

Non-Invasive Neuromodulation of the Central Nervous System: Opportunities and Challenges: Workshop Summary

DETAILS

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NON-INVASIVE NEUROMODULATION OF THE CENTRAL NERVOUS SYSTEM

Opportunities and Challenges

WORKSHOP SUMMARY

Lisa Bain, Sheena Posey Norris, and Clare Stroud, *Rapporteurs*

Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

Institute of Medicine

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **ERIC B. LARSON**, Group Health Research Institute. He was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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1

Introduction¹

Based on advances in biotechnology and neuroscience, non-invasive neuromodulation devices are poised to gain clinical importance in the coming years and to be of increasing interest to patients, clinicians, health systems, payers, and industry. Evidence suggests that both therapeutic and non-therapeutic applications of non-invasive neuromodulation will continue to expand in coming years, particularly for indications where treatments are currently insufficient, such as drug-resistant depression.

Given the growing interest in non-invasive neuromodulation technologies, the Institute of Medicine's Forum on Neuroscience and Nervous System Disorders convened a workshop, inviting a range of stakeholders—including developers of devices and new technologies, researchers, clinicians, ethicists, regulators, and payers—to explore the opportunities, challenges, and ethical questions surrounding the development, regulation, and reimbursement of these devices for the treatment of nervous system disorders as well as for non-therapeutic uses, including cognitive and functional enhancement (see Box 1-1).

Three non-invasive neuromodulatory devices are currently cleared for the treatment of depression and several others for the treatment of migraines, and many more devices and conditions are being explored.

¹The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

There is also a proliferation of over-the-counter (OTC) and do-it-yourself (DIY) device usage. Yet the neuromodulation field also faces significant business-related challenges, including a lack of clarity about how to navigate through regulatory and reimbursement environments to bring a device to market successfully, according to Jeffrey Nye, vice president of Neuroscience Innovation and Scientific Partnership Strategy at Janssen Research & Development, LLC, Johnson & Johnson Innovation. By contrast, he said the pharmaceutical industry has a much more well-developed understanding of these issues. Another hindrance for companies developing therapeutic neuromodulatory devices is that these organizations are typically small relative to those developing drug therapies, and therefore they may have fewer resources to devote to the pursuit of endorsement by regulators and payers, said Ana Maiques, chief executive officer of Neuroelectrics.

Non-invasive neuromodulation is not likely to provide a “magic bullet” for the treatment of conditions such as depression, said Thomas Insel, director of the National Institute of Mental Health (NIMH). He surmised that in the future, device companies may join with pharmaceutical companies to produce combined treatments that are more effective than either of the two alone. Yet while the potential benefits of combination therapy are substantial, so are the developmental, technical, regulatory, and business barriers to such collaborative approaches.

Excitement about the potential for neuromodulation technologies is tempered by concerns the development may be getting ahead of regulation and scientific insight, said Alvaro Pascual-Leone, professor of neurology and associate dean for clinical and translational research at Harvard Medical School. Several workshop participants noted that little is known about the mechanisms of action affecting clinical improvement, and therefore, more evidence is needed. Hank Greely, director of the Stanford Program in Neuroscience and Society at Stanford University, agreed, noting that the use of neuromodulation devices has been creeping up without as much attention as in other areas of medical product development. He and several other workshop participants also discussed the ethical considerations around the use of non-invasive neuromodulation, such as off-label OTC use.

BOX 1-1
Statement of Task

An ad hoc planning committee will plan and conduct a 2-day public workshop to explore opportunities, challenges, and ethical questions surrounding therapeutic and non-therapeutic uses of non-invasive neuromodulation of the central nervous system (CNS).

Presentations and discussions will be designed to:

- Highlight potential benefits and risks of non-invasive neuromodulation based on known short- and long-term CNS mechanisms of action.
 - Explore the scientific landscape of non-invasive neuromodulation device development for both therapeutic and non-therapeutic uses.
 - Consider issues concerning vulnerable populations such as children.
- Consider the regulatory landscape for non-invasive neuromodulation devices.
 - Discuss potential outcome measures for therapeutic uses in regulatory processes.
 - Explore pathways for regulatory approval of therapies utilizing a combination of non-invasive neuromodulation devices and pharmaceuticals.
 - Discuss differences in regulatory pathways among countries.
- Explore current and potential use reimbursement practices for therapeutic use of non-invasive neuromodulation devices.
 - Explore the evidence base and acceptable therapeutic outcome measures utilized in reimbursement decisions.
 - Consider economic outcome measures used to determine payer practices.
- Examine ethical questions around the use of non-invasive neuromodulation devices.
 - Consider ethical issues of off-label and over-the-counter use on regulation, reimbursement, and patient safety.
 - Discuss the use of these devices for enhancement in individuals without an impaired baseline.
 - Consider the implications of involuntary or coercive use (e.g., children, court-ordered treatment).

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. An individually authored full-length workshop summary will be prepared by a designated rapporteur based on presentations and discussions held during the workshop in accordance with institutional guidelines.

ORGANIZATION OF REPORT

The following report summarizes the workshop presentations and discussions. Chapter 2 provides an overview of the gaps, challenges, and potential opportunities for future research and policy action identified by individual participants. Subsequent chapters elaborate on these topics. Chapter 3 provides an overview of what is known about the neurobiological basis of non-invasive neuromodulation and the technologies that have been developed to deliver neurostimulation to the brain. Chapters 4 and 5 discuss therapeutic and non-therapeutic uses of neuromodulation, including its use as a tool for diagnosis, presurgical mapping, and research. Chapter 6 explores the use of neuromodulation to enhance brain function and performance, followed by a discussion of the ethical issues related to the use of neuromodulatory technologies in Chapter 7. Chapter 8 provides a brief overview of the regulatory pathways for both therapeutic and non-therapeutic devices in the United States and Europe. Included in this chapter is a discussion of the challenges of conducting clinical trials of neuromodulatory devices. In Chapter 9, challenges of reimbursement are discussed. Chapter 10 provides an industry and venture capital perspective on the challenges for businesses that are developing non-invasive neuromodulatory devices.

2

**Overview of Gaps, Challenges,
and Potential Opportunities**

Non-invasive neuromodulation provides the neuroscience community with a unique ability to gain fundamental insight into brain function while at the same time helping patients, Alvaro Pascual-Leone explained. He suggested that, in combination with other therapies and other methods to assess brain function (such as quantitative behavior assessment, electroencephalography [EEG], or brain imaging), non-invasive neuromodulation also may offer the ability to personalize treatment by enabling a better understanding of the specific neural substrates underlying the symptoms of disease, then targeting the specific neurobiological circuits involved. However, along with many participants, he also emphasized the need for more basic research, as well as larger and longer clinical studies with suitable control interventions to better understand the long-term benefits and risks of non-invasive neuromodulation.

Given the way the market is progressing, particularly the rapid growth of non-therapeutic uses of neurostimulation for cognitive and performance enhancement, several participants called for more attention to consumer, DIY, and off-label uses of non-invasive neuromodulation. Ethical, legal, and safety implications of non-medical uses deserve particular scrutiny, they said. Should consumer-targeted devices take hold in the marketplace, they will inevitably have implications for medical device research and innovation, said Hank Greely. Indeed, Jeffrey Nye suggested that these devices could essentially disrupt the regulatory approval of medical devices by further blurring the distinction between medical and non-medical approaches. They could also disrupt clinical trials by making it increasingly difficult to identify treatment-

naïve patients and by making it more difficult to blind patients as to whether they are receiving treatment or placebo.

Throughout the workshop, many participants discussed the research gaps and challenges associated with non-invasive neuromodulation and identified potential opportunities to address them. In addition, policy issues were examined, and workshop participants focused their discussions primarily on challenges and potential opportunities related to ethical, legal and social implications, regulation, reimbursement, and the current business development environment for non-invasive neuromodulation, all of which are further discussed in subsequent chapters. While there are a number of barriers to address, including the need for a greater understanding of the underlying mechanisms and long-term effects of neuromodulatory devices, many participants acknowledged the vast opportunities of such devices and how all sectors (e.g., regulatory, payers, researchers, companies, and society) might contribute to bring this technology forward to clinicians and patients.

RESEARCH GAPS AND CHALLENGES¹

During the workshop presentations and discussions, many participants identified research gaps and challenges associated with non-invasive neuromodulation. The suggestions, listed here and attributed to the individual(s) who made them, are expanded on in succeeding chapters. Their full names and affiliations are listed in Appendix C.

Limited Understanding of the Fundamental Neurobiology of Non-Invasive Neuromodulation

- Knowledge gaps exist regarding basic mechanisms of action of non-invasive brain stimulation, and the neurophysiologic effects of non-invasive neuromodulation on the brain (Lisanby, Pascual-Leone).
- Knowledge gaps exist in the brain circuitry, and neurobiology of core symptoms and disabilities caused by many of the brain diseases being targeted with non-invasive brain stimulation (Lisanby, Pande, Pascual-Leone, and others).

¹The points in this list were made by the individual(s) to which they are attributed; they are not intended to reflect a consensus among workshop participants.

- Although there are clear anatomical and physiological differences between the brains of children and adults, as well as developmental changes in plasticity, little is known about the effect of non-invasive neuromodulation on the immature brain given that most studies exclude children (Rotenberg).
- A better understanding of why some people do not respond to non-invasive neuromodulation is needed at the neurobiological level (Pascual-Leone and others).
- Genetic and epigenetic factors of individual variability of the effects of non-invasive neuromodulation need to be explored further (Pascual-Leone and others)

The Large Number of Parameters Involved in Non-Invasive Neuromodulation: Challenges for Understanding the Neurobiological Effects

- The efficacy of non-invasive neuromodulation is highly variable, most likely because of both individual differences, patient differences, differences in stimulation characteristics of the various devices, and failure to engage the appropriate neurobiological target (differences in the brain substrates of similar symptoms and disabilities) (Pascual-Leone).
- The large number of coil designs and the various options for placement on the head make it important to systematically evaluate the corresponding electric field distribution of various devices (Lisanby).

The Large Number of Parameters Involved in Non-Invasive Neuromodulation: Challenges for Understanding the Clinical Effects

- Effects on cognition are influenced by many factors, including the intensity of stimulation, where the stimulation is applied and the anatomy of the targeted network, and the cognitive construct of interest (Hamilton).
- Clinical studies in children are particularly challenging because of limits in the number of patients, lack of homogeneity, interactions with other treatments, and limited access to tissue (Rotenberg).
- The ability to determine effectiveness is hindered by varying definitions and treatment parameters in clinical trials (Gaynes).

Additional Study of Long-Term Safety and Efficacy

- Strategies to optimize the efficacy while preserving the safety of non-invasive neuromodulation are in need of further study and development, in particular, the long-term safety and the impact on the developing brain (Farah, Hamilton, Lisanby).
- Home use of these devices could enable more individualized treatment, but requires a better understanding of the effects of more frequent patterns of stimulation and raises concerns about clinical supervision, regulation, and reimbursement (Maiques).

Knowledge Gaps Associated with Depression and Other Therapeutic Uses

- The most well-developed therapeutic use of non-invasive neuromodulation is for the treatment of medication-resistant depression; less is known about the wide variety of other potential therapeutic uses (Hallett, Pascual-Leone, and others).
- Comparative effectiveness studies of non-invasive neuromodulation for treatment-resistant depression concluded that the quality of evidence was low or insufficient for the effect of repetitive transcranial magnetic stimulation (rTMS) on improving functioning or maintaining remission (Gaynes).

Knowledge Gaps Regarding Appropriate Control Conditions and Clinical Trial Designs

- Better design of sham stimulation and control conditions are critical to assess the effects of non-invasive neuromodulation in clinical trials (Hallett, Pascual-Leone, and others).
- Clinical trial design, including adaptive designs and other approaches, is needed to optimize and speed up solid evidence of clinical efficacy (Connor, Tariah).

POTENTIAL RESEARCH OPPORTUNITIES²

During the workshop presentations and discussions, many participants identified potential opportunities to improve the available evidence on non-invasive neuromodulation. These suggestions, listed here and attributed to the individual(s) who made them, are expanded on in succeeding chapters.

Improving Our Understanding of the Fundamental Neurobiology of Non-Invasive Neuromodulation

- Research is needed to better understand whether neural oscillations are an epiphenomenon of brain function or a signal of information processing, and whether abnormalities are associated with psychiatric and neurological conditions (Lisanby, Pascual-Leone).
- Research is needed to better understand the impact of non-invasive brain stimulation on distributed brain networks—the effects of brain stimulation does not remain limited to the directly targeted brain area and, in fact, the behavioral and ultimately therapeutic effects may be mediated by impact on distant brain regions reached via trans-synaptic network effects. Better characterization of such neurobiological effects can help gain fundamental insights on brain function and brain-behavior relations, while enabling improved therapeutic approaches (Fox, Lisanby, Pascual-Leone).
- Research studies and new tools are needed to better understand the functional role of extracellular currents and the interaction between the stimulation and the brain's electrical activity (Lisanby).
- Research is also needed to focus on the neurophysiological effects when extracellular currents are exogenously applied compared to when they are endogenously generated, as well as the interaction of the two (Lisanby).
- Similarly, there is a need for a better understanding of basic brain circuitry and the effects of different electromagnetic fields

²The points in this list were made by the individual(s) to which they are attributed; they are not intended to reflect a consensus among workshop participants.

on those circuits. Without this, we will be in the position of being able to work with only the clinical phenotype (Pande).

- A better understanding of the neurobiological substrate of various symptoms may reveal additional targets of non-invasive neuromodulation (Pascual-Leone).
- Various types of modeling, including realistic head modeling of the induced electric field distribution in the brain, and animal models of the physiological responses to stimulation provide opportunities for better understanding the effects of different types of non-invasive neuromodulation (Lisanby).
 - An international collaboration of scientists, including those from the Food and Drug Administration (FDA), have developed and are making freely available to the scientific community a realistic head model to study the effects of non-invasive neuromodulation on the brain (Iacono et al., 2015).
- More preclinical studies and animal models are needed to assess the long-term effects of non-invasive neuromodulation on adults and children (Farah, Rotenberg).
 - The large number of animals that can be employed in studies enable investigators to test and tweak systematically a range of different stimulation protocols and different doses to determine the optimal parameters to test in clinical studies. In addition, laboratory models enable studies of mechanisms of action at a resolution not available in humans, for example, by assessing regional gene expression, changes in neurotransmitter receptor subtypes, and other molecular consequences of non-invasive neuromodulation (Rotenberg).
- More research is needed to determine dose–effect relationships and appropriate washout periods for different stimulation protocols (Hamilton and others).

Using Non-Invasive Neuromodulation for Diagnosis and Research

- Because stimulating a part of the brain can evoke a measurable response, neurostimulation coupled with electrophysiologic recording techniques may provide biomarkers for disease states that could be modulated by non-invasive neuromodulation, or even serve as stand-alone biomarkers (Rotenberg).

Developing a Taxonomy or Classification Scheme for Non-Invasive Neuromodulation

- The lack of a consensus taxonomy or classification scheme for non-invasive neuromodulation technologies, in combination with sometimes unclear specification of clinical and performance standards for different devices makes it difficult for clinicians to extract relevant information from the literature about safety, efficacy, risks, etc. that are unique to a form of device or are generalizable across all device types within a category (Demitrack and others; see Box 2-1).

BOX 2-1

Variables Associated with Non-Invasive Neuromodulation

The box lists the various uses, settings, technologies, parameters, and conditions for which non-invasive neuromodulation has been indicated or researched, as mentioned by individual workshop participants.

1. Uses of non-invasive neuromodulation
 - a. Therapeutic
 - b. Non-therapeutic
 - i. Diagnosis
 - ii. Research
 - iii. Presurgical mapping
 - iv. Enhancement
2. Conditions for which non-invasive neuromodulation has been indicated/researched
 - a. Psychiatric conditions
 - i. Depression
 - ii. Posttraumatic stress disorder
 - iii. Obsessive-compulsive disorder
 - iv. Aggression
 - v. Addiction
 - b. Neurologic conditions
 - i. Epilepsy
 - ii. Migraine
 - iii. Movement disorders
 - iv. Neuropathic pain
 - v. Tinnitus
 - c. Neurorehabilitation

3. Settings for delivery of non-invasive neuromodulation
 - a. On-label use by clinicians
 - b. Off-label use by clinicians
 - c. Over-the-counter use by consumers
 - d. Do-it-yourself use by consumers
4. Technologies
 - a. Electromagnetic
 - i. Electroconvulsive therapy
 - ii. Transcranial electrical stimulation (TES), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS)
 - iii. Transcranial magnetic stimulation
 - b. Ultrasound
5. Technical performance specifications (select)
 - a. Coil geometry and placement on the head
 - b. Temporal characteristics of the magnetic pulse
 - c. Patterning of pulse sequence
 - d. Number and spacing of sessions
 - e. Use as an add-on or substitute treatment
 - f. Patient differences (e.g., baseline level of depression)

DISCLAIMER: This box presents variables discussed by one or more individual workshop participants. Because this is a summary of workshop comments and is not intended to reflect consensus, this table and its content should not be attributed to the rapporteurs of this summary as informed by the workshop.

Optimizing the Therapeutic and Non-Therapeutic Uses of Non-Invasive Neuromodulation Through an Improved Understanding of Clinical Effects, Safety, and Efficacy

- The field of non-invasive neuromodulation, and stimulation in combination with pharmacotherapy, would benefit from an experimental medicine approach where various parameters, dosing, duration, intensity, etc., are tested against a variety of constructs (e.g., cognitive constructs) and electrophysiological recording techniques (Insel and others).
- The tools of cognitive neuroscience, including neuroimaging and neurophysiologic approaches, could be used to guide the development of safer and more effective non-invasive neuromodulation strategies in heterogeneous populations (Pascual-Leone).

- Pre-registration of studies and/or the establishment of a repository for null results (a “file drawer” repository) might improve information on both safety and efficacy by reducing the problem of publication bias, which is most pronounced with underpowered studies. Given the likely small effect sizes for enhancement uses, supporting well-designed larger scale studies would also improve assessment of efficacy (Farah).
- Adaptive and other innovative trial designs may be useful for clinical trials of non-invasive neurostimulatory devices and for combination trials (Connor).
- Combining non-invasive neuromodulation with pharmacotherapy, cognitive therapy, or behavioral approaches could provide novel and more efficacious interventions (Hallett, Pascual-Leone).
- There is a need to know more both about the neurobiological characteristics that differentiate between those who do and do not respond to neurostimulation, and the synergies among different therapies (Pascual-Leone).
- Animal studies could enable investigators to examine the effects of combining pharmacologic agents with non-invasive neuromodulation, both to design combination trials where neuromodulation and pharmacotherapy are complementary, and to avoid drugs that may interfere with a desired neuromodulation effect (Rotenberg).
- Realizing the potential for home use of neuromodulatory devices under clinical supervision will require more research on the effects of more frequent patterns of stimulation as well as attention to regulatory and reimbursement issues (Maiques).
- There is a need for comparative effectiveness studies to provide efficacy information for decision-making on the part of payers, providers and patients. With the availability of this type of information, improvements would follow in the consistency of clinical decision making and reimbursement policies (Robinson-Beale).
- Non-invasive neuromodulation combined with monitoring of brain activity using technology such as EEG could enable individualized approaches to treatment (Maiques).

Improving Understanding of the Use of Non-Invasive Neuromodulation for the Enhancement of Brain Function and Performance

- Performance enhancement applications have the potential to be used by a wide range of individuals, from the very elite to the severely disabled and from school children to pilots; and aside from important ethical issues, questions that need to be addressed include where they would use these devices and under what kinds of supervision and training (D. Edwards).
- Much more work is needed to demonstrate the mechanisms underlying enhancement, the reproducibility and long-term effects of these approaches, and the potential of combining neurostimulatory approaches to cognitive and performance enhancement with exercise training and cognitive training (Cohen Kadosh, D. Edwards).

POLICY ISSUES AND POTENTIAL OPPORTUNITIES³

During the workshop presentations and discussions, many participants identified issues and potential opportunities related to ethical, legal, and social issues; the regulation of non-invasive neuromodulation devices; reimbursement for treatment using these devices; the business environment in which these devices are being developed; and education/awareness about these devices among clinicians, the general public, and others. These suggestions, listed here and attributed to the individual(s) who made them, are expanded on in succeeding chapters.

Ethical, Legal, and Social Issues

Challenges

- Non-physical harms, such as effects on a person's sense of "self," may result from non-invasive neuromodulation (Parens).

³The points in this list were made by the individual(s) to which they are attributed; they are not intended to reflect a consensus among workshop participants.

- The fuzzy line between treatment and enhancement follows from unclear definitions of what is normal (Parens).
- The use of non-invasive neuromodulation is expanding, despite incomplete understanding of safety and efficacy (Farah and others).
- The effects of non-invasive neuromodulation on cognition, attention, memory, learning, visuomotor perception, and other neuropsychological functions have led to a growth industry in non-therapeutic enhancement tools, although the possible negative consequences of these technologies are not completely understood (Cohen Kadosh, D. Edwards, Fox).
- Ethical concerns are raised by the use of neuromodulation on people unable to consent for themselves, for example parents choosing non-invasive neuromodulation to treat or enhance their child's capacities or behavior, and by the involuntary or coercive use of non-invasive neuromodulation, such as the offer of neuromodulation to criminal offenders in exchange for a better sentence (Chandler).
- The DIY movement raises questions about the responsibility of researchers to educate the public (Maslen).

Potential Opportunities

- Concerns about physical and non-physical harms demand a cross-disciplinary conversation among clinicians, epidemiologists, health psychologists and sociologists, welfare economists, philosophers, and many others (Parens).
- A better understanding of the safety and efficacy of non-invasive neuromodulation is needed to make decisions about whether it is appropriate to put neurostimulatory devices in the hands of clinicians, patients, and consumers. To enable adequately powered studies, Farah advocated for the introduction of social structures, ranging from preregistration registries to funding along with education of consumers, and she suggested coming together as a community to articulate a research agenda to accomplish this (Farah).
- As these technologies become more normalized, they may become part of the cultural wallpaper, the “new normal,” but this should not stop the community from considering whether limits should be in place to prevent harmful use (Chandler).

Regulation

Challenges

- Different regulatory paths for neuromodulatory devices in the United States and Europe have resulted in different availability of these devices around the world (Marjenin, Tariah).
- The complex regulatory pathway for non-invasive neuromodulatory devices presents unique challenges for device developers (Marjenin, Tariah).
- The regulatory requirements for non-invasive neuromodulatory devices will vary depending on the perceived level of risk, with non-therapeutic neuromodulatory devices facing less stringent regulatory requirements (Marjenin, Tariah).
- Many transcranial magnetic stimulation (TMS) studies use sham controls, but because TMS is intrinsically multisensory, blinding the patient and therapist is difficult (Pascual-Leone).
- Important and challenging aspects of clinical trials for neuromodulatory devices include the choice of control or comparison condition, determination of dose–effect relationships, and patient heterogeneity (Hamilton, Lisanby).

Potential Opportunities

- Regulatory policies for medical devices in the European Union (EU) should be extended to brain stimulation devices for enhancement. The goal of this proposal is to promote safe use of the devices; however, Maslen acknowledged it would have no effect on DIY uses. (Maslen)
- International harmonization of regulatory policies, though difficult to implement, could expedite regulatory approvals (Hallett).
- Novel clinical trial designs may be needed because clinical trial methods developed in the pharmaceutical sphere may not be appropriate for device-based treatments (Demitrack).
- For sponsors seeking regulatory approval of devices in the United States, the FDA has encouraged the use of new tools, including innovative clinical trial designs, adaptive trials, and modeling and simulation (Connor).

- Preclinical approaches and collaborations with the FDA could be useful to better understand how the various technologies affect the brain (Reppas).
- Regulators from both the United States and Europe encourage sponsors to consult with them early in the development process about the development of their medical device, including clinical trial design issues (Marjenin, Tariah).
- Data submitted to one regulatory agency may possibly be leveraged in a subsequent submission to another agency. This will require developers to consult with regulators to determine which data will be accepted (Marjenin, Tariah).

Reimbursement

Challenges

- Reimbursement for TMS has grown considerably in recent years as devices become more widely accepted by the clinical community, and both patients and clinicians are requesting reimbursement for appropriate clinical care (Demitrack, Maiques, Robinson-Beale).
- Health plans individually determine whether treatment will be reimbursed based on multiple types of data, research-randomized control trial, population-based, comparative effective (often incomplete or conflicting in this arena), comparative efficiencies and cost considerations, and the existence of practice guidelines. These data needs are frequently not available nor included in research protocols. This leads to significant inconsistency in provider application within practice and variation in medical policies and reimbursement decisions (Robinson-Beale).
- The lack of practice guidelines is a barrier to reimbursement. Without such guidelines, decisions may be based on the opinions of independent practitioners who may or may not have experience with a technology. This includes decisions about the coverage of maintenance therapy (Robinson-Beale).
- Inconsistent reimbursement decisions may limit patient access to treatment and business development (Hailey, Reppas).

- Regulatory and reimbursement pathways in different countries complicate the approval process for companies developing non-invasive neuromodulatory devices (Marjenin, Tariah).

Potential Opportunities

- Practice guidelines from professional societies would assist health plans in making appropriate reimbursement decisions and improve the consistency of reimbursement practices (Jaffe, Robinson-Beale).
- There is also a need for comparative effectiveness studies to help determine the relative value of new technologies in comparison to standards and the indications for application (Robinson-Beale).
- When practice guidelines are missing or not explicit enough to clarify practice application to create necessary medical policy, insurance companies would need to include in the technology review process expert or seasoned clinicians who have treated patients using the new technology in providing input into medical policy (Robinson-Beale).
- Organized registries could help capture additional data needed to further inform applications of technologies (e.g., unresponsive subpopulations, longer-term effects, adverse reactions, etc.) on the use of devices after marketing approval has been granted (Morales, Robinson-Beale).
- Standard criteria for reimbursement could help enable universal coverage and access (Morales).

Business Environment

Challenges

- Interest in non-invasive neuromodulatory devices is high among both clinicians and industry. However, growth of the industry is hampered by a number of factors, including low awareness of the technology among the broader practitioner base, lack of direct to consumer education, a limited understanding of the mechanism of the effect of these technologies, a lack of funding from federal grant sources, and sometimes unclear regulatory pathways to approval (Demitrack, Maiques, Pande, and others).

- Development of neuromodulatory devices has been largely the province of small companies with limited resources (who may be interested in selling the devices to larger companies). Small companies may lack sufficient resources to undertake the complicated and lengthy processes required for regulatory and reimbursement approval (Maiques).
- Despite excitement in the field, investors have shied away from medical device companies because of unproven business models for some technologies, lack of regulatory predictability, challenges obtaining reimbursement, and the long development time frame for investors to see a return on their investment (Jaffe).

Potential Opportunities

- Funding sources for large-scale innovative research demanded by clinicians and patients are limited, while such large, time-consuming and often expensive studies are needed in order to clarify the most effective methods of dosing and appropriate short- and longer-term treatment regimens (Demitrack).
- There could be tremendous opportunities for operational synergies between device and pharmaceutical companies in the development of innovative therapies. Potential synergies could include the use of common sales and marketing forces that call on psychiatrists or other clinicians, combined regulatory departments, etc. However, many challenges from a business and regulatory perspective will need to be addressed (Nye).
- Education/awareness efforts (as described below) may help enhance the business environment for device manufacturers and investors (Demitrack).

Education/Awareness

Challenge

- Clinicians and the public have a low awareness and understanding of neuromodulation. Although the brain is responsive to both chemical and electrical stimulation, clinical practice has been dominated by a largely pharmaceutical or

neurochemically-based understanding of the treatment of disease (Demitrack).

Potential Opportunities

- Professional societies should take a more active role in establishing practice standards and addressing the needs of practicing clinicians who utilize these technologies (Demitrack).
- Providers need improved education and training about the risks and benefits of TMS, as well as efforts to raise awareness among the public (Morales).
- Cross-disciplinary discussions among clinicians, epidemiologists, health psychologists and sociologists, and others are needed to address concerns about the non-physical as well as physical harms that may result from non-invasive neuromodulation (Parens).
- Scientists may need to take more responsibility for educating the public about their work to avoid misinterpretation and misuse of technologies (Maslen and others).

3

The Science and Technology of Non-Invasive Neuromodulation

Highlights

- Any part of the brain is a potential target for neurostimulation, and a better understanding of the neurobiological substrate of various symptoms could open the way to other therapeutic uses of non-invasive neuromodulation. (Hallett)
- Neurostimulation causes anatomical and functional changes of brain circuits; prolonged stimulation can affect metaplasticity. (Hallett)
- Because of the connectivity in brain circuits, the effects of brain stimulation extend beyond the stimulation site. (Fox)
- Neurostimulation affects children differently than adults, due both to anatomical differences and developmental changes in the brain. (Rotenberg)
- A range of transcranial electromagnetic devices and ultrasound have been shown to effectively modulate activity in the human brain. (Chen, Edwards, Elias, Krauthamer, Lisanby)
- Investigation of neurostimulation approaches in animal models helps scientists understand the molecular consequences and pharmacology of neurostimulation. (Rotenberg)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

The history of neuromodulation goes as far back as ancient times, when electric fish were used to treat pain, explained Mark Hallett, chief of the Human Motor Control Section at the National Institute of Neurological Disorders and Stroke (NINDS). Today's broad range of non-invasive neuromodulatory devices includes electroconvulsive

therapy (ECT), transcranial electrical stimulation (TES), transcranial magnetic stimulation (TMS), static magnet stimulation, transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), random noise stimulation, ultrasound and focused ultrasound (FUS), and peripheral nerve stimulation, including stimulation of the cranial nerves. These tools not only provide insight into brain physiology, but can be used to modify the brain circuitry for a variety of therapeutic and non-therapeutic purposes, including neuroenhancement.

TARGETS AND MECHANISMS OF ACTION

Hallett suggested that any and every part of the brain could potentially be a target for neurostimulation. At this time, therapeutic applications of neurostimulation, such as repetitive pulse TMS (rTMS), have primarily been successful for the treatment of medication-resistant major depression. In these applications, stimulation is typically delivered to the dorsolateral prefrontal cortex (DLPFC), which has been identified as being hypometabolic in patients with depression (George et al., 1995; Martinot et al., 1990). However, Alvaro Pascual-Leone suggested that assuming the effects of neurostimulation come only from effects on the prefrontal cortex may miss the contribution of other brain areas. A better understanding of the neurobiological substrate of various symptoms may reveal other brain areas and neural circuits that may be modifiable through neurostimulatory approaches. For example, resting state functional connectivity maps may enable the identification of networks that may be modifiable using different stimulation approaches, possibly in combination with other interventions.

NEUROSTIMULATION EFFECTS ON THE BRAIN

Neurostimulation can alter brain function by creating a lesion or in some other way inducing an anatomical or functional change that will interrupt brain circuits or modulate oscillations within a circuit, said Hallett. In terms of non-invasive neuromodulation, most lesions are transient, although high-intensity focused ultrasound will create a more permanent lesion with longer lasting effects.

Neurostimulation interventions can produce either acute or persistent effects; however, the ability of a neurostimulatory device to produce a prolonged effect depends on its ability to use plasticity to change the brain. Neurostimulatory devices may produce a plastic change through multiple mechanisms, including strengthening or weakening synaptic strength and inducing anatomical changes such as increases in dendritic spines or axonal sprouting. According to Hallett, synaptic change and anatomical change are likely to occur sequentially. Moreover, it appears that treatments need to be repeated multiple times in order to get a long-lasting effect. This may reflect a transition from a physiologic to an anatomic change.

Michael Fox, assistant professor of neurology at Harvard University, noted that the physiologic effects of brain stimulation extend far beyond the site where stimulation is administered. For example, in order for TMS administered to the primary motor cortex to cause a muscle twitch, the polysynaptic neural response to the pulse must travel through the mid-brain and pons, cross the medulla, down the spinal cord, across a synapse to the alpha motor neuron, along that neuron down the limb and cross a neuromuscular junction, thus causing the muscle to contract. In other words, focal brain stimulation does not stay focal, but affects multiple areas of the brain (Fox et al., 2012b). Yet, for the goal of inducing long-term neuroplastic changes, a few participants noted that there is importance in direct repetitive stimulation of the relevant brain structures (Pell et al., 2011).

Propagation of the neural response to the stimulation occurs outside of the motor cortex as well. For example, Fox and colleagues have shown, using several different imaging techniques, that when TMS is administered to the DLPFC for treatment of depression, there are also effects on the subgenual cingulate (Fox et al., 2012a). One implication of this is that connectivity in the brain can be used to identify locations on the surface of the brain that are accessible to non-invasive brain stimulation and that enable modulation of circuits and deep targets (Fox et al., 2012a). This work also demonstrates the usefulness of neuroimaging as a means of studying the different areas of the brain that may be affected by neurostimulation of a specific target.

The effects of non-invasive neuromodulation also depend on frequency and duration of stimulation. Administration of repeated pulses at low frequency or cathodal tDCS results in a reduction in the strength of the twitch, suggesting that excitability has been modulated, whereas administration of a high-frequency pulse of TMS or anodal tDCS results

in an excitatory effect and a stronger twitch. In addition, the behavioral and physiologic effects of stimulation last longer than the stimulation itself, although how long they last is unclear. For example, one study showed that effects on memory and changes in functional connectivity following multiple-day stimulation persisted for 2 weeks (Wang and Voss, 2015). Roi Cohen Kadosh, Wellcome Research Career Development Fellow and university research lecturer at the University of Oxford, showed data from another study where learning effects persisted for 6 months following transcranial random noise stimulation (tRNS) stimulation (Snowball et al., 2013).

NON-INVASIVE NEUROMODULATION IN CHILDREN

Several participants spoke about special medical and developmental considerations when using non-invasive neuromodulation in children. In addition, ethical issues arise with regard to children's capacity to cooperate and to make informed decisions about the treatment; these are discussed in Chapter 7.

The brains of a child and adult have obvious anatomic differences, such as the density of the skull, the distance from the scalp to the brain, and the fact that the head and brain grow with time, said Alexander Rotenberg, associate professor of neurology at the Harvard Medical School and senior associate in neurology at Boston Children's Hospital. In addition, throughout childhood there are changes in excitability, and with those changes come potential special vulnerability to injury. For example, the immature brain has an immature cortical inhibitory pattern, which makes it especially vulnerable to excitotoxic injury and seizures. Indeed, GABA, the inhibitory neurotransmitter in the mature brain, is actually excitatory in early life (Rakhade and Jensen, 2009). Rotenberg suggested that genetic mechanisms that switch GABA from excitatory to inhibitory may develop improperly in some disease states, such as autism and epilepsy.

The immature brain is also undergoing more neurogenesis, synaptogenesis, synaptic pruning, and myelination than the adult brain, yet little is known about how applied electric fields and other forces will affect these processes, or if prolonged exposure to current may have unexpected consequences. For example, Rotenberg mentioned a study in boys with autism that used TMS to assess synaptic plasticity. After delivering a train of repetitive TMS to the motor cortex, the investigators tested how long it took for corticospinal excitability to return to baseline.

The results indicated that there is a developmental trajectory to motor plasticity in this population, suggesting that frequency and duration of stimulation in children should take into account age and other developmental characteristics (Oberman et al., 2014). Rotenberg noted, however, that there have been few clinical trials that have segmented the pediatric population in order to examine mechanisms and neuroplasticity across the developmental trajectory.

One reason for the paucity of evidence regarding the effects of neurostimulation in children is that most human neuromodulation research excludes young people. In addition, studies in children are particularly challenging because of limits in patient availability, lack of homogeneity, interactions with other treatments, and limited access to tissue. Rotenberg said that more preclinical studies and animal models are needed to address these challenges. These models enable investigation of mechanisms at a resolution that is simply unavailable in humans, for example, looking at changes in regional gene expression or neurotransmitter receptor subtypes. The biggest advantage of animal models is found when large numbers of test animals are available, enabling systematic tweaking of protocols to identify the optimal dose, pattern and frequency of stimulation, etc. The molecular and electrophysiologic mechanisms are also accessible in isolated brain slices, which can be derived from experimental animals, and also (following brain surgery) from humans. Interestingly, said Rotenberg, because clinical applications of neurostimulation devices have been deployed well in advance of the basic science to support them, when data are acquired in the laboratory they can be rapidly translated to the clinic because the devices are already there.

MODELING ELECTRICAL DOSE AND EXPOSURE

Victor Krauthamer oversees a group of scientists at the FDA that aims to understand the fundamental mechanisms of neurostimulation as they are applied in devices seeking regulatory approval. Krauthamer directs the Division of Biomedical Physics in the Office of Science and Engineering Laboratories at the FDA's Center for Devices and Radiological Health (CDRH). The studies undertaken in these labs are especially important to understand the safety of various modalities of electromagnetic stimulation on nerve cells. They have been able to predict, for example, the effects of high-frequency stimulation on

unmyelinated and myelinated cells (Krauthamer and Croscheck, 2002), illustrating the relative importance of the type of fiber that is being stimulated. Krauthamer's group also has been working to understand the cellular mechanisms underlying emerging neurostimulation approaches such as those using near-infrared light (Katz et al., 2010), as well as the physiological and anatomical effects of low- and high-frequency ultrasound.

The FDA scientists use modeling and simulation at both the macroscopic, or anatomical, level, and the microscopic, or neuronal, level, to assess the effects of various neurostimulation devices on the brain, said Leonardo Angelone, research biomedical engineer at CDRH. For example, to study the electric fields generated by a given source applied transcranially, they are using an anatomical model of the human head that was developed through an international collaboration. This model will be made freely available to the scientific community, said Angelone (Iacono et al., 2015). It has been used, for example, to demonstrate how changing the location of electrodes on the head makes the field more focal.

Modeling also has been used to evaluate the differences among technologies—such as TMS compared with tDCS (Wagner et al., 2007)—to better understand the neuronal response and influence on behavior (Miniussi et al., 2013), and to examine the differences in electric field distribution with different TMS coils (see Deng et al., 2013, for example).

ELECTROMAGNETIC DEVICES

A range of transcranial electromagnetic devices has been shown to effectively activate the human brain, although it is less clear how to leverage this for adaptive and durable neuromodulation, according to Dylan Edwards, director of the Non-Invasive Brain Stimulation and Human Motor Control Laboratory at Burke Medical Research Institute and Weill Cornell Medical College.

Electroconvulsive therapy is one of the earliest technologies developed for therapeutic purposes, used primarily for the treatment of depression and other psychiatric conditions. Though often not thought of as a “non-invasive” approach because it induces seizures, Sarah H. Lisanby, professor and chair of psychiatry and behavioral sciences at Duke University, said it remains a potent and rapidly acting treatment for

depression. The FDA has approved the use of ECT for six indications, although concerns about side effects and incomplete knowledge about the mechanisms of action limit its use primarily to those with severe, treatment-resistant depression (Kellner et al., 2012).

Transcranial electrical stimulation includes both tDCS and tACS, which are among the most readily available and cheap neurostimulatory devices in use. Indeed, a method used in 1804 by Giovanni Aldini to treat melancholia is not that different from the tDCS approaches that can be downloaded from the Internet today, said Krauthamer (Parent, 2004). Essentially, it involved delivery of a constant, low-intensity electric current over tens of minutes.

Transcranial magnetic stimulation was introduced in 1985 by Barker and colleagues as a non-invasive and painless method of electrically stimulating the human motor cortex (Barker et al., 1985). TMS devices deliver very brief, high-intensity magnetic pulses, with the neuromodulatory effect resulting from multiple pulses being delivered. Pascual-Leone and colleagues showed more than 20 years ago that a short burst of rapid rTMS increases excitability in the brain (Pascual-Leone et al., 1994). A few years later, Robert Chen and colleagues showed that low-frequency rTMS reduces excitability in the brain (Chen et al., 1997). In other words, just modulating the frequency will alter the effect on the brain, said Hallett. These differences can be converted into different therapeutic approaches for a variety of conditions, such as depression, stroke, movement disorders, epilepsy, and pain. In addition, said Rotenberg, because one can stimulate over a part of the brain and then quantify the response, TMS has robust diagnostic capacity, especially when coupled with other electrophysiological recording techniques.

The spatial distribution of the TMS field is controlled by coil design and placement on the head. Thus, the different coils differ in terms of coil focality and precision of stimulation (Deng et al., 2013). For example, the two coils approved for the treatment of depression—the figure 8 iron core by Neuronetics and the H-coil from Brainsway—have very different spatial distribution. The figure 8 coil is fairly superficial with minimal spreading, while the H coil has deeper penetration and greater spreading (see Figure 3-1). There are many other coil designs, each with a different corresponding electric field distribution (Deng et al., 2013). Lisanby noted how daunting it is to systematically evaluate these different devices, but added that this is where modeling and animal models are essential.

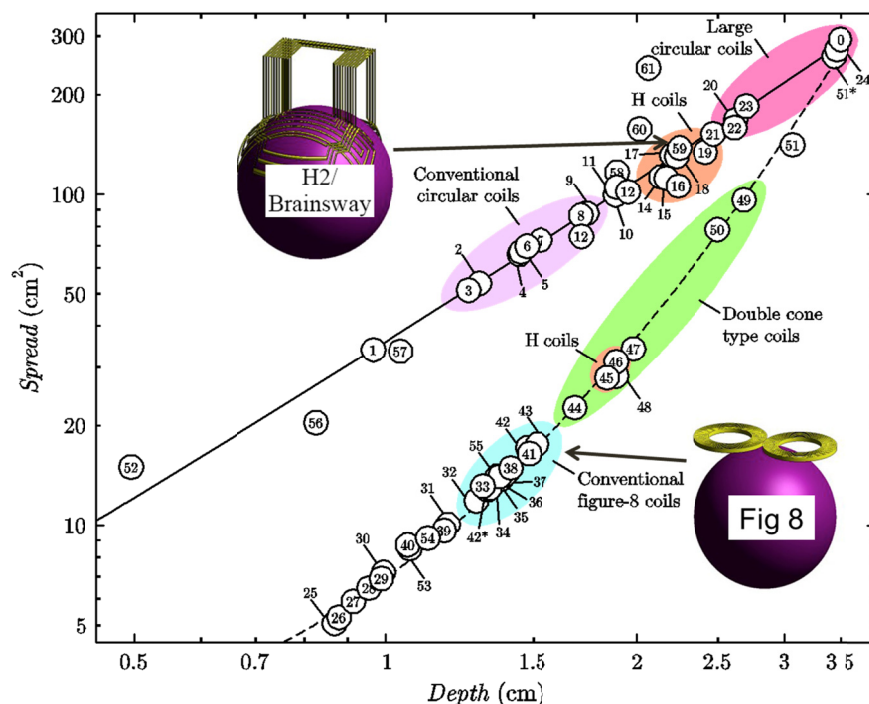


FIGURE 3-1 Focality/depth trade-off of 61 coils.
 SOURCE: Presented by Sarah Lisanby at the IOM Workshop on Non-Invasive Neuromodulation of the Central Nervous System on March 2, 2015. Modified from Deng et al., 2013.

A few novel coil designs are also being tested in humans. One uses multiple magnetic coils to improve magnetic field focality (NCT01431001). Another uses low-frequency magnetic stimulation (LFMS, NCT01654796), a technology that grew from the serendipitous observation that one of the pulse sequences used in functional magnetic resonance imaging (fMRI) resulted in mood improvements in patients with bipolar disorder (Rohan et al., 2004). A third (NCT01370733) synchronizes the stimulation to a patient’s alpha frequency as measured by EEG (Leuchter et al., 2013).

ULTRASOUND

Non-invasive neuromodulation with ultrasound is at a much earlier stage of development than TMS or tDCS. It has received CE Mark

clearance¹ for therapeutic brain lesioning indications, indicating it is approved to be marketed in Canada and Europe; however, it has not yet been approved by the FDA.

Diagnostic ultrasound typically uses high-frequency waves that do not move through the skull very well. However, according to Jeffrey Elias, associate professor of neurological surgery and neurology and director of stereotactic and functional neurosurgery at the University of Virginia School of Medicine, there are some therapeutic frequencies that move through the skull better. Indeed, as far back as the 1950s, neuroscientists William and Frank Fry conceived the idea of focusing ultrasound beams deep inside the brain to treat movement disorders (Fry et al., 1958). Their technique could hardly be called non-invasive, however, because it required making a cranial window in the skull, which limited its development. Now that ultrasound can be delivered through the intact skull, non-invasive neuromodulation with lower intensities is receiving considerable attention.

For example, Elias's lab is investigating the use of ultrasound's mechanical effects to activate or inhibit brain circuits (Elias et al., 2013). Slice preparation studies have indicated that pulsing neurons with low-intensity ultrasound causes, through an unclear mechanism, an electrical stimulation of excitable or inhibitory response at the neurons (Tufail et al., 2010). Several labs are pursuing this line of research, mostly in small animals. They have shown that by pulsing the cortex, they can induce a behavioral response without causing any histological effect. Legon and colleagues have also tested this technology in humans. In this study, they were able to enhance performance on sensory discrimination tasks by targeting a specific area of the somatosensory cortex with transcranial focused ultrasound (tFUS) (Legon et al., 2014), and similar effects were later replicated by Yoo's lab (Lee et al., 2015).

Elias said an advantage of low-intensity focused ultrasound is that it can be delivered deep in the brain without causing permanent damage or effects, thus lowering the bar for testing and brain mapping (Bystritsky et al., 2011). Potential indications include acute symptoms such as seizures as well as chronic conditions such as depression where plasticity might be affected. The main disadvantage is that much work remains to understand mechanism and refine the parameters to optimally activate or

¹ See <http://www.jtultrasound.com/content/2/1/17> (accessed October 5, 2015).

inhibit neuronal circuits. The concepts and technology need to be further developed in the laboratory, he said, and then brought to the clinic.

PRECLINICAL STUDIES IN ANIMAL MODELS

Although TMS and other types of non-invasive brain stimulation have already been deployed in the clinic, Rotenberg noted that the basic science to support their use is lacking, and advocated increased use of preclinical studies in animal models to fill this gap. The large number of animals that can be employed in studies enable investigators to test and tweak systematically a range of stimulation protocols and doses to determine the optimal parameters to test in clinical studies. In addition, laboratory models enable studies of mechanisms of action at a resolution not available in humans, such as assessing regional gene expression, changes in neurotransmitter receptor subtypes, and other molecular consequences of neurostimulation. For example, *in vitro* slice cultures enable scientists to assess the effect of different levels of stimulation on different cellular populations within different brain regions, providing access to molecular mechanisms such as plasticity in a simplified structure (Vlachos et al., 2012). Animal studies also enable investigators to examine the effects of combining pharmacologic agents with neurostimulation, both in order to design combination trials where drugs facilitate the neurostimulation effects, and to identify drugs that may interfere with neurostimulation, said Rotenberg.

In summary, looking across non-invasive neuromodulation technologies, Lisanby compared the current state of knowledge to trying to develop a new drug without a complete understanding of the pharmacology, including the pharmacokinetics and pharmacodynamics, and many workshop participants identified gaps that need to be addressed in order to advance the field, ensure the safe application of devices, and develop devices with better efficacy. These research gaps, challenges, and opportunities were outlined in Chapter 2.

4

Therapeutic Uses of Non-Invasive Neuromodulation

Highlights

- Neuromodulation enables the translation of insights from cognitive neuroscience into targeted therapies in psychiatry and neurology. (Pascual-Leone)
- Currently, the only FDA approved use of non-invasive neuromodulation is for medication-resistant depression. Its utility in other psychiatric disorders is currently under study. (Lisanby)
- Non-invasive neurostimulation also appears to be promising for post-stroke treatment of hemiparesis, aphasia, visuospatial neglect, pain, attention disorders, and movement disorders, as well as migraine and neuropathic pain. (Hamilton, Pascual-Leone)
- Neurostimulation may facilitate the reorganization of injured neural networks. (Hamilton)
- Combining neuromodulation with other therapies, such as drugs, cognitive therapy, or behavioral approaches, may be necessary to achieve maximal efficacy. (Hallett)
- Combining neuromodulation with EEG monitoring of brain activity could enable specific and individualized adaptation of stimulation to appropriate areas of the brain. (Maiques)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Neuromodulatory devices provide tools that can translate insights from cognitive neuroscience into targeted therapies for disorders of the

central nervous system. These tools have been most well developed in the field of psychiatry, but applications for neurorehabilitation and the treatment of neurologic disorders such as migraine, epilepsy, and movement disorders were also discussed by several workshop participants.

According to Alvaro Pascual-Leone, neuromodulation forces clinicians to think from the patient-system point of view, enabling them to personalize interventions by understanding the patient's particular pathophysiology; in a sense, it is reverse engineering the disorder. Doing that requires the disorder to be deconstructed, moving from concepts such as dementia or depression to specific symptoms, and then characterizing them on the basis of the neural substrate of those symptoms, that is, the specific circuits affected. In other words, he said, these neuromodulatory approaches enable targeting not of the disease itself, but specific symptom complexes that map onto specific neural substrates.

Most of the work on developing therapeutic applications of neurostimulation has focused on transcranial current stimulation (tDCS and tACS) and transcranial magnetic stimulation; however, more recently tRNS has captured the imagination of scientists, clinicians, and even the general public, said Pascual-Leone. At the time of the workshop, two TMS devices targeting treatment-resistant depression are FDA approved and covered by insurance and Medicare in most states: the Neuronetics device with the NeuroStar protocol and the Brainsway device with H-coil, both for the treatment of medication-resistant depression. Since the workshop, a third device has been cleared by the FDA—Magtim Super Rapid.¹ The NeuroStar TMS Therapy alone has treated more than 25,000 patients (NeuroStar TMS Therapy, 2015). With a remission rate, based on both controlled trials and clinical experience, of about 30 percent, Pascual-Leone said this means that perhaps 24 or 25 remitters per day are being helped with TMS.

These results beg the question of why only some people respond to treatment and, indeed, whether neurostimulation is actually responsible for the responses seen. Beatrix Krause and Roi Cohen Kadosh examined individual differences that impact the effectiveness of TES, concluding that patient characteristics that impact the effectiveness of treatment include genetic factors, head or tissue morphology, and state factors (e.g., fatigue, attention, alertness); disease characteristics, including symptoms

¹See <http://www.magstim.com> (accessed June 1, 2015).

and co-morbidities; and stimulation characteristics (Krause and Cohen Kadosh, 2014).

Pascual-Leone reviewed the literature on therapeutic applications of neurostimulatory devices, specifically TMS and tDCS, looking at randomized sham-control, parallel-group, multisession studies across multiple indications. For every indication and every device, he found both negative and positive studies. For some indications such as epilepsy and stroke, the specifically targeted area for stimulation was especially important. For example, in studies of generalized epilepsy where the target is unclear, the results were poor; however, when the target was known, and the stimulation was delivered appropriately to the ipsilateral or contralateral cortex, the results were greatly improved.

Most studies reviewed were small and were affected by a high risk of bias for a variety of reasons (e.g., selection bias, performance bias from blinding, etc.). Thus, noted Pascual-Leone, Cochrane reviews² of the quality of evidence across multiple indications concluded that while there may be some indication of efficacy of non-invasive brain stimulation, the evidence is weak. He concluded that larger studies with more diverse groups and settings are needed to avoid bias.

Despite the weak evidence, Pascual-Leone sees great promise in these neurostimulatory approaches if interventions can be individualized. That, he said, requires thinking about the disorders in a different way and demonstrating that the appropriate substrate is being engaged for a specific patient. For example, to address cognitive function, cognitive neuroscience insights might be able to help guide the interventional applications. For this he advocated combining brain stimulation techniques with neuroimaging and neurophysiology, that is, by using magnetic resonance imaging (MRI)-guided approaches for optimal spatial precision and EEG-guided approaches for optimal frequency for a given cortical location or condition. He also stressed the need to combine neurostimulation with behavioral, pharmacologic, and other interventions and the importance of exploring how these devices can be used safely in children, the elderly, and other special populations.

Experimental medicine approaches, where as part of a clinical trial a target is tracked in response to dose of stimulation, could also help understand contributors to efficacy, said Thomas Insel. TMS is well suited

²See http://www.cochrane.org/CD008208/SYMPT_stimulating-the-brain-without-surgery-in-the-management-of-chronic-pain (accessed July 1, 2015).

for this approach, especially coupled with other electrophysiologic recording techniques, functional imaging, and other outcome measures, said Alexander Rotenberg. However, Roy Hamilton, assistant professor of neurology at the University of Pennsylvania, pointed to the complexity of the problem, which arises from the multidimensionality of the parameter space. For example, with tDCS, factors that must be controlled for include the intensity and location of stimulation, the cognitive construct of interest and how it is measured, the anatomy of the network, and the baseline state of the brain.

PSYCHIATRIC DISORDERS

According to Sarah H. Lisanby, electroconvulsive therapy has “unparalleled efficacy” in terms of benefits to patients with depression, particularly those who have failed to respond to pharmacologic treatments (Greenberg and Kellner, 2005). In one study of depressed patients who reported suicidal thoughts and acts, treatment with ECT resulted in a resolution of suicidal intent in 80.9 percent of those enrolled, some (15.3 percent) after only one ECT session, while most required multiple sessions (Kellner et al., 2005). However, the downside of ECT is memory loss, including loss of memories about the world as well as memories about events in a person’s life (autobiographical memory) (Lisanby et al., 2000).

Innovations, including the use of realistic head modeling to optimize the location of electrodes on the head so that the stimulation is more focal, as well as the use of ultrabrief pulse ECT (Sackeim et al., 2008), have attempted to resolve some of the problems associated with ECT, noted Lisanby. Magnetic seizure therapy (MST), in which magnetic stimulation is used to induce focal seizures, is another experimental technique that provides more focal stimulation in comparison to ECT, and this increase in focality is associated with a reduction in cognitive side effects (Won et al., 2014).

TMS is also used at subconvulsive levels for the treatment of depression. In one study comparing active TMS to sham TMS, TMS was significantly superior to sham after 4 and 6 weeks of five sessions per week (O’Reardon et al., 2007). Similar results were shown in a recent multicenter study with 212 patients diagnosed with major depressive disorder (MDD) with 20 sessions in 4 weeks acutely, and then biweekly for 12 weeks (Levkovitz et al., 2015). Another recent meta-analysis concluded that both high- and low- frequency TMS demonstrated a significant ef-

fect in patients with posttraumatic stress disorder (PTSD) using continuous scale measures of PTSD and depression symptom severity (Karsen et al., 2014). Lisanby noted that the benefits of TMS include a good safety profile, the ability to stimulate focally, and the lack of adverse effects on memory.

Bradley Gaynes, professor of psychiatry at the University of North Carolina School of Medicine, discussed the comparative effectiveness review on non-pharmacologic interventions for treatment-resistant depression in adults, conducted by the Agency for Healthcare Research and Quality (AHRQ) under his direction (Gaynes et al., 2011). AHRQ strives to identify the highest quality evidence available and synthesize that information quantitatively to answer key questions that are of public health or medical importance. Gaynes noted that these efforts are limited by the information available; thus as the evidence evolves, conclusions evolve as well. He further noted that absence of evidence does not equate with absence of effect.

The standard used by AHRQ is to determine whether evidence is of high, moderate, low, or very low quality, reflecting the level of confidence the agency has that evidence supports a claim. In their assessment of non-pharmacologic interventions for treatment-resistant depression, they found that rTMS does not clearly differ from ECT in terms of benefits or harms; however, the strength of evidence was low (Gaynes et al., 2011).

With regard to rTMS compared with sham treatment, they concluded the following:

- rTMS produced a greater decrease in depression severity based on high strength of evidence.
- rTMS was three times as likely to produce a response based on high strength of evidence.
- rTMS was six times as likely to achieve remission based on moderate strength of evidence.
- rTMS produced a greater improvement in health status and daily functioning based on low strength of evidence.
- There was insufficient evidence on the ability of rTMS to maintain response or remission (Gaynes et al., 2011).

In terms of benefits, noted Gaynes, they concluded that rTMS produced better outcomes for depression severity and response rates for young adults and for depression severity in older adults with post-stroke depression, although the strength of evidence was low. In terms of

harms, rTMS produced more scalp pain at the stimulation site than sham treatment, again only with low strength of evidence. The AHRQ report also included other analyses to try to compare effect sizes among trials designed to assess different treatment strategies such as those that used augmentation or switching designs, but there was not enough evidence to come up with any firm conclusions.

Gaynes said the ability to quantitatively synthesize data from TMS studies was hindered by varying definitions of treatment-resistant depression; an unclear number of prior treatment episodes; varying parameters such as coil location, motor threshold, stimulus pulse, and number of pulses; whether TMS was used as an add-on or substitute treatment; and baseline levels of depression. In addition, journal articles from which data were derived often report only group effects, making it difficult to answer simple questions such as how depression severity affects outcomes. He and several other participants also commented that data published in journals may be biased in favor of studies with positive outcomes. He noted other knowledge gaps as well, including information on health-related outcomes such as quality of life, levels of functional impairment, and patient reports as well as efficacy in specific population subgroups.

Moreover, TMS is not without risks. The most common risk is headache, and there is also a risk of hearing loss; however, the most serious risk is seizures (Rossi et al., 2009). Medications can raise or lower the risk of seizures depending on their effects on seizure threshold, said Lisanby, but the safety guidelines that are used to guide TMS dosing were derived in healthy subjects who were not taking medications. Certain populations may be especially vulnerable; for example, children and individuals with comorbidities such as autism, substance abuse, and addiction.

The devices that have been cleared by the FDA for the treatment of depression have the capability of doing both high and low frequency stimulation, but the dosage approved for depression is high frequency. A range of other devices are in development, as noted in Chapter 3, many of which deliver low-frequency stimulation, which carries with it a much lower risk of seizures. A recent meta-analysis that included nearly 250 patients across eight studies found no detectable difference in terms of therapeutic effect between the two frequencies (Chen et al., 2013). tDCS has also been tested as a treatment for depression, and a recent study showed that the combination of sertraline and tDCS was more effective than either in monotherapy for the treatment of depression (Brunoni et

al., 2013). Relative to TMS, tDCS is safe, with no known risk of seizure, said Lisanby. However, similar knowledge gaps remain with regard to mechanism of action and optimization of dose in space and time.

Non-invasive neurostimulation has been used for other psychiatric disorders as well, including PTSD (Karsen et al., 2014), obsessive-compulsive disorder (Berlim et al., 2013), aggression (Dambacher et al., 2015), and addiction (Bellamoli et al., 2014).

NEUROREHABILITATION

The ability of neurostimulation to help patients recovering from stroke also holds great promise, Hamilton said. Because recovery from a focal brain injury depends on the reorganization of networks that serve specific cognitive operations, non-invasive brain stimulation offers both a window into the brain to reveal those networks and a way to leverage change and improve recovery, said Hamilton. Moreover, because stroke is so prevalent—affecting nearly 800,000 Americans each year—and responsible for tremendous morbidity (Go et al., 2014), and given the paucity of effective therapies, there is great unmet need in this area.

According to Hamilton, TMS and tDCS are being applied to three main areas in stroke recovery: hemiparesis, which is motor weakness of one side of the body; neglect, which is the inability to attend to or act upon stimuli on one side of one's body or space; and aphasia, or problems producing or understanding language. His group starts by understanding how intact cognitive systems work and how injured systems differ from normal systems, using this knowledge to guide the development of brain stimulation protocols. For example, a meta-analysis from his group looked at functional imaging data from aphasic subjects during language tasks compared to normal subjects, and determined that while normal subjects activate left-dominant networks, aphasic subjects also activate additional areas in both the left and right hemispheres (Turkeltaub et al., 2011).

Hamilton and others have pursued the notion that neurostimulation might facilitate reorganization of injured neural networks. This work is predicated on the idea that the two hemispheres are richly interconnected so that, for example, if you inhibit the intact hemisphere or stimulate the damaged area, you restore some degree of balance between the two hemispheres (Hamilton et al., 2011). Indeed, in the Contrastim Stroke Study, 20 subjects received 18 sessions of rTMS stimulation to the non-lesioned

hemisphere prior to task-oriented upper limb rehabilitation. Ten subjects received sham stimulation. More than 88 percent of the subjects receiving rTMS stimulation had a meaningful clinical response compared to only 38 percent who received sham stimulation (Harvey et al., 2014), prompting a much larger Phase III trial that is currently ongoing, said Hamilton.

Studies of tDCS in aphasia have also been promising although more heterogeneous, said Hamilton (Monti et al., 2013). This variability may be due to differences in study design as well as patient factors, including lesion shape and location and the constellation of symptoms. The use of TMS and tDCS for neglect is at an even earlier stage, he said. His lab has shown, for example, that tDCS facilitates visuospatial processing (Medina et al., 2013); and at least one study has shown that a type of TMS called theta-burst stimulation (TBS) may accelerate recovery from spatial neglect (Koch et al., 2012). Michael Fox mentioned another study where TMS was administered to the parietal cortex, resulting in enhanced ability to detect targets on the ipsilateral side (Hilgetag et al., 2001).

OTHER NEUROLOGIC DISORDERS

Neurostimulation has been investigated as a treatment for a variety of other neurologic disorders, including epilepsy, migraine, movement disorders, amyotrophic lateral sclerosis (ALS), tinnitus, and chronic pain. For example, Mark Hallett's group investigated the use of rTMS delivered to the left and right motor and dorsolateral prefrontal cortex as a treatment for gait abnormalities and bradykinesia in Parkinson's disease (PD) patients (Lomarev et al., 2006). In comparison to patients receiving placebo, those receiving TMS showed gradual improvement in gait as well as reduced upper limb bradykinesia. The effects lasted for at least 1 month after treatment ended.

The eNeura TMS device is FDA approved for medication-resistant migraine with aura (FDA, 2013). Pascual-Leone said that while this device may have limited clinical impact because most patients with migraine have unpredictable auras and those with aura are often resistant to treatment, the device nevertheless paves the path for patient-applied home use of this technology.

COMBINING NEUROSTIMULATION WITH OTHER THERAPIES

Hallett and several other participants also mentioned the potential of combining multiple neurostimulation technologies or a combination of neurostimulation with behavioral interventions or drugs in order to provide even better results. For example, Yang et al. (2013) combined rTMS with treadmill training in patients with PD. After 12 sessions of rTMS followed by treadmill training over a 4-week period, the combination was shown to improve walking performance and modulate corticomotor inhibition better than either treatment alone in patients with PD (Yang et al., 2013).

Pascual-Leone's group has also investigated the combination of tDCS with visual illusion for the treatment of neuropathic pain in patients with spinal cord injury. In a sham-controlled study, patients receiving tDCS and visual illusion together reported a reduced intensity of neuropathic pain in comparison with those who received either intervention alone or placebo (Soler et al., 2010).

Many participants commented on the likelihood that effective treatment of many brain disorders may require combinatorial approaches that deliver neurostimulation in combination with pharmaceutical treatments or behavioral-based interventions. Mark Demitrack, vice president and chief medical officer of Neuronetics, for example, said he believes combinatorial work across device platforms as well as combinations of neurostimulation with behavioral interventions are ripe for study now. Ana Maiques, however, said she believes the barriers separating pharmaceutical and device companies are diminishing; and Atul Pande, chief medical officer at Tal Medical, added that most studies are currently conducted against a background of existing pharmacotherapy. Regulatory challenges would likely be complex for a combinatorial strategy; in addition, business models for combination approaches, including potential operational synergies among companies, have yet to be explored, said Jeffrey Nye.

5

Using Non-Invasive Neuromodulation for Diagnosis and Research

Highlights

- The assessment of brain responses to non-invasive neurostimulation may be useful in the diagnosis of upper motor neuron involvement in neuromuscular disorders, spinal cord lesions, multiple sclerosis, PD, and Alzheimer's disease. (Chen)
- These techniques may also be useful to assess disease progression, predict response to therapy, presurgically map eloquent areas of the brain that should be protected during surgery, and employ as a research tool to better understand the neurobiologic processes underlying normal and abnormal brain performance. (Chen)
- Neurostimulation coupled with electrophysiologic recording techniques may provide biomarkers for disease states that could be modulated by non-invasive neuromodulation, or even stand-alone biomarkers. (Rotenberg)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

The effects of non-invasive neuromodulation provide not only potential therapeutic benefits, but also a window into the workings of the human brain. Thus, non-therapeutic uses of neuromodulation are being developed in parallel with therapeutic devices as research tools and for diagnosis and presurgical mapping to protect eloquent brain areas from damage during surgery.

DIAGNOSIS

Unlike therapeutic modalities of TMS, which use repetitive stimulation, diagnostic applications of TMS typically involve single-, paired-, or multiple-pulse techniques that enable the measurement of motor evoked potential (MEP) amplitude, central motor conduction time (CMCT), and cortical inhibition and excitation. As summarized by Robert Chen, professor of medicine at the University of Toronto, CMCT is used to detect myelopathy, upper motor neuron involvement in ALS, and the location of spinal cord lesions, and to document lesions in multiple sclerosis. In ALS, multiple TMS measures may be used to better characterize the disease. For example, in patients with ALS, motor cortex excitability may be increased while CMCT is typically delayed. These measures can thus be used to distinguish ALS from mimic disorders such as Kennedy's disease or spinal muscular atrophy, or other neuromuscular disorders (Vucic et al., 2011). In addition, cortical hyperexcitability appears to be an early feature of ALS; thus it may be useful as a diagnostic biomarker (Vucic et al., 2011). TMS techniques may also enable the assessment of disease progression and treatment effectiveness in drug trials (Vucic et al., 2013).

Assessment of cortical inhibition with TMS may also be useful to predict response to acetylcholinesterase inhibitors in patients with Alzheimer's disease (AD) (Di Lazzaro et al., 2005) and as a possible biomarker of mild cognitive impairment in patients with PD (Yarnall et al., 2013).

PRESURGICAL MAPPING

During surgery for brain tumors, arteriovenous malformation, epilepsy, or other brain conditions, surgeons often rely on mapping of the motor cortex to identify eloquent areas of the brain such as the speech area so they can avoid damage to those areas. TES has been used for this purpose, although it can only be done intraoperatively. However, Chen described recent studies using TMS presurgically to map the motor cortex; those studies indicate that this approach reliably predicts TES responses (Galloway et al., 2013; Krieg et al., 2013; Picht et al., 2013).

NEUROMODULATION AS A RESEARCH TOOL

Chen also described how TMS and tDCS are being widely used in both human and animal studies to gain a better understanding of the neurobiologic processes underlying normal and abnormal brain performance. For example, Vesia et al. (2010) used TMS to disrupt cortical activity in normal human volunteers, thus creating “virtual lesions” that identified the specific areas responsible for performing saccade (eye movement) and reach tasks, and Chen’s group has used TMS to study the physiologic underpinnings of levodopa-induced dyskinesias in individuals with PD (Morgante et al., 2006). These studies suggest that cortical plasticity is deficient in PD patients, particularly in dyskinetic patients. Chen’s group has also shown that plasticity can be restored with subthalamic nucleus deep brain stimulation (Kim et al., in press; Udupa and Chen, 2013).

Alexander Rotenberg noted that because stimulating a part of the brain can evoke a measurable response, neurostimulation coupled with electrophysiologic recording techniques may provide biomarkers for disease states that could be modulated neurostimulation, or even serve as stand-alone biomarkers.

6

Enhancement of Brain Function and Performance

Highlights

- Research is expanding on non-therapeutic applications of neurostimulation in healthy people. (Cohen Kadosh, Pascual-Leone)
- Transcranial electrical stimulation can improve cognitive and non-cognitive performance in educational, military, athletic, gaming, and occupational settings, although more evidence is needed to determine its effectiveness. (Cohen Kadosh, Edwards)
- Cognitive and non-cognitive enhancement through neurostimulation may have negative consequences, and the long-term effects have not been well studied. (Fox, Pascual-Leone, Maiques)
- An emerging market for direct-to-consumer non-therapeutic products raises questions about safety and efficacy, as well as attention to safety and efficacy in the home setting. (Wetmore)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

The effects of non-invasive brain stimulation technologies on cognition and performance has both therapeutic and non-therapeutic applications, depending on whether they are used to ameliorate symptoms of a disorder or enhance otherwise normal function. Indeed, according to Alvaro Pascual-Leone, the range of non-therapeutic applications is growing even faster than therapeutic applications. One reason for the growth of research in this area is that because most investigational interventions are initially tested in groups of healthy individuals before being tested in

patients, most of the available evidence about the effects of these technologies are from healthy subjects, noted Roi Cohen Kadosh.

In addition, a rapidly expanding DIY movement and direct-to-consumer devices are promoting self-experimentation in healthy subjects to enhance abilities and prompting the need for carefully controlled studies to assess effects, evaluate risks, and identify mechanisms

tDCS has been widely used in non-therapeutic applications. However, other types of transcranial electric stimulation are also being used and investigated, including transcranial alternating current stimulation and transcranial random noise stimulation; all of these modalities have different effects on the brain, but ultimately appear to manipulate neuroplasticity (Antal and Paulus, 2013; Fertonani et al., 2011). Moreover, while tDCS appears relatively safe in studies of limited duration, the long-term safety and the long-term effects on the brain have not been well established, according to Ana Maiques and others.

Cognitive enhancement is perhaps the most well known and widely publicized non-therapeutic application of brain stimulation (Coffman et al., 2014). Many studies have shown that TES can improve cognitive and non-cognitive performance with even a single session or multiple sessions of stimulation, particularly when used in combination with cognitive training, said Cohen Kadosh (Cohen Kadosh, 2013). For example, his lab has shown that tRNS, given in combination with two different arithmetical training approaches, improved both the speed of calculation as well as memory-recall-based learning. They further showed that these effects endure for at least 6 months (Snowball et al., 2013). In another study, Reis and colleagues showed that anodal tDCS stimulation over 5 days of training on a visuomotor skill also led to increased learning rate and better performance (Reis et al., 2009). Again, these improvements lasted beyond the neurostimulation period, suggesting a neuroplastic change, said Cohen Kadosh.

Cohen Kadosh noted that most of these studies have focused on young healthy adults. However, his group has also shown that students with math anxiety perform better when they receive tDCS stimulation to the DLPFC. They had not only improved reaction time in comparison to those who received the sham stimulation, but also decreased salivary cortisol concentrations, indicating lower stress. Interestingly, however, when the same stimulation protocol was used in individuals who did not have math anxiety, reaction time increased compared to sham stimulation and cortisol levels increased (Sarkar et al., 2014).

Performance enhancement through neurostimulation is also being actively pursued for military, athletic, educational, gaming, and occupational settings. Dylan Edwards said there is an overwhelming array of applications and many papers published, but few studies replicated. He described one effort to enhance perception using a virtual reality, real-world training application used to train military personnel to detect concealed objects such as bombs (Clark et al., 2012). In this study, tDCS was used to deliver stimulation to brain networks identified by fMRI as important for this task, that is, the right front and parietal cortex. The study in 96 healthy subjects showed that tDCS stimulation resulted in significant improvements in learning and performance, and that these improvements were sustained after training.

Another study designed to investigate the perception of fatigue on performance in elite cyclists showed that tDCS stimulation of the temporal cortex delivered prior to an incremental maximal cycling test resulted in a reduction in heart rate as power increased, and a 4 percent improvement in performance (Okano et al., 2013). The investigators who conducted the study concluded that tDCS modulated the autonomic nervous system and the sensory perception of effort and exercise performance. Edwards said this is important because fatigue is considered a balance between motivation and perception of effort.

In assessing the effects of neurostimulation on cognition, multiple parameters are important, including the cognitive construct of interest, how that construct is measured, when the stimulation is given in relation to the assessment, and the baseline state of the brain, according to Roy Hamilton. Moreover, cognitive enhancement can come with a cost, said Michael Fox. As described in Chapter 3, Fox noted that focal stimulation propagates throughout brain circuits, enabling the stimulation of targets far from the stimulation site. For non-therapeutic use, this propagation can have negative consequences. For example, one might stimulate the DLPFC to enhance cognition, but because of connectivity with limbic regions, the stimulation might also affect mood.

Trade-offs are also seen in studies aimed at improving working memory by stimulating the DLPFC. Pascual-Leone's lab has shown, for example, that rTMS of the right DLPFC enhanced verbal working memory, but reduced spatial working memory (Fried et al., 2014). Although TMS delivered to the parietal cortex may enhance the ability to detect a visual target on the ipsilateral side, at the same time it can reduce the ability to detect a target on the contralateral side (Hilgetag et al.,

2001). In patients with spatial neglect on one side, this form of therapy may be useful, but should be used with caution in normal subjects.

DIRECT-TO-CONSUMER PRODUCTS

Non-therapeutic neuromodulation devices are also being developed as direct-to-consumer products, avoiding the regulatory barriers that can slow development of therapeutic products. Throughout the workshop, many participants raised concerns about ethical and safety issues that arise when providing devices outside the medical sphere. However many participants also said that despite these concerns, consumer-targeted devices will represent a substantial part of the market in the future. Ethical issues are discussed further in Chapter 7.

Thync, a neuroscience and consumer technology company based in California and Massachusetts, positions itself outside of the medical or cognitive enhancement spheres, setting as its goal improvement of brain health. Daniel Wetmore, director of intellectual property and usability at Thync, described their device as a wearable *Bluetooth*[®] technology controlled unit that snaps into electrodes worn on the temple area of the head with a second electrode either behind the ear or on the back of the neck to deliver electrical stimulation. The company claims its device can modulate psychophysiological arousal by delivering pulsed neurostimulation waveforms (called “Vibes”) to increase energy, enhance focus, boost motivation, reduce stress, and improve the quality of sleep.

In terms of efficacy, Thync has published a preprint in *bioRxiv* demonstrating that, compared with sham stimulation, the Thync device significantly suppressed the acute stress response without affecting cognition (Tyler et al., 2015). Both self-report and physiologic measures of stress were evaluated. Wetmore said they believe the mechanism of action involves modulation of cranial and cervical spinal nerves with limited direct stimulation of the brain transcranially.

7

Ethical, Legal, and Social Issues

Highlights

- The use of neurostimulation, including off-label use, is rapidly expanding, without a full understanding of safety and efficacy. (Farah, Pascual-Leone, and others)
- Non-invasive neuromodulation has the potential to cause not only physical, but non-physical harms as well. (Parens)
- The safety and efficacy of long-term stimulation is not well understood. (Farah)
- The involuntary or coercive use of neuromodulation presents many ethical concerns. (Chandler)
- The do-it-yourself movement raises questions about the responsibility of researchers to educate the public. (Maslen)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Ethics in the context of neuromodulation extends far beyond what Aristotle would have recognized as classical ethics issues in his day, said Hank Greely. With regard to neuromodulation, the topic spans ethical, legal, social, and even political implications, indeed, all things in society that affect the use and potential misuse of these devices now and in the future. For example, Alvaro Pascual-Leone mentioned the reality that off-label application of neurostimulation is rapidly expanding, without examination or a full understanding of safety and efficacy implications. Patients are making devices, buying devices, and getting clinicians to

prescribe devices; companies are developing new consumer-targeted devices with non-medical aims that ultimately get leveraged into the medical setting.

IMPACT ON “SELF”

Erik Parens, senior research scholar at The Hastings Center, focused his comments on what he called non-physical harms, that is, how a technology might do harm not to our bodies, but to us as human beings. He cited four major concerns: inauthenticity, complicity, mechanization, and inequality. The first, inauthenticity, threatens to separate us from who we really are or how the world really is. Complicity relates to how these technologies could be used so people can live up to social norms that may be problematic, such as the idea that making money is the greatest good. Mechanization refers to the concern that these technologies could make us think of ourselves as machines that need fixing rather than persons who need and want engagement. Finally, these technologies may exacerbate inequality by providing advantages only to those who have the resources to access the technology. Social inequality is bad for the health of society as well as for the health of individuals, particularly those at the bottom, said Parens.

ENHANCEMENT VERSUS TREATMENT

Parens said that the distinction between treatment and enhancement is abstract and fuzzy, and also unavoidable and potentially useful if we're trying to articulate what, for example, should go into a basic package of medical care. Since the 1990s, enhancement has been defined in contrast with treatment, where treatment restores normal functioning and enhancement produces something better than normal functioning. Yet, because there is no bright biological line between normal and better than normal functioning, there is no bright line between treatment and enhancement. Even if there was such a bright biological line, it would not follow that there is a bright ethical line. It does not follow from the fact that an intervention is an enhancement that is unethical; to reach that conclusion, one would need to be explicit about additional reasons regarding, for example, the likelihood of harms, either physical or non-physical. Nor does it follow from the fact that an intervention changes the

brain directly (as with neuromodulation) rather than indirectly (as with traditional education) that is unethical; to reach that conclusion, one would again need additional reasons—perhaps about the different values embodied in the direct versus indirect means of achieving the desired end.

Nobody is against true enhancement, said Parens. People are, however, opposed to things that purport to deliver a benefit but in fact cause harm. For example, soma, the drug in Aldous Huxley's *Brave New World*, was supposed to give people the experience of happiness but did so in the absence of engagement in the kinds of activities that normally make human beings feel happy. Parens suggested that people do not object to soma because it is an enhancement, but because it is not.

SAFETY AND EFFICACY

Martha Farah, Walter H. Annenberg Professor of Natural Sciences at the University of Pennsylvania, cast ethical concerns into four overlapping categories: safety, efficacy, freedom, and fairness, focusing her comments on safety and efficacy. It seems clear that a single session of TMS or tDCS is safe if done properly, she said, although much less is known about their use in repeated sessions over months or years, which is how they will be used for treatment and enhancement. Through empirical experience, the field may eventually arrive at some knowledge of how risky or safe these devices are. Alternatively, a deep understanding of the mechanisms by which these devices work could point to theoretically possible downsides of these methods. Farah suggested that we do not have either the necessary experience or a firm grasp of mechanism.

Roi Cohen Kadosh noted that further study is needed on the long-term safety of neurostimulation and the impact of neurostimulation on the developing brain. He added that there can be trade-offs with neurostimulation, that is, it may improve some cognitive processes while worsening others. Farah commented that this finding should come as no surprise given what we know about neurons wiring and firing together and the competitive nature of plasticity. However, there is much that we don't know. She suggested that animal research may be one place to begin to understand the long-term physiological effects of neurostimulation.

Atul Pande raised the concern that, in the case of low field magnetic stimulation (LFMS), it may be possible to compact the technology enough so that it can be used easily at home. But, he asked, if it is prescribed for say, 20 minutes, what might the effect be if a person uses it

for 8 hours? Indeed, the safety of unsupervised use was mentioned by several participants as a poorly addressed area of concern. Ana Maiques said the short-term safety of tDCS in adults is relatively well established, but less is known about the long-term safety or the use of tDCS in children or other special populations. Neuroelectrics' solution to this concern is to permit sales only to individuals who have a prescription from their physician, and to control the device through the cloud, so that the device can only be activated for the number of minutes prescribed.

An additional concern raised by several participants is that devices marketed for enhancement to well-being are not currently regulated as medical devices either in Europe or the United States, and are subject to general, non-specific safety requirements. Hannah Maslen, Postdoctoral Research Fellow in Ethics at the Oxford Center for Neuroethics, showed some examples of the claims manufacturers are making about their devices. While noting that the devices are not FDA approved, they often include statements such as "it has been tested to all of the required standards," or "scientific papers are being published every day and the results are incredible." In some cases, they include disclaimers suggesting that the data presented may be inaccurate and encouraging users do their own research.

With regard to efficacy, Farah noted that we are also in the very early days of figuring out whether repeated long-term brain stimulation is helpful. Some studies indicate that it is, particularly in combination with training and maybe in combination with drugs or other modalities. Early studies by many labs suggested that a single treatment with tDCS or TMS enhanced cognitive processes such as working memory, but subsequent meta-analyses of multiple studies found systematically smaller and smaller effect sizes, in some cases zero (Brunoni and Vanderhasselt, 2014; Horvath et al., 2015). Several participants strongly urged caution in interpreting these meta-analyses because of the many types of heterogeneity across studies. This phenomenon may, in part, reflect publication bias, wherein only studies that show an effect are published. Another possible reason for the lack of demonstrated effect in meta-analyses is the heterogeneity of subjects, stimulation parameters, and assessments, all of which result in substantial noise. Farah's group recently completed a meta-analysis of tDCS studies of working memory, correcting for publication bias and with a fairly homogeneous set of parameters. It showed small effects, some but not all of which were statistically reliable. She noted, however, that this analysis included a range of healthy normal individuals with no classification by ability level or genotype.

Farah suggested that a communal effort is needed to improve what we can learn from the research, ideally pre-registering studies (as done with pharmaceutical trials), archiving null results in a “file drawer” repository, and encouraging studies with higher power to overcome the factors that limit the conclusions that can be drawn from existing studies.

FREEDOM/COERCION/INVOLUNTARY USE

Invuntary or coercive uses of non-invasive neuromodulation, applied for the purpose of changing behavior or gaining compliance with socially accepted norms, present additional complex ethical challenges, although data supporting these uses are sparse, according to Jennifer Chandler, professor of law at the University of Ottawa. One recent paper showed that application of tACS to the right DLPFC reduced aggressive behavior in men (Dambacher et al., 2015), and another showed that tDCS of the right lateral prefrontal cortex (rLPFC) increased compliance with social norms in a computerized simulation (Ruff et al., 2013).

Chandler illustrated the ethical issues presented by two contrasting hypothetical cases: one involving parents who want their child to undergo non-invasive brain stimulation in order to improve their academic or physical performance, and another involving criminal offenders who are offered a reduced sentence if they undergo neuromodulation. Both of these cases raise numerous ethical concerns related to issues of safety, efficacy, justice, fairness, self-identify, and authenticity. For the first case, the primary considerations would be the best interests of the child; in the second case, the issues are less clear, that is, is the intent to punish or treat the offender? Chandler says in the criminal realm, forensic psychiatrists are bound by what is in the best interest of the offender; however, this is also open to interpretation.

In cases involving enhancement in children, one must consider the definition of benefit, that is, is it in the best interest of the child to satisfy the expectations and demands of parents, schools, peers, or society in general? For instance, children may be better off if improvements in their behavior cause their parents to have less stress or their teachers or peers to like them better, but are those reasons enough to subject the child to a procedure with potentially negative consequences? Similarly with criminals, the object of rehabilitation is often compliance with social norms, yet by whose definition are these social norms established? Chandler pointed to the example of the mathematician Alan Turing, who was sub-

ject to antilibidinal drugs, or chemical castration, at a time when homosexuality was considered a criminal offense.

Another concern is that blaming the brain for a social or behavioral “problem” may have self-fulfilling prophecy effects, affecting motivation, self-efficacy, and locus of control by convincing the person that their brain is “broken,” which can result in unanticipated behavioral consequences, noted Chandler. For example, studies have shown that a disbelief in free will can increase aggression and reduce helpfulness (Baumeister et al., 2009). In the criminal context, blaming the brain can support a perpetrator’s belief that he or she is not responsible for his or her acts, perhaps undermining efforts at rehabilitation.

THE DO-IT-YOURSELF MOVEMENT

The schematics and directions for building a tDCS device can be easily found on the Internet, and the parts can be purchased for about \$25, Greely explained. Thus, it is no surprise that the DIY tDCS movement is rapidly expanding, said Maslen. One of the richest sources of information for the community is the Reddit tDCS forum (in press).¹ While contributors to the forum include many people who base their comments on what they glean from scientific papers, there are also a number of people who come to the forum with comments indicating a lack of understanding of tDCS and uses that appear to be unsafe or dangerous. Greely added that one of his graduate students performed an analysis of the Reddit tDCS forum (Jwa, 2015). Anna Wexler, a doctoral student in the Department of Science, Technology, and Society at the Massachusetts Institute of Technology, said she is also doing research on the DIY community using qualitative, in-depth interviews.

Given that people are experimenting with these devices and the near impossibility of preventing this experimentation, Maslen asked whether researchers have a responsibility to laypersons who appropriate their research for parallel purposes. Should appropriation of research be explicitly considered by ethics committees when researchers obtain ethical approval? Should research results be made freely available in order to better inform those engaging in DIY practices?

¹See <http://www.reddit.com/r/tDCS> (accessed July 1, 2015).

Questions were raised about the obligation of scientists to better educate consumers. Should they, for example, provide a lay summary in their publications to avoid misinterpretation and misuse of the technology by individuals who may lack the scientific background to understand the technical details of the paper? Or should they work with the DIY community to provide expert commentary on questions that arise? Maslen said she could imagine some sort of public engagement initiative to set up such a community. However, other participants raised potential issues of liability. Greely took this one step further, asking to what extent scientists doing their research should think about the possible downstream negative effects, including nefarious or unsafe use by the DIY community. Interestingly, at least in the United States, institutional review boards are forbidden from considering social harms according to the Common Rule, he said.

8

Regulatory Issues

Highlights

- Different regulatory paths for neuromodulatory devices in the United States and Europe have resulted in different availability of these devices around the world. (Marjenin, Tariah)
- The regulatory requirements for non-invasive neuromodulatory devices will vary depending on the perceived level of risk, with non-therapeutic neuromodulatory devices facing less stringent regulatory requirements. (Marjenin, Tariah)
- For sponsors seeking regulatory approval of devices in the United States, the FDA has encouraged the use of new tools, including innovative clinical trial designs, such as adaptive trials as well as modeling and simulation. (Connor)
- Many TMS studies use sham controls, but because TMS is intrinsically multisensory, it is difficult to blind the patient and therapist. (Pascual-Leone)
- Important and challenging aspects of clinical trials for neuromodulatory devices include the choice of control or comparison condition, determining dose–effect relationships, and patient heterogeneity. (Hamilton, Lisanby)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

REGULATORY PATHWAYS

The FDA in the United States, and the European Commission (EC) in Europe, are charged with regulating neuromodulatory devices. Their different paths to device approval have resulted in varying availability in different countries. For example, while the Neuronetics Neuro-Star system for the treatment of depression received FDA approval in 2008, CE Mark approval¹ was not obtained until 2012 (PR Newswire, 2012). Meanwhile, the Brainsway TMS system for the treatment of depression received CE Mark approval several years prior to receiving FDA clearance in 2013 (Brainsway, 2013). Also in 2013, the FDA approved the Cerena TMS system for the treatment of migraine headaches that are preceded by an aura. This device was approved through the *de novo* pathway as a Class II device, indicating that it is a low- to moderate-risk device not substantially equivalent to an already marketed device (FDA, 2013). The different classes of devices are described below. In 2014, the FDA also cleared eNeura's SpringTMS device for migraine (PR Newswire, 2014a).

At the FDA, responsibility for regulating most non-invasive neurostimulatory devices lies primarily with the Neurostimulation Devices Branch in the Division of Neurological and Physical Medicine Devices at the Office of Device Evaluation. By contrast, EC has 28 member states, represented by "Competent Authorities," equivalent to the FDA but for individual countries. Competent Authorities have enforcement powers and designate "Notified Bodies" to assess applications for CE marking, which indicates that a product complies with European Union (EU) regulations and may be marketed in that country.

The FDA defines devices as things that are "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man . . . intended to affect the structure or any function of the body of man and which does not achieve any of its primary intended purposes through chemical action" (FDA, 2015b). What that means, according to Tim Marjenin, chief of the Neurostimulation Devices Branch at the FDA, is that even if a product is non-therapeutic and non-diagnostic, it may still be regulated as a medical device. However, he emphasized the word "may," noting that the

¹See <http://www.emergogroup.com/resources/europe-process-chart> (accessed June 1, 2015).

decision on whether or not to regulate a device depends on many factors. Sponsors who wish to know whether their product is considered a “medical device” are advised to contact the Device Determination Group in the FDA Office of Compliance.

According to Ibim Tariah, technical director at British Standards Institution (BSI), the EC definition of a medical device is similar to that of the FDA, specifying that it is intended to be used in human beings for diagnosing, preventing, monitoring, or treating a disease and does not achieve its action by pharmacologic, immunologic, or metabolic means. Non-medical devices are not subject to EC regulations; however, Hannah Maslen noted that the European Commission has proposed a revision of the Medical Devices Directive that would include a new annex covering implantable and invasive devices with a non-medical purpose.

ENSURING SAFETY AND EFFICACY

Regulators’ primary concern is ensuring that products reaching the market demonstrate both efficacy and safety. According to Marjenin, most neurostimulatory products are thus classified into one of three classes of devices based on the level of regulatory control needed to “provide a reasonable assurance of safety and effectiveness.”

- Class I: These devices are subject only to general controls. Excluded from this class are devices that are life supporting or life sustaining, or that are needed to prevent impairment of human health or that present a potential unreasonable risk of illness or injury.
- Class II: General controls alone are insufficient to provide a reasonable assurance of safety and effectiveness and there is sufficient information available to establish special controls. Devices in this class typically require submission of premarket notification 510(k) if the technology is similar to something already classified, or a new device regulation if a device is not comparable to something on the market. Clinical data are generally not needed for a 510(k) submission, but are typically needed for a *de novo* application.
- Class III: General controls are not sufficient, and not enough information is available to establish special controls. Devices considered Class III generally require premarket approval

(PMA). Clinical data are always needed for a PMA (FDA, 2014).

Marjenin said non-invasive devices are generally not Class III, but they may be assigned to this class if there is insufficient evidence to establish special controls. Marjenin said that special controls can mean a number of things, such as postmarket surveillance or performance standards. In Europe, classification of devices is based on four risk classifications. Devices with higher risk classifications receive more scrutiny by the appropriate authorities, said Tariah. At the two highest levels, both notified bodies and competent authorities may be involved in regulatory approval.

In 2012, the FDA issued a Guidance on *Factors to consider when making benefit-risk determinations in medical device premarket approval and de novo classifications* (FDA, 2012). This Guidance describes the FDA's approach to making benefit–risk determinations, including an evaluation of the possible and probable risks; the type, magnitude, and duration of benefit; the level of uncertainty; patients' tolerance for risk and perception of benefit; and the availability of alternative treatments.

With regard to off-label use, neither the FDA nor the notified bodies in the EC regulate the practice of medicine, including off-label use of products, according to Marjenin and Tariah. Victor Krauthamer concurred, noting that his division would not necessarily investigate an off-label use unless it had some relevance to public health as a general question, such as if a safety concern popped up.

Marjenin also discussed the regulatory perspective on products that present a low risk to user safety and are intended to be used to maintain or encourage a general state of health or healthy activity. In January, 2015, the FDA issued a General Wellness Draft Guidance (FDA, 2015a) that outlines their proposed approach to evaluating such general wellness products. Importantly, said Marjenin, a product's inclusion under this guidance does not mean it has been shown to be safe and effective, and not misbranded for its intended use.

Maslen noted that the regulatory approach to assessing risks and benefits for non-therapeutic devices, including enhancement devices, diverges from the approach used for medical devices. She suggested that more thought needs to go into how best to evaluate the risk–benefit profile of enhancement devices. Both objective and subjective benefits should be considered, along with the value of the enhancement effect on

the individual. For example, the objective benefit of an improvement in working memory might be very valuable to a mathematician, but of less value to an athlete; the subjective benefit of feeling sharper or more alert might have more value for an elderly person who is starting to worry about cognitive decline than for a healthy 20-year-old who does not have such concerns. Maslen suggested that effects labeled as treatment, because they are more fundamental and more universally valued, are more amenable to cost–benefit or risk–benefit analyses, compared to enhancement benefits, which are harder to weigh against risks. For this reason, she proposed that more consumer freedom is appropriate for enhancement devices.

Alvaro Pascual-Leone added that the neuroscience community may not currently have the expertise to address outcomes for specific indications, which is why it is especially important to listen to patients and clinicians. Marjenin concurred, noting that regulators typically ask sponsors to demonstrate clinical meaningfulness in particular patient populations. In addition, patients’ perception of risk and their perspective on risk–benefit trade-offs is an important part of risk–benefit considerations, said Marjenin.

CLINICAL TRIAL DESIGN

In 2004, the FDA published the Critical Path Initiative (CPI), which recognized that the “tools used today to predict and evaluate product safety and efficacy are badly outdated.” Clinical trial design was one area they cited as needing reform to make possible smaller and smarter trials (FDA, 2004). Publication of the CPI led to the founding in 2005 of the Critical Path Institute, a public–private partnership comprising eight consortia established to develop tools in precompetitive space to accelerate drug development.

Jason Connor, an adaptive clinical trial designer with Berry Consultants, addressed issues related to clinical trials for neurostimulatory devices. Connor serves on the FDA’s Neurologic Devices Advisory Panel. He emphasized the importance of communicating with key stakeholders—including the FDA, clinicians, patients, and statisticians—early in the trial design process. The FDA, and particularly CDRH, has a wealth of experience in clinical trial design and can often give key clinical insights as well as help navigate the regulatory landscape, he said. Moreover, he said, the FDA is far more

innovative than most people realize, and he urged investigators to be creative and seek the help of statisticians to design a trial that will answer relevant clinical questions.

One of the innovations supported by the CPI was the use of modeling and simulation. Connor noted that these tools allow investigators to simulate different population groups, different levels of effectiveness of the device, different dose–response curves, and different study designs enabling trials to be tailored to a specific patient population where a benefit is most likely to be seen. Simulations also allow key stakeholders to imagine why the trial might fail and what could have been done differently, for example, by changing dose, selecting a different study population, etc. For example, many investigators overestimate treatment effects or underestimate variability and thus fail to reach their primary endpoints.

Adaptive designs may maximize the potential for success in a trial, Connor said. Adaptations can be made for a variety of parameters, including sample size, randomization, dose, etc. When you adapt according to prespecified rules, he said, you can overcome some obstacles in the trial and better understand the error rate. Adaptive randomization may be especially valuable in combination therapy and for testing treatments in a variety of subpopulations. Many questions arose regarding the regulatory requirements for combination therapies. Marjenin said the FDA has an Office of Combination Products that will work with the drug and device divisions at the FDA to advise sponsors on the appropriate design of combination trials.

Another important issue with regard to trial design for neurostimulation is the choice of control or comparison condition. The gold standard for pharmacologic studies is the placebo-controlled, double-blind study; yet neurostimulatory devices present challenges with regard to the control. Many studies use sham controls, and according to Sarah H. Lisanby, much work has been done to develop shams that accurately as possible simulate the effects of active TMS. A more powerful approach, she said, is to use an active control, where subjects receive active stimulation to a region of the brain not expected to exert the desired effect but are blinded to the expected outcome. However, with regard to sham controls, Pascual-Leone noted the difficulty of mimicking or masking the clicks and taps that accompany TMS. Some devices switch current direction, but for the most part do not completely blind the patient or therapist. He suggested that alternative trial designs may be needed with active as well as task controls.

Other challenges that sponsors must address when conducting clinical trials for neurostimulatory devices mirror those encountered for drug trials, but require different tools. For example, determining the appropriate dose–effect relationships and addressing recruitment and eligibility concerns, blinding issues, and patient heterogeneity are particularly challenging in trials of neurostimulation devices, said Roy Hamilton. Another issue is the washout period, which according to several participants differs with stimulation modalities and parameters (e.g., duration of stimulation), although very few studies have been done to address this question.

The question was raised about whether independent assessments are needed for different devices with similar mechanism, or if data can be pooled from studies of devices with a similar mechanism. John Reppas, director of public policy for the Neurotechnology Industry Organization, said there is no good way to establish dose equivalence among devices, making it difficult to pool results.

REGULATORY OVERSIGHT FOR OVER-THE-COUNTER USE

OTC products typically need human factors and usability testing to ensure that users can determine themselves whether they are appropriate candidates to use the product and that they can use the device properly. Marjenin emphasized that not all devices are appropriate for OTC use.

The Foc.us gamer headset is a prime example of a consumer device that is not regulated by the FDA. Marjenin said his office is typically aware of devices marketed to consumers and may be discussing it internally; however, they are bound by confidentiality not to discuss their deliberations publicly. More generally, he said that for any marketed product that seems, for all intents and purposes, as if it should be considered a medical device, there may be an ongoing action or correspondence, but this also would be confidential. Krauthamer added that the regulatory science group does not typically look at specific devices, but only general endpoint; examples include running animal and cell tissue experiments at the field strengths covered by a range of devices, but not specifically that device.

Hank Greely asked whether there is any way for consumers to find out if a product that is on the market has been approved or cleared by the FDA and considered to be a “wellness product” not requiring regulation,

or if it is still “in limbo.” Marjenin said that unless the FDA has weighed in on it, consumers would not be able to find out.

9

Reimbursement Issues

Highlights

- Reimbursement for TMS has grown considerably in recent years as devices become more widely accepted by the clinical community, and both patients and clinicians are requesting reimbursement for appropriate clinical care. (Demitrack, Maiques, Robinson-Beale)
- Health plans individually determine whether treatment will be reimbursed based on multiple types of research data—RTC, population-based, comparative effective (often incomplete or conflicting in this area), comparative efficiencies and cost considerations, and the existence of practice guidelines. These data needs are frequently not available nor included in research protocols. This leads to significant inconsistency in provider application within practice, and variation in medical policies and reimbursement decisions. (Robinson-Beale)
- The lack of practice guidelines is a barrier to consistent application of the technology in practice, coverage, and reimbursement decisions. Without such guidelines, clinical decisions may be based on the opinions of independent practitioners who may or may not have experience with a technology and health plans setting coverage policy. (Robinson-Beale)
- Inconsistent reimbursement decisions may limit patient access to treatment and business development. (Hailey, Reppas)
- Regulatory and reimbursement pathways in different countries complicate the approval process for companies developing non-invasive neuromodulatory devices. (Marjenin, Tariah)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Reimbursement for TMS is constantly evolving as the devices become more widely used and accepted in the clinical community. Rhonda Robinson-Beale, senior vice president and chief medical officer of Blue Cross Idaho, said that pressure from the clinical community has even led payers to consider reimbursement for TMS despite conflicting evidence about efficacy.

Oscar Morales, founding director of the TMS Service at McLean Hospital, described the evolution of coverage for TMS at McLean Hospital, which is a psychiatric affiliate of the Harvard Medical School. The TMS Service at McLean was inaugurated in 2009, following FDA approval in 2008 of the Neuronetics TMS system for depression. For the first 2 years, TMS at McLean was an entirely self-pay service; however, over the years 2011 to 2015, Medicare and insurance companies gradually approved reimbursement, such that there is now universal coverage for TMS. Over the past year, the TMS Service averaged about 200 clinical treatment sessions per month, using the NeuroStar and Brainsway systems for the treatment of depression, noted Morales. In addition, the TMS Lab conducts clinical research.

DECISION-MAKING PROCESSES

Robinson-Beale said most health plans have a technology assessment committee that reviews available information from peer-reviewed sources as well as third-party organizations to decide whether reimbursement is warranted. They will also look at what is generally accepted practice, in particular off-label use of a treatment. Typically, the studies they review are the same as were used to inform the FDA's decision on granting marketing approval for a therapy, but health plans may reach different conclusions, in part because they must assess the cost of a treatment compared to the cost of standard treatment. Moreover, each health plan conducts its own review process, creating an array of funding policies.

For example, in the case of TMS, the FDA concluded that TMS was appropriate after one failed trial of an antidepressant. Different health plans reached different conclusions: One decided to cover TMS after the fourth failed antidepressant trial; another stipulated that TMS would be covered only in patients who had adverse effects from antidepressant therapy, or who could not tolerate antidepressant treatment, or who preferred TMS as an alternative to ECT. Coverage decisions also differ by

region, adding to the disparity across the country. In addition, Robinson-Beale said, a decision by the Centers for Medicare & Medicaid Services (CMS) ripples across the reimbursement landscape because it covers approximately 100 million people in the United States, and their associated health care expenditure (CMS, 2015). Other payers thus have to validate why they will not cover something that CMS covers.

Health plans also have to consider how other parameters of treatment affect reimbursement decisions, said Robinson-Beale, such as the dose, duration, and frequency of treatment required for a beneficial effect. For TMS, frequently raised questions include whether TMS is more efficacious than antidepressant medications, and if so, for which patients.

Cost plays an important role in reimbursement decisions, particularly with the high cost of some newer technologies and pharmaceutical products such as biologics that can cost hundreds of thousands of dollars per year per patient, according to Robinson-Beale. To reach decisions on covering these new technologies, health plans may require very good comparative analyses of cost versus efficacy with standard treatments, she said. Indeed, Eric Liebler, vice president of scientific, medical, and governmental affairs at electroCore, suggested that cost may have a positive impact on reimbursement for neurostimulatory devices because the costs of these devices may be materially less than some of the new pharmaceutical therapies coming out today.

Practice guidelines are another important factor in coverage decisions, said Robinson-Beale, but the American Psychiatric Association has provided very little detail regarding TMS other than to mention it as a possible treatment for depression, without identifying a clear target population. The American Medical Association also presents a potential roadblock to reimbursement because it issues Current Procedural Terminology (CPT) codes, which physicians need in order to be reimbursed. According to Ross Jaffe, managing director of Versant Ventures, it can take 2 to 5 years after FDA approval to obtain a CPT code, and the process is heavily influenced by specialty societies such as national medical societies or professional interest medical associations.

IMPROVING THE EVIDENCE BASE FOR REIMBURSEMENT

As noted by Robinson-Beale, the key issue for payers is whether a treatment is medically necessary and whether there is sufficient evidence to support that determination. Most of that evidence comes from peer-

reviewed journals; however, she maintained that data analysis in published research studies may not be designed to demonstrate effectiveness or comparative effectiveness to standard treatment or in certain subpopulations. For example, many randomized clinical trials exclude patients with co-morbidities, thus failing to answer the question of whether a treatment will be effective in real-life populations. These studies may also lack clarity with regard to dosage, frequency, outcome measures, frequency of relapse, etc. Comparative effectiveness studies, such as the one described by Bradley Gaynes in Chapter 4 to evaluate TMS for depression, are also used by payers in determining reimbursement policies. In addition, some insurers have used FDA reports to evaluate treatment effectiveness, although they lack access to the actual data for further analysis. Administrative claims may provide additional data with regard to outcomes.

Other sources of evidence for payers include consensus guidelines from expert groups or observational data from large registries across heterogeneous populations. Robinson-Beale noted that in the absence of conclusive, comprehensive data, decisions on coverage and reimbursement must be made with gaps in information, resulting in a diversity of interpretations. She said payers would prefer to see comparative effectiveness of a treatment against the standard of care rather than sham treatments, as well as objective efficacy analysis that includes cost as a factor. If researchers and other data sources were able to answer key questions that are important to that application of a technology in real life practice, health plans would have more opportunity to make clear decisions on medical policy, and less of an opportunity to reject coverage reimbursement, she said.

IMPACT OF NON-REIMBURSEMENT

The disparity of coverage across different health systems limits patient access to innovative and potentially beneficial treatments and leads to fragmented and inconsistent care, said Mary Hailey, vice president of health policy and government relations at Neuronetics. It also impedes business development if there is no market for a new device, said John Reppas.

Reppas added that when the value of a technology is the ability to deliver individualized treatment, reimbursement decisions may be further complicated because payers have been slow to value patient-centric as-

pects of non-invasive approaches. In fact, they may focus instead on the additional costs that will arise from a higher level of patient engagement.

Hailey said the standards that devices must meet to gain coverage continue to rise over the years; several other workshop participants commented on inconsistencies (a “double standard”) between the regulatory and reimbursement requirements for devices compared to drugs. For example, Thomas Insel asked if there is a separate standard for medicine versus behavioral health, citing the insulin pump, a much more expensive device that has received positive reimbursement decisions from CMS and most insurers. Robinson-Beale attributed this disparity to the fact that medical devices enjoy a longer history of acceptance, whereas behavioral devices are relatively new, requiring a new way of thinking on the part of those making decisions. Another factor that may explain a lower level of acceptance for behavioral indications such as depression is the lack of clarity regarding how neurostimulation fits in with existing psychotherapy and pharmacotherapy approaches, said Robinson-Beale. Liebler added that more objective measures are often available for outcomes “below the head,” whereas behavioral outcomes are often more subjective.

Robinson-Beale suggested that as mental illness becomes better defined from a neuro-circuitry perspective, devices will be driven into accepted practice. She said this has started as the American Psychiatric Association working in conjunction with the NIMH on such projects such as the Research Domain Criteria (RDoC) project.¹

However, she also predicted that as these devices move into the consumer market and people come to believe that neurostimulation can safely be delivered over the counter, the medically reimbursed landscape may change dramatically.

¹See <http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml> (accessed June 1, 2015).

10

The Business Environment

Highlights

- Interest in non-invasive neurostimulation devices is high among both clinicians and industry. However, growth of the industry is hampered by a number of factors, including low awareness of the technology among the broader practitioner base, and a limited understanding of the mechanism of effect of these technologies, a lack of funding from federal grant sources, and sometimes unclear regulatory pathways to approval. (Demitrack, Maiques, Pande, and others)
- Despite excitement in the field, investors have shied away from medical device companies because of unproven business models for some technologies, lack of regulatory predictability, challenges of obtaining reimbursement, and the long development time frame for investors to see a return on their investment. (Jaffe)

NOTE: The points in this list were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

INDUSTRY PERSPECTIVES

Given that current treatment options for psychiatric illnesses such as depression are suboptimal, increased recognition that the underlying mechanisms of disease involve neural networks is needed, according to several participants. Particularly given the demonstrated responsiveness of these networks to electrical stimulation, along with a changing reimbursement landscape, there is considerable interest in industry to develop new neuromodulation devices, according to Mark Demitrack.

Clinical interest is also high, he said. In the United States, Demitrack noted that more than 600 NeuroStar TMS devices are currently in use in a variety of clinical, academic, and hospital-based settings. About 80 percent of these devices are used by non-academic, office-based practitioners who see TMS as a welcome addition to the standard armamentarium of treatment options for depression when initial pharmacotherapy options do not provide benefit. As one of the only non-invasive and non-systemic treatment options, TMS therapy has been well received by patients. Acceptance of TMS as a proven safe and effective antidepressant treatment has also been established in large, independent meta-analysis of existing research, such as the recent analysis conducted by AHRQ (Gaynes et al., 2011). A reflection of its emerging acceptance as a treatment option is the incorporation of TMS therapy as recommended treatment consideration when initial pharmacotherapy has failed in various international practice guidelines (see, for example, the American Psychiatric Association, the World Federation of Societies for Biological Psychiatry, and the Royal Australia and New Zealand College of Psychiatrists).

Interest in other neurostimulatory devices is also high, said Ana Maiques, noting that Neuroelectrics currently sells its tDCS/EEG device in 35 countries. EEG provides a powerful tool to dynamically study brain activity, while tDCS delivers stimulation through multiple electrodes in order to target precise areas of the brain (Ruffini et al., 2014). The promise of this approach, said Maiques, is that EEG measures could be used to adapt the transcranial current stimulation (tCS) parameters (either tACS or tDCS) to better target certain cortical circuits (Fröhlich, 2014; Fröhlich and Schmidt, 2013). Other assessment tools, such as accelerometry or electromyography (EMG), may also be integrated into future iterations of the device.

While TMS and, to a lesser extent, tDCS have demonstrated relatively strong uptake in the market, other approaches such as LFMS remain relatively unknown, said Atul Pande. As mentioned in Chapter 3, LFMS emerged from the clinical observation that patients with bipolar depression reported feeling better after a single 20-minute echo-planar magnetic resonance spectroscopic imaging (EP-MRSI) procedure MRI spectroscopy scan (Rohan et al., 2004). A venture fund in Boston created Tal Medical around this observation.

Uptake in the market has also been limited by the fact that neuro-modulation is a new paradigm, according to Jeffrey Nye. He said that while the pharmaceutical industry has a fairly streamlined understanding

of the expectations for sponsoring companies to bring a product to the market, that is, the investments and studies that are needed to achieve regulatory and payer approval, these expectations are less clear for the neuromodulatory device market. He added that while several participants cited the great potential of drug-device synergies, particularly for combination therapy, it will be necessary to figure out the best business model, build operational synergies (sales, etc.), and manage the complexities of regulatory clearance.

A VENTURE CAPITALIST'S PERSPECTIVE

Innovation in the area of non-invasive neurostimulation requires a strong business case and investment from both public and private sources, what Ross Jaffe calls the innovation ecosystem. Jaffe founded and directs Versant Ventures, a large health care-focused venture capitalist firm based in California that has raised about \$1.9 billion over the past 15 years to invest in early stage companies (PR Newswire, 2014b). Neuromodulation is a particularly exciting area, said Jaffe, as our increased understanding of the electrobiochemical nature of the brain has provided insight into new ways to attack chronic disease. Electricity has been used to modulate end-organ function not only in the brain but in other parts of the body as well (e.g., pacemakers, implantable cardioverter defibrillator [ICD]), and is now being applied at the molecular level to affect human physiology, providing new device opportunities in what have traditionally been pharmacological space.

Medical devices provide the opportunity to improve the quality of care and reduce costs, said Jaffe, and excitement about medical device innovation is high. However, success in medical innovation requires building a sustainable business around the technology that can develop and deliver the device at a profit; that requires a clear understanding of the market as well as the regulatory, reimbursement, and clinical paths. Intellectual property and patent issues are also important. Hank Greely commented that, unlike drugs and biologicals, there is no regulatory exclusivity for devices, making it even harder to attract investment.

Despite excitement in the field, Jaffe said there has been a less than 70 percent drop in the amount of funding for early-stage medical device companies since the peak in 2008 (Norris, 2013); although, there has been an increase in funding for devices that monitor chronic illnesses and a person's overall health (Laird Wireless Connectivity Blog, 2015; RnR

Market Research, 2015). The reason is the significant capital requirements and the long development time frame required for investors to see a return on their investment, which Jaffe blamed primarily on issues of regulation and reimbursement. The FDA has taken steps to encourage innovation over the past few years, he said, while reimbursement has gotten much worse. Investors now see a much clearer and more attractive path to generating financial returns in the biotech industry than in the medical device industry. On the device side, investors are shifting toward investing in later-stage companies, after FDA approval, in order to lower their risk and improve their rates of return.

From a business point of view, Jaffe said the ability to distribute a product directly to patients can be attractive, particularly if the technology is disposable and needs to be replaced on a regular basis. In addition, as opposed to invasive neuromodulation, non-invasive approaches can be less expensive to start up and human clinical data can often be obtained with relatively little expense. Devices in the consumer space also face fewer barriers in terms of regulation.

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B

Workshop Agenda

**Non-Invasive Neuromodulation of the Central Nervous
System: A Workshop
March 2 and 3, 2015**

Institute of Medicine
500 Fifth Street, NW, Room 100
Washington, DC 20001

Background:

Based on advances in biotechnology and neuroscience, neuromodulation devices are poised to gain clinical importance in the coming years and to be of increasing interest to patients, health care providers and payers, and industry. Emerging evidence suggests that the potential therapeutic and non-therapeutic uses of non-invasive neuromodulation devices for the central nervous system are broad and will continue to expand. Along with the growing number of opportunities, there are challenges and open questions associated with the use of these devices. Currently, there is a need for greater understanding of the potential benefits and risks; in particular, of the short- and long-term impact of using these devices. From a regulatory standpoint, there are scientific and clinical questions that are important for regulatory approval and usability for consumers. A third area of consideration is the existing, and appropriate, levels of evidence for reimbursement. Several issues raise ethical questions, including the potential for off-label, over-the-counter, or do-it-yourself uses or for enhancement. Given the growing interest in non-invasive neuromodulation devices for the central nervous system, the goal of this workshop is to explore opportunities, challenges, and ethical questions

surrounding the development, regulation, and reimbursement of such devices.

Meeting Objectives:

- Highlight potential benefits and risks of non-invasive neuromodulation based on known short- and long-term central nervous system mechanisms of action.
 - Explore the scientific landscape of non-invasive neuromodulation device development for both therapeutic and non-therapeutic uses.
 - Consider issues concerning vulnerable populations.
- Consider the regulatory landscape for non-invasive neuromodulation devices.
 - Discuss potential outcome measures for therapeutic uses in regulatory processes.
 - Explore pathways for regulatory approval of therapies using a combination of non-invasive neuromodulation devices and pharmaceuticals.
 - Discuss differences in regulatory pathways among countries.
- Explore current and potential use reimbursement practices for therapeutic use of non-invasive neuromodulation devices.
 - Explore the evidence base and acceptable therapeutic outcome measures used in reimbursement decisions.
 - Consider economic outcome measures used to determine payer practices.
- Examine ethical questions about the use of non-invasive neuromodulation devices.
 - Consider ethical issues of off-label and over-the-counter use on regulation, reimbursement, and patient safety.
 - Discuss the use of these devices for enhancement in individuals without an impaired baseline.
 - Consider the implications of involuntary or coercive use (e.g., children, court-ordered treatment).

March 2, 2015

8:30 a.m. Opening Remarks

ALVARO PASCUAL-LEONE, *Workshop Co-Chair*
 Professor of Neurology
 Associate Dean for Clinical and Translational
 Research
 Harvard Medical School

JEFFREY NYE, *Workshop Co-Chair*
 Vice President
 Neuroscience Innovation and Scientific
 Partnership Strategy
 Janssen Research and Development, LLC
 Johnson & Johnson Innovation

HANK GREELY, *Workshop Co-Chair*
 Director, Stanford Program in Neuroscience and
 Society
 Stanford University

8:40 a.m. Mechanisms and Targets of Action

- Provide an overview of what is known about mechanisms and targets of action.
- Discuss what technology is needed to further develop the field.

MARK HALLETT
 Chief, Human Motor Control Section
 National Institute of Neurological Disorders and
 Stroke

9:05 a.m. Non-Invasive Neuromodulation Technology

- Provide an overview of non-invasive neuromodulation devices, including electromagnetic devices and other developing devices, such as those involving ultrasound and light.

- Discuss what is known and unknown about engineering neuromodulation devices.
- Discuss how electrical dose and exposure of different brain locations to electric fields can be modeled.

VICTOR KRAUTHAMER
 Division of Biomedical Physics
 Office of Science and Engineering Labs
 Food and Drug Administration

LEONARDO ANGELONE
 Division of Biomedical Physics
 Office of Science and Engineering Labs
 Food and Drug Administration

SESSION I: THERAPEUTIC AND NON-THERAPEUTIC USES

Session Objectives: Discuss potential benefits and risks of non-invasive neuromodulation devices based on known short- and long-term central nervous system mechanisms of action. Explore the scientific landscape of device development for both therapeutic and non-therapeutic uses. Discuss the scientific controversies behind the potential uses. Consider issues concerning vulnerable populations.

Part One: Therapeutic Uses: Current and Developing

- What are common clinical applications of non-invasive neuromodulation devices?
- What are the known benefits and risks associated with use? What are the scientific controversies behind this evidence?
- Are mechanisms and outcomes of use different between adults and children?
- What opportunities and challenges exist around increasing understanding of effects of treatment?
- “In place of current therapeutics”: How do non-invasive neuromodulation devices compare to current treatment options?
- “In combination with current therapeutics”: What is the potential for use in combination with other therapies, and what is known about interactions?

9:30 a.m. Overview Talk and Session Objectives

ALVARO PASCUAL-LEONE, *Moderator*
Professor of Neurology
Associate Dean for Clinical and Translational
Research
Harvard Medical School

9:55 a.m. Panel Remarks

ROY HAMILTON
Assistant Professor of Neurology
University of Pennsylvania

SARAH “HOLLY” LISANBY
Professor and Chair
Department of Psychiatry & Behavioral
Sciences
Duke University

ALEXANDER ROTENBERG
Associate Professor of Neurology
Harvard Medical School
Senior Associate in Neurology
Boston Children’s Hospital

W. JEFFREY ELIAS
Associate Professor of Neurological Surgery and
Neurology
Director of Stereotactic and Functional
Neurosurgery
University of Virginia School of Medicine

10:35 a.m. Discussion Among Speakers and Workshop Participants

11:10 a.m. BREAK

Part Two: Developing Non-Invasive Neuromodulation Devices for Therapeutic Uses

- What is the level of interest in development of these devices?
- What are the opportunities and barriers to development?

11:25 a.m. Session Overview and Objectives

JEFFREY NYE, *Moderator*
Vice President
Neuroscience Innovation and Scientific
Partnership Strategy
Janssen Research and Development, LLC
Johnson & Johnson Innovation

11:30 a.m. Panel Remarks

MARK DEMITRACK
Vice President and Chief Medical Officer
Neuronetics

ATUL PANDE
Chief Medical Officer and Executive Vice
President
Tal Medical

ANA MAIQUES
Chief Executive Officer
Neuroelectrics

12:00 p.m. Discussion Among Speakers and Workshop Participants

12:30 p.m. LUNCH

Part Three: Non-Medical and Investigational Uses

- What is the type and extent of non-medical use?
- What are the known benefits and risks associated with use?
- What opportunities and challenges exist around non-therapeutic use, including over-the-counter and consumer-initiated use?
- Are mechanisms and outcomes of use different between adults and children?

- How is non-invasive neuromodulation used for diagnostic and investigational purposes?

1:15 p.m. Session Overview and Objectives

FRANCES JENSEN, *Moderator*
Professor and Chair of Neurology
Perelman School of Medicine
University of Pennsylvania

1:20 p.m. Overview Talk

ROBERT CHEN
Professor of Neurology
University of Toronto

1:40 p.m. Panel Remarks

DYLAN EDWARDS
Director, Laboratory for Non-Invasive Brain
Stimulation and Human Motor Control
Burke Medical Research Institute
Associate Professor, Department of Neurology
Weill Cornell Medical College

ROI COHEN KADOSH
Wellcome RCD Fellow and University Research
Lecturer
University of Oxford

DANIEL WETMORE
Director, Intellectual Property and Usability
Thync

MICHAEL FOX
Assistant Professor of Neurology
Harvard University

2:20 p.m. Discussion Among Speakers and Workshop Participants

2:45 p.m. BREAK

SESSION II: REGULATORY

Session Objectives: Consider the regulatory landscape for non-invasive neuromodulation devices. Discuss potential outcome measures for therapeutic uses in regulatory processes, pathways for regulatory approvals for therapies using a combination of non-invasive neuromodulation devices and pharmaceuticals, and differences in regulatory pathways among countries, then consider the impact.

3:00 p.m. Session Overview and Objectives

JEFFREY NYE, *Session Moderator*
 Vice President
 Neuroscience Innovation and Scientific
 Partnership Strategy
 Janssen Research and Development, LLC
 Johnson & Johnson Innovation

Regulatory Pathways for Non-Invasive Devices

- How does the regulatory landscape contrast for non-invasive devices versus other medical devices?
- What is the current regulatory position regarding the balance between risk and benefit standards of evidence and fostering innovation?
- How are medical devices defined in the context of regulatory approval?
- When do preexisting device-based indications (e.g., presurgical mapping) impact other potential uses?
- What regulatory oversight exists for over-the-counter use?
- What are the regulatory issues regarding combination non-invasive neuromodulation devices and pharmaceutical therapies?
- Consider country differences in regulatory pathways, including
 - How are regulatory pathways for non-invasive neuromodulation devices different?

- What challenges exist for companies targeting domestic and foreign markets?
- What is the impact of differences in regulations?
- How does the Food and Drug Administration coordinate with overseas regulatory agencies?

- 3:05 p.m. TIMOTHY MARJENIN
Chief, Neurostimulation Devices Branch
Food and Drug Administration
- 3:25 p.m. IBIM TARIAH
Technical Director
British Standards Institution
- 3:40 p.m. Conducting Clinical Trials
- What levels of evidence are needed to warrant clinical use?
 - What considerations are important when designing clinical trials (e.g., timing, length, magnitude)?
 - What challenges exist for developing clinical trials for non-invasive neuromodulation devices?
 - How can clinical trials be conducted effectively?
- JASON CONNOR
Adaptive Clinical Trial Designer
Berry Consultants
- 3:55 p.m. Discussion Among Speakers and Workshop Participants
- 5:00 p.m. Day-One Wrap-Up
- Workshop Co-Chairs
- 5:15 p.m. ADJOURN DAY ONE

March 3, 2015

8:30 a.m. Day Two Opening

Workshop Co-Chairs

SESSION III: ETHICAL CONSIDERATIONS

Session Objectives: Examine ethical questions around the use of non-invasive neuromodulation devices. Consider ethical issues of off-label and over-the-counter use on regulation, reimbursement, and patient safety. Discuss the use of these devices for enhancement in individuals without an impaired baseline. Consider the implications of involuntary or coercive use.

8:35 a.m. Session Overview and Objectives

HANK GREELY, *Session Moderator*
 Director, Stanford Program in Neuroscience and
 Society
 Stanford University

8:40 a.m. Neuromodulation, the Self, and Enhancement

- Explore questions about the use of these devices and the impact on “self.”
- Consider the impact of use of these devices for enhancement in individuals without an impaired baseline.
- Identify ways of incorporating these considerations into the development and use of non-invasive neuromodulation devices.

ERIK PARENS
 Senior Research Scholar
 The Hastings Center

MARTHA FARAH
 Walter H. Annenberg Professor of Natural
 Sciences
 University of Pennsylvania

9:20 a.m. Neuromodulation and Unsupervised Use

- What are considerations when using non-invasive neuromodulation devices outside of therapeutic use?
- What are potential risks for use of these devices by consumers? Are there differences in risks/benefits between clinical oversight and non-clinical settings?
- How well are users protected from potential malfunctions?

HANNAH MASLEN
Postdoctoral Research Fellow in Ethics
Oxford Center for Neuroethics

9:40 a.m. Neuromodulation and Coercion

- Consider the impact of use in vulnerable populations (e.g., in children or individuals with mental illness) or involuntary use of these devices (e.g., court ordered or psychiatrist ordered).

JENNIFER CHANDLER
Professor of Law
University of Ottawa

10:00 a.m. Discussion Among Speakers and Workshop Participants

10:30 a.m. Break

SESSION IV: REIMBURSEMENT

Session Objectives: Explore current and potential use reimbursement practices for therapeutic uses of non-invasive neuromodulation devices. Explore the evidence base and acceptable therapeutic outcome measures used in reimbursement decisions. Consider economic outcome measures used to determine payer practices.

10:45 a.m. Session Overview and Objectives

RHONDA ROBINSON-BEALE, *Session Moderator*
Senior Vice President and Medical Officer
Blue Cross of Idaho

10:50 a.m. Current Reimbursement Practices

- Are payors currently reimbursing for these treatments?
- How are insurance companies currently evaluating these treatments in comparison to other options?
- Are there state differences in reimbursement practices?
- What is the impact of non-reimbursement?

RHONDA ROBINSON-BEALE
Senior Vice President and Medical Officer
Blue Cross of Idaho

OSCAR MORALES
Founding Director, Transcranial Magnetic
Stimulation Service
McLean Hospital

11:20 a.m. Improving the Evidence Base for Reimbursement

- What is the current evidence base used for reimbursement?
- What evidence is needed from research to align with insurance policies and evidence criteria?
- How might greater information of comparative effectiveness between these devices and other therapeutics impact reimbursement practices?

RHONDA ROBINSON-BEALE
Senior Vice President and Medical Officer
Blue Cross of Idaho

BRADLEY GAYNES
Professor of Psychiatry
Associate Chair of Research Training and
Education
University of North Carolina at Chapel Hill
School of Medicine

11:50 a.m. Industry Panel

- What is the impact of non-reimbursement or of reimbursement that is fragmented regionally or internationally?
- How do reimbursement decision-making processes differ for pharmaceutical products and medical devices, given the differences in safety profile (i.e., the view of regulators)?
- How different do devices need to be for independent assessments and how important is pooling of studies of devices with a similar mechanism?

MARY HAILEY
Vice President of Health Policy and Government
Relations
Neuronetics

ERIC LIEBLER
Vice President, Scientific, Medical, and
Governmental
Affairs
electroCore

JOHN REPPAS
Director of Public Policy
Neurotechnology Industry Organization

12:20 p.m. Discussion Among Speakers and Workshop Participants

12:45 p.m. LUNCH

1:15 p.m. Non-Invasive Neuromodulation: A Venture Capitalist's Perspective

ROSS JAFFE
Managing Director
Versant Ventures

SESSION V: MOVING FORWARD

Session Objectives: A panel will synthesize and discuss key highlights from the workshop presentations and discussions, including identifying next steps and promising areas for future action and research.

1:35 p.m. Panel Discussion: Session Moderators

ALVARO PASCUAL-LEONE, *Workshop Co-Chair*
Professor of Neurology
Associate Dean for Clinical and Translational
Research
Harvard Medical School

JEFFREY NYE, *Workshop Co-Chair*
Vice President
Neuroscience Innovation and Scientific
Partnership Strategy
Janssen Research and Development, LLC
Johnson & Johnson Innovation

FRANCES JENSEN
Professor and Chair of Neurology
Perelman School of Medicine
University of Pennsylvania

HANK GREELY, *Workshop Co-Chair*
Director, Stanford Program in Neuroscience and
Society
Stanford University

RHONDA ROBINSON-BEALE
Senior Vice President and Medical Officer
Blue Cross of Idaho

APPENDIX B

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- 2:25 p.m. Discussion Among Speakers and Workshop Participants
- 2:45 p.m. Closing Remarks from the Workshop Co-Chairs
- 3:00 p.m. Adjourn Workshop

C

Registered Attendees

Tom Acklin
All is Well Centers for Mind
and Body Integration

Susan Amara
National Institute of Mental
Health

Leonardo Angelone
Food and Drug
Administration

James Aulds
Department of Defense

Mitchell Belgin
Washington Square
Psychiatry

Heather Benz
Food and Drug
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Alexander Beylin
Food and Drug
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Sabine Biset-Meunier
National Institute of
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Eric Blumberg
George Mason University

Aaron Boes
Beth Israel Deaconess
Medical Center
Harvard Medical School

Kristen Bowsher
Food and Drug
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Timothy Brindle
Department of Veterans
Affairs

Mark Brody
Brain Matters Research

John Campo
The Ohio State University
Wexner Medical Center

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NON-INVASIVE NEUROMODULATION

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University of Maryland
School of Medicine

Franklin Carrero-Martinez
National Science Foundation

Pablo Celnik
Johns Hopkins University

Jennifer Chandler
University of Ottawa

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National Center for
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William Jeffrey Elias
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Jennifer Evans
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Martha Farah
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Gregory Farber
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Michael Fox
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Mark Gorman
Member of the Public

Anupama Govindarajan
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Hank Greely
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Pamela Greenwood
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Mary Hailey
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Mark Hallett
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Roy Hamilton
University of Pennsylvania

Michelle Harris-Love
Georgetown University

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NON-INVASIVE NEUROMODULATION

Cathy Hart
New Hope TMS Depression
Therapy

Elizabeth Katz
Food and Drug
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Dietrich Haubenberger
National Institute of
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Erin Keegan
Food and Drug
Administration

Mi Hillefors
National Institute of Mental
Health

Brain Kidwell
George Mason University

Stanley Huang
Food and Drug
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Inhwa Kim
American Association for the
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Maria Iacono
Food and Drug
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Randy King
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Jenna Koschnitzky
Hydrocephalus Association

David Jones
Battelle Memorial Institute

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Doe Kumsa Food and Drug Administration	David Markowitz Scitor Corporation
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Nate Lakshmi Medtronic	Hannah Maslen Oxford Center for Neuroethics
Gary Levin Digital Health Space	Matthew McClain McClain and Associates, Inc.
Eric Liebler electroCore	Shelly Menolascino Shelly Menolascino, M.D., LLC
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Sarah H. Lisanby Duke University	Angela Morris St. Jude's Medical Center
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Ana Maiques Neuroelectrics	Deepti Mughal TMS of Jacksonville
Stefano Marengo National Institute of Mental Health	Matthew Myers Food and Drug Administration

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