data collection and statistical analyses, and assisted in manuscript development.

Katie Ryan is a Research Professional in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. She serves as the lead coordinator for research projects focused on the ethical implications of innovative interventions and technologies in psychiatry and medicine. Ms. Ryan contributed to survey development, led data collection, and assisted in manuscript development.

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Asees Waraich is a medical student at the Keck School of Medicine of the University of Southern California. She is interested in geriatric psychiatry and neurology, and in particular the ethics surrounding research. Ms. Waraich assisted in the literature review as well as in drafting and revising the manuscript.

Laura Weiss Roberts serves as Chairman and the Katharine Dexter McCormick and Stanley McCormick Memorial Professor in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. Over two decades, Dr. Roberts has received scientific, peer-reviewed funding from the National Institutes of Health, the Department of Energy, and private foundations to perform empirical studies of modern ethical issues in research, clinical care, and health policy, with a particular focus on vulnerable and special populations. Dr. Roberts was the principal investigator for the study that is the topic of this manuscript. Dr. Roberts helped conceived the study design, participated in data analysis, helped revise the manuscript, and approved the final version.

Barton Palmer is Professor in the Department of Psychiatry at University of California, San Diego, and a Staff Psychologist at the Veterans Affairs San Diego Healthcare System. Dr. Palmer has a strong track record of scholarly productivity over the past two decades in the area of empirical research on ethical issues in clinical research and care. Dr. Palmer helped design the study, participated in data analysis, and helped lead manuscript drafting and revision.

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Table 1.

Sociodemographic characteristics of respondents (n=240)

Demographic Characteristic	At Risk Group (n=56)	Caregiver Group (n=60)	Comparison Group (n=124)	p-value[2]
Age, Mean (SD)	38.1 (10.1)	42.1 (13.8)	37.5 (10.5)	**0.035**
Gender, n (%)				
Female	27 (48.2%)	35 (58.3%)	47 (37.9%)	**0.034**
Male	29 (51.8%)	25 (41.7%)	76 (61.3%)	
Ethnicity, n (%)				
Hispanic or Latino	4 (7.1%)	10 (16.7%)	7 (5.6%)	**0.043**
Not Hispanic or Latino	52 (92.9%)	50 (83.3%)	116 (93.5%)	
Race[1], n (%)				
Asian	1 (1.8%)	4 (6.7%)	12 (9.7%)	0.182
Black or African American	3 (5.4%)	10 (16.7%)	12 (9.7%)	
White	50 (89.3%)	44 (73.3%)	98 (79%)	
Other	2 (3.6%)	2 (3.3%)	5 (4%)	
Education, n (%)				
Some college/College degree	14 (25%)	17 (28.3%)	39 (31.5%)	0.606
Bachelor's degree (e.g., BA, BS)	6 (10.7%)	9 (15%)	10 (8.1%)	
Graduate degree	36 (64.3%)	34 (56.7%)	74 (59.7%)	
Employment status, n (%)				
Work full time/Self-employed	42 (75%)	47 (78.3%)	102 (82.3%)	0.371
Work part-time (up to 35 hours per week)	3 (5.4%)	6 (10%)	8 (6.5%)	
Other	11 (19.6%)	6 (10%)	13 (10.5%)	
Marital status, n (%)				
Married/partnered	34 (60.7%)	34 (56.7%)	55 (44.4%)	**<0.001**
Divorced/Separated/Widowed	2 (3.6%)	12 (20%)	7 (5.6%)	
Never married	20 (35.7%)	14 (23.3%)	62 (50%)	
Total household Income, n (%)				
Less than $35,000	18 (32.1%)	12 (20%)	27 (21.8%)	0.127
$35,000 to $69,999	13 (23.2%)	29 (48.3%)	49 (39.5%)	
$70,000 to $99,999	16 (28.6%)	11 (18.3%)	24 (19.4%)	
>$100,000	9 (16.1%)	7 (11.7%)	22 (17.7%)	
Current health insurance, n (%)				
Yes	48 (85.7%)	52 (86.7%)	96 (77.4%)	0.229
No	8 (14.3%)	7 (11.7%)	26 (21%)	
No health insurance in past 12 months, n (%)				0.109
Yes	12 (21.4%)	21 (35%)	28 (22.6%)	
No	44 (78.6%)	37 (61.7%)	95 (76.6%)	

[1] Respondents were able to select more than one race.

[2] p-values correspond to chi-square for categorical variables and one-way ANOVAs for continuous variables.

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Table 2a.

TMS Protocol: At Risk Group vs. Comparison Group for At Risk (Comp-AR)

Item	At Risk[2] (n=56)	Comparison (Comp-AR) (n=64)	p-value[1]
	Mean (SD)	Mean (SD)	
Willingness to participate	6.1 (1.0)	5.5 (1.4)	0.005
Would feel lucky to participate	5.8 (1.0)	5.1 (1.4)	0.002
Would feel obligated to sign up	3.4 (2.0)	3.2 (1.9)	0.553

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Table 2b.

DBS Protocol: At Risk Group vs. Comparison Group for At Risk (Comp-AR)

Item	At Risk[2] (n=56)	Comparison (Comp-AR) (n=64)	p-value[1]
	Mean (SD)	Mean (SD)	
Willingness to participate	4.4 (1.6)	4.1 (1.8)	0.235
Would feel lucky to participate	5.1 (1.7)	4.0 (1.8)	**0.001**
Would feel obligated to sign up	3.3 (2.0)	2.9 (1.9)	0.314

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Table 2c.

TMS Protocol: Caregiver Group vs. Comparison Group for Caregiver (Comp-CG)

Item	Caregiver[3] (n=60)	Comparison (Comp-CG) (n =60)	p-value[1]
	Mean (SD)	Mean (SD)	
Willingness to participate	5.4 (1.4)	5.4 (1.5)	0.949
Would feel lucky to participate	5.4 (1.6)	5.2 (1.4)	0.637
Would feel obligated to sign up	4.4 (1.8)	4.3 (1.7)	0.838

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Table 2d.

DBS Protocol: Caregiver Group vs. Comparison Group for Caregiver (Comp-CG)

Item	Caregiver[3] (n=60)	Comparison (Comp-CG) (n=60)	p-value[1]
	Mean (SD)	Mean (SD)	
Willingness to participate	4.6 (1.5)	4.3 (1.9)	0.353
Would feel lucky to participate	5.1 (1.3)	4.7 (1.5)	0.134
Would feel obligated to sign up	3.8 (1.6)	3.3 (1.9)	0.086

[1] p-values correspond to one way ANOVAs.

[2] At Risk group + Comp-AR were asked:
"How willing would you be to sign up if you were in Mary's/Joe's shoes?" (1 = "not at all willing" to 7 = "very willing");
"If I were in Mary's/Joe's shoes, I would feel lucky that I was offered the opportunity to participate in this study" (1 = "strongly disagree" to 7 = "strongly agree"); and
"If I were in Mary's/Joes shoes, I would feel obligated to participate in this study" (1 = "strongly disagree" to 7 = "strongly agree").

[3] Caregiver group + Comp-CG were asked:
"How willing would you be to sign up Mary/Joe to participate in this study if you were in Casey's/Pat's shoes?" (1 = "not at all willing" to 7 = "very willing");
"If I were in Casey's/Pat's shoes, I would feel lucky that Mary/Joe was offered the opportunity to participate this study" (1 = "strongly disagree" to 7 = "strongly agree"); and
"If I were in Casey's/Pat's shoes, I would feel obligated to sign Mary/Joe up for this study" (1 = "strongly disagree" to 7 = "strongly agree").