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Closed-Loop Rehabilitation of Age-Related Cognitive Disorders

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Abstract

Cognitive deficits are common in older adults, as a result of both the natural aging process and neurodegenerative disease. Although medical advancements have successfully prolonged the human lifespan, the challenge of remediating cognitive aging remains. The authors discuss the current state of cognitive therapeutic interventions and then present the need for development and validation of more powerful neurocognitive therapeutics. They propose that the next generation of interventions be implemented as closed-loop systems that target specific neural processing deficits, incorporate quantitative feedback to the individual and clinician, and are personalized to the individual's neurocognitive capacities using real-time performance-adaptive algorithms. This approach should be multimodal and seamlessly integrate other treatment approaches, including neurofeedback and transcranial electrical stimulation. This novel approach will involve the generation of software that engages the individual in an immersive and enjoyable game-based interface, integrated with advanced biosensing hardware, to maximally harness plasticity and assure adherence. Introducing such next-generation closed-loop neurocognitive therapeutics into the mainstream of our mental health care system will require the combined efforts of clinicians, neuroscientists, bioengineers, software game developers, and industry and policy makers working together to meet the challenges and opportunities of translational neuroscience in the 21st century.

Keywords

closed loop; neurotherapeutics; cognitive training; neuroplasticity; personalized medicine

The field of medicine has had many successes over the last century, paramount among which are innovations that have prolonged average human lifespan to nearly 80 years.[1] In fact, the United Nations projects a life expectancy of 100 years for one in three newborns today.[2] Although extended lifespan is one metric of medical success, a fundamental challenge facing modern medicine is the preservation of healthy neurocognitive status and/or rehabilitation of deteriorating cognition with age. In this context, human cognition is defined as the brain's core information processing abilities of attention, perception, memory, emotion, language, and decision making. Furthermore, this challenge to preserve/rehabilitate cognition is not only relevant to cognitively impaired older adults, but also

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children with deficient cognitive functioning associated with delayed neurodevelopment.[3] In fact, accumulating evidence suggests that developing cognitive reserve during early life delays the functional manifestations of Alzheimer disease (AD) later in life.[4–7] In contrast, stress and abuse-related adversity early in life are shown to impair cognition and compromise both mental and physical health in adulthood and relate to early morbidity.[8–12] Together, this evidence base makes a strong case for early neurocognitive intervention in children that continues to be implemented throughout life as a critical component of the preventive health care model.[13]

Unfortunately, neurocognitive interventions that engender robust and sustainable impacts on mental health are not currently available as highlighted in the following clinical case and current methods of care.

Clinical Case

To illustrate the deficits of our present-day therapeutic approach, let us consider the clinical pathway that is likely to occur for an older adult who presents to his or her clinician with symptoms of mild cognitive impairment (MCI), such as increasing memory loss related to daily life tasks, events, and conversations; decreased ability to plan and execute daily life decisions; heightened impulsivity and distractibility; and/or diminished spatial navigation abilities in familiar environments. First, they are likely to receive a traditional cognitive evaluation that does not include any functional brain imaging. We now have evidence that MCI compared with healthy aging is associated with greater neural network dysfunction characterized by diminished or abnormal recruitment of frontal, parietal, and temporal top-down control regions during attention and memory-related encoding and recognition, which in turn is related to gray matter volume reductions in these regions.[14–17] Functional integrity of hippocampal and thalamocortical networks is also more impacted in MCI versus healthy controls.[18,19] Even resting state cortical neural synchronization dynamics quantified by electroencephalography- (EEG-) based spectral power and coherence measures during rest (or by default mode network activity using functional magnetic resonance imaging [fMRI]) can help distinguish MCI and AD compared with healthy aging.[20–22] Moreover, healthy older adults with intact brain volumes have been shown to exhibit reduced neural activity in fMRI during some cognitive operations compared with MCI patients who show increased brain activity with reduced volumes, perhaps as a compensatory mechanism to minimize functional manifestations.[23] Despite this, we have been unable to incorporate such basic research evidence into our diagnostic pathway in any systematic manner.

Following a traditional evaluation that likely poorly characterizes the precise neurocognitive deficits, the starting dosage and prescriptive medication plan for the patient is based solely on population data. This lack of personalization also often occurs without accompanying prescriptions for cognitive/ behavioral training to assist in the remediation of the underlying neurocognitive deficits, representing a unimodal approach. After a couple of months, she or he returns to the physician for an in-person meeting to assess efficacy and side effects, often with no quantitative data collected, and drug dosage adjusted without a clear empirical basis of how it will impact symptoms, leading to another round of extended and imprecise treatment adjustments reflective of an “open-loop system” (i.e., an intervention lacking

precise and rapid quantitative feedback during its course, which in turn leads to uninformed adaptive adjustments in the intervention).

Those top-notch physicians who recognize the inherent flaws of this clinical approach will modify their therapeutic regimen so that it is somewhat more personalized (e.g., starting with half dose for patients in their 80s), multimodal (e.g., encouraging physical exercise), and "closed loop" (i.e., more precise feedback, such as asking family members to assess and communicate results by phone more frequently). However, it is clear that even this well-motivated attempt falls tragically short of the impactful cognitive interventions we should be delivering. Not only is this common treatment practice for conditions in neurology, such as MCI and dementia, this disheartening scenario is pervasive across therapeutic approaches for all psychiatric conditions (e.g., depression, schizophrenia, traumatic brain injury, posttraumatic stress disorder, and attention deficit/hyperactivity disorder [ADHD]). Increasingly, cognitive deficits assessed in such cases are now referred under the common umbrella of *neuropsychiatric*, as neurologic and psychiatric boundaries were artificially created by our medical system, while the root of all of these disorders is neural network dysfunction.[24]

Current Methods of Care or Management

As is evident from the clinical case example, standard mental health care practices based solely on our current pharmaceuticals suffer many inadequacies:

1. They are usually *unimodal*, as medical prescriptions are largely made in isolation of other therapeutics. It is often only in cases where psychiatric symptoms are experienced along with cognitive symptoms that other complementary treatments are prescribed. For example, medications and psychotherapy for MCI patients with anxiety may secondarily relieve some of the cognitive impairments due to interactions between networks underlying stress responses (hypothalamic–pituitary–adrenal network) and frontoparietal cognitive control networks.[25]
2. The approach is *open loop*— it does not involve real-time, quantitative feedback to guide rapid adaptive, dynamic adjustments of the intervention.
3. It *poorly targets* the specific neural network dysfunction that underlies different aspects of cognition. For example, when medications are prescribed for patients with MCI, they are the same as those used to provide symptomatic relief in Alzheimer disease (i.e., cholinesterase inhibitors: donepezil, rivastigmine, galantamine, and the NMDA-receptor-blocker memantine), regardless of differences in presenting cognitive deficits (e.g., memory vs. attention vs. visuospatial). Apart from medications, there is a long list of health-style modifications (e.g., exercise, nutrition, and stress management) that can improve brain health, which while frequently prescribed by cardiologists are often overlooked in the mental health world.[26]
4. Lastly, our current approach suffers from a *lack of personalization* due to overreliance on population data and poorly characterized individual differences in neural processing and cognition.

It is now becoming clear that the brain and cognition are too complex to impact in a meaningful and sustainable manner via a single modality, especially when that modality utilizes the blunt instruments available in our current pharmaceutical toolbox. Without attaining network-specificity and the ability to selectively target drugs to deficient neural processes and underlying pathophysiology, it is inevitable that to achieve beneficial effects, medication dosages will be pushed to high levels that cause excessive negative side effects. In fact, pharmaceutical companies are now retreating from research and development in mental health therapeutics, as it is becoming evident that approaches using nonselective agents in an open-loop and nonpersonalized way are often ineffective.[27] The National Institute of Mental Health refers to this as the "valley of death" in the development of interventions targeting neuropsychiatric disorders, akin to a similar standstill in anticancer drug development. The time is thus ripe to develop and rigorously evaluate new approaches to complement the current molecular therapies for enhancing cognition in neuropsychiatric disorders. This may allow us to reduce drug doses and minimize side effects, perhaps even eliminate pharmaceutical agents that have low efficacy and high side effects.

Evidence-Based Compensatory or Restorative Treatments

There have been many challenges in generating evidence for an effective therapeutic approach for individuals with cognitive impairment. Cooper et al recently conducted a comprehensive systematic review of all treatments evaluated for MCI.[28] They concluded that cholinesterase inhibitors are ineffective and do not reduce the incidence of dementia, and hence should not be prescribed clinically for MCI. Studies that involved cognitive rehabilitation through computerized cognitive training were (1) underpowered and did not improve global cognition relative to an active control group, or (2) only influenced neurocognitive measures, but did not generalize to daily life function.[29,30] Even a year-long study of aerobic activity versus a relaxation/balance/flexibility exercise control group did not move cognitive measures, and another systematic review of physical exercise interventions in MCI found null effects.[31] Of note, these findings differ from modest yet statistically significant cognitive improvements observed after cognitive training and physical exercise training in healthy older adults as analyzed in another recent quantitative review.[32] On a positive note for MCI, a single trial of a multimodal heterogeneous psychological group therapy (memory training combined with psychomotor recreational activities and social interaction) succeeded in improving cognition. Another single trial evidenced benefits of a dopamine agonist (piribedil) over 3 months. But further high-quality randomized clinical trial evidence is clearly needed for these new multimodal therapies and pharmaceutical targets.[28]

There are several likely reasons for the lack of success. The MCI patient population is a heterogeneous group and the diagnosis is unstable over time and across practitioners, all contributing to the variable outcomes in these clinical trials and hence limited positive results; indeed no therapeutic approved by the U.S. Food and Drug Administration (FDA) exists for MCI. Consistent with this notion, trials that are confined to homogenous subpopulations defined by biomarkers have shown some beneficial outcomes, such as vitamin E intake in MCI individuals who carry alleles of apolipoprotein E ε4.[33] Overall, it seems that future diagnostics and therapeutics should focus on isolating genetic and

neurophysiological biomarkers in MCI subpopulations and apply precisely targeted pressure on the deficient systems.

Interesting Developments in the Therapeutic Pipeline

Persuaded by the shortcomings of the current system, and capitalizing on recent advances in high tech, both hardware and software, we now enter a new era of novel intervention development and validation. We propose that new interventions in this domain should aim to be multimodal, closed loop, personalized, and targeted to specific neural markers that underlie network dysfunction. One such personalized and neurally targeted intervention that is being increasingly adopted in mainstream neurotherapeutics is deep-brain stimulation (DBS), an FDA-approved neurosurgical procedure applied in movement disorders such as essential tremors, Parkinson disease, and dystonia.[34] Deep-brain stimulation is an example of a promising closed-loop intervention for neural, especially motor, disorders that is worth discussing.

Deep-brain stimulation involves implantation of electrodes in specific brain regions as pacemaker devices delivering electrical pulses to the implanted brain site; the pulse generator is usually implanted subcutaneously below the clavicle. Generally, feedback from the patient during the awake portion of surgery is used to determine optimal placement of a permanent electrode, and the stimulation rate is adjusted by the neurosurgical team to suppress symptoms and control side effects. More recently, there have been advances in closed-loop DBS for movement disorders that incorporate neural signals from the subthalamic nucleus or electromyography- (EMG-) based muscle activity to adaptively adjust the stimulation parameters.[35,36] Furthermore, in an extended closed-loop DBS system the clinician can review the stimulation parameters selected by neural/ muscle signal adaptive algorithms via telemetry. In general, these recent closed-loop DBS approaches have been found to show greater efficacy than the first-generation open loop protocols, as they continuously adjust to the individual patient's neural dysfunction.[36]

Despite requiring invasive surgery, DBS has recently been investigated as a possible treatment for psychiatric disorders, included treatment-resistant major depression, chronic pain, obsessive–compulsive disorder, and even for improving cognitive function in AD.[37–39] This is largely because the method is adjustable, reversible, can be personalized to the patient, and offers neuromodulation targeted to a specific neurologic site of action. But this method has not yet been FDA-approved for any psychiatric condition, as controlled trial studies concluded the need for further evaluation and two recent multisite controlled trials of DBS for major depression were discontinued due to inefficacy.[40,41] Indeed, safety and efficacy of DBS has to be carefully evaluated, especially given that the treatment requires invasive neurosurgery and its high cost is a deterrent to general use.

With regard to MCI and AD, initial positive evidence for cognitive benefit is emerging from one open-label feasibility study and a couple of case reports that have targeted stimulation in the fornix and the nucleus basalis.[39] One year of fornix stimulation was associated with improved clinical outcomes in cognition, memory, and quality of life; glucose metabolism improved in fronto-temporal-parietal-striatal-thalamic and fronto-temporal-parietal-

occipital-hippocampal networks, which is not typical for the spontaneous evolution of AD. The investigators also observed a positive association between better prestimulation cognitive functionality/higher preoperative glucose metabolism in the fornix and beneficial cognitive and quality of life outcomes, suggesting DBS may benefit patients with MCI and non-advanced AD. One aging Parkinson dementia patient implanted with a nucleus basalis DBS showed almost immediate improvements in attention, alertness, and motivation, which was further associated with better mood and enjoyment of former activities; a phase I investigation based on this case report is underway.[39] Although human DBS studies on MCI/AD patients are still in infancy, animal research suggests that the caudate nucleus, dorsal striatum, certain thalamic nuclei, hippocampus, and amygdala could all be potential future targets.

There is also increasing promise of noninvasive approaches. Overall, the lower cost, feasibility, and large-scale accessibility of noninvasive, closed-loop systems make them very attractive for all neuropsychiatric disorders.[36] Among current noninvasive and nonpharmaceutical interventions for neuropsychiatric disorders, computerized cognitive training is emerging as a potentially promising therapeutic. In addition to studies in neuropsychiatric populations, cognitive training has also shown benefits in healthy individuals. Trainees perform cognitive tasks that engage various aspects of cognitive control, including training fundamental abilities of visual and auditory perception, attention, and working memory. The tasks are made adaptive to the trainee's real-time behavioral performance, presenting progressively greater challenge with accurate performance and reducing challenge for inaccurate responses.[42] The trainee is also continuously aware of his or her performance during adaptive training via continuous feedback reward cycles that occur at multiple time scales, from feedback every few seconds in training to daily, weekly, and monthly progress summaries until the end of training. In more recent years, cognitive training has employed Internet and mobile technologies, which allow online training data to be immediately transferred to the training supervisor. This provides the supervising researcher/clinician with the opportunity to continuously track progress on the intervention, perform immediate follow-ups in case the trainee is nonadherent, and even make performance data-informed changes to the training schedule and dosage if desired. Cognitive training thus (1) generates a behavioral closed-loop system between the human trainee interacting with a cognitive task on a computer, (2) is personalized to the trainee's performance capacities driven by underlying adaptive progression mechanics, and (3) the cognitive training tasks can be selected to strengthen specifically deficient neurocognitive domains as determined in a quantitative pretraining diagnostic assessment. Additionally, the deployment of cognitive-training technology to large samples of the population is relatively low cost. In combination, these characteristics make cognitive training an attractive neurotherapeutic tool, but of course only when treatment efficacy is demonstrated.

Healthy aging studies from our laboratory and others have shown that cognitive training interventions based on principles of neuroscience can generate beneficial neuroplasticity in underlying cognitive control neural systems, and further leads to some degree of generalization of improvements from the training domain to untrained cognitive tasks known as "transfer of benefit."[43–50] Two studies have now demonstrated long-term endurance of cognitive benefits in 5- and 10-year follow-ups for older adults who performed

10 sessions of training and brief booster training at the 1- and 3-year mark.[51,52] However, evidence of transfer of benefit being reported is still quite limited and it is now becoming understood that cognitive transfer occurs in domains that invoke similar underlying neural processes and cortical activations as the training task.[49,53–56] Thus, increasingly researchers are developing and testing training program regimens with varied exercises that focus on multiple aspects of cognition. Such programs are showing combined neuroplastic and cognitive benefit beyond aging, in other neuropsychiatric conditions, with evidence emerging for cognitive training in schizophrenia to the extent that the method is being evaluated in multisite controlled trials for FDA approval.[57–59] Finally, there is an opportunity for cognitive training to become integrated within multimodal treatment programs for neuropsychiatric illness, combining training with psychotropic medications or with other behavioral therapies to enhance treatment outcomes. However, much work remains in carefully evaluating the feasibility and efficacy of cognitive training, especially in terms of multimodal combinations and interactions with other treatment modalities.

We are optimistic that multimodal, closed loop, targeted, and personalized interventions will be part of the future of mental health therapeutics. In addition, development of noninvasive closed-loop systems should make treatments feasible and accessible to large numbers of individuals. Rather than generic diagnosis and treatment formulations, such therapeutics can be tailored to the patient's specific pathophysiology and disease severity, and then continuously tracked by neuroimaging tools, most feasible among which is EEG given its low-cost and high millisecond-level temporal resolution. In addition, as simultaneous tracking of other physiological measures, including heart rate variability, galvanic skin responses and sleep-wake cycles are performed, adaptive algorithms would track the progressively changing state of the patient, and automatically adjust the parameters of intervention delivery.

While progress is being made in the development and validation of closed-loop systems for movement disorders, there is a dearth of such solutions in cognitive therapeutics, partially due to the complexity of neural network dynamics underlying cognition.[36] Scientific teams developing closed-loop rehabilitation systems for movement disorders have relied on progress in key areas of basic science research before further advanced therapeutics emerge that can be integrated in mainstream mental healthcare. These key research foci overlap with the need to advance the development of cognitive closed-loop therapeutics and include (1) improved understanding of distributed neural networks and brain function dynamics that underlie healthy and pathophysiological conditions; (2) development of more sensitive, robust, ideally wireless noninvasive neural sensors that have high spatial resolution and low latency, as well as high usability and comfort for the individual[60] (3) development of more sophisticated and sensitive adaptive algorithms that map the dynamic nature of underlying neurophysiology onto the observed behavior (closed-loop decoder adaptation is an excellent example of such algorithms[61]); (4) implementation of both model-free (i.e., neurophysiological data driven) and computational model-based elements within the closed loops, where the model-based scheme allows short-term prediction of the system state; (5) software algorithms interfaced with fast-computing hardware, such as high-end graphic processing units (GPUs), to deliver near real-time closed-loop functionality[62] and finally (6) development and integration with mobile device interfaces (e.g., phones and tablets) with

minimized demands on battery power, which will ultimately enable long-duration device deployment in the home setting and global scalability.[36,63]

To make true headway in such technologically and scientifically challenging research areas, traditional university laboratories may not be sufficient. We need to create state-of-the-art, immersive virtual environments that mimic the real world, and integrate recent technological advances in interactive video game mechanics with the latest in multimodal brain–body imaging, such as wireless EEG, cardiac and respiratory function sensors, eye tracking, and three-dimensional motion capture. These can further be coupled with neuromodulation tools such as transcranial electrical stimulation (tES) and neurofeedback. Our Neuroscape laboratory at the University of California San Francisco is one such effort to build a platform for development and rigorous validation of novel closed-loop diagnostics and therapeutics that translate neuroplasticity findings from bench to bedside.[64,65]

New closed-loop therapeutics are anticipated to refine upon existing approaches. For example, neurofeedback is a conventional closed-loop therapy where individuals learn to self-regulate their ongoing neural rhythms through audiovisual feedback; it has even shown promising therapeutic outcomes in neurodevelopmental disorders, such as in ADHD and in older adults.[66–68] However, conventional neurofeedback operates on long timescales that involves the capture of tens of seconds of neural activity data, and signals that are usually read and modulated by scalp channels that do not have the spatial resolution localized to the specific underlying neural source. Moreover, the traditional procedure does not incorporate adaptive algorithms to personalize the approach to the evolving performance capacities of the individual. These technological limitations have contributed to variability in neurofeedback performance success across individuals, hindering large-scale adoption of the method despite some promising studies. The fact that currently a highly trained professional needs to administer every neurofeedback session to a patient with 30 to 50 hours of typically recommended treatment, has led to escalating costs that are usually not covered by health care insurance, again limiting mass adoption.

Ideally, the next-generation neurofeedback technologies will have the ability to target specific cognitive-task related neural processing in a precise brain region at subsecond time scales, both pre- and poststimulus onset. This vision is consistent with cognitive neuroscience research that shows task-related, stimulus-evoked neural activity patterns are distinct from ongoing baseline rhythms, which correlate with functional and behavioral performance in healthy and cognitively impaired populations, young and old.[69–71] Aligned with this vision, we are developing novel brain computer interface technology at the Neuroscape laboratory known as the *Glass Brain* (►Fig. 1). Within the Glass Brain, closed-loop computations occur in near real-time at a temporal resolution of less than one second; the neural signals are artifact-corrected in real-time and more precisely decoded from cortical source space instead of scalp space.[62,63,72–74] Further, the neurofeedback procedure is presented using an immersive video game environment that is constantly adapting to the capacities of the individual within the context of a cognitive task. The hope is that in the future, individuals who engage in a Glass Brain cognitive closed loop will have neural processes targeted by a preintervention diagnostic that assesses their information-processing strengths and weaknesses. Thus, like a surgeon wielding a gamma knife, the closed-loop

system will place selective pressure on the most deficient neural processes, fine-tuning function of specific networks. Furthermore, such a neurocognitive closed loop could be applied either alone or in a multimodal manner with behavior-based cognitive training closed loops or even closed loops that incorporate real-time neural stimulation (tES).[75] It is with such technological breakthroughs that we hope to bridge the fields of neuroscience, bioengineering, and neuropsychiatry to successfully prolong the quality of cognitive life for new centenarians.

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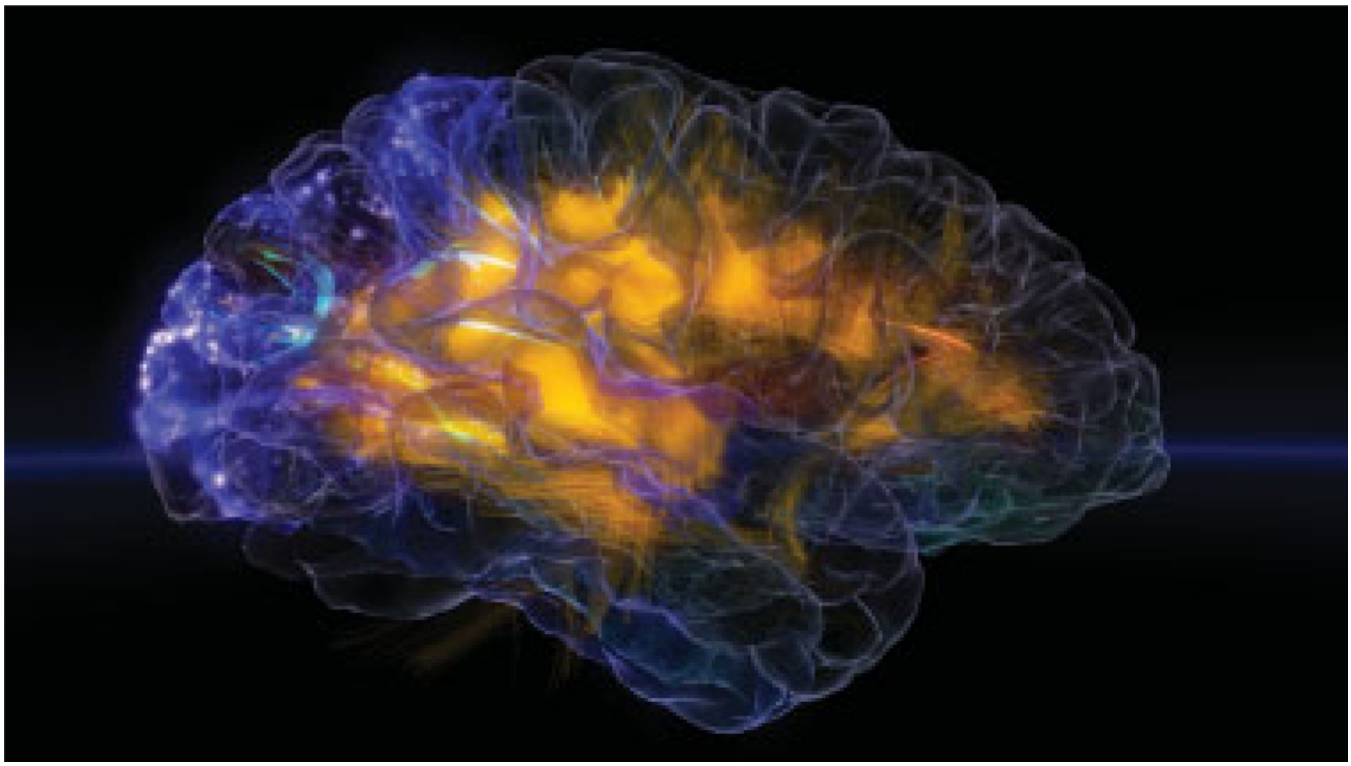

Fig. 1.

A snapshot of the "Glass Brain," an anatomically realistic three-dimensional (3D) brain visualization rendered in the Unity game engine, depicting real-time source-localized activity (power and effective connectivity) from electroencephalographic signals. Each color represents source power and connectivity in a different frequency band (θ, α, β, γ) and the golden lines are white matter anatomical fiber tracts. Estimated information transfer between brain regions is visualized as pulses of light flowing along the fiber tracts connecting the regions. The modeling pipeline includes brain magnetic resonance imaging to generate a high-resolution 3D model of an individual's brain, skull, and scalp tissue; DTI (diffusion tensor imaging) for reconstructing white matter tracts; and BCILAB/SIFT to remove artifacts and statistically reconstruct the locations and dynamics (amplitude and multivariate Granger-causal interactions) of multiple sources of activity inside the brain from signals measured at electrodes on the scalp.[64]