Translational Neuroethics in Neuromodulation for Neuropsychiatric Disorders

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Parkinson's Foundation
CENTER OF EXCELLENCE

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Disclosures

- National Institute of Neurological Disorders and Stroke, Award Number RC1NS068086
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- Executive Board, Ethics Committee, American Psychological Association
- I am NOT a Bioethicist or a Philosopher

The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health or the American Psychological Association

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Goals

1) Apply a process of resolving neuroethical dilemmas
2) Identify clinical and research neuroethical dilemmas in neuropsychiatric neuromodulation
3) List some of the current demographic challenges to accessing advanced neuromodulation treatments/clinical trials

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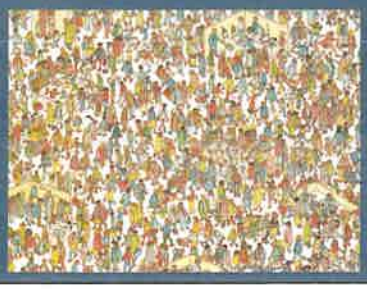
Where in the brain is the human soul?



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CP Snow and the 1959 Rede Lecture

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Two Forms of Blindness

- Favor the Sciences: minimize the importance of narratives/lived experiences, culture, and history
- Favor the Humanities: anti-science, anti-reductionist

Ritcher (2010) Technology and Society

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Ethics

- Values
- Language
- Consistency

Consistency is the hobgoblin of little minds....
A foolish consistency is the hobgoblin of little minds

Emerson

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Neuroethics, History

- A Harvard physician, Anneliese A. Pontius (1973) coined the term neuroethics to highlight potential detrimental long-term consequences of different forms of early intervention to accelerate walking in the newborn
- In 1989, Ronald Cranford, a US neurologist, discussed the ethical and legal issues uniquely associated with clinical neurology (e.g., infant anencephaly, brain death, dementia). He emphasized the role of the neurologist in ethics discussions and the importance of ethical issues in neurological care.

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Neuroethics, Safire and the 2002 Meeting

- 2002 Neuroethics: Mapping the Field Conference assembled dozens of experts in neuroscience, law, ethics and other fields. This meeting was fundamental to the field and has helped propel the field forward.

- Neuroethics is "a distinct portion of bioethics, which is the consideration of good and bad consequences in medical practice and biological research. But the specific ethics of brain science hits home as research on no other organ does" Safire, 2002

➡ Specificity of the brain or *neuroexceptionalism*

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What is neuroethics?

- "The ethics of neuroscience and the neuroscience of ethics"
- Philosophers, bioethicists, neuroscientists, biomedical engineers, clinicians
- Criticized for being too speculative and insufficiently skeptical
- Translational Neuroethics: Integrated, Inclusive, Impactful

Rosslee, 2002; Wexler & Specker Sullivan, 2021

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Pragmatism

- Empirical methods are a useful tool for addressing questions, including ethical questions
- Experiential knowledge is important (e.g., different stakeholders' perspectives, impact of context on moral agents, fallibilism)
- "Truth in ideas is their power to work"

Dewey,1922, Kögg, 2020, Kubs et al. 2019, Racine 2010

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Pragmatism in the Neuropsychology Clinic

- Rely on empirical methods
- Recognize the importance of experiential knowledge in gaining a better understanding
- Fallibilism – knowing what we don't know and having the humility to seek different perspectives
- Ensure that the work is patient centered and clinically relevant ("truth in ideas is their power to work")

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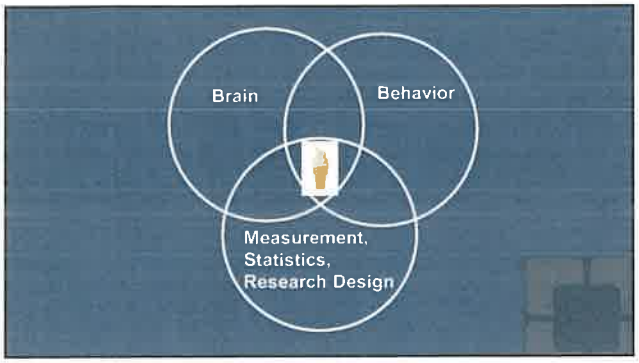

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APA Code of Ethics

Principles

- Beneficence and Nonmaleficence
- Fidelity and Responsibility
- Integrity
- Justice

Ethical Principles of Psychologists and Code of Conduct, APA, 2017

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Criticisms of APA Code of Ethics

- Not a coherent theory of ethics
- Based on unclear meta-ethical commitments
- Unclear relationships with normative ethical accounts
- May fall short, especially when the General Principles are in conflict.

O'Donohue, 2016; Ethics and Behavior; Kubo, 2021

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What is ethics?

"Ethics is a generic term for various ways of understanding and examining the moral life" (p4)

- Normative ethics: "Which general norms for the guidance and evaluation of conduct are worthy of moral acceptance and for what reasons?" (These generally emerge in the context of an ethical theory)
- Practical ethics: "The attempt to work out the implications of general theories for specific forms of conduct and moral judgment"
- Theory and principles are used to develop action guides, shaped by paradigm cases and empirical data

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Moral Dilemmas

1) Some evidence indicates that act *X* is morally right, and some evidence indicates that act *X* is morally wrong, but the evidence on both sides is inconclusive
2) An agent believes that, on moral grounds, he or she both ought and ought not to perform act *X*.

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Moral vs Practical Dilemmas

1) Conflicts between moral principles or rules are moral dilemmas
2) Conflicts between moral principles and self-interest sometimes produce a practical dilemma that is not a moral dilemma (e.g., employer pressure to shorten protocols)

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Resolving Dilemmas: Method, Justification, Truth

- Deliberation begins with "an imaginative rehearsal of various courses of action" Dewey
- To demonstrate justification for a moral belief, it is important to provide good reasons for one's belief/decision
- Not all reasons are good reasons, and not all good reasons are sufficient for a justification

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Models of Justification

1) Deductive (i.e., top down) : justified moral decisions are deduced from a pre-existing theoretical structure of normative precepts that cover the judgment.
2) Strength: If a "fairly settled…body of general guidelines" exist, moral judgements should follow those general guidelines
3) Weakness: This doesn't work if there is not a clear precedent; can also lead to an infinite regress of justification

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Models of Justification

1) Inductive: Individual case model. "Inductivism maintains that we must use existing social agreements and practices as a starting point from which to generalize to norms such as principles and rules"; emphasis on the particular and contextual aspects.
2) Strength: History and philosophy do not produce static systems of moral norms
3) Weakness: What is the role of general rules (moral principles) over particular judgments?

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Models of Justification

1) Coherentism: relies on dialectical approach. "We develop theories to illuminate experience and to determine what we ought to do, but we also use experience to test, corroborate and revise theories".
2) A process that entails pruning and further refining our moral judgments so that they are coherent with our ethical theory (i.e., coherence between particular and general judgments).

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Specification

- A strategy for resolving moral problems
- Moral principles are very abstract; specification allows us to connect them with concrete action-guides and practical judgments.
- Appropriate specification "conserves or elevates the coherence already present in a theory"
- Example: Non-maleficence - Are assisted suicide and voluntary active euthanasia harmful actions absolutely proscribed by the principle of non-maleficence?

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Balancing

- Prima facie obligation - an obligation that must be fulfilled unless it conflicts on a particular occasion with an equal or stronger obligation
- Actual obligation – determined by the balance of the respective weights of the competing prima facie obligations
- Justified acts of balancing entail that good reasons be provided for one's judgment
- Balancing can be "viewed as a specification of norms that incorporates one's reasons"

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Conditions that Restrict Balancing

- Better reasons can be offered to act on the over-riding norm than on the infringed norm
- The moral objective justifying the infringement has a realistic prospect of achievement
- No morally preferable alternative actions can be substituted
- The form of infringement selected is the least possible, commensurate with achieving the primary goal of the action
- The agent seeks to minimize the negative effects of the infringement

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Superiority of Balancing

- "Specification is an attempt to populate our moral universe with a wide variety of additional moral rules"
- "Casuistry relies on concrete cases as moral guidelines…."
- Both involve generation of a large set of specified norms or cases
- DeMarco and Ford argue that, even if such a large set existed, neither process is ideal in assisting health care professionals solve moral problems

DeMarco & Ford, 2009, Journal of Medicine and Philosophy

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Superiority of Balancing, 2

- Unlikely that a sufficient number of specifications or cases can be developed, learned and applied
- Specification relies on formulaic rules and casuistry relies on similar, yet different, case paradigms
- "Using these techniques tends to hide actual conflict and impedes moral debate. Both obscure the fact that in actual moral decision-making, conflicting moral considerations need to be carefully considered in relation to each other"

DeMarco & Ford, 2005; Journal of Medicine and Philosophy

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Link between Coherentism and Scientific Method

- Coherentism: relies on dialectical approach. "We develop theories to illuminate experience and to determine what we ought to do, but we also use experience to test, corroborate and revise theories".
- Coherentism relies on testing specific hypotheses; it combines theoretical knowledge with practical implications

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Ethics in Neuropsychological Clinical Decision-Making

Beauchamp and Childress

- Non-maleficence
- Beneficence
- Autonomy/Respect for persons
- Justice

APA Principles

- Beneficence and Nonmaleficence
- Fidelity and Responsibility
- Integrity
- Justice

Reliance on empirical data and incorporation of diverse perspectives (Pragmatism)

Beauchamp & Childress, 1994; Dewey,1922; Kaag, 2020; Kobu et al, 2019; Racine 2010

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Psychiatric Neuromodulation and Ethics

Focus: Deep brain stimulation (DBS) for treatment resistant depression (TRD)

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Neuropsychology's Responsibilities in DBS for Neuropsychiatry

- Evaluate cognitive status and potential risk
- Evaluate neuropsychiatric status and potential risk
- Evaluate level of support
- Evaluate goals for surgery
- Research design and outcome assessment

Ford & Kubu, 2006; Rezai et al, 2008; Kubu, 2013

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Neuropsychiatric Disorders are Incredibly Complex

- Motor
- Sensory
- Cognitive
- Affective
- Social
- Physiological

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What I'm not going to discuss…..

- Importance of solid empirical data to justify human studies
- Need for interdisciplinary teams (neurosurgery, psychiatry, neurology, physiatry, neuropsychology, bioethics)

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What I am going to discuss…..

- History and Stigma
- Are we measuring what matters? And, why that matters.
- Consent and vulnerability
- Non-abandonment
- Access and healthcare equities

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History of Neuropsychiatric Modulation

- 1883 Corning proposes VNS for treatment of epilepsy
- 1891 Burckhardt performs "modern" psychosurgery for the first time
- 1910 Puuseep cuts fibers between FL and PL to treat BAD
- 1935 Fulton and Jacobsen present NHP research in London
- 1935 Moniz and Lima perform the first frontal leucotomy
- 1936 Freeman and Watts begin frontal lobotomy to ease burden on overcrowded asylums
- 1948 Freeman popularizes transorbital lobotomy (>3500 procedures)

Heller et al. (2006) Neurosurgery

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Historical Types of Psychosurgery

- Cingulotomy
- Capsulotomy
- Subcaudate tractotomy
- Limbic leukotomy: Cingulotomy and Subcaudate tractotomy

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History of Neuropsychiatric Modulation

- 1948 Scoville publishes his technique of cortical undercutting to reduce incidence of post-leukotomy syndrome
- 1949 Spiegel and Wycis perform first stereotactic psychosurgery in DM thalamus for agitation related to psychosis
- 1949 Moniz shares Nobel Prize for "discovery of the therapeutic value of prefrontal leucotomies in certain psychoses"
- 1949 Talaraich proposes anterior capsulotomy for affective and anxiety disorders
- 1954 Introduction of chlorpromazine

Heller et al. (2006) Neurosurgery

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History of Neuropsychiatric Modulation

- 1962 Foltz and White perform the first stereotactic anterior cingulotomy
- 1964 Knight develops stereotactic subcaudate tractotomy for affect and anxiety disorders
- 1972 Leksell modernizes anterior capsulotomy – thermocoagulation and gamma knife radiosurgery
- 1973 Kelly performs the first limbic leukotomy
- 1987 Benabid introduces use of implantable stimulating electrodes (DBS) for treatment of PD tremor

Heller et al. (2006) Neurosurgery

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History of Neuropsychiatric Modulation

- 1988 Penry and Dean implant first VNS in human for epilepsy
- 1997 DBS approved in US for treatment of PD tremor
- 1999 Nuttin, Cosyns, and Demeulemeester publish results of DBS for treatment-resistant OCD
- 2000 Elger et al and Rush et al document improvement in depression in VNS for epilepsy
- 2005 Mayberg and Lozano publish first results of DBS for TRD
- 2005 VNS approved in US for medically refractory MDD
- 2005 – present, expansion of targets, disorders, and interventions

Heller et al. (2006) Neurosurgery

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History of Neuropsychiatric Modulation

Increasing minimalism and precision guided by

- Increased knowledge of functional neuroanatomy
- Surgical and neuroimaging innovations
- Reducing tissue destruction
- "Non-invasive"

Heller et al. (2006) Neurosurgery, Lacruz et al. (2013) World Neurosurgery

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Psychosurgery and Public Opinion

- Freeman's Evangelism: Between 1945-1955 ~ 50,000 lobotomies were performed in the US. Intense media support for the procedure. "Lobotomobile"
- Federal Support: VA recommended lobotomy for treatment of psychiatrically disabled soldiers returning from WW II
- Nobel Prize awarded to Moniz in 1949

Heller et al. (2006) Neurosurgery

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Psychosurgery and Public Opinion

- 1950s Backlash and concerns raised, especially regarding Freeman (Rosemary Kennedy, Frances Farmer)
- 1959-1962 Popular culture, Tennessee Williams "Suddenly Last Summer", Ken Kesey "One Flew Over the Cuckoo's Nest"
- Antiestablishment Fervor and Mistrust of Authority
- 1970s Social Paranoia: Mark and Ervin's "Violence and the Brain": thesis that "psychosurgery could be used for widespread mind control by government, military, or law enforcement agencies"
- Delgado "... We must electronically control the brain. Someday armies and generals will be controlled by electric stimulation of the brain"

Heller et al. (2006) Neurosurgery

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More Contemporary Views on Neurosurgery in Psychiatry

- Focus groups of citizens without a mental health diagnosis from four cities (Berlin, Vancouver, Montreal, Madrid) regarding different kinds of neuromodulation, including VNS, ablative microsurgery, radiosurgery, MRgFUS, and DBS. Themes included:
  - Authentic self (can surgery negatively impact true self vs role of psychiatric illness in true self)
  - Psychiatric surgery is viewed as a last resort (irreversible)
  - Stigma of mental illness
  - Consent

Cabrera et al (2021) Curr Med Psychiatry

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More Contemporary Views on Neuromodulation in Psychiatry

- Focus groups of 16 psychiatrists in Michigan
- Convenience sample
- Examined attitudes toward ECT, TMS, DBS, Adaptive Brain Stimulation
- Generally positive
- Most support ECT or TMS if failed several medication trials (i.e., last resort)
- Lack of knowledge about DBS and, even more so, ABI
- Spoke to stigma associated with stimulation therapies
- Need for complementary and ongoing therapies

Cabrera et al (2021) Psychiatric Quarterly

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Psychosurgery Guidelines in the US

- 1949 First Research Conference on Psychosurgery at the NIMH – call to adopt a "universally accepted rating scale, with patients individualized by diagnosis or other category…[to] provide an effective method for both case-selection and evaluation of operative results"
- 1972 Psychosurgery Report authored by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Research Act, 1974) argued for rigorous patient selection and follow-up
- US. Congress considered a ban on psychosurgery in 1974 as part of the National Commission but based on the evidence did not support that stance

Heller et al. (2009). Neurosurgery. Fins, Rezai, Greenberg (2006) Neurosurgery

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International Psychosurgery Guidelines

FINDINGS: The proposed consensus document highlights that

- While stereotactic ablative procedures such as cingulotomy and capsulotomy for depression and obsessive-compulsive disorder are considered 'established' in some countries, they still lack level I evidence.
- Further, it is noted that deep brain stimulation in any brain target hitherto tried, and for any psychiatric or behavioural disorder, still remains at an investigational stage.

Nuttin et al (2014). Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. JNNP

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International Psychosurgery Guidelines

- Researchers are encouraged to design randomized controlled trials, based on scientific and data-driven rationales for disease and brain target selection.
- Experienced multidisciplinary teams are a mandatory requirement for the safe and ethical conduct of any psychiatric neurosurgery, ensuring documented refractoriness of patients, proper consent procedures that respect patient's capacity and autonomy, multifaceted preoperative as well as postoperative long-term follow-up evaluation, and reporting of effects and side effects for all patients.
- **Multidisciplinary teams include neuropsychologists**

Nuttin et al (2014). Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. JNNP. Fins, Rezai, Greenberg (2006). Neurosurgery

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Translational Neuroethics

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Neuroethics in the Lab

- Patient Centered
  - Directly solicit patients' and care partners' perspectives in their own language
- Clinically relevant
  - Use this information to improve patient care
- Team based
  - Incorporate different perspectives and disciplines
- Stewardship (Patient, Profession, Science, Public)
  - Respectful, Communication, Resources, Scientific Methods

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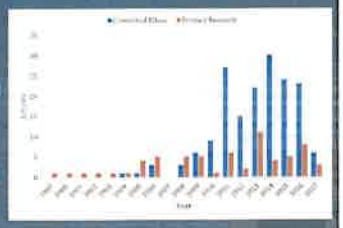
DBS and Control

- Gisquet (2008) argued that DBS can be a uniquely disruptive experience for patients due to the associated loss of control of the illness and loss of control of one's life and unwanted personality change
- Many neuroethics papers focus on the invasiveness of the DBS device and loss of control



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Does DBS result in unwanted personality changes?

- Studied 150 patients with PD and their Care Partners.
- Standard clinical personality measures were administered
- Mixed methods were used to more closely examine participants' most valued personality characteristics

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Methods

- Participants
  - Cohort 1: 50 patients with PD diagnosed ≤1 year + Care Partner
  - Cohort 2: 50 patients diagnosed within 5 – 7 yrs + Care Partner
  - Cohort 3: 50 patients approved for DBS + Care Partners (assessed prior to DBS and followed prospectively at Post-Op 6 & 12 months)

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Methods

- Semi-structured interview in which patients and care partners described patient's personality
- Follow up question eliciting participants' most valued personality characteristics (i.e., those they don't want to lose)
- Participants rank ordered top 3 characteristics
- Participants indicated extent to which the patient demonstrates embodiment of that characteristic on visual analogue scales:
  - Present Rating
  - Retrospective Historical Rating

Least — Most

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Methods

- 32 codes developed in response to "how would you describe your family member's personality throughout their lifetime?"
- Care Partners provided 886 unique responses
- Two independent raters indicated how much each unique, verbatim response was reflected in each of the 32 codes on a 4-point Likert scale
- The average score was computed and subjected to an exploratory factor analysis

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Eight Big Buckets of "Personality"

- Prosocial (e.g., loving, kind, generous)
- Physical (e.g., basic motor, athletic)
- Cognitive (e.g., intelligence, memory, curiosity)
- Self-Discipline (e.g., hard worker, reliable, fortitude)
- Virtues (e.g., faith in God, integrity, humility, loving fidelity/commitment to family/friends)
- Positive Emotionality (e.g., extravert, positive, high energy)
- Internalizing Negative Emotionality (e.g., sad, anxious)
- Externalizing Negative Emotionality (e.g., irritable, inflexible, angry)

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Proportion of top ranked Characteristics Patients fear losing most

- Positive Emotionality 29%
- Cognitive 20%
- Virtues 19%
- Self-Discipline 15%
- Prosocial 11%
- Physical 6%

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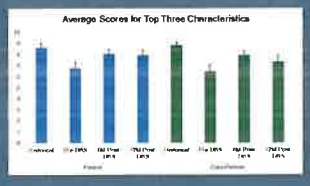
Does DBS Change Valued Personal Characteristics?

N=48 patient – care partner dyads recruited from a consecutive series of patients with PD. Studied prospectively pre-DBS and post-op months 6 and 12. Completed visual analog scales on self-identified personal characteristics they were most afraid of losing



Patients: Wald chi-square = 16.194, p < .001, d= .69 and Care Partners: Wald chi-square = 5.746, p < .001, d= .43

Merner ... Kubu. 2024. JAMA Network Open

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Does DBS Change Personality at the Individual Patient level in a Meaningful Way?

- Examined all changes >/= -/+ 1 SD from Pre to Post-Op Month 6
- 43/150 change scores (28%) met criteria
- 11.6% were negative changes (5 changes in 4 patients)
- 88.4% were positive changes (38 changes in 23 patients)
- 92% of all patients did not have a negative change

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Does DBS Change Scores on Personality Tests?

N=49 patient – care partner dyads recruited from a consecutive series of patients with PD Studied prospectively pre-DBS and post-op months 6 and 12

- No significant changes on most standard personality scales* per patient and care partner ratings (NEO, Iowa Scales of Personality, Frontal Systems Behavior Scale; Wald Chi^2 range = 0.004 – 0.649, all p's>.0125)
- *NEO, Agreeableness Scale from the care partners' perspective which indicated a negative change (Wald Chi^2 = 11.15, p<.001). This appeared to be driven by a few outliers and the absolute magnitude of the mean change was negligible from a clinical perspective (i.e., <0.5 SD)

Mainio et al. in preparation

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Summary

- Existing personality measures do not comprehensively assess what matters most to patients
- DBS is associated with personal characteristic ratings closer to retrospective historical scores
- DBS does not result in negative valued personal characteristic changes in 92% of participants
- DBS may be restorative to valued personal characteristics in patients with PD
- Few changes were apparent on standard personality tests

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Limitations

- Limited diversity in our samples
- Conclusions limited to the measures we used/questions we asked

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Implications

- The notion that neural implants can result in unwanted, deleterious changes to important aspects of personality is viewed as a truism by many
- Even though empirical data based on patients' values and standard personality tests suggest otherwise
- Stigma and fear may dissuade patients from seeking out viable therapies, especially historically marginalized, under-represented patients

Mainer & Kahn, 2023

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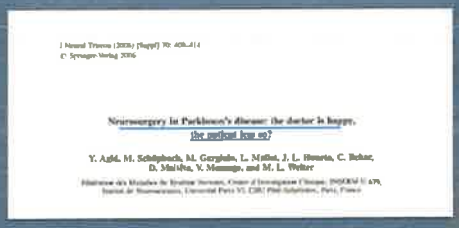
Satisfaction gap



Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so?

Y. Agid, M. Schüpbach, M. Gargiulo, L. Mallet, J. L. Houeto, C. Behar, D. Maltête, V. Maisonge, and M. L. Welter

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Methods

- Semi-structured interviews with a consecutive series of 52 patients approved for DBS to treat Parkinson's disease (PD)
- Participants identified the top three symptom and personal goals for surgery and extent to which they were in control of those goals. Control ratings were completed prior to and following surgery

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Methods

- Symptom control refers to one's ability to alter disease symptoms, such as tremor.
- Personal control refers to one's ability to autonomously and volitionally act to achieve functional personal goals.
- Device control refers to one's ability to adjust the actual stimulator settings.
- Global control

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Methods

- Content analysis was used to identify the broad categories of the participants' goals.

0 No Limitations — 10 Severe Limitations

- Participants indicate extent to which they can fully participate in those rank ordered goals on a visual analogue scale and changes were assessed prospectively using mixed effects linear models

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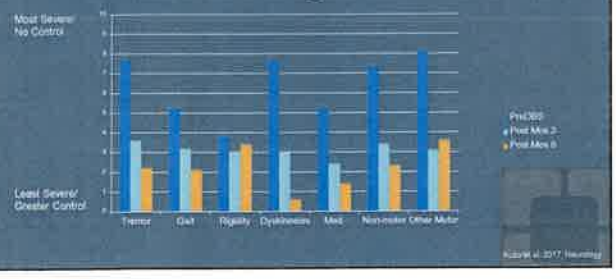
Changes in Symptom Control following DBS



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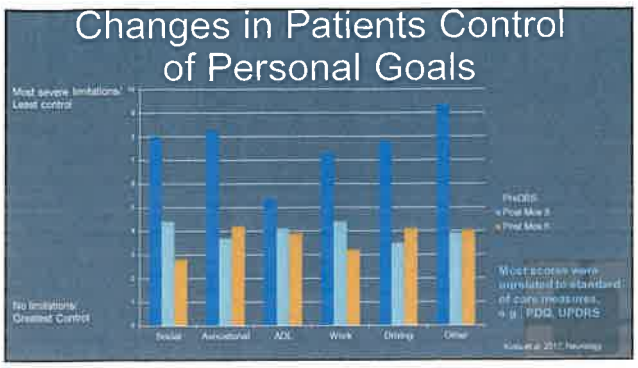
Changes in Patients Control of Personal Goals



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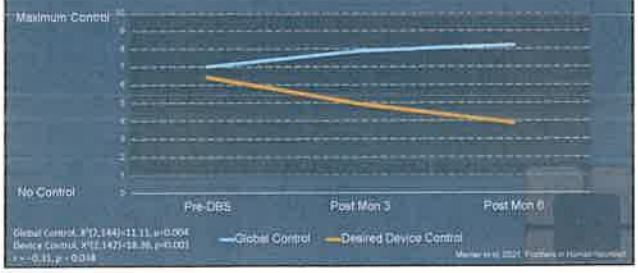
Changes in Device and Global Life Control with DBS



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Summary

- Despite conversations with multiple team members regarding expectations, symptoms that typically don't respond as well to DBS were among the most often cited symptom goals
- Patients' motivations to seek out DBS were primarily related to larger life goals including relationships, avocational pursuits, and working - illustrating the importance of identifying the underlying motivations and functional goals for DBS
- Improvements in patients' goals were unrelated to standard metrics
- Patients desire less control of their device while they experienced greater control in their lives

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Do these findings generalize to other patient groups (PD, Tremor, Epilepsy)?

- Symptom goals include the core features of the disorders for all three groups (e.g., tremor, rigidity, seizures)
- Participants in all groups also included psychiatric symptoms (e.g., anxiety, depression), fatigue, motor/sensory, and medication side-effects as symptom goals

Preliminary data

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What about functional goals?

- Social – PD, tremor, epilepsy
- Avocational – PD, tremor, epilepsy
- ADL – PD, tremor, epilepsy
- Work – PD, tremor, epilepsy
- Education* – epilepsy
- Driving – PD, tremor, epilepsy
- Other – PD, tremor, epilepsy

Preliminary data

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Summary

- Standard of care measures do not fully capture what is most important to patients
- This contributes to poor communication and mismatched expectations
- This can impact translational science, treatment planning, and informed consent discussions

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Why does this matter? (or Implications)

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Meaning of a failed trial

- EVEREST – cortical stimulation + rehab vs rehab in motor recovery
- RECLAIM and BROADEN: Industry sponsored DBS trials for treatment resistant depression
- "Failed" futility analyses, studies terminated based on financial decisions. Not because of patient safety concerns

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Ethical Concerns

- Focus on those who didn't respond vs those who did
- Loss of benefit to those patients who did respond when trial ended
- Lost knowledge opportunity in patients already implanted
- Public and scientific misperception of "failed" therapy; "failed" hypothesis

Fins, Kubu, Mayberg 2016

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Implications for translational research

- Importance of trial design
- Constraints of arbitrary end points – should we consider more iterative, fluid designs?
- Limitations of current outcome measures which may not reflect the treatment goals of a diverse, broad sample of our population
- Public perception and continued viability of a potential therapy

Fins, Kubu, Mayberg 2016

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Ethical Implications

- Neuropsychiatric disorders are among the most complex brain diseases.
- Goals and expectations for treatment may potentially be even more complex in these patients
- Outcome measures, including standard personality measures, may not assess what neuropsychiatric patients value most
- DBS may be restorative to traits patients value

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Ethical Implications

- If patient care is truly patient centered, we need:
  - To listen to what matters to patients
  - Incorporate what matters to patients in our outcome measures
- Why are these perspectives important?
  - Improves communication
  - Improves informed consent
  - Improves patient satisfaction
  - Improves science

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Neuropsychologist's/ Neuroethicist's role

- Partner with others to advocate for other ethical trial designs
- Challenge negative and stigmatizing narratives
- Integrate patients' values into study design and develop new measures that prioritize patients' perspectives and understandings of treatment "success"

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Neuropsychologist's/ Neuroethicist's role

- Better define the specific symptoms and behaviors we want to address
- Develop new measures with better construct validity (cf., Meehl's concept of "fuzzy constructs")
- Consider the underlying potential etiology/ phenotype
- Identify predictors of success
- Be mindful of the window of opportunity

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Informed Consent

- Cognitive/capacity issues
- Coercion

Kubu & Ford, 2017

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Informed Consent in Intracranial Studies

- "Invasiveness" and risk
- Role conflict (competing values) for physician-investigator
- Ability to provide and/or Voluntariness of consent (capacity, desperation, power differentials)
- Therapeutic misconception

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Informed Consent in Intracranial Studies

- Patients perceive implanted electrodes as more invasive and riskier than medications and MRI guided focused ultrasound

Kubu, unpublished data

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Role Conflict for Physician-Investigator

- Hippocratic oath
- Fiduciary responsibilities
  - Patients
  - Public
  - Profession
  - Science

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Vulnerability and Neuropsychiatric Disorders

- Patients with neuropsychiatric disorders have been abused and exploited in research studies - increased vulnerability
- Vulnerability often linked to concerns re: decisional capacity
- Persons with neuropsychiatric conditions do not automatically lack decisional capacity
- Paternalism and stigma

Bracken-Rache/Bell, Racine, 2016

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Therapeutic Misconception

- The inappropriate assumption by research participants "that decisions about their care are being made solely with their benefit in mind"
- Patients with treatment resistant depression can provide informed consent to participate in a DBS trial but still demonstrated therapeutic misconception

Appelbaum, Roth, & Lidz 1982; Fisher, Dunn, et al, 2012

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Informed Consent Best Practices

- If patient can provide consent
- Surgeon best equipped to discuss R/B and introduce study
- BREAK
- Research personnel further review the study and get informed consent relying on a "teach back" method
- Clinical trials – may necessitate a consent monitor

Feinsinger, Pouratian, et al. 2022, Chiong, Leonard, Chang, 2018

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Post-Trial Obligations

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Post-trial obligations is a Wicked Problem

93

Wicked Problems

- The roots of wicked problems are
  - complex and tangled
  - without a clear set of choices,
  - or path to a solution.

Webber & Rittel, 1973; Pretz, Naples & Sternberg, 2003; Weber & Khademian, 2008

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Wicked Problems

- The subsets of problems involved are all interconnected, so that multiple stakeholders and conflicting values are involved, leaving uncertain how one or even several approaches might adequately address the problem.

Webber & Rittel, 1973; Pretz, Naples & Sternberg, 2003; Weber & Khademian, 2008

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Wicked Problems

- Thus, wicked problems are not readily resolved through traditional linear decision-making approaches of problem-definition, solution development, and execution.

Webber & Rittel, 1973; Pretz, Naples & Sternberg, 2003; Weber & Khademian, 2008

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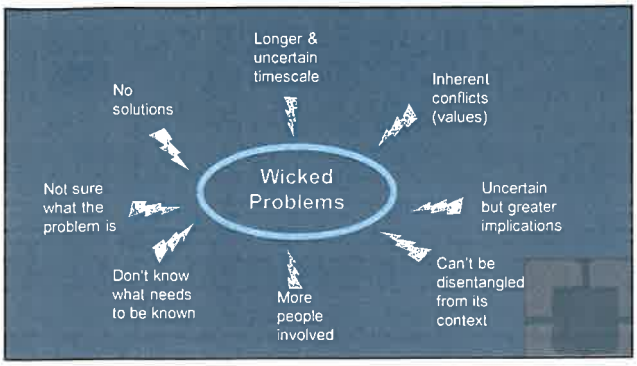

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Addressing a Wicked Problem

- Recognize when we have a wicked problem

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Addressing Our Wicked Problem

- Recognize when we have a wicked problem
- Reflection

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Addressing Our Wicked Problem

- Recognize when we have a wicked problem
- Personal reflection
- Engage in discussion with various stakeholders and those from other disciplines who might provide important perspectives

100

Addressing Our Wicked Problem

- Recognize when we have a wicked problem
- Personal reflection
- Engage in discussion with various stakeholders and those from other disciplines who might provide important perspectives
- Map out the core issues and values in conflict. Use balancing to identify a justified way forward.

101

Non-Abandonment

- Defining implanted neurological device abandonment
- Conducted a systematic English language PubMed search to investigate any existing definitions of neurological device abandonment (7/734 articles)
- The expert consensus group reviewed these findings, supplemented by additional literature and personal experience to propose a definition

Okun et al., (2024) JAMA Open Access

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Definition of Implanted Neurological Device Abandonment

1. Failure to provide information relevant to (the existence or absence of) plans for medical, technical, and/or financial responsibility as fundamental aspects of patient consent during and after a clinical trial

Okun et al., (2024) JAMA Open Access

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Definition of Implanted Neurological Device Abandonment

2. Failure to fulfill reasonable responsibility for medical, technical, and/or financial support prior to the end of an implantable device's labeled lifetime.

Okun et al., (2024) JAMA Open Access

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Definition of Implanted Neurological Device Abandonment

3. Failure to address any immediate needs (e.g., infection or device programming) of the individual using the implanted device, which may result in safety concerns and/or the deterioration of the device effectiveness.

Okun et al., (2024) JAMA Open Access

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Definition of Implanted Neurological Device Abandonment

4. Failure of a clinical research trial if or when (1) informed consent has failed to address ongoing access to and management of the implanted device and/or

(2) Trial organizers have not made reasonable efforts to facilitate access and support

Okun et al., (2024) JAMA Open Access

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Access and Addressing Healthcare Inequities

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Race, Ethnicity, and Mental Illness

- 21% of US Adults experienced mental illness in 2020
- Average delay between symptom onset and treatment is 11 years
- 150 million US citizens live in a designated mental health shortage area
- Fewer under-represented minorities (20.8-43%) receive mental health treatment than white patients (51.8%)
  - Stigma
  - Limited access
  - Distrust

NAMI, https://www.nami.org/mhstats

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Ethical Implications

- Women and minorities have been under-represented in healthcare research historically leading to inappropriate assumptions that impact care (e.g., gender differences in cardiac symptoms)
- We may be inappropriately imposing our values and goals on what we think patients want/value.
- This may exacerbate existing communication challenges and healthcare disparities

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Addressing Ethical Dilemmas

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Balancing

- Prima facie obligation - an obligation that must be fulfilled unless it conflicts on a particular occasion with an equal or stronger obligation
- Actual obligation – determined by the balance of the respective weights of the competing prima facie obligations
- Justified acts of balancing entail that good reasons be provided for one's judgment
- Balancing can be "viewed as a specification of norms that incorporates one's reasons"

Beauchamp & Childress, Principles of biomedical ethics, 6th edition, 1994

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Conditions that Restrict Balancing

- Better reasons can be offered to act on the over-riding norm than on the infringed norm
- The moral objective justifying the infringement has a realistic prospect of achievement
- No morally preferable alternative actions can be substituted
- The form of infringement selected is the least possible, commensurate with achieving the primary goal of the action
- The agent seeks to minimize the negative effects of the infringement

Beauchamp & Childress, Principles of biomedical ethics, 4th edition, 1994

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Balancing, Example 1

- A 36-year-old man is a candidate for neuromodulation to address severe symptoms of TRD
- He lives in a rural region with limited access to a DBS team
- Is it ethically permissible to have him undergo an ablative neurosurgery rather than DBS?

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Balancing, Example 1

- Relevant Values
  - Benefit
  - Risk
  - Cost
  - Equity

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Balancing, Example 1

- Benefit
  - Should potential benefit be denied due to geographical constraints?
  - Ablative lesions can provide relief to TRD symptoms
  - DBS offers greater flexibility to maximize benefit than a lesion
  - DBS may also provide a greater opportunity to understand basic scientific mechanisms

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Balancing, Example 1

- Risk
  - An ablative procedure requires fewer surgeries (and associated risks) but results in a permanent lesion
  - A DBS procedure also carries risk, albeit rare yet significant, but also provides flexibility with respect to stimulation to minimize potential side-effects and is reversible
  - What happens if the DBS device suddenly stops functioning and suicide risk?

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Balancing, Example 1

- Costs
  - Who pays for the surgery/surgeries?
  - If the procedure is done as part of a clinical trial, who assumes responsibility for the device and patient care after the trial?
  - Multiple visits to the DBS team may result in additional burdens/costs to the patient vs an ablative lesion

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Balancing, Example 1

- Equity
  - Should everybody have access to the best and most updated technologies?
  - If the patient is offered an ablative procedure, does this contribute to potential inequities in healthcare for geographic reasons?

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Balancing, Example 1

- Patient care takes precedence over research opportunities
- Need to share all information with patient and their care partners
- Need to explicitly assess patient's values and preferences
- A lesion may be ethically permissible to reduce suffering, although the reasons supporting that decision should be specified

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Balancing, Example 2

- How do we address "failed" clinical neuromodulation trials. What is the best design for a neuromodulation clinical trial?

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Balancing, Example 2

- Relevant Values
  - Scientific reproducibility, generalizability
  - Obligations to participants
  - Obligations to scientific progress

Fins, Kubu, Mayberg ...2016

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Balancing, Example 2

- Scientific reproducibility, generalizability
  - Clear, well-defined methods and measures are necessary
  - But if chosen incorrectly, they may hinder science and potentially harm patients
    - Inter-operator variability
    - Importance of inter-patient variability with white matter pathways and stimulation parameters
    - Time points
    - Measures

Fins, Kubu, Mayberg ...2016

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Balancing, Example 2

- Obligations to participants
  - Do no harm; unethical to continue a study that results in harm or there is clear evidence of lack of efficacy
  - Participants have undergone the risks associated with an implanted device
  - Participants' motivations often include contributing to the scientific enterprise to help future patients

Fins, Kubu, Mayberg ...2016

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Balancing, Example 2

- Obligations to participants
  - Some participants may have experienced benefits; what happens to them?
  - Can we leverage what we've learned from participants who benefited to help participants who haven't experienced benefits?
  - Who will cover the costs of the implanted devices and related care?

Fins, Kubu, Mayberg 2016

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Balancing, Example 2

- Obligations to scientific progress
  - Intracranial neuromodulation clinical trials offer a unique opportunity to study neural networks which may help alleviate suffering in the future
  - "Failed" trials may result in misperception that future work in this area is futile
  - History has taught us that the significant modifications to stimulation parameters helps increase benefit (i.e., flexibility is an advantage)

Fins, Kubu, Mayberg 2016

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Balancing, Example 2

- Obligations to scientific progress
  - We don't want to be limited by…"the insufficiency of methodological directives, by themselves, to dictate a unique substantive conclusion to many sorts of scientific questions" (Kuhn)

Fins, Kubu, Mayberg 2016

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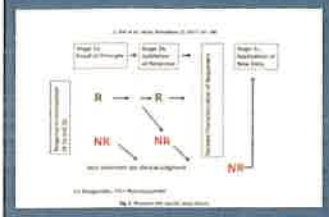
Balancing, Example 2



- Increase flexibility for those who failed to sustain a response or
- Failed to respond in a successful trial or
- In trials deemed to have failed

Fins, Kubu, Mayberg , 2015

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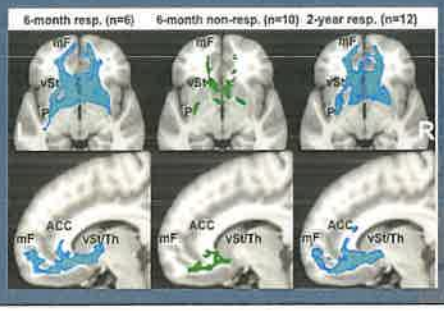
Mayberg's Lab
Riva-Posse et al (2014) Biological Psychiatry



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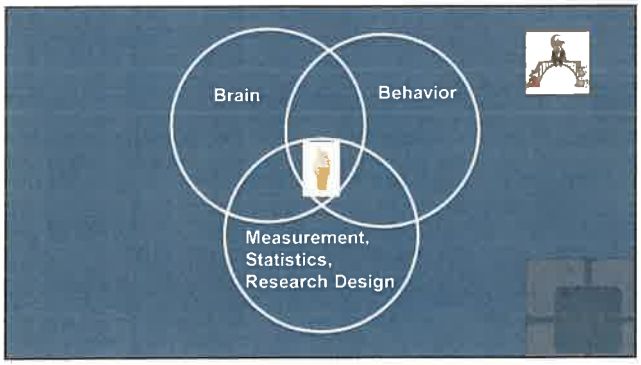

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Reflect on....

- How do our values and ideas about what constitutes health influence our clinical care?
- How do our values and ideas about what constitutes "proper science" influence how we conduct research?
- How do we avoid scientific reductionism without sacrificing empirical rigor?

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Recommendations

- Listen to our patients and their families
- Ascertain their underlying functional goals, motivations, and values
- Partner with minority community leaders to develop relationships and learn from them how to incorporate their voices in research and healthcare decisions
- Embrace interdisciplinarity and diverse voices
- Include additional outcome measures more reflective of patients' values

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How do we move forward in establishing the most ethical and scientifically robust way?

- Rely on data
- Acknowledge limitations and temper conclusions
- Clearly articulate the ethical principles in conflict

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William James and The Principles of Psychology

"The task was twofold – to make the budding field of psychology accountable to the most rigorous methods of the natural sciences and to simultaneously explain how this empirical study of the human mind avoided scientific reductionism" p 69

"....the objective method of science can only go so far in explaining the subjective experience of human beings" p98

Kaag, 2020

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Good ethics are based on good data

Questions?

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