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ARTICLE

Subject and Family Perspectives from the Central Thalamic Deep Brain Stimulation for Traumatic Brain Injury Study: Part I

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Abstract
This is the first article in a two-part series describing subject and family perspectives from the central thalamic deep brain stimulation for the treatment of traumatic brain injury using the Medtronic PC + *S* first-in-human invasive neurological device trial to achieve cognitive restoration in moderate to severe traumatic brain injury, with subjects who were deemed capable of providing voluntary informed consent. In this article, we report on interviews conducted prior to surgery wherein we asked participants about their experiences recovering from brain injury and their perspectives on study enrollment and participation. We asked how risks and benefits were weighed, what their expectations and fears were, and how decisions were reached about trial participation. We found that informed consent and enrollment decisions are fraught. Subjects and families were often split, with subjects more focused on putative benefits and families concerned about incremental risk. Both subjects and families viewed brain injury as disruptive to personal identity and relationships. As decisions were made about study enrollment, families struggled with recognizing the re-emergent agency of subjects and ceding decision-making authority to subjects who had previously been dependent upon them for protection and guidance. Subjects and family members reported a hope for the relief of cognitive disabilities, improved quality of life, normalization of interpersonal interactions, and a return to work or school as reasons for study participation, along with altruism and a desire to advance science. Despite these aspirations, both subjects and families appreciated the risks of the intervention and did not suffer from a therapeutic misconception. A second essay to be published in the next issue of *Cambridge Quarterly of Healthcare Ethics—Clinical Neuroethics* will describe interviews conducted after surgery, the effects of cognitive restoration for subjects, families, and challenges presented to the social structures they will call upon to support them through recovery. This subsequent article will be available online prior to its formal publication in October 2023.

Keywords: brain injury; deep brain stimulation; cognitive restoration; narratives; neuroethics; disability rights

Disrupting the Trajectory of Brain Injury

Following hospital discharge for traumatic brain injury (TBI), many patients will experience significant long-term disability including chronic cognitive impairments that disrupt vocational, social, and emotional functioning[1,2,3] but imagine if a novel neuroprosthesis could disrupt this life-long trajectory of disability. What significance would that have for lives that have been suddenly and permanently upended?

While we are still a long way from an established treatment for moderate to severe brain injury, the recently concluded central thalamic deep brain stimulation for the treatment of traumatic brain injury using the Medtronic PC $+$ S (CENTURY-S) study represents a promising step toward a novel therapeutic. The objective of this invasive neurological device trial was to assess whether focus and attention could be improved via stimulation of the centrolateral thalamus in people with moderate to severe TBI. It was hoped that this intervention would foster cognitive restoration for individuals who had regained functional independence but whose vocational and social reentry remained limited by their injury.

As will be reported elsewhere in detail,[4] the results of the CENTURY-S study were encouraging. The devices were safely implanted at the thalamic target in all six subjects enrolled. Objective neuropsychological testing in the five subjects completing the study demonstrated improved processing speeds indicative of remediation of impaired cognitive function. Nicholas D. Schiff, Christopher R. Butson, and Jaimie M. Henderson presented preliminary results at the *Ninth Annual Deep Brain Stimulation Think Tank* held on August 25–27, 2021 in Orlando, Florida.[5] All subjects in this report exceeded the primary endpoint of 10 percent improvement in the time to complete Trail-Making Test part B, a measure of processing speed. This finding was consistent with subject self-reports on standardized TBI-specific quality-of-life measures assessing attention and executive function. Even after a brief open label period of 3 months, two of four subjects had a one-point increase on the Glasgow Outcome Scale-Extended (GOS-E) from their preoperative baselines. Without indulging in a therapeutic misconception,[6] these data suggest an historic inflection point and a promising new intervention for individuals for whom no effective treatments currently exist.

Though this objective evidence is encouraging, these metrics only tell part of the story. They fail to capture the subjective experience of subjects who decided to participate in the trial and their families. To that end, we conducted semi-structured interviews with subjects and their families.[7] Our work as investigators embedded in both the parent CENTURY-S study and this qualitative research falls in the lineage of *participant observation* pioneered by the great American sociologist, and sometimes bioethicist, Renée Fox.[8,9,10] This gave us a unique perspective on translational neuroscience as the study was conceived and implemented. This methodological "binocularity," to invoke Erik Parens's framework,[11] has informed our approach.

Prospectively, we elicited the perspectives of subjects and family members about their experiences with brain injury, how they reached decisions about trial participation, and their hopes and fears. After implantation, we asked whether restoration had been achieved and if it had an impact on personal identity, self-determination, dependency, personal responsibility, and interpersonal relationships. Finally, we asked whether cognitive restoration prompted a reassessment of life goals and challenges, or barriers encountered en route to social reintegration as they rethought their lives. Data from the preoperative interviews will be presented here. Postimplantation data will be reported in the October 2023 issue of *Cambridge Quarterly of Healthcare Ethics—Clinical Neuroethics.*

Through the integration of ethics research into the fabric of this novel neurological device clinical trial, we have had the opportunity to accompany subjects and families in this first-in-human study. Their narratives suggest that informed consent and enrollment decisions are fraught. Subjects and families are often split, with subjects more focused on putative benefits and families concerned about incremental risk.[12] As subjects made decisions, families struggled with recognizing the autonomy of subjects and ceding authority to now capacitated subjects. Both subjects and families appreciated the experimental nature of the study and did not suffer from a therapeutic misconception.

Scientific and Normative Antecedents

The application of neuromodulation to brain injury follows in a scientific lineage that began when Benabid pioneered deep brain stimulation (DBS) to treat drug resistant Parkinson's disease (PD).[13,14] Since then,[15] DBS has evolved as an investigative intervention for a number of neuropsychiatric conditions, most notably depression,[16] obsessive compulsive disorder,[17] and brain injury, notably the minimally conscious state (MCS).[18]

Patients in the MCS, a state of liminal consciousness,[19] were chosen as an initial subject population because these individuals have intact but under activated neural networks with the potential for *integrative* neural function with thalamic stimulation. Such stimulation activates the *mesocircuit*, a complex brain circuit involving the thalamus, basal ganglia, brain stem, and cerebral cortex and reestablishes integrative cortical function.[20] In 2007, our group demonstrated that thalamic stimulation could restore executive function, spoken language, and motor control in MCS in a single subject.[21,22] Importantly, that subject also regained some degree of personal agency with the ability to participate in decisions at the level of assent and dissent. He was able to voice preferences, tell his mother he loved her, and express emotions.[23]

For consent in the MCS study, we utilized a legally authorized representative with the proviso the subject would be consented should decision-making capacity return. While neuromodulation did restore elements of agency, autonomous decision-making capacity was not achieved.[24]

The *current* trial follows in this scientific and normative lineage. Having demonstrated the safety and putative efficacy of thalamic stimulation in MCS, the risk-benefit ratio made intervention in moderate to severe brain injury ethically proportionate. These subjects started with a higher functional status and could provide voluntary consent.

This capacity for communication and consent makes this study normatively and methodologically distinct from the MCS study, providing *an opportunity to engage subjects in conversation* about their views and experiences. These conversations are complemented by interviews with family members.

Previous scholarship described patient experiences with DBS in PD and psychiatric conditions.[25,26,27,28,29] The only report of a patient receiving DBS for severe brain injury is a surrogate account found in *Rights Come to Mind: Brain Injury, Ethics and the Struggle for Consciousness.*[30] Here we add to this scholarly literature so that subjects and families in the landmark CENTURY-*S* trial can tell their own story.

Methodology

Our subjects were drawn from the "Central Thalamic Stimulation for Traumatic Brain Injury" [UH3 NS095554, NCT 02881151], a study designed to assess the safety and efficacy of DBS for patients with moderate to severe brain injury (GOS-E levels 5–7). The CENTURY-S study enrolled six decisionally capacitated research participants. Each participant was assessed by an independent consultation-liaison psychiatrist to confirm their decision-making capacity and ability to provide voluntary informed consent.

Once enrolled in the CENTURY-S study, subjects were approached by Dr. J. M. Henderson regarding their willingness to participate in this study. If the subject agreed, permission was obtained to ask at least one family member about participation. We then obtained informed consent from subjects and family members.

Using existing scholarly literature, as well as prior narrative work with families touched by brain injury, we created a semi-structured interview schedule that included questions about the subjects' and family members' experiences of brain injury, recovery, recruitment and consent for the CENTURY-S study, their hopes and concerns for study participation, their experiences in the study, and their future hopes and concerns. Interviewing both subjects and their family members allowed us to identify perspectival similarities and differences. The semi-structured format yielded standardized questions and provided respondents the freedom to direct parts of the interview and for follow-up questions. This approach allowed for "expansions and clarification"[31] and identification of "unanticipated data."[32]

Interviews were conducted before and after surgery to follow perceptions over time. The first set of interviews were conducted prior to device implantation. The second set were done after the study's "treatment phase." When the second set of interviews occurred, subjects had been exposed to at least 3 months of stimulation. Stimulation continued after the formal CENTURY-S study concluded.

Interviews were audio-recorded and transcribed. We analyzed transcripts using Atlas.ti, computer-assisted qualitative data analysis software,[33] to organize and systematically code qualitative data.[34] Data were coded deductively and inductively. Standard interview questions allowed the use of predetermined codes. Using the method of grounded theory, inductive coding was employed for unanticipated responses. Transcripts were coded line-by-line and aggregated into conceptual codes, reflecting emerging themes or patterns.[35,36,37] Quotations were edited for clarity without altering intended meaning.

In-person interviews were conducted for the pre- and postimplantation interviews of the first subject and family member and the first interview of the second subject. Thereafter, due to COVID-19 restrictions all interviews were conducted over Zoom.

Stanford University School of Medicine served as the delegated Institutional Review Board for partner institutions on the CENTURY-S study. This qualitative study received IRB approval from Weill Cornell Medical College, Stanford School of Medicine, and Pennsylvania State University.

Demographics

Eighteen subjects were interviewed of whom eight were surgical candidates and 10 were family members. The eight surgical candidates were drawn from 419 potential candidates who were screened for the CENTURY-S study and referred to us. Of the eight candidates who underwent formal presurgical evaluation, two opted not to proceed to surgery: one whose symptoms were deemed less amenable to the study's goals; another who withdrew consent because of family opposition. These interviews (two subjects and one family member) were excluded from analysis.

Six subjects (four males; two females) underwent surgery and had preimplantation interviews. All subjects were white and spoke English as their first language. Their age range was between 22 and 60 years, average 36.2 years, with five to six subjects in their 20s or 30s. Time since their injury was 2–18 years, with an average time to implantation of 7.7 years.

Interviews of subjects and family members ranged from 30 minutes to 2 hours. Subjects had shorter interviews than family respondents. Total preoperative interview word count for subjects was 69,094 (range 6,843–14,921) and 74,507 (range 3,804–18,313) for families.

One subject had her stimulator removed because of a postoperative wound infection. Given this adverse event, she was disenrolled from the CENTURY-S study and follow-up interviews were not conducted. With this disenrollment, there were six preoperative and five postoperative interviews involving six subjects and nine family members.

What Brain Injury Has Wrought: Personal Identity and Dependency

Brain injury is a life-altering event for patients, families, and caregivers, making these events socially constructed and relationally significant. Families, when they are present, are integral to the recovery process and deeply affected by brain injury.[38] As one survivor reflected, "The difficulties and struggles that I have faced through this time have not been mine alone, my loved ones have been right there with me on this wild, confusing and frustrating ride."[39]

Beyond the burdens of surrogate decision making during periods of incapacity in acute care,[40] families assume longitudinal decisional responsibilities for which they may be ill-prepared.[41] After a loved one survives a brain injury, families report changes in family caregiving roles,[42] the burden of ambiguous loss coupled with the paradoxical presence and absence of their relative with whom there may be altered, lost, or reformed identities,[43] and behavioral changes.[44] These stressors can result in relational identity reconfigurations between patients and relatives that are further reflective of the interpersonal instability that can follow severe brain injury.[45] These dynamics can be exacerbated by deficient or inadequate access to rehabilitation[46] and psychosocial support.[47,48]

Our study sought to understand how DBS affects personal identity, interpersonal relationships, functional status, and dependency. Studies show that patients may view their injuries as deficits and express a sense of abandonment related to perceived dependency,[49] challenges mitigated by the reemergence of self-identity, resilience, and recovery.[50]

Subjects and families in our study were keenly aware of the changes that brain injury had wrought….

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A subject in early middle age was injured decades earlier as she was about to start graduate school reports how brain injury had caused amnesia and subsequent memory problems; an inability to filter (she described herself as less "polished," more "blunt"); anxiety, obsessive compulsive disorder (OCD), and panic attacks; irritability; physical numbness; and the inability to read and understand a book or operate a cash register. The subject has insight into her lost capabilities. Following her injury, her mother reports that the subject is irritable, impulsive, dependent, anxious, naïve, and has trouble focusing, difficulties with short-term memory, and insight into lost abilities. They also report that the subject has left foot drop and often falls. The subject lives next to her family who pay her expenses. The subject reports good family relationships but desires more independence.

Her mother reports that the subject is a "totally different person" after brain injury[51] [P210]. She told us that the person "… you met today is the improved version, who is really nothing like who she was. And my husband got very angry at me in the very beginning because I turned to him and—I was grieving—I said I've lost my daughter. My daughter's dead. I do not know who this is. And he got very mad … He could not understand what I saw: the essence of my daughter had changed forever." She grieved the loss of her daughter, "Knowing that she could never be who she was before." She took months off from work to provide care noting, "I raised her all over again."

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Another subject in her late 30s whose injury was more recent reports "blackouts," possible seizures, headaches, and memory impairment as well as problems with multitasking, organization, disorientation, daytime somnolence, and emotional lability. Some friends thought she was her old self and others did not. The subject felt she was not the same person as before her accident. Speaking in the plural first person she observes, "The way of life changed, that we were not feeling who we were. We did not feel like we were up to par of our own selves" [P137]. Before the accident she was confident and self-sufficient, "I made myself this really bad ass woman that was going to make it no matter what without anybody's help. I prided in the person that I became. Almost every day I could almost work some job or be on call somewhere."

But it all changed after her injury. She recalled a friend told her, ""Look at you now. You ain't worth shit.'" Painfully, she acknowledges that her friend was, "Right to an extent that I wasn't the same person." She laments, "I miss the me that I was where I knew who I was every day." She reports problems with executive function and dependency, "Every single problem is a brand-new start. It may take you in different directions. It's very, very, very hard. To have the right support system around you that's not going to push you down at the same time." Friends and society were impatient with her pace of recovery, "They're like, 'You just bumped your head. Let's go.'" While her friend reports that she is becoming more like the person "that 1 know" she remained a "shell of herself."

It has been a struggle to regain independence and self-sufficiency, "Now you are just supposed to build it and figure it out. There's not anybody really there to help you learn the day-by-day stuff. When you do find people, they cannot be there all the time because they need to go to work. You've got to try to rely on yourself and trying to figure out like a little baby tries to figure out what they can. They start crawling. They start walking. You're doing the same thing, but you are at a different level in your life when you are expected to know how to do all that."

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A subject in his early 20s who resides with his family reports that he had significant postinjury amnesia, impaired memory, an inability to "multitask," sleep problems and fatigue during waking hours, poor concentration, immaturity, "literal" thinking, and difficulty in making cognitive "connections." He reports daily headaches and effects on libido. His mother reports confabulation and immaturity. She feels he is not as smart, has a juvenile sense of humor, is more naïve, and that thinking is more difficult for him.

The subject is aware of how his injury has changed his relationship with his family which prides itself as a "smart" family. The subject's mother notes, "… we were accustomed to having quick, witty …

conversations very commonly and it just is not as easy for him now" [P308]. After the injury, the family had to slow their pace and accommodate the subject. He reports that "… it's taken a fair while for my family to also slow down to my speed and to predict the speed I'm going to have to catch up with them … I did not realize how nice it was for them to … calmly wait and patiently wait the whole time." His mother reports that "I mean we just have more concrete conversations now … It was hardest at first when he was the most regressed … it was just exasperating to have … the entire family dynamic then revolved around a lower plane of abstract thought because we were not gonna exclude him from conversations." As she put it, "… our family's really bright and it just felt like, you know—Not that he was dumb, but I just did not know how to interact with him because what he considered interesting and amusing just did not—I did not know how to relate to it anymore."

Both the both subject and his mother report that he is not the same person. The subject told us, "I would say I'm similar, but I'm not sure I would say I'm the same." His mother reports that he is an *immature* version of himself, so much so that "… he's enough different that it feels like he's a different person. He's less mature … he thinks the dumbest things are funny." When asked if this was a cognitive deficit or a developmental regression she told us, "I definitely felt like he was regressed … he would refer to, [himself], 'Uh, look what seven-year-old [name deleted] is doing or saying.' And I would say that to him … 'Now you are a seven-year-old.' "And she would try to explain why this was happening, "That part of your brain is making you act this way,' you know?"

Remarkably her son, reminded her "… of a younger self. I do not know if it was his same younger self … I mean he still had experiences that his seven-year-old self had never had … I do not feel like [he's]… not smart enough in a way or something … it just felt like he could not access that … he just used to have a much, more advanced ability for abstract reasoning…"

There was mourning in her voice, for what was lost, as well as the novelty of meeting someone familiar *for the very first time*, "In a lot of ways it's like, greeting someone and nobody else can tell why because he's still right there but it's not him, right? You're meeting someone new and getting to know them and learning how to be with them … in one way it's still someone you care a lot about because you care a lot about this person that was. *But you do not even know this new person* and it takes a while for you to decide if you even like them because it's a new person."

This felt like an irretrievable loss: her old son would never return. With resignation she told us, "… I'm forgetting who that person was to a certain degree at this point. This is five years later… There's damage to parts that did things and gave him characteristics that—it's not magically gonna come back. He's gonna grow into something else, something new."

Her husband was more accepting of the new version of their son, but the subject's brother, "… wishes really hard that-that the old [subject] would come back. They were good friends. And I guess I would like that, but … it's not something I hope and wish for anymore." When asked if it might be possible to get her "old son" back, she was philosophical and realistic, "I do not even know what that would mean … I mean you have to separate getting the old him back from getting him to a place where he's suffering less and happy in his life … I think at this point I just would like him to be able to get the degree of functionality that would make him feel good in the world."

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A middle-aged man injured 3 years before enrollments reports headaches, vision and memory problems, difficulty sleeping and nightmares, depression, neurofatigue, and challenges with routine tasks like bill-paying. He reports that his partner thinks he is nonempathetic and meanspirited. The subject's adult son reports that his father can no longer multitask, has difficulty with operating computer technology and email, lost his work ethic, is overly argumentative, and more emotional. He also reports that the subject has neurofatigue. The subject's partner reports that he has become immature, irresponsible, impulsive, and manipulative.

The subject reports, "I think I'm different" [P336] but is surprised when his partner, "… tells me things about my personality that I had never heard in my whole life. I was married the last time for … 21 years; and… she called me on a lot of things, but she never called me insensitive or ….

non-empathetic; never heard that …" He also reports an old friend who wanted to remember the subject as he used to be. The subject reports that although he is different, his core is the same, "I still have a big heart. I'm still a good guy that way." He is saddened "… because I always think I'm thinking of somebody else … But apparently that's changed … have I really changed?" He added, "I can accept that I'm not the same person, being able to do certain things; but when your personality changes, and you are not the person you strived to be your whole life … it's demoralizing. It's really frustrating …" He told us, "I'm hoping to be able to work through that … and … self-regulate better."

The subject's partner says that he is a "new person." His son observes, "… he lost his identity, because he identified himself as someone who worked hard and [was] a successful businessman." After the injury he has become dependent on his partner. "One thing I have to learn to do is accept help and also ask for help" to compensate for "… my deficiencies…" He thought "… I was paying my bills just fine. Then [his partner] decided to take a look, and it was a disaster. I was paying thousands of dollars to people that I did not even owe money to… that was quite a shock … So she pays my bills now… I really do not trust myself on anything important … ".

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Many of the themes about cognitive capacity and personal identity are reprised in this subject in his late 20s/early 30s whose injury occurred a decade earlier. Per his report, the injury limited how much information he can "hold in [his] mind", decreased his "wit," caused memory problems, and made it difficult to make decisions or process several emotions concurrently [P378]. It caused introversion, social aversion, and learning challenges which has altered his interests and hindered his ability to work. His mother observes he is often nonemotional and not as social as she thinks he should be. He is unable to maintain focus and read much, and has memory and attention issues, which impacts his ability to keep a job. This frustrates him because he is unable to do the types of things (e.g., advanced college level math) he used to do. In addition, he has massive mood swings that can frighten others. His mother notes, "He's totally frustrated. There's been times where he has, his mood swings … can be very huge. And he gets extremely frustrated because he cannot do what he wants to do. He cannot live the life he wants to live. He cannot remember to do a lot of things."

Both the subject and his mother think that he is different after injury. The subject observed, "… I'm a different person. The day I woke up, I liked different things. I hated different things. I acted different ways … I liked different things, like different genres of movies, different types of movies, different types of books…" And then insightfully appreciating how his life had changed he pointed to his bookshelf telling us that, "… the most common theme is a fiction book involving time travel, where the main character goes back in time or forward in time … to fix things; and you can see there's a correlation with that and my life, obviously … I now like that type of book, which I never really read before, time-travel books."

As the subject seeks to repair his life, his mother mourns a lost past. She confesses, "And you know, when you see me get teary eyed with you, there are many times that to this day where I … just have myself a good cry, because it just never goes away. You know … it's really, really hard." The subject mother's reports how caregiving has transformed her life. As she told us, "… life is never the same. Nor will it ever be, I do not think. There's a saying you are only as happy as your least happiest child … And so [he] is my least happiest child right now. Sometimes it flip flops, but [he] is not happy. And so you know, his life is not on track."

Her life trajectory has also been altered, "It took me a long time to get my life going again where I would actually live my life … start dating again, start going away even on a little weekend trip. I was afraid to do anything. And so that took a long time and now I do. But even when I do that, it's not like [he's] not capable of living alone…"

Her son's prolonged dependency changed their relationship and her sense of obligation. She told us, "… for a while after the accident he would tell me everything, almost to a fault. You know, TMI … And then it's gotten now where it's almost like he does not want to share a lot of stuff with me. And that's OK … But life is not the same. Our relationship is good. You know, [he] and I, we [have]—this thing, you know, it bonds you. When you are with somebody 24/7, you know, from pretty much a year of rehabbing him, you bond."

It is a bond borne of experience that is even stronger than what she experienced in bringing up her children, “You know, more so than with a regular child that you just live a normal life with. So we have a special bond, I think, as a mom. He may not see it like that. Because he does not have children. So you do not get it. But we do—there is a certain love between us. Knowing he knows I’m there for him no matter what. I know that [he] knows that. And I think he would say that in a heartbeat, ‘My mom will do anything for me at any time.’ And I know that if I needed [him] for something, I know that he would be there for me. Because he appreciates and loves me for all that we have been through. So the relationship is very good. Yet he has over the course of the last few years, has kind of kept private things private now. And that’s OK. He thinks I’m nosy. *I’m a mom. It’s what we do.*”

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A final subject in his late 20s was injured, nearly a decade earlier while attending college. He has weakness on the right side and memory difficulties. His parents, who were both interviewed, note he has significant short-term memory impairments (e.g., cannot remember the plot of a movie a couple of days after watching it), occasional fits of anger, problems with “self-organization” (i.e., executive functioning), and is slowly regaining the ability to understand and learn a joke. They told us he “performed his own lobotomy” [P410].

The subject’s speech is sparse and halting. When interviewed he would lose his train of thought. Asked whether his personality changed after his injury he told us, “I am told that I’m apparently a lot more calm … apparently. I would not recommend to anyone, going through the procedures that I went through to mellow out …“When one of us observed that he seemed like an “easy going person” he replied, “… apparently I wasn’t really always like this.”

His father wondered “if sometimes we baby him” noting that, “He’s not a kid anymore, but he’s still a kid.” His mother has had to help him organize his college work, “I had to sit next to him for the whole class and read every assignment with him and read the work, and then we’d go through the test … and I’d ask him a question, and he would not know the answer. I’d tell him the answer, and he would forget immediately after.” Over time he made progress, but it was tenuous. Once he mistakenly forgot an assignment and realized he had overlooked it and asked his mother for help. As she recalled, “…we spent all day Saturday on one problem. And I was like, you cannot—there’s no way. So he failed that class.”

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All subjects and family members reported that brain injury caused profound changes to the subject’s abilities and personalities. Phrases such as “old self” were used frequently to describe subjects before their brain injury. Interviewees also reported that brain injuries changed family relationships with altered caregiving responsibilities. These ruptures to personal identity and agency often prompted subjects and their family members to seek out new treatments or research opportunities to mitigate the negative effects of the brain injury, which will be discussed in the subsequent section.

Finding the Study

One of the challenges of novel neuroprosthetic trials is meeting enrollment expectations. This is especially difficult in a first-in-human neuro-invasive phase I study where electrodes are implanted into a recovering brain. Several respondents heard about the trial through PatientWing.com a service with which CENTURY-S contracted and from a *New York Times* article[52] that profiled the study following a presentation at the 2019 NIH BRAIN Initiative meeting reporting results in the first study subject.[53]

Many subjects and their family members scanned the scientific and clinical trial literature for possible therapies. The mother of the first subject told us, “…we [my husband and I] always watch what’s being studied … So we are always cruising the research sites. And it popped up on … And [he] goes, ‘… look at this. It’s stem cells’ and I go, ‘It’s not stem cells … that’s deep brain stimulation.’ And I read it, and you described our daughter" [P210]. When asked what it felt like to find what appeared to be a match she replied, "You have no idea. Yeah. Literally … Actually, my heart started to beat faster. It clicked. I immediately grabbed this phone, and sent an email …"

Another subject was encouraged by friends to search online for research opportunities, "… a couple of my friends, they know the medical world. They're like, 'There's something else out there for you.' I'm like, 'I know there is, but I'm frustrated.' I kept looking on the internet. I'm like I could not find the right websites to find anything" [P137]. She was also exhilarated when she found the PatientWing.com listing, "I'm like there's no way that study is really out there. I'm hitting every single thing going down it. I'm like no way… I was just like everything just hit." She elaborated, "It was the whole memory thing, the cognitive things … It was just like every little piece, everything going down the organization to your whole day. I'm like wait a second. It's out in California. I still go out there."

She read in disbelief, "I just stared at it for a minute. I'm like no way. Am I really reading this? I actually went outside for a little bit. I came back in. I'm like read it again. It really is there…. [My friends would] be yelling at me and kicking me if I did not do this. I put in all my information." She heard back in a couple of days, not ever expecting a response.

One mother first read about the study in *The New York Times*, "It was about a year and a half ago. And I was like, 'Oh my God.' And it's at Stanford. It was just amazing… from how they described it looked to me like he'd be a perfect candidate. So I was just really excited and hopeful … he would be accepted" [P308]. One subject found it via advertising on Facebook. Worried it might be "suggestive advertising" he was assuaged when he saw the Stanford affiliation [P336].

Another subject made it a habit of perusing the internet for new studies. He told us, "Every six to 12 months, I google any ongoing or … starting studies that might improve brain injuries, and then if I think it's worthwhile, I'll try to get into one. And that's what I did" [P378]. He also found the study via *The New York Times* article. When asked how he found the study he told us, "… this specific study… I have it on my phone, actually … I have this tab saved … from *The New York Times*, that says, "Doctors Use Electrical Implant to Aid Brain-Damaged Woman."[54]

The subject's mother confirmed this account, "He found this all. [He's] been researching for 10 years… So this is something that's been ongoing for 10 years, and [he] has adamantly been researching for 10 years straight. And then he came across this study."

Another mother discovered the study by accident having heard a story on National Public Radio on stem cells and paralysis. Out of curiosity she googled it to learn more and stumbled on "…experimental therapies for TBI, and this study popped up at Stanford and I called" [P410].

These accounts of study discovery suggest challenges of unequal access to such trials and a bit of luck. Whether the study was discovered by subjects or their families all had access to smart phones and computers, along with the requisite computer literacy, and educational attainment necessary to process the information. But beyond that, discovery was a random event, and it was a close call as one family reminded us, "… And if we had not kept, just every month or two, gazing, we never would've seen this study" [P210].

Reasons for Participating

A previous study using semi-structured interviews with patients with drug resistant depression who passed screening to enroll in a DBS trial found that motivations for participating in this particular neuromodulation trial varied. Many patients cited: exhausting treatment options and desiring to take initiative with respect to their depression; thinking that DBS would be an effective treatment for them and that they will receive direct benefit from participating in the study; and interpreting messages from their physician or the researcher that DBS will be efficacious. Others cited altruism.[55,56]

Three of our six subjects spoke about altruism, contributions to science, or giving back to help others. One subject spoke altruistically and about having a sense of purpose through study participation. She knew this was a first-in-human trial and told us, "I think it's kind of cool. I mean it could be groundbreaking. I could be helping a lot of people. I mean not only am I going to help myself, but …

I mean there could be lots of people that I could be helping who have head injuries" [P410]. Reflecting on life's disappointments following her injury, she found solace in being a study participant, "I mean at least I served a purpose. You know what I mean? Like, okay, I've suffered, but look at all the other people that I'm going to help. So that's really cool. I've always wondered: what's my purpose in the world? Maybe this is a purpose. That's kind of cool… I [had not had] a purpose, and maybe this is my purpose."

Her mother explained her daughter's rationale, "She said, 'You know, mom, I have not been able to do anything I wanted to do with my life. I really have not done anything in my life. Maybe this is what I was supposed to do with my life. Maybe I can make a difference for somebody else.' And I agree with her. I think all of us as human beings should strive to leave everything we do, or whatever we experience, better than how we found it."

A second subject reported a desire to "give back" to medicine and to others suffering from brain injury [P137]. She told us, "… it's more than just for me. If I get nothing out of it, so be it. I tried. At least then that's part of the study for the future as well. It's also me giving back to the medical world as well… for the future down the road that changes the medicine." Like other subjects, she felt a sense of accomplishment through participation, "I made it out here. I did this on my own. I found this study on my own." Her friend acknowledges her noble motivations and says the subject is pleased with her participation and hopes to give back to others, "Yes. I think she understands it. One thing she did mention was that she's proud to be part of the first cases like this. She hopes that something positive comes out of it." But he also notes that "her primary concern was to get well."

The parents of another subject report that their son wants "to make progress" and "help science" [P210]. His parents interpreted his motivations as mixed, "… he feels it's important to help science and be part of a study, and Stanford, obviously he has a lot of respect and reverence for … and trust … but, I think maybe you'll find out when you ask him [that]… he wants to help science and be a part of that, or if it's more because he wants to … progress. I think it's both."

Beyond altruism and a sense of purpose, the first of these subjects had hopes for a better life, "… there's so much I've suffered … I mean, I have not been able to work, I have not been able to do anything for 18 years." And with a sense of desperation,[57] "So it's more like might as well try it. I've lost everything" [P210]. She told us, "I just want to be happy again." When asked if she ever had a good day, her reply was mixed, "Yeah, I do … No, I do not feel like I have happy days. I just feel like they are boring." She did not report being sad but rather unfulfilled. She had memories of her former life and she knew her current state was intellectually impoverished by comparison.

Her mother shared this metaphor, "We're in this room. The door cracked. If I can pull my door open, I'll get to see more. She'll get to do more. There might be opportunity there. Should we take it? Of course. We know what's in this room. We've been in this room for 18 years. I'm sick of this room. I'd like her to be able to do more. She's sick of this room. Hope. A little light. Opportunity. We could see something else. Why would not you go?"

Another subject expressed the hope that the study would decrease headaches and regularize his sleep. His mother took the long view about a successful outcome given his life expectancy, "I do not know the extent to which the researchers look at this, but from my perspective he's young enough that if this works for him, he's got the whole rest of his life to benefit from it. And this is, you know, potentially 60 more years of benefit, and so that's a long lever I guess as far as improved quality of life" [P308].

One subject quantified his reasons for participating, "I just figure, if I have this surgery, and I can improve even 10 percent of my thinking, it might help everything along the way; the depression, everything; just because … it will not be quite as hard to get through daily struggles" [P336]. His son also frames it numerically, "He's so ambitious… [it is]… harder to do those things, but he can never multitask. And now he's getting like an overload of information … he just wants that 5 percent, that 10 percent. But he does not have the ability to put in that work to achieve that 5 or 10 percent. And I think that's what drove him to this operation, because he thinks that it will do it itself."

Another subject had a greater degree of desperation because "his life cannot get much worse." Given this there was no reason not to participate in the study [P378]. As he told us, "I do not go anywhere or do anything, and I'll never have … have a full-time job, so worst-case scenario, I still sit at home doing nothing all day." Given these prospects he asks himself, "… can I find any excuse not to have brain surgery? And I'm still here, because I cannot find any reasons why I should not have brain surgery; because basically what that means to me is, I do not want to live this life currently. So let us try to find a way to change it."

Participants in our study reported several motivations for study participation. Similar to subjects in a trial of DBS for depression, many were motivated by altruism and wanted to help scientific advancement and other people who have severe brain injuries. Some framed their decision to participate in the study as their "purpose." Many were also motivated by a hope of improving their own lives. None of the subjects reported their healthcare providers or the CENTURY-S research team suggesting that subjects participate in the study to obtain relief from suffering caused by their brain injury. This is likely due to the quality of the informed consent process and screening out prospective participants if there was evidence of a therapeutic misconception.

Informed Consent Process

Decisions to participate in neuromodulation trials with indwelling devices are complex choices, requiring conventional elements of decision-making capacity. This process is complicated by conditions that compromise decision-making capacity and the complexity imposed by the reemergence of agency following severe brain injury. Adequately assessing the burdens and benefits of participation and avoiding therapeutic misconception are especially important goals given the enduring nature of implants.

Beyond the vulnerabilities that might stem from liminal decision-making capacity and heightened expectations of study success, a participant's choice to consent to an invasive neuromodulation trial ultimately depends on the weighing of risks and benefits and how goals of care are understood and formulated.[58] When weighing risks of research participation, prospective participants in the DBS for drug resistant depression trial cited inconvenience, surgical risks, and possible lack of efficacy,[59] but varied in how they rated the study's risk.[60] Scholars have noted the presence of therapeutic misconception in DBS depression trials with less misconception the greater the depression.[61]

Discussion of Risks and Benefits

All the subjects and families felt they were given enough information to make a choice about study enrollment. They also reported they had ample opportunity to ask questions and were satisfied with the amount of information provided. A mother of a subject noted the care with which information was conveyed, "It was kind of cute how it was repeated … they are kind of double-checking and go over it again, and then one more time before you go we are going over this again. So, yes, I think they do a very good job of explaining" [P210]. One subject reported formulating a list of questions with his family, all of which were answered by the research team.

Several subjects and family members reported being told of risks but were unable to recall them all during our interviews. Others were more precise in their recollections citing risks of death, infection, or incremental injury from a stroke. One subject told us, "I know there is of course the, albeit tiny, risk of death. There was a risk of receiving an infection at the surgery spot, similar to … the pneumonia I had years ago, but in the brain" [P308].

His mother focused on the paradoxical risk of additional injury to the brain when the intervention was meant to ameliorate deficits, not augment them. She told us, "…the scariest thing is that he could have a stroke if they hit a blood vessel in the, during the surgery. Obviously that can make his condition similar, but worse, I guess. A stroke is not all that much different than a brain injury in terms of the deficits it causes. I mean it is, but you know on a macro scale. But also just sort of neurological issues like changes in mood or tremors or, zapping feelings or you know, the things that you associate with issues with the brain. Confusion and balance issues and headaches of course, difficulty concentrating—all the things that it's supposed to fix…"

Subjects noted that the consent documents focused more on risks than on benefits. One described the document as "…it's like two or three pages full of anywhere from stroke to infection to pinching something … at least two pages long full of them, and very small section of plus side things" [P336].

This subject's partner was told of a previous subject whose putative benefits were described,"… the one person that they have had go through the surgery at Stanford and how she was able to participate more in social situations, that she was able to read a novel, that she had more energy, after the surgery … cognitively she did not have near as much neurofatigue." She felt that this was relevant to her partner's needs, "Well, that goes right down [his] alley. These are all the things I'm looking for. These are all the things I want …" The description of the team having to turn the stimulator down in a previous subject, "… because she had too much energy; and in his mind, that's a huge drug. It was like, yeah, 'Give me some some of that; give me extra; turn it up. That's exactly what I'm looking for.'"

Another subject resorted to sarcasm when recalling the risks and benefits in "… a packet that was emailed to me about the study and all the *wonderful* things that could go wrong, so many things"[P378]. But added that, "I chose not to remember the details, just keep in mind that the surgery has a 95 percent chance of success, 5 percent chance of likely impacting motor difficulty or cognitive function, 8 percent of mild difficulties arising, and … less than 1 percent serious injury and/or death."

Like others he was influenced by *The New York Times* article profiling our work,[62] "… the number one benefit I was looking for was the ability to read a book, and that seems to be a huge side effect of this person in the article … She can do a lot of reading now. She's finished a few books. Processing speed was also mentioned, which—everyone can use better processing speed to some extent. So that's good, plus it's one of my bigger weaknesses."

A final respondent whose memory was the most impaired of all the subjects was unable to recall study risks or benefits when we initially asked him in the interview. He politely told us, "Actually do not remember too many of the risks too clearly, but if you would like to inform me about the risks, I'd happily listen to you" [P410]. Similarly when asked about study benefits he initially replied, "Sorry, but my memory is a little bit foggy when it comes to certain things … I'm not too sure." Later when asked about what he would like the study to achieve, recalled that, "… my father has told me that some benefits of this study include me being able to clear up, like make clear my former memories. So that would be very interesting … processes that were made a little bit earlier, because of the study, then that would be greatly beneficial in my opinion." When asked what he meant by processes he replied, "Like remembering things a little bit more efficiently or being able to comprehend and—or achieve certain aspects of life a little bit more efficiently … Like smoothly, and you know what, you can do this, and you do it without many hitches, if any at all…Less of a struggle …."

While they came to fully understand the risks and benefits prior to surgery, this same family reported initial difficulties understanding risks because they were presented as a list without any context for their likelihood. They had a difficult time distinguishing the signal from the noise, "… you know, there's a litany of risks that just seem … horrible, but, at the same time, every time you see an ad on TV about medicine, you hear about all these horrible risks of taking medicine. So it's kind of hard for me to understand if it's much higher risk …" When asked if it would be constructive to present risks based on their probabilities, they thought this would be useful. They told us, "I think [that if] there was, like, likelihoods in the consent form, but again, I do not know if that's kind of normal likelihoods, or—like, for me, I would think they have to say risk of death with any, you know, surgery." She also suggested that the risks be contextualized for a particular subject wondering if generic risk profiles would suffice. She asked would they be different for her son, "… someone who's in as good a shape as he in, and he's young … is his risk much less because of his health and his youth than, you know, somebody who were in their 80s doing this surgery? You cannot say—you cannot tell me that's the same risk."

Another issue related to risk for this family's risk/benefit calculus was their confusion about whether the device would be removed at the end of the study and what effect this might have. His mother worried about loss of function with device explantation and the loss of any enduring benefits, "… I'm hoping, that maybe … it's like exercise. It will help us create pathways."

Despite this complexity, participants in our study were all satisfied with the amount of information they received from the research team and the opportunity to ask questions throughout the enrollment process. Our study demonstrated that although subjects and their families were not able to recall all the risks in detail, they were under no misapprehension that the study had no risks, and they were appropriately aware that some of the risks were quite serious. Further, subjects understood potential benefits not just from the consent documents but also from the media coverage of the benefits experienced by the first CENTURY-S study subject. Some participants wished the written consent forms detailing the risks were easier to understand.

Therapeutic Misconception

Despite their hopes for the study—and anecdotal information about subjects from the team and media accounts—neither the subjects nor the families appeared to harbor a therapeutic misconception, mistaking this phase I trial for a vetted therapy. One subject used humor as a defense precisely because she appreciated experimental nature of the surgery and that it was not an established therapy. Asked about the distinction she replied, "Yes. I know this is research. We're not sure it works," after first jokingly imploring us, "You need to tell me that this works … This works, darn it. Do not tell me this is not proven" [P210].

Another subject appreciated the distinction between research and therapy, " … research … follows a guideline. Your therapies do that too, but those are already okayed by the whole entire system. They've been out there for quite some time. They just tweak and change their ways. Research is something that's experimental at the same time" [P137]. Her friend felt that the novel nature of research was adequately explained by investigators and that, "… she's proud to be part of the first cases like this."

One subject spoke of the portrayal of the study during the consent process and the caution taken to neither convey nor promise a benefit. The researcher had, "… been very careful and selective in what he says; because we really do not know, because we are in the early stages of this" [P336]. He also hedged on the possible benefits seen in an earlier subject "… although it could go the other way, too… he'd been very careful, which I know he has to be."

While this subject *objectively* understood the difference between research and therapy, there was a transference to the investigator and his prestigious university that might have led to a belief in as yet unproven efficacy. The subject told us, "I do know, from going to one of the top universities with one of the top doctors … that gives me [the hope that] something good's going to come out of it."

This bias toward the positive was appreciated by the subject's son and partner who believe that the subject is focusing on potential benefits over risks. Speaking of his father, the son observed, "… he can say, yeah, there's two pages of bad things; but he'll just focus on the four lines … maybe it'll help with this."

Another subject discussed the possible benefits of "… having more self-control… So I can kind of pull away from the computer and get to bed more, so I can be more rested, which helps reduce headaches" [P308]. But he was clear that he was not counting on them. He told us, "… those those extra add-ons are not directly expected, they'll be nice if they happen. But do not plan for them. So like I said it'll be really nice if they happen, but until they do I will not know. But they will be nice benefits to it … if it works out that way."

Another subject was clear that DBS for brain injury is, "… still being evaluated. It may not do anything for me. It might change everything for me. My hope is that, after a year, I will have a solid reason whether or not I should keep it" [P378]. He added, "…I do not have any expectations that something's going to work. That would be crazy."

A final subject was clear about the research-therapy distinction, "An established treatment is something that will happen, like 100 percent of the time. Or maybe 99.7 percent of the time and so a study is something that helps establish the said treatment … studies are potential, and things might happen but it's not 100 percent sure that it's going to happen" [P410]. His father dealt with the uncertainty by turning to humor. With a laugh, he told us, "He's a guinea pig… I'm kidding, I'm kidding, I'm kidding. *No worries.*"

Only one respondent, the close friend of one of the subjects, seemed to harbor a variant therapeutic misconception. When asked if he was nervous about his friend's surgery, he responded, "No. When she said Stanford, no. I thought she's in the right hands" [P137]. While not a therapeutic misconception about efficacy, his faith in Stanford could viewed as a misconception about the safety of the study. This is worth additional inquiry as phase I studies seek to establish both the safety and efficacy of an intervention. Several other respondents were impressed and comforted by the reputation of Stanford as a premier academic medical center and this institutional transference could have led to distortions about perceptions of risk.

Who Decides?

One of the great challenges in the informed consent process is *who decides*? While all of the CENTURY-S participants were evaluated for decision-making capacity and the ability to provide voluntary informed consent by an independent psychiatrist, making choices about research participation is far more complicated than a question of capacity or competence. Following their injury, our subjects existed in a liminal space of re-emergent agency which at the time of the study reached a clear threshold for capacity. As they recovered and regained capacity, the locus of decisionmaking moved from family members acting as surrogates to the subjects.

This evolutionary process is especially complicated because subjects and their families are enmeshed in relational complexity.[63] Even as subjects recover and regain agency, they continue to have ongoing impairments. Family members see the subject's progress and continued vulnerability recalling their utter dependency following injury.[64]

This makes for a complex negotiation. People with brain injury seek to individuate and make their own choices as their families feel the desire to protect them from incremental harm. In our study, this tension between agency and paternalism becomes apparent. That the decision to participate in the CENTURY-S study is a high-stakes one involving an invasive phase I trial makes it all the more challenging.

Some of the variability centered on the family constellation, whether subjects were still in the parental orbit, living more independently, or had children of their own. But whatever the family dynamics, no subject made a decision without consultation with, and input from, family and friends.

With this web of relationality, decisions were collaborative. While subjects had to make the final call, both normatively and legally, they sought the advice and blessing of their family members. One subject recalled consulting, "… with my parents … they were both there to back me, and we talked about it for the last three months" [P210]. She thought it was "good" they were involved and grateful for their input, "… because I think they have guided me throughout my life, in good ways. I think they look out for me and protect me. So I'm not against it."

Despite her gratitude, she was unequivocal that the decision was hers alone and not her parents. When asked if she would proceed with surgery even if her parents objected she replied with a manifesto of self-determination:

> Respondent: I would still do it.
> Interviewer 1: You'd still do it. You think it's your decision?
> Respondent: It's my decision…Yeah. And if they didn't want me to do it, too bad. Because it's my life.
> Interviewer 1: Why is it your decision?
> Respondent: Because it's my body… And I'm an adult… And I have legal consent over myself …

The subject reports that her parents strongly support study participation in part because she and they trust the Stanford CENTURY-S principal investigator. While her parents were supportive, they were nonetheless ambivalent. They recognized their daughter's prerogative to make decision as emblematic of her recovery of independence. They gave her "every ounce of information that we have" and wanted her to make "as many decisions as we can possibly have her make." They aspired to neutrality, "I did not want to influence her, so I will not tell her where I stand on it," although the subject's mother told us, with a nervous laugh, "It scares the holy crap out of me."

They coached her to independently write out questions and appreciated delays in the research schedule that gave her, "… time to truly think about the ramifications of her choices, both good and bad. And this is a life decision." Placing this in a broader narrative, her mother reflected, "I look at it as I gave her life, and what she chooses to do with it is up to her." She encouraged her daughter to ask questions so it "was part of her decision-making process" and get her own answers so she had "confidence in the procedure."

Her mother intentionally brought self-restraint to their discussions knowing that she could easily "sway her." She added, "I did not want to influence her, so I will not tell her where I stand on it." Was that hard? "You bet." But that was the only way it could be, "It's got to be her decision. I could not handle it if it was my choice, and something went wrong. If it was my choice and something went right, I would not want to take credit for it. She's the brave person facing this. This is her life, not mine."

Ultimately, it was about her daughter's autonomy and self-determination, "That's freedom. That's where hope and happiness lies." Ultimately, she was proud of her daughter's courage, "I admire her, because I do not know if I would be brave enough to undergo this procedure. That's me personally."

Another mother was concerned about influencing her son, but in the *opposite* direction: she was more favorably disposed towards the surgery. She showed him *The New York Times* article,[65] "… and told him why I was excited about it for him, and I encouraged him to apply …" [P308] but also held back on expressing her views. Although she reported, "… I'm really excited about this study and I'm as much worried about me affecting his decision-making too much. I mean like I do not wanna push him if he's not interested."

The subject seemed less interested in whether it was his decision or his parents as he was predisposed to consenting. He recalls, "… my mother is the one that brought it to my attention. So I was discussing it with her and discussing it with my father, and I forget if they had to convince me of it or anything. I believe I was fairly accepting … or interested in it in the first place initially" [P308].

For him it was less about *who* made the decision than a proper risk–benefit calculation related to his chronic headaches, a question only he could answer. He noted, "Now, keep in mind this is a big thing, it'll be brain surgery … which I do understand. But you know, I have a risk-reward state of it, like if it does nothing beyond get rid of the headaches or reduce them a little bit more it's worth it."

Another subject affirmed that the decision was his, that his father was encouraging, and his mother concerned, "… [my] mother and father gave their input on it … but it was mainly my decision … I think my mom does not want me to do it. My dad does want me to do it…" [P378]. He explains that his father is sympathetic to the surgery because he underwent risky medical procedures previously, "My mom does not understand what I go through or been through… and my dad also does not understand, but he thinks that, since I think it has potential, that I should give it a try. And he's done similar things in the past, where he had to risk paralysis to fix a neck issue; and it was a 95 percent chance of success … so and there's some medical comparison. He needed it for that issue. I need it for this issue."

The subject's mother reports initial opposition but has become more accepting as she appreciates she has only so much influence: ultimately it was her son's choice. She recalled, "… when he first approached me on it, I was like, I do not think we want any wires going into your brain … But he really, he was adamant. He was doing it. It did not matter. Right? He makes his own decisions at this point … but his dad was a little bit more supportive than I am … which as I've learned I should have been doing from the beginning. But you know, hindsight's great."

Her thinking evolved, "… like I told you, initially I was totally against it. I tried to talk him out of it. I did not like this whole idea of wires going through the brain. But in the past year or so… as I discussed it with his dad and I discussed it with my husband … they have made me understand, why [he] wants to do it. OK? Because he's so unhappy … that it's worth trying anything to get him a little bit better. So because of that, I want that for him too. And I will say, as I said before, [the subject] has made some decisions that I have been totally against, and he's been right … So I'm going to go with him, his gut has been correct in the past. I'm going with his gut on this one. I believe—he's extremely intelligent. He does his research.

And I know he's researched this extensively. And so … I support him in it … I hope it works. Any little bit. But yeah, I do support him, and I trust his judgment."

When pressed if there were limits to her trust in his judgment she replied, "If there was something extremely dangerous, first of all, for me to try to step in and he was totally opposed, he would not let me. But I'd have to then gather forces, like I said, like his dad [and]… bring in his brother … I would go to his dad first and discuss it and see how he felt. Which is kind of what I did the first time this came about. You know, I discussed it with my husband, but then I go to [his] dad and I say, what do you think and see his opinion on it." But that was not necessary because her thinking had evolved. And echoing other parents, she told us she still worried because, "I'm still his mom and they are still wires go[ing] into the brain."

Two of our subjects had lives that were less tethered to their parents and because of this dynamic, the decision-making process differed. The first of these subjects sought the approval of family and friends in a less consultative and more confirmatory manner regarding a decision that she had already made. To that end, she spoke with her father, grandmother, and children about the study, and they were all supportive. She bonded with her father, himself a brain injury survivor, through their discussions about the surgery. He helped her financially, "He paid for my ticket to come out here and dropped me off at the airport. Me and my dad, we finally started telling each other that we love each other. We never said that before. He gave me a hug. He goes, "Get the hell out of here and you go. You get better. You do it. You do it for us" [P137].

She also talked to her ex-partner about the study. Even with their estrangement she sought his approval, because she "…gave him my kids when the accident happened when I knew that possibly any day could be my last one." She also sought the counsel of "elders" in her community and informed them of her decision, "Hey guess what I'm going to do? They're like, 'That's awesome. I'm so proud of you. If something happens, it does. If it does not, it does not. You tried. You went for one more thing.'"

Another subject's family constellation consisted of a significant other, an adult son, and siblings. He encountered more resistance about participation than the other five subjects. They were concerned about his fitness as a surgical candidate and the soundness of his decision-making process.

The subject also sought the input of his personal neurologist who felt the risks were not worth the potential benefits. He was frustrated about the lack of "continuity between doctors" [P336]. He could not facilitate a conversation with his neurologist and study personnel "… to make everyone feel better, including myself." He later sought out a favorable second opinion "… that carried a lot of weight for me personally."

The subject and his partner spoke with the research team about his medical suitability and the incremental risk of operative injury. While this was addressed by the surgeon through consultation with other Stanford faculty, neither the subject's partner nor son was fully satisfied. They worried about the subject's pre-existing medical co-morbidities, "You know, from my perspective, he's already had at least one stroke in his cerebellum, and for me, it's a concern."

The subject's partner remained concerned because other doctors had advised against participating, advice that was diluted by their acknowledgement that it was the subject's choice and not their professional judgement that was determinative. They told the subject, "… 'given everything that you have going on this is not something that I would do; and yet, you know, it's your life, and your choice…'" It was a complicated message that could be framed depending upon one's goals.

The subject also consulted his siblings. Initially, they did not support his participation but changed their minds after realizing the extent of his suffering. He came to appreciate his own needs after communicating the "… extensive reasons why I wanted the surgery… and it did not occur to me till after I wrote … I was struggling as much as I was." He invoked the metaphor of brain injury as an unseen wound, "… you know, the invisible onus part of it … they thought I was doing much better and did not have … all the things I struggle with … after that most of them have been on board."

While his siblings were supportive, his partner remained "… more reluctant than me." While she was supportive of research in general and knew about DBS from a family member with PD she was uncertain about its role in brain injury. More importantly, she felt that her partner's hopes were not realistic, "…I have major concerns that … his expectations were way above what reality was ever going to be, and he was not weighing the risks."

Part of this was what his son characterized as "information overload" and an inability to properly balance risks and benefits. The subject's partner characterized this as their "… major concern with this whole thing with Stanford … as you can hear, just any, teeny tiny bit of improvement will be worth it … for him being able to weight the risks and the benefits, he just—he cannot." His partner and son wondered if they should step in and "… talked a lot about, do we have to help him make a better decision… What's this going to look like if there's disappointment at the end? Because I have major concerns that, if he does not feel like he's getting an improvement, and especially because of the way it's randomized, and not knowing what's happening and what's not happening; and he does not deal with knowing what's not knowing what's happening; I'm concerned about his emotional state."

Despite their misgivings about the surgery and his ability to choose wisely, his partner and son resigned themselves to supporting the subject, hoping that the surgery would not make things worse. His partner told us, "You know, especially—my God—if something, you know, does not go right or he has some other kind of a side effect … I've pushed pretty hard, honestly, for him not to do this, because I'm concerned. And, and yet, it's his life…" His son agreed, "…if he gets worse, then it's going to be hell for [us], and worst of all, it's going to be hell for him. So, as long as things do not get worse, I'll be really okay. And I support him. There's nothing else I can do, because … he decided the second he got accepted. He was in. I know I cannot do anything to change that, so all I can do is try to get him to be as in a good mindset going into it, be supportive, be loving, be here for him. And that's the best I can do now."

The subject acknowledged their concerns and genuinely appreciated their support amidst ambivalence. Speaking of his son and partner, "… who… I'm closest to, of course, they are the most concerned… but… you know, here they are today, with me, right? We're driving to Northern California … So obviously, apprehensive, or not, they are here for me; and that's awesome."

While the characteristics of the families presented their own variability, a common characteristic amongst subjects was that they were more focused on the burdens imposed by their injury than the risks of the surgery as they considered its putative benefits. Family members were in general more risk aversive. Despite their concerns about harms from study participation, conditioned in part by their earlier protective roles when the subjects were incapacitated, family members came to appreciate that they should not and could not make decisions on the subjects' behalf. Family members demonstrated "generosity and gravitas" as they bore witness to the subjects' re-emergent agency and affirmed the dignity of decisions only the subject could make.[66]

Hopes

On the cusp of surgery, subjects and family members were cautiously optimistic but remained sober. Similar to the findings of Lázaro–Muñoz and colleagues reported in their study of adaptive DBS, our subjects hoped for symptom relief and improved quality of life, with some motivated by altruism.[67] With respect to study participation, many reported hoping to avoid complications. Beyond this concern, they hoped for better cognitive function—improved memory, less impulsivity, greater focus, and executive function as well as improved relationships with friends and family. Goals were often framed in terms of returning to work or school and normalizing social interactions. More altruistically, one friend said he hoped "that science advances, that she gets better and that you guys learn something…" [P137].

One family member hoped for the most basic of aspirations that, "She could hold a job where she would have a place to get up and go every day. A reason to get dressed and a reason to interact with a variety of people, and not be so isolated. Isolation is killing. And I think she's capable of more, but the isolation curtails it" [P210].

As has been reported in DBS in treatment-resistant depression,[68] most of our subjects desired a better quality of life. One family member wanted to overcome the "… fear of the future. It's the sadness that there may be no future. Or that the future's—the sameness of the future … And that's the sadness. Because I think as parents we always want our children to have it better than we did, or at least equal to. And there's no hope of that. But this may give her hope … and a more experiential existence than what she has now. It's so constrained, and so limited…." [P210].

One subject simply hoped to be able to spend a day with her daughter, "To have her for a whole entire day that I remember …[and] Wake up and be able to help her with her hair in the morning or to be able to go to school events because I actually remember to go, or I feel that I can make it by the end of the day" [P137].

Despite their injuries, subjects held on to their dreams. They retained aspirations for their professional and personal lives. One subject hoped to "do more thinking stuff" [P308]. He spoke of "…being able to focus … take multiple thinking classes on different subjects without breaking down as I struggled…" He hoped to return to his pre-morbid function, "…going back to what I was kind of before the accident where I'm able to do it." He told us that "… if what I hope for happens … I would like to be able to go to college and take a full-time course load, go into my field [early childhood education]."

The subject's mother hoped her son could gain more independence, although she wanted to be realistic. "I mean we both have hopes. I think both of us are working to stay realistic about it and not overburden it with more than is really possible or, more than what we think is reasonable. … I would love to be surprised … maybe it sounds like I'm intentionally keeping my expectations low and maybe that's the case." If that were the case she hoped that "… it's not rubbing off on him." More hopefully she told us, "I want him to be able to hold a job … have his own place and pay his own bills … and, maybe meet someone and—I do not know how much of that is really possible."

Two subjects quantified their hopes for improvement in quality of life at 1 percent [P137] and another 5–10 percent better [P336]. The latter's partner put it at 50 percent so "… he can go and do what he wants to do." The subject described it as overcoming his daily challenges "where every day is a battle although I try and be upbeat … it's not the quality of life I really want to live. And so I'm willing to take the chance, to even get—if I can even get five or 10 percent better, it's better than the quality of life I have now … that's the reason I want to go forward with this." If he could have concentration and stamina for cognitive tasks so he could work it would indirectly help his feelings of depression. Like other subjects he recalls who he once was and his former capabilities, but this has been frustrated, "… there's days that I can put together that I can be solid, but it does not usually last more than a couple days, and then I get knocked back down again."

Another subject analogized neuromodulation to "a RAM upgrade" on a computer, "… I feel like my brain is just being bottlenecked by my processing speed and my focus. So if those, if that area can just be expanded slightly, I feel it would exponentially increase the output that I'm capable of giving, if that makes sense." [P378] With that restored capability he hoped to be able to read longer and to regain quickness in his conversation, "Like, I used to be witty … That has not happened in 10 plus years. So I do not really see that as likely, but it'd be nice … something amazing."

Like other parents, his mother craved a new normal for her son, "My hopes and dreams are [for him to] get back to hopefully living a normal life somewhat. Normal or better than it is. You know, normal, the new normal, as I learned, right now the new norm is not so great. So I'm hoping for another new norm of maybe this will help give him maybe a little more self confidence … But he does not seem to want to step out. And that's the part that I say maybe self-confidence in getting yourself back out there."

One subject focused on improved memory so he could recall earlier parts of his life as well as clearer thinking and comprehension. He hoped that this would help him do things with "less of a struggle … without many hitches" and do well in school and then have a career as a medical professional [P410]. He would also like to get married and have children. Without memories, he felt disconnected from his former life.

Like other subjects he had unrealized hopes and dreams that remained despite his injuries. Before he was injured he had planned to become a pediatric oncologist, "And I would still pursue in the future. But if I do not achieve as high. I do not achieve that rank … I would be completely fine with becoming someone who helps other people; a rehabilitationist (sic) … because I've had a number of individuals in my life help me in the way a rehabilitationist helps other people. And I would enjoy that greatly." He also hoped to find a partner and start a family. His parents hoped their son might "reconnect with his goals and dreams."

Concerns

Although one subject had no concerns stating she was, "… a little bit scared … [but that]… I'm just more excited than anything" [P137], most respondents voiced concerns about the surgery. Concerns included the aesthetics of implantation, unfulfilled expectations, posttrial access to devices, surgical complications, and the possibilities of further disability, dependency, and death.

Aesthetics

One subject asked herself, "…do I really want a big pack on my chest for a pacemaker? I've been like, that's kind of ugly. And like this thick vein coming down my neck, I'm like, that's not real attractive either. So it's not like I've been like, hmm, let us do it. It's not like they are paying me for this. So it's not like I'm all on board" [P210].

Unmet Expectations

Some respondents worried about disappointment if the study did not result in improvement. One subject's partner worried, "My biggest fear is … unmet expectations and a depression that will come from that … he says, even just 5 percent would be better. What I believe is 5 percent and what I think he believes is five percent are two different things." She was concerned that, "… he will not feel like he's improving and will be depressed … especially because of the—the way it's randomized… I'm concerned about his emotional state … my God—if something does not go right or he has some other kind of a side effect … I've pushed pretty hard, honestly, for him not to do this, because I'm concerned."

As parents of one subject thought about the risks of surgery, one felt their son had a good quality of life while the other disagreed, "Not in my book—not in my book." [P410] His mother responded that her "… biggest fear is—he's OK now, and he's still showing signs of progress … if he has to live with us the rest of his life, it's, a pretty good life … I would rather have that than …. if this therapy did not work and caused more brain damage and then he was in a wheelchair or worse." They pondered the risks of a "regression," a scenario neither was willing to accept. They only would assume risks encountered in routine medical care, "But if it's a much higher risk … then I'm not sure I'm comfortable with it."

Posttrial Access

Unprompted by a direct question, three respondents voiced concerns about posttrial access during preoperative interviews.[69] One subject reported that his father had questions about ongoing support of the device after study completion. He told us, "… my dad … asked how long the the implant would be supported or maintained by Stanford?" [P308] He posed the hypothetical, "… if we went through the study and if it worked … super well, or it's nice… [was] Stanford … going to continue paying for it or supporting it? If insurance was likely to pay and support it … I do not think we asked the cost to replace the battery if not. But it's just of working out … where insurance would be standing on it, and where supporting the implant would be…" The subject was unsure of the answer but said he thought that the research team said the plan "… if it goes forward and works out then join the kind of longer-term study. And Stanford will continue to help maintain and care for it. I do not believe it's what's like the phrase? In [perpetuity], but you know, four or five years of these benefits would already be massively helpful."

When asked if he thought that the study should be responsible in perpetuity the subject calibrated this responsibility against efficacy, "… depending on the exact degree of benefit gained from it, I would like it to be in perpetuity." But he appreciated there could be limited resources, "… I also understand that this is a nice little study. And now the costs are going to be X times the life span of the participants is as much as insurance does not want to pay for it, the school they have, they have a budget. There is only so much that they can pay for, so. It would be nice if they were able to, but I understand why at least the school might be forced to stop after a while."

The mother of a subject was also concerned about longitudinal care for an in-dwelling device. If, "… he stays in the study for about five years. He'll be monitored so to speak? And then—but what happened? … he's got, all of this in him. And what happens down the road … What happens down the road when [the subject] turns 40 and he's got wires in his head and Dr. Henderson's not around anymore?" [P378] Because all of this was so new, "… I want to know who's going to be able to take care of all of this if something needs to be taken care of? I do not know what—nobody knows. I guess that's for me the scary part, is nobody knows what the long term issues are going to be. He's only 30 years old. He's got a good 50 or more years …"

She asked about contingency plans if the Stanford surgeon were no longer available, "… first of all I do not know how old is Dr. Henderson. Not that it even matters, but … stuff happens at any given moment, as I have learned, and I tell people all the time. You know, you never know [my son] walked out the door, 1:30 on a Sunday afternoon and life changed, right? So I know that stuff happens. So Dr. Henderson, again, I refer to his age because is he going to be around practicing for a long, long time? And then again, of course he could be, you know, 35 for all I know, and something could happen to him … who's going to be overseeing [my son], or if something needs to be done down the road, or what if these wires are affecting something else that [he] needs to have done—who's around for another doctor to refer to…"

The partner of another subject worried about insurance coverage should there be a surgical complication, "… God forbid, he has a stroke or if something goes wrong during this surgery. What are those costs? Does his insurance [cover] the cost?" [P336] When asked whether she raised her question with the surgeon's office, she replied, "I believe that was—but they do not have an answer. No one has an answer, and even the health insurance company does not have an answer, because there's so many variables, because he's doing something that is not medically necessary. Does his insurance no longer cover him? … there's so many unknowns there from a financial standpoint."

These concerns about posttrial access to device maintenance and associated care speak to the lack of infrastructure to support subjects as they leave the trial and become patients.[70] While this problem will be resolved should these interventions evolve into therapies, there will be an intermediate period when subjects are potentially unsupported with in-dwelling devices. As will be discussed in our follow-up article, questions of posttrial access became more prominent with the demonstration of proof of principle in the CENTURY-S trial.

Complications

Understandably, many study participants relayed concerns about complications from study participation. One subject worried, "I do not want to come out of it more mentally impaired than when I went into it, or physically impaired with any of the wonderful side effects … that would be terrible. From what I've heard, all the patients have had zero side effects so far. I know the one with the infection, but other than … So as long as I do not have any new deficits, I'd be pretty happy" [P378].

The mother of a subject was more sober, "My fear is a very selfish one, is what am I getting myself into? What if she has a stroke on the table? What if she's disabled? Now what am I going to have to take care of, and how long will that last? It's going to complicate my life. Those were my fears. Those were my genuine concerns" [P210].

Two subjects had advance care planning discussions with their families, each of which discussed the burdens of a bad outcome and quality of life considerations. One subject worried he would be a burden on his caregivers, "the things I'm afraid of—I'm not really afraid of dying, to be honest with you; but I am afraid of being a vegetable or a burden to my loved ones. That would be the worst thing … I would rather die than be a burden to my loved ones … if that makes sense" [P336]. To that end he articulated his preferences in a living will. His partner told us, "… whatever that is you write at the hospital he does not want any heroics. He does not want to be a vegetable. If I get to that, I want you to end my life… he wanted it very clear: I do not want to live like that."

The mother of another subject told us that her daughter, "…made me make a horrible promise that if she has a stroke and she's severely debilitated, that she not live in a convalescent hospital, that I take her to

Oregon and let her end her life [using physician aid in dying]… And that was one of the things that bothered me, because I said, '… there's risk. You know the risk.' She goes, 'Yeah, I know. But I know you'll do the right thing'" [P210]. In the end, even as she made her own choices, the subject placed her trust in her mother to make decisions on her behalf.

Creating Community

One subject and his mother were interested in meeting other study participants to compare notes and overcome their isolation. They asked, "Are all the subjects in this trial going to meet each other, or are we just going to stay anonymous? "[P378] When pressed if he thought that would be helpful he replied he did not know, "… but it would be interesting to hear some other experiences."

His mother also desired meeting others, "… I think the patients themselves interacting—one is kind of a support group in one sense, for the patients and for the family members to just have somebody else that understands what you are going through … I do not know who the other family members are if it's other moms or dads or siblings or wives and husbands. But whoever it is, you are going through this kind of alone, blind, and so if there was somebody else there that kind of gets what you are going through, that's number one. It would be interesting just to—I think for the patients, and again, I'm not the patient so I'm speaking as if I were, but I think it would be interesting for them to be able to kind of go through it with somebody else and see … is this happening to you? Is that happening? I do not know."

While she appreciated the need for privacy and confidentiality, she saw the advantage to building a community of subjects to get, "… information from each other and kind of like a little mini support group in a sense. And then sometimes, you know, somebody might have a question that somebody else did not think of as you are going through it. And so it's just kind of more information, you know, the more information, the better we deal with things."

The desire of this subject and his mother points to the sequestration of subjects participating in novel clinical trials and the advantages of creating supportive communities. This utility of such groups warrants additional study along with the logistics of bringing groups together while respecting privacy and confidentiality.

Limitations

The study is limited by the small number of participants who may not be representative of a much larger pool of potential participants. Demographically, participants were all white and endorsed a belief in scientific progress, which is not representative of all people with brain injury. Our findings may not be generalizable to other invasive neurotechnologies of other conditions. While the sample was small, we did interview the full cohort of subjects and at least one of their family members who participated in the CENTURY-S study which provides rich accounts of their experiences. While none of our subjects held a therapeutic misconception [see above], this could be a consequence of eligibility criteria which excluded candidate subjects unable to distinguish research from therapy.

Conclusion

When commentators discuss neuroprosthetics, they often fear that a novel technology will alter personhood and personal identity.[71] Our interviews revealed that it was the brain injury itself that was disruptive to personal identity, family relationships, and life trajectories. These disruptions were burdensome enough to prompt subjects to enroll in the CENTURY-S study and assume the risks associated with trial participation, a stance less willingly taken by family members who worried that surgery could lead to complications, further disability, dependency, and death. Concerns also included questions about posttrial access for their devices. Despite their reservations, family members recognized—and at times celebrated—the re-emergent agency of the subjects and supported them in their decisions.

Respondents reported that they were provided enough information and time during the informed consent process to make decisions about participation. Hope for relief of cognitive disabilities, improved quality of life, normalization of interpersonal interactions, and a return to work or school were cited as reasons for study participation, as was altruism and a desire to advance science. Despite their hopes for the surgery, neither subjects nor their families operated under a therapeutic misconception, appreciating the intervention as research. Both subjects and family members viewed the study as safe, reassured in part by the reputation of the surgical investigator and the prestige of his academic medical center which might reflection the distortion of institutional transference.

These data form the backdrop for a forthcoming article in this journal which will report on the effects of subsequent cognitive restoration on subjects and their families. In this follow-up article, we consider the challenges of adaptation to neuromodulations, including improvements in cognitive function, altered (and restored) relationships, and family dynamics. While these changes were welcomed—and to some degree unexpected—they exposed new barriers to social reintegration now made relevant because of a recovery once thought inconceivable. These changes prompted deep reflection by subjects and families about life goals once thought to be immutable and the need to reimagine supporting social structures.

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