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Review

Techniques and devices to restore cognition

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ABSTRACT

Executive planning, the ability to direct and sustain attention, language and several types of memory may be compromised by conditions such as stroke, traumatic brain injury, cancer, autism, cerebral palsy and Alzheimer's disease. No medical devices are currently available to help restore these cognitive functions. Recent findings about the neurophysiology of these conditions in humans coupled with progress in engineering devices to treat refractory neurological conditions imply that the time has arrived to consider the design and evaluation of a new class of devices. Like their neuromotor counterparts, neurocognitive prostheses might sense or modulate neural function in a non-invasive manner or by means of implanted electrodes. In order to paint a vision for future device development, it is essential to first review what can be achieved using behavioral and external modulatory techniques. While non-invasive approaches might strengthen a patient's remaining intact cognitive abilities, neurocognitive prosthetics comprised of direct brain–computer interfaces could in theory physically reconstitute and augment the substrate of cognition itself.

Contents

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1. Introduction

A range of medical devices to restore or augment human functions are becoming available with the swift engineering and biomedical advances in the new field of neurotechnology. Cochlear implants have restored hearing to thousands of people, while devices to restore sight and movement are progressing rapidly. Sensory devices inject signals into the nervous system, while motor prosthetics extract signals from the nervous system and send them to control devices such as robotic arms or stimulators to re-activate paralyzed muscles [136]. Other types of neurotechnology devices improve health by modulating pre-existing systems: deep brain stimulators, for example, deliver targeted electrical stimulation to the basal ganglia to relieve the symptoms of Parkinson's disease. Non-invasive techniques under development include transcranial magnetic or direct current stimulation, and biofeedback delivered from quantitative electroencephalography (EEG) or functional magnetic resonance imaging (fMRI).

Medical devices seek to restore lost function and leverage remaining, intact aspects of the patient's physiology. Deep brain stimulators appear to unfetter an otherwise intact voluntary motor control system from the aberrant activity of one or more nuclei of the basal ganglia in patients with Parkinson's disease or dystonia, whereas cochlear implants bypass a dysfunctional organ of Corti to activate an intact vestibulocochlear nerve to re-instate audition. A major area not addressed by these devices is that of higher cognitive functions, such as memory, language and executive planning, all of which can be compromised in a wide range of neurological diseases.

Cognitive function may be improved by using both non-invasive techniques and invasive medical devices. Non-invasive techniques range from behavioral techniques or assistive software that provide new strategies to restoring memory and planning to electromagnetic stimulation and biofeedback that modulate activity in a patient's brain as part of a rehabilitation program. Whereas the non-invasive approaches may improve cognition by strengthening retained skills or reorganizing the activity of intact brain, implantable medical devices that are able to record and stimulate ensembles of neurons could, in theory, physically restore the substrate of cognition. Though pharmacotherapy will not be a focus of this review, it will be touched upon in the context of implantable microfluidic systems.

The central premise of direct brain–computer interfaces is that lost function can be recovered by artificially recreating or bypassing the neural substrate lost by disease or injury. A successful implementation of such a strategy would be marked by a return to baseline function as measured both by standardized neuropsychological testing, activities of daily living, and a person's subjective appreciation of independent function. Such systems would ideally be transparent and effortless to use. Yet to proceed with clinical trials developing such devices, it is essential to lay out what can be achieved with a variety of non-invasive means. To accept the risk of any invasive intervention, patients and physicians must understand what, if any, alternatives exist. Thus, this paper will begin by reviewing behavioral and assistive device techniques aimed at helping patients with cognitive impairment, and proceed to approaches that increasingly attempt to physically modulate or interface with a patient's brain to improve function.

2. Behavioral techniques

2.1. Assistive devices

Simple, low-cost interventions such as a memory book or wallet, containing pictures of familiar places or people, can help patients with impaired episodic memory better navigate conversations and daily activities [16,119]. Mobile phones and pagers can be set up to actively remind patients of tasks [165,173]. Off-the-shelf systems (e.g., PDAs) can be modified to improve access and usability for people with cognitive impairment by creating a linear flow of use, making the system more resilient to user errors, and consistently repeating items that users need help with [150].

Cognitive orthotic software can facilitate skill acquisition and self-sufficient management of daily tasks [13,36]. These systems can be highly customized to take into account the deficits and rehabilitation goals of a particular patient. Expert systems comprising mobile phones and palm-top computers linked by radio to web-based central workstations have been found to help remind patients with brain injury, stroke and dementia that certain tasks must be performed such as taking a medication or calling a relative [128]. A palmtop computer can literally step a patient through a task: it might alert them that it is time to call a sister, and then either to provide the phone number and await confirmation the task was completed, or give the patient the option to defer the task and follow-up later [88,128]. Patients with brain injuries may benefit from both wearable computers that facilitate interaction with the environment [46], and computer-based diaries, with auditory alarms and linked entries [174]. Wearable cameras and microphones that continually record and monitor a person's environment, coupled to sensors placed throughout the home which all then feed into pattern recognition algorithms to alert a person to perform certain tasks, are in development [42,43,51]. Preliminary field tests of these systems find that considerable challenges remain: as with able-bodied people, patients are averse to having their privacy invaded by cameras and are wary of conspicuously placed sensors; they do not want to be awoken from a nap to take a medicine a specific time [51]. To compensate for a patient's deficit, computer-based memory-aids must be adaptive to the individual and incorporate input of multiple family members and health care givers. A fundamental challenge for automated memory-aids is to devise a method by which computers could recognize the correct situation when a particular reminder should be triggered.

Computerized memory-aids have been found to be useful for simple reminding tasks but fall short of the kind of ongoing guidance that patients with severe cognitive impairments would require to become independent. Another approach is to train the patient herself in order to improve cognition and memory. In theory such cognitive training approaches could help a patient in all aspects of daily life.

2.2. Virtual reality (VR)

VR has been shown to promote learning in people with memory impairments; furthermore, this learning appears to transfer to improved real-world performance [19,96,178]. Virtual worlds based on a patient's own home enable safe practice of daily activities and memorization of the location of items [34,78]. Just as VR tools can

be used for data management by scientific teams to capture and manage complex data [100], so too the annotated display might be adapted to help individuals with memory impairment. Given that enriched environments increase new neuron production in rodents, elaboration of gray matter and remyelination in white matter [86], the mere act of having patients navigate through complex VR worlds may yield clinical benefits.

2.3. Cognitive training

A range of behavioral training techniques have been developed to help impaired patients by leveraging remaining, intact cognitive structures. Animal studies have shown that experience can yield long-lasting effects on brain plasticity and morphology, hence training techniques might likewise induce beneficial changes in the human brain [18]. The approaches vary in sophistication from the use of simple mnemonic aids to complex training regimens designed to reorganize cortical representations. In humans, epidemiological studies have explored a wide number of factors that have been suggested to reduce age-related cognitive decline including both formal and informal education, leisure pursuits, intellectual engagement, physical fitness training, and expertise in different skill domains such as music, computer-game playing, language translation or meditation [75]. Playing computer games appears to improve certain aspects of visual attention such as spatial resolution and number of objects being tracked, which in turn could improve visual memory [48]. Perhaps the best established techniques for cognitive enhancement are healthy diet and physical exercise; several epidemiological studies have revealed significant correlations between physical exercise and cognition [27,124]. Simple procedural changes in the ways people are trained to learn can have dramatic effects: testing retrieval, rather than merely studying items, can significantly improve retention [70]. Here we shall define and review the application of mnemonic techniques, errorless learning, spaced retrieval, vanishing cues, and a technique named plasticity-based learning.

Mnemonic strategies range from verbal techniques such as verbal mediations, acronyms or poems, to spatial techniques such as imagery and the "method of loci." In method of loci, a fact or memory is associated with a particular place in a real or imagined environment such that by mentally walking through this space and visiting particular locations, a person can sequentially recall the memories 'stored' there. Method of loci has been shown to be helpful in adults and children with memory and other cognitive impairment [11,85]. People who are exceptionally good memorizers often use mnemonics techniques to organize, remember and recall large amounts of visual and verbal memories that do not *a priori* have spatial organization by using brain areas, as shown by fMRI, related to spatial navigation and memory (right cerebellum, left medial superior parietal gyrus, bilateral retrosplenial cortex, right posterior hippocampus) [85]. In addition to spatial-location mnemonics, preliminary evidence suggests that musical mnemonics (simply incorporating melody or rhythm in words to be remembered) can improve memory [159].

Errorless learning comprises a technique in which patients are shown both the question and its answer during training, thus providing participants ongoing positive feedback as they are given the right answer. While a meta-review of different techniques in amnesic patients found that errorless learning yielded the greatest effect size [73], a small cohort study of elderly with early-stage dementia suggested high-effort semantic learning was more effective [30]. Incorporating errorless learning and spaced retrieval, in which newly acquired information is recalled at increasingly longer intervals or with more intervening items, was most effective for patients with Alzheimer's [47]. At best, the evidence suggests that these approaches have a mild benefit on attention and memory, in a manner similar to cognition-enhancing drug trials, such as acetylcholinesterase inhibitors (e.g., donepezil) [47].

Patients who have severely impaired episodic memory due to encephalitis and other conditions may be able to learn new skills using remaining, intact implicit memory [45]. In teaching these patients word pairs to memorize, implicit learning can be leveraged by systematically showing more and more letters of a word to be remembered (e.g., for the word 'cursor' showing 'c' then 'cu' then 'cur', etc.) and then subsequently removing the added letters. This technique is termed 'vanishing cues,' and while it appears to benefit certain patients, a meta-review found it lacking [45,47]. In people with brain injuries explicit strategies such as mnemonics and practicing attention, were found to be the most effective in improving performance on the Stroop-Color task and digit span memory [156,162].

Cognitive training approaches suffer from numerous drawbacks including a lack of statistical power due to small groups of participants, absence of long-term follow-up, and failure to measure the impact of the intervention on measures of quality of daily life [23,47]. Another common critique of behavioral techniques to enhance cognition is that the training effects are specific to the tasks used and generalize poorly to the kind of situations an impaired person needs to navigate in daily life [75]. Given that real-world skills involve a variety of cognitive processes, it has been proposed that training interventions ought to *a priori* incorporate multiple processes (e.g., reasoning, verbal episodic memory, processing speed) rather than focus on a single one. Two large-scale, randomized trials addressed several of these concerns and provided some evidence that cognitive training in well-functioning older adults improved cognition in a manner that generalized to daily tasks and that was sustained for up to 5 years after the intervention [7,172]. Memory training comprised teaching mnemonic strategies (organization, visualization, association) for remembering verbal material [172]. Reasoning training involved teaching techniques to find a pattern in a series of words or letters, and then identifying the next item in the series. Participants were also tested on applying the strategies to everyday problems (e.g. a mnemonic strategy to recall a grocery list; a reasoning strategy to comprehend a bus schedule [172]). Improvements appeared to generalize to a positive effect on daily function on the accuracy of verbal memory, self-ratings of how independent they were on daily tasks such as preparing a meal, and the speed and accuracy of tasks such as finding a number in a phonebook and reading a road sign [172].

An approach termed "plasticity-based learning" comprises exercises in which participants must: (1) identify whether a frequency-modulated sweep is upward or downward, (2) identify a synthetically generated syllable from a confusable pair (e.g., /ba/vs./da/), (3) match spoken confusable consonant–vowel–consonant words (e.g., bat, vat) from a spatial grid, (4) reconstruct a sequence of short spoken words, (5) reconstruct spoken instructions by dragging icons on a computer screen, and (6) answer questions about short narratives. Exercises increase in difficulty, dynamically matching the participant's performance. In a small study of children with language-learning impairment, 1 month of daily training was associated with significant improvement in the ability to follow complex auditory stimuli [154]. In a randomized, controlled study of elderly adults, 8–10 weeks of training improved performance on immediate recall of list of words, copying a figure, naming a picture, serial recall of digits, and recalling a figure or a story [87,120]. However, as with the other cognitive training paradigms, it is not clear how much plasticity-based learning generalizes to the real-world environment.

Training techniques such as mnemonic aids, motivational techniques to enhance attention, customization to individual differ-

ences in personality and ability level, and integration of the training to ongoing medical care have been shown to help patients with memory impairment [157]. New techniques should be developed with an understanding of both what has been shown to be effective in holistic approaches to neuropsychological rehabilitation and upon an understanding of the neurophysiology of synaptic plasticity [25,87]. Both assistive devices that a person can carry with them, or which are integrated into sensors in the home, and training techniques ranging from physical exercise to mnemonics, all promise to bring some benefit to patients with cognitive impairment. Yet, even as these assistive devices and techniques are improved it is likely there will be an upper limit of the degree to which they can help patients overcome their impairments. Hypothetically, attempts to modulate or restore the substrate of cognition itself could yield more fundamental benefit. The next two parts of this review cover non-invasive and invasive approaches to modify cortical function in order to restore cognitive abilities.

3. Non-invasive modulation

3.1. Visual entrainment

Steady-state visual stimuli may be used to probe EEG responses: recent work comparing EEG and fMRI of human participants exposed to flickering light found that medial frontal cortex metabolic activity depended on the temporal frequency of visual input implying that during visual stimulation, input frequency can be used to activate distinct functional networks [146]. Indeed the use of visual flicker to purposefully modify cortical activity in order to improve memory has been explicitly tested [169,170].

The alpha rhythm is an oscillation in range of 8–12 Hz, with an average peak of 10–11 Hz in healthy adults. The peak alpha frequency (PAF) corresponds to the discrete frequency with the highest power estimate in the alpha range. The specific discrete frequency of this oscillation appears correlated with mental performance at all ages, although it tends to be slowest in children and the elderly [2]. Alpha oscillations are associated with memory function: they decline in old age and Alzheimer's disease and can be restored by anti-dementia drugs. In a study of 550 normal participants (aged 11–70 years) in the Brain Resource International Database, both performance on reverse digit span tests and PAF were found to significantly decrease with age [123]. For each increasing additional 1 Hz of alpha peak frequency, a corresponding 0.21 digit increase in reverse digit span occurred, when age was held constant [123]. Inasmuch as alpha activity reflects memory performance, one might hypothesize that enhancing alpha might likewise enhance memory.

Recent studies suggest that by exposing human participants to light flickering at particular frequencies, episodic memory can be improved. Visual flicker at 9.5–11.0 Hz (in 0.5 Hz intervals) displayed briefly before presenting a three-letter word to be remembered after a distracter, was found to improve word recall in both young adults and the elderly [169,170]. In the study of 51 young adults, participants recognized more three-letter words that had followed 0.5–1.5 s of 10.0 Hz flicker during learning, compared to those that had followed 0, 8.7 and 11.7 Hz flicker [170]. In the study of 30 elderly, cognitively normal adults, flicker at frequencies close to 10.2 Hz, but not below 9.0 or above 11.0 Hz, improved later recognition of words from the learning phase [170]. While oscillating visual and auditory stimuli have been shown to increase frequency-matched power spectra in the EEG, the mechanism by which flicker improves episodic memory is not known. Rhythmic EEG activity induced by flicker may serve as a gain signal in recurrent cortico-cortical or thalamo-cortical loops, or may predispose LTP at hippocampal synapses.

3.2. Transcranial magnetic stimulation (TMS)

TMS comprises a non-invasive method of induction of focal currents in the brain and transient modulation of the function of targeted cortex [80]. The direction of current flow in an overlying coil determines which neural elements are activated. A review of magnetically induced stimulation of non-motor areas revealed that adverse effects were infrequent and usually mild [84]. rTMS has been shown to ameliorate symptoms in conditions ranging from migraine (the disappearance of abnormal visual evoked potentials by 1 Hz over visual cortex [39]) to depression (5 Hz over left prefrontal dorsolateral cortex [80]). The energy generated by TMS is estimated to be about 0.05% of that applied in a burst of electroconvulsive therapy.

In a study of four aphasics who were 5–11 years post-stroke, 1 Hz rTMS applied daily for 10 days to an anterior portion of Broca's area induced significant and lasting improvement in picture naming [103,104]. In addition to picture naming, rTMS may also be able to inhibit cortical areas responsible for forming concepts such that areas concerned with spatial detail are made directly accessible to conscious perception. In a small single-blind, randomized, sham-controlled study of the ability to estimate the number of discrete elements visually presented immediately after their presentation, 15 min of 1 Hz rTMS applied to the left anterior temporal lobe was found to significantly improve number estimation accuracy [144]. Seven seconds of rTMS at 5 Hz over the parietal precuneus area, applied immediately before a response was required in a delayed-match-to-sample working memory task, was found to significantly decrease reaction time in a sham-controlled study of healthy young adults [83]. rTMS has also been found to ameliorate age-related impairments in memory. In a randomized, double-blinded, sham-controlled study of 39 non-demented elders with mild memory problems, 5 min of periodic 5 Hz stimulation over the left prefrontal cortex was found to significantly improve learning of novel face–name associations [145]. Furthermore, this behavioral improvement was mirrored by changes in fMRI activation, namely increased activity in the left anterior cingulate, right middle and frontal gyri. Magnetic stimulation hence provides a promising, non-invasive approach to improving memory and cognition in patients with a wide range of disorders, both by activating networks that subserve these memory functions or by de-activating networks that may interfere with performance.

3.3. Transcranial direct current stimulation (tDCS)

Whereas rTMS induces currents in the brain using electromagnetic induction, tDCS involves placing metal electrodes on the scalp to directly apply a small (and harmless) current across the cranium. The effects are highly dependent on the polarity and geometry of the electrodes on the head. The current can hyperpolarize or depolarize neurons in the path of the current depending on the electrode polarity [37]. A small trial of Parkinson's disease patients with cognitive impairment suggests that tDCS applied to dorsolateral prefrontal cortex might increase its excitability in turn improving performance on short-term verbal memory tasks [15].

Transcranial direct current stimulation over the motor cortex, premotor cortex, visual cortex, and left dorsolateral prefrontal cortex may improve working memory, implicit learning and verbal fluency in healthy adults [37,60,106]. In a study of 15 young women where each subject served as her own control, 10 min of anodal tDCS over left dorsolateral prefrontal cortex was found to improve performance in a three-back letter working memory task, as compared to control conditions of sham stimulation or tDCS over primary motor cortex [37]. Transcranial application of poten-

tials oscillating at 0.75 Hz, a similar range as seen in endogenous slow-wave sleep, has been shown to induce the appearance of oscillations at that specific frequency on the EEG. The induction of these oscillations during sleep appeared to significantly improve the retention of hippocampus-dependent declarative memories in healthy humans [93]. Specifically, bilateral tDCS over frontal cortex during slow-wave sleep (five 5-min trains at 0.75 Hz, applied 4 min after entering stage 2 non-REM sleep for the first time) enhanced retention of word pairs learned during the preceding day [93].

Though both TMS and DCS ultimately modulate neural activity by inducing the passage of current, the way they achieve this and the nature of the stimulation effect are distinct. TMS is thought to induce neuronal depolarization and induction of action potentials, while DCS, when applied at low currents (e.g., 1 mA) is thought to only cause a slight change in the resting potential of stimulated cells [37]. By causing this change in resting potential, DCS may improve information processing by bringing neurons closer to depolarization thresholds in response to appropriate inputs or by strengthening effects on glutamatergic synapses. In addition, DCS may induce extracellular potential oscillations comparable to those that would occur naturally, and that reach the extracellular space before transmission by chemical signals would [93]. The two techniques or rTMS and tDCS may have distinct and complementary roles in clinical applications that have yet to be fully characterized. The efficacy of either technique appears highly dependent on such parameters as polarity, cortical region stimulated, frequency, duration, and precise timing relative to an ongoing task and preceding brain activity. While rTMS and tDCS appear to focally activate particular brain areas, biofeedback in which participants view their own brain-activity in real-time, represents another method to 'stimulate' the brain and potentially modify cognition.

3.4. Neurofeedback

Given that gross patterns in scalp recorded potentials correlate to states of arousal, it is intuitive to hypothesize that gaining voluntary control over EEG signals might provide better regulation of arousal. Indeed, the most widely tested application of EEG biofeedback, also known in the literature as neurofeedback, is to treat attention-deficit disorder, which can be considered a disorder of abnormal arousal. The use of neurofeedback as a therapeutic intervention has been tainted by controversial claims and a dearth of clinical trials to assess its efficacy. Fortunately, controlled studies are being conducted and the procedure appears to pose no physical risks to patients.

Neurofeedback comprises self-modulation of the EEG by positively reinforcing the production or suppression of specific EEG frequencies. Neurofeedback originated out of studies conducted in the 1960s in which operant conditioning was used to train cats to increase the power of the 12–15 Hz EEG rhythm over somatosensory cortex (the so called 'sensorimotor' or mu rhythm) while remaining alert and motionless [149]. The conditioning took place within a NASA study to investigate the toxic effects of a rocket fuel component (hydrazine) on cats and it was fortuitously noticed that the cats that had undergone the sensorimotor training had significantly elevated thresholds to developing seizures after being administered the hydrazine. These findings spurred investigations on neurofeedback in humans: in the 1970s it was found that occipital theta (4–7 Hz) amplitude was negatively correlated with vigilance and that by conditioning human participants to increase or decrease occipital theta amplitude, performance on a visuospatial task worsened or improved, respectively [10]. In terms of seizure control, several labs have gathered evidence that reinforcing production of 12–15 Hz, while simultaneously suppressing theta 4–7 Hz, activity appears effective at reducing seizure frequency in humans with epilepsy. Most of these studies were underpowered, however, and this approach is not part of standard clinical care [98,149].

Small, randomized controlled trials of neurofeedback in children with attention-deficit hyperactivity disorder (ADHD) have demonstrated that the technique improves attention and appears to induce changes in fMRI. Unlike those in control groups, children operantly conditioned to enhance 12–15 and 15–18 Hz rhythms, and to concurrently suppress the 4–8 Hz theta rhythm, display activation of areas in the right (anterior cingulate and ventrolateral prefrontal cortices) and left (caudate nucleus, substantia nigra, thalamus) hemispheres. Neurofeedback might modulate the activity of brain regions that mediate selective attention and response inhibition [9,79].

As the neurophysiological underpinnings to the complex waveforms of the EEG are just beginning to be elucidated [148], the mechanism behind how neurofeedback exerts its effect on these systems remains unclear. The sensorimotor rhythm develops when a subject is motionless yet remains attentive. By remaining alert yet stationary, motor output to the thalamus and brainstem might be reduced, in turn leading to decreased red nucleus activity and reduced stretch reflex and muscle tone. The net effect of such decreased tone would be reduction of somatic afferent activity and a state shift of the ventroposterior lateral and reticular nuclei of the thalamus into oscillatory bursting, with the consequent development of the sensorimotor rhythm on the EEG. The sensorimotor rhythm appears similar in location and quality to sleep spindles; in fact, sensorimotor rhythm training appears to enhance spindle activity during quiet sleep [98]. Another class of neurofeedback focuses on modifying slow cortical potentials: these shifts are thought to reflect widespread depolarization of apical dendrites of cortical pyramidal cells. Negative slow cortical potential shifts are thought to reflect cortical arousal, attention and active processing, whereas positive shifts might represent relaxation. In contrast to 12–15 Hz entrainment, self-regulation of slow cortical potentials is correlated with significant changes in metabolic activity in the basal ganglia and thalamus, implying that people can learn to regulate a cortico-striatal-thalamic loop modulating local excitation thresholds of cortical assemblies [55].

As discussed earlier, PAF appears to be related to memory and cognition. A small pilot study of elderly people evaluated the distinct effects of either reinforcing the production of a higher frequency for peak alpha or reinforcing increased amplitude of alpha-range activity regardless of specific frequency. Increasing PAF appeared to improve processing speed (e.g., Stroop Task speed), but not memory, whereas increasing amplitude improved memory but actually worsened processing speed [3]. Though the study had too few participants to assess whether alpha feedback training might be a clinically useful tool for improving cognitive skills, the findings reveal that improving one set of skills might compromise others. Another small study found a correlation between augmenting the sensorimotor rhythm (12–15 Hz) while suppressing neighboring frequencies improved performance on word list recall, a measure of semantic working memory [163].

While the various pilot neurofeedback studies imply that the technique can induce lasting cognitive processing changes in humans, and while certain mechanisms based on thalamocortical circuitry have been proposed, most investigation remains largely exploratory. In order to assess potential clinical benefits, therefore, studies must not only be better powered, with appropriate randomization and controls, but they also must attempt to build upon our growing knowledge of the relationships between oscillations and cognition.

Inasmuch as cognitive abilities depend on a person's ability to induce a particular neurophysiological state, neurofeedback may

improve cognitive function. Research on neuromotor EEG prosthetics has shown that people can learn to modulate oscillatory activity at a wide range of cortical locations and frequencies [14]. Possibilities for future research include the investigation of whether training people to increase oscillatory activity within the neural networks supporting memory function can significantly enhance learning or recall. In particular, recent studies have shown that oscillatory activity in the gamma frequency band, especially in hippocampus and temporal cortex, increases during successful encoding of study items (as measured by whether those items are subsequently recalled) [131]. The same pattern of gamma activity over hippocampus and cortex is recapitulated just prior to successful retrieval of previously learned items [132]. Training people to increase gamma activity (recorded from the scalp or subdurally) in these regions, while decreasing alpha and beta activity over widespread sites [131], could potentially result in improved learning and recall. In addition to operant conditioning to consciously increase the magnitude or precise frequency of gamma activity, participants could be engaged in closed-loop systems in which stimuli to be recalled were repeatedly presented until the system detected gamma activity signatures that predict later successful recall.

In addition to increasing (or decreasing) the power of a given frequency band, neurofeedback could be used to increase the coherence and synchronization of a particular frequency band across electrode sites. Coherence, a frequency domain metric which describes the linear association between two variables, may reflect the number and strength of corticocortical connections between neural ensembles when applied to EEG signals [155]. Synchronization refers to the temporal alignment of signals and has been thought to play a role in binding disparate ensembles together to form conscious percepts. Like oscillatory power, coherence and synchronization have been associated with successful memory processing [38]. It currently is unknown to what degree humans can achieve voluntary control of the coherence and synchronization of oscillating local fields simultaneously recorded from spatially separate electrodes.

Other physiological signals may play a role in neurocognitive rehabilitation. The P300, a marker related to unexpected stimuli [152], has been used in brain–computer interfaces to allow paralyzed people to control software [133]. The P3b component, derived from temporo-parietal activity, appears to be related to memory processing and may serve as a useful neurofeedback target [114]. In addition to the EEG, functional magnetic resonance imaging can also be used as a form of biofeedback. A recent study reported that adult participants, who visually monitored the metabolic activity of their own anterior cingulate cortex, were able to control this brain activation and reduce chronic, medically refractory pain [28]. Recent evidence suggests that humans can achieve voluntary control of the metabolic activity of other specific brain regions, such as insular cortex or the amygdala, via fMRI neurofeedback [22,32]. Adults and children with memory and other cognitive impairment could use variations of this closed-loop real-time fMRI biofeedback to either boost the baseline activity in medial temporal lobe structures known to serve as a substrate of memory, or to improve spatial mnemonic techniques by increasing the activity of areas such superior parietal cortex, right posterior hippocampus [85] while engaging memory tasks. Although considerable work remains before the full potential clinical benefit of non-invasive modulatory techniques is characterized, approaches that attempt to directly interface with substrate of cognition might promise the most comprehensive therapy. The next section reviews preliminary animal and human studies of implantable systems to enhance cognition and outlines new approaches that might re-instate lost function.

4. Invasive techniques

4.1. Frequency-contingent learning

Implanted electrodes can capture high-frequency electrical activity that would otherwise be spatially filtered by the skull, and can provide high signal-to-noise recordings of oscillations at precisely defined anatomical locations within the brain. Work in animal models has established that fairly simple closed-loop systems can augment memory. The theta rhythm (usually defined as 4–8 Hz in humans, and as 3–10 Hz in animals) is known to enhance hippocampal plasticity and accelerate learning in rats, cats, rabbits, and other animal species [67], and thus manipulations based on theta activity could be used to counteract impairments in learning due to abnormal development, aging or pathology of the hippocampus and other memory structures. Rabbits that receive training trials in the presence of theta were found to learn twice as fast as those receiving trials in the absence of theta [130]. By comparing the performance of two groups of animals to yoked controls trained with matched intertrial intervals, it was found that instead of theta benefiting learning, rather nontheta was especially detrimental in tasks that do not require the hippocampus such as delay conditioning. Pre-task theta activity was strongly associated with the subsequent learning rate in operant conditioning [130]. Whereas cerebellar and oculomotor pathways are clearly essential substrates of eyeblink conditioning, hippocampal influences appear to be parallel and modulatory in nature. Theta-triggering accelerated both the learning rate and the firing rate of individual hippocampal neurons as rabbits engaged in a difficult, hippocampus-dependent task [49].

The presence of high levels of theta may be optimal for learning because this oscillatory activity facilitates hippocampal plasticity at a cellular level. The approximately 200 ms period of the theta rhythm matches the optimal window for coincident pre- and post-synaptic activity for long-term potentiation induction at CA3 synapses in the hippocampus [139]. The processes that increase theta power may be due to increased attention or awareness of environmental stimuli; awareness itself of stimulus contingencies has been shown to enhance the learning rate in human eyeblink conditioning [90]. The growing body of evidence that theta activity is present in human participants during performance of both spatial and verbal memory tasks [68] raises the possibility that learning could be optimized by presenting information to be learned contingent on a person's ongoing brain activity. In order to be practically useful for people with cognitive impairment, scalp electrodes would have to be used during training sessions to monitor theta, or intracranial electrodes implanted for chronic recording. The ability of oscillatory-contingency to affect learning could itself be used as a diagnostic test to assess the nature of memory impairment in children with different cognitive disorders.

Contingency could be based on coherence across sites, such as theta synchronization between hippocampus and entorhinal or frontal cortex. In addition to enabling frequency-contingent learning, invasive recordings with subdural grids and multi-electrode arrays could pave the way for neurofeedback based on high-gamma frequencies not recordable by scalp electrodes, and on the more precise anatomical localization [77]. Intracranial neurofeedback could be used to operantly condition increased phase synchronization between perirhinal cortex and the hippocampus, or to train patients to selectively increase oscillatory power within, or coherence between, any number of medial temporal lobe and frontal cortex structures. As more is learned about the specific oscillatory features associated with human cognition, these features in turn could be used for a principled exploration of intracranial contingency-based training.

4.2. Cell-triggered recall

Individual neurons recorded in the human medial temporal lobe fire selectively to images of faces, animals, objects or scenes [118]. A subset of these neurons have an invariant representation of individuals, namely they fire when patients are presented with strikingly distinct pictures of a given individual, landmark or object (or even the name written as text on the screen) [118]. The idea that individual neurons could carry an invariant representation has exciting implications for a neurocognitive prosthetics. For people with memory impairments, this raises the possibility that within their temporal lobes there may exist neurons whose individual ability to classify external stimuli may outperform that of the individual. A chronically implanted microelectrode array could pick up the activity of such a neuron, and based on a previous calibration session, use a look-up table to identify what the person perceived. This in turn could drive an explicit cue (such as the name of the identified person or object whispered into the child's ear via a speaker in the auditory canal or text appearing on an external computer screen) or a perception induced by stimulation of auditory or visual cortex.

One might reasonably counter that a camera and microphone, coupled to already-available pattern recognition algorithms and relational databases, could help patients remember certain items or perform certain tasks. Indeed, a prototype system uses inconspicuous motion sensors and an automated phone system to monitor an elder's activity pattern at home, and appropriately call them with reminders to take medications or perform other tasks [51]. However, no external sensor system will ever be able to detect memory associations in the absence of external stimuli: a patient wandering through a particular landscape or talking to a person may struggle to remember an important association. Talking to a brother might remind a person to call a son, or walking by a supermarket might trigger thoughts of a certain meal they want to cook. While databases could conceivably be programmed to capture some of these spontaneous associational triggers, it is difficult to fathom how it might fully emulate the combinatoric complexity of actual networks in the brain. Pattern detection based on temporal lobe firing could decode items that are imagined and have no simultaneous referent in the external word, and identify items that are embedded in networks of associations.

Research in neuromotor prosthetics has revealed that humans can bring the activity of both individual neurons and ensembles of neurons under direct voluntary control [33,56]. Just as the behavioral correlate of motor cortical neuron discharge is real or imagined movement, patients with cognitive impairment could learn to voluntarily control neurons in temporal cortex as part of memory rehabilitation training. Implanted devices might also extract multimodality information about the identified invariant object with other cues not so easily measured by external microphones and cameras, such as emotional salience and the degree of covariance in firing rate with other neurons recorded elsewhere in the brain.

4.3. Cortical microstimulation

The neurosurgeon Wilder Penfield and his colleagues recognized that the experiential phenomena induced by microstimulation of the temporal cortex were similar to the symptoms experienced by patients during spontaneous seizures [110]. Microstimulation could thus be used to localize the seizure focus in order to guide therapeutic resection for refractory epilepsy. Penfield found that while gross microstimulation usually induced a vague, generalized memory, in certain cases it could cause a vivid re-living of a recollection by 'replaying' a memory in a way analogous to that of a tape player. In one case, so long as the stimulation continued, a patient heard an orchestra playing a song proceeding at the same tempo as it was originally experienced. The moment the electrode was withdrawn, however, the song stopped, and when stimulated again, the song would restart at the beginning [111]. A more recent investigation found that a patient experienced, depending on which subdural electrode was stimulated, a female voice singing, particular childhood songs, and the voice of a sports announcer whom he had listened to [99]. That microstimulation can reliably induce realistic perceptions to guide behavior has been shown in numerous animal studies [107,125,153]. When the brain 'induces' a memory, it is not the same as hearing a semantic fact recited "an apple is a fruit," but a complex, brain-wide re-living of the item in which the sweetness of the apple and other associated memories lights up a particular activation pattern of a collection of neurons and all of their related connected ensembles [115]. By activating these other ensembles, such a microstimulation-induced process would induce not just a recollection but also a panoply of associations that could not be activated any other way. The notion that an experience can be replayed may not be merely a metaphor: the temporally structured ensemble spiking patterns that occur in the hippocampus and cortex of rats during awake exploration were recently found to be repeated during REM and slow-wave sleep [65]. Not only might a transiently synchronized activation pattern carry perceptual, mnemonic, and affective information, it might also, by virtue of emerging from the activity of an entire ensemble, resist noise and tolerate the loss of individual neurons [65]. All medical devices must be able to restore lost function without compromising the patient's remaining function: microstimulation meets this criterion inasmuch as it can induce these phenomena without compromising a person's consciousness and ongoing experience of the world [64,110,177]. Given that the target beneficiaries of neuroprosthetic devices may have severe cortical and subcortical abnormalities, it is reassuring that microstimulation can induce distinct experiential memories even in patients who have already undergone resection of the anterior temporal lobe in previous attempts to treat seizures [99].

Neuromotor prosthetics research has demonstrated that complex information can be reliably be decoded from neural ensembles on subsequent days even if particular neurons may have been removed or added to the ensemble [135]. Furthermore, the information encoded in the ensemble activity of multiple, simultaneously recorded individual neurons, can be decoded in real-time and be used in behaviorally useful manner [137]. A central goal of neurocognitive prosthetic development will be the determination of how to apply the real-time decoding techniques developed in neuromotor prosthetics to the growing body of data on how ensembles of neurons throughout cortex and subcortical structures represent cognitive features, such as spatial position in the environment [41,82,136].

In addition to anatomically organized spatial and temporal topographies, the ongoing oscillatory state of underlying brain regions could be exploited. In one case study, the induction of memory experiences was found to occur only when the particular brain structure being stimulated was synchronized in the theta range [8], perhaps as part of a synchronized hippocampal-limbic-visual-cortex network. The effect of microstimulation on the brain is thus defined by ongoing behavioral context [52], the underlying oscillatory state of the target brain region and the recent history of previous microstimulation episodes [20].

Whereas the cortical microstimulation described in the neurosurgical mapping cases occurred in the context of mapping prior to resection, the approach could be systematized to create a kind of percept-stimulation database. A memory neuroprosthetic based on stimulation of the cortex could induce memories and perceptions when cued by an external computer in an attempt to help a person

remember a fact or an association. A lookup table could be built associating stimulus parameters with induced memories. If memories comprise combinations of simpler 'eigenmemory' components, then perhaps one could retrieve nearly any memory using a combinatorial microstimulation approach. For example, a patient could perceive or imagine a certain person and associations with that person. Upon next meeting this person in real-life, the memory-impaired patient could use the look-up table to engage the electrical stimulation to induce the brain-state associated with that person. In a sense, a patient could be trained to perform a kind of procedural task of linking items to contexts such that he effectively becomes his own hippocampus [31].

4.4. Non-electrical neural stimulation

Although electrical microstimulation may occasionally induce specific percepts, the inadvertent activation of nearby neurons and passing white fibers might render precise activation of cortical ensembles representing a particular memory impossible [65]. Recent advances in transgenic engineering have made it possible to achieve just such a type of selective stimulation of individual neurons with light. Photoresponsive proteins isolated from algae (channelrhodopsin) have successfully been transfected via viruses into neurons, in both *in vitro* and in vivo experiments, making individual neurons fire action potentials when exposed to focused light [17]. In one recent proof-of-concept study, optical stimulation of layer 2/3 neurons transgenically encoded with light-gated channelrhodopsin in the mouse primary sensory cortex was shown to modify behavior [59]. Hence arrays of optical fibers chronically implanted into genetically modified cortical areas in a patient, could in theory be used to activate specific ensembles or individual neurons.

Direct infusion of chemicals might serve as another method to stimulate neurons to induce specific local changes or diffuse modulatory effects. The ability to deliver neurotransmitters, medications and other compounds to precise anatomical locations at precise times may be possible with new devices such as chronically implantable hydrogel or microfluidic probes [105,122]. Arrays that release chemicals could be used to stimulate, inhibit or modulate cortical activity or effect more nonspecific antinflammatory interventions.

4.5. Subcortical and peripheral stimulation

Stimulation of several subcortical structures, such as the thalamus and the septal nuclei, has been shown to improve memory and other aspects of cognition. These nuclei play a role in modulating and facilitating memory, both as part of diffuse neuromodulatory systems ascending from the brainstem and as sites of memory storage or addressing. In one case study, activation of a deep brain stimulator implanted in the thalamus (area Vim) in a man with Parkinson's disease was found to improve performance on a semantic memory task, yet impaired verbal fluency and recall from a word list [158]. Deep brain stimulation (DBS) has recently been used to ameliorate symptoms in patients with severe psychiatric disorders; a recent study suggests that DBS improves memory in patients with severe psychiatric illness in a manner that does not depend on the particular illness. In a recent study of 18 patients (8 with treatment-resistant depression and 10 with obsessive compulsive disorder), activation of bilateral DBS electrodes in the anterior limb of the internal capsule was associated with significantly improved immediate and delayed recall of prose passages [76].

The thalamus may also be a target of stimulation. Left thalamus stimulation appears to improve verbal memory when audition is delivered to the contralateral ear [168]. Continuous high-frequency (100 Hz) electrical stimulation of the central thalamus generates widespread cortical activation and facilitates global arousal, goal-directed seeking behavior, and object recognition memory in rodents [141]. DBS targeting the central thalamus could restore sustained attention, working memory and awareness in patients with traumatic brain injury [126] and appears to have achieved some of these goals in at least one patient [127].

The septal nucleus is part of an ascending pacemaker system that induces hippocampal theta activity in rodents. Direct electrical stimulation of the septal nucleus in rodents has been shown to induce the release of acetylcholine in the hippocampus and improve memory in rodents in a frequency-dependent manner [66,86]. Stimulation of the septal nuclei in aged rats at 5 or 50 Hz were found to be effective whereas 0.5 Hz or less had no effect. Likewise stimulation at 7.7 Hz improved active avoidance memory and brightness discrimination in young rats, whereas stimulation at 77 or 100 Hz had no effect [66]. Pathological changes in Alzheimer's disease affect both the hippocampus and the deep septal nuclei. Direct electrical stimulation of the deep septal nuclei may be an opportunity to improve memory in patients with Alzheimer's disease and other memory disorders. Such stimulation might recruit remaining septo-hippocampal fibers and promote theta activity and hence improved memory encoding throughout the hippocampus. Humans have been implanted with electrodes in their septal nuclei for durations greater than 10 years to treat neurogenic pain [129], thus establishing a preliminary safety record.

Aside from the thalamus and the septal nuclei, other subcortical targets for the restoration of memory and cognition might include other neuromodulatory nuclei. Other cholinergic nuclei such as the diagonal band of Broca or the nucleus basalis of Meynert could be stimulated; electrodes implanted in the noradrenergic locus coeruleus or GABAergic basal forebrain could improve mental alertness and attentional focus; serotonergic raphe nucleus stimulation might improve regulation of the time scale of reward prediction [86,89]. Other sites include the substantia nigra, caudate nucleus, nucleus accumbens, and the ventral tegmental area. A case study of bilateral stimulation of the ventromedial nuclei of the hypothalamus in a human induce sensations of déjà vu, vague flashes of memory, and appeared to show improved hippocampal-dependent memory [53]. High-frequency (200 Hz) electrical stimulation of the caudate, striatum or anterior cingulate during reinforcement might accelerate learning acquisition [171]. The hippocampus itself can be a target of open-loop stimulation: in-vivo stimulation given at 5 Hz (i.e., in the theta range) has been found to induce stable LTP in rats [147].

In evaluating the effects vagal nerve stimulators have on patients who receive it to reduce seizure frequency, numerous investigators have coincidentally noticed a benefit on cognition [175]. In a study of ten epileptic participants implanted with vagus nerve stimulators, 2 min of stimulation at 0.50 mA 30 s after reading text was found to enhance subsequent word recognition [26]. Animal studies have shown that vagus nerve stimulation may enhance the rate of recovery from brain injury, as measured by time to remember a hidden platform in the Morris water maze [143]. Several small studies have explicitly investigated the potential benefit of VNS on cognition in patients with Alzheimer's disease and preliminary evidence implies a mild improvement might be achieved [44,97,142]. Although the studies are reassuring in the sense that the device did not appear to pose any safety risk to the patients, the small number of subjects makes it difficult to assess reliability and how any benefits might extrapolate to daily life. Just as the precise mechanism by which VNS reduces seizure frequency is not understood, the method by which it might enhance cognition likewise remains a matter of speculation. VNS may induce widespread release of norepinephrine by directly (via the vagus nerve up to the brain-

stem) or indirectly (via peripheral arousal changes) stimulating the locus coeruleus, in turn increasing activity in the hippocampus and amygdala in a manner that enhances retention [44,143,179].

4.6. Connectivity as cognition

The number and strength of local intra-cortical and long-distance white matter interconnections between neurons is directly correlated with cognitive function [86,147], hence devices that restore or augment such connections may restore cognition. Neural prosthetics could conceivably address two aspects of such damage induced by ischemia or injury: first, they could recapitulate the functionality due to loss of gray matter modules in cortex or subcortical areas, and second, they could restore connectivity between areas lost by interruption of white matter tracts. Fig. 1 shows graphically the principle of how a pair of stimulating and recording electrode arrays could bridge cortical areas whose connectivity was lost due to stroke or injury. The activity of a neuron in one area could induce the stimulation of one or more neurons in another area. Even if the exact nature of recording and stimulation were modified (for example, optical stimulation of neurons instead of electrical) the principle of reconnection would be the same. The prefrontal cortex, non-relay nuclei of the thalamus, basal ganglia and the hippocampal formation are all thought to play crucial roles in binding together of distributed cortical representations. Hence, pairs of stimulating-recording arrays can be used to not only re-instate lost connectivity, but to reinforce existing connectivity or induce completely new connectivity. In this manner a direct brain–computer interface could take on some of the organizing memory functions that might be compromised due to damage to the medial temporal lobe or other structures.

Pairs of electrodes chronically implanted in the cortex of a non-human primate can artificially link two cortical areas that were not initially tied together such that the linkage induces an observable behavioral effect [62]. Such linking can be achieved by spike-triggered stimulation, namely the activation of a stimulating electrode contingent upon a sufficiently high firing rate of neuron recorded by a second, nearby electrode. Although these preliminary studies [63,95] used only two electrodes, the number of channels could in principle be increased. One might imagine the neurologist of the future, given a patient implanted with hundreds of recording and stimulating electrodes throughout the brain, could have at her disposal a workstation in which she could view the neural activity (individual units or focal high-gamma oscillations) and set stimulation parameters for selected electrodes or optical fibers. This future clinician could thus artificially reconnect any number

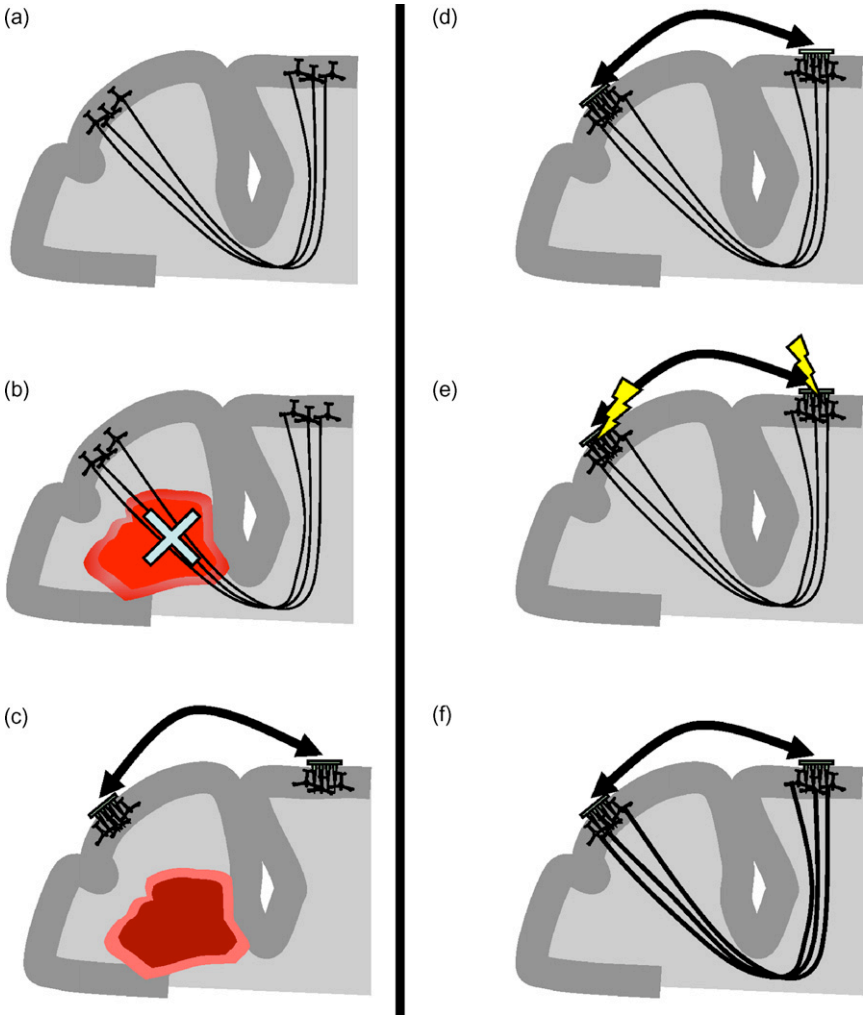

Fig. 1. Restoration or augmentation of a connection between two brain areas by means of paired electrode arrays. (a) Two brain areas are reciprocally linked by uncinate fibers in the white matter. (b) A subcortical stroke destroys the white matter tract that linked the areas. (c) Multi-electrode arrays implanted in each area are connected to a medical device or computer system that functionally restores the interconnection by means of recording and stimulation. (d) Two cortical areas are already physically linked by uncinate fibers. (e) Correlated spike-triggered stimulation or firing induces plasticity in connecting synapses. (f) The two areas are now more strongly coupled.

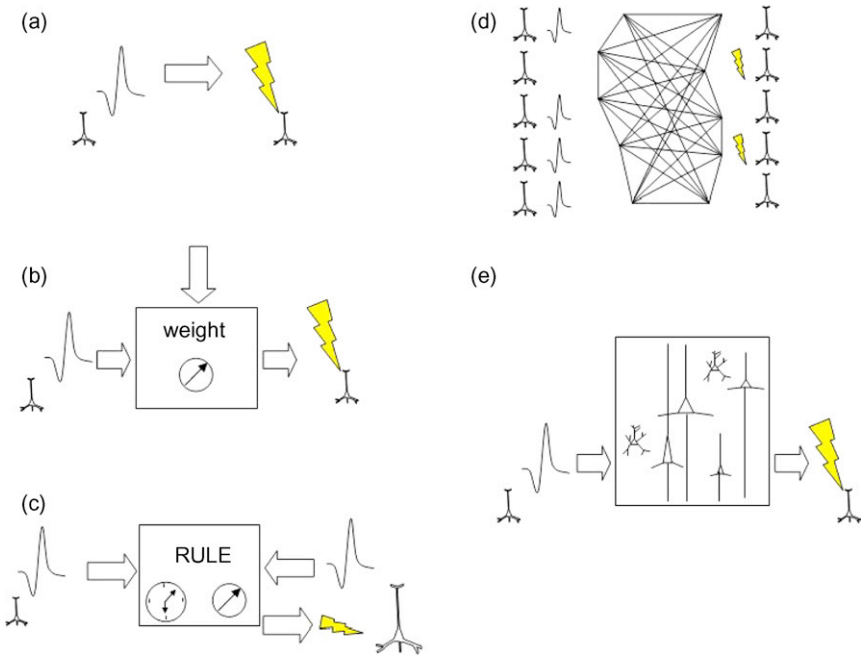

Fig. 2. Connection rules. (a) Spike-triggered stimulation. (b) Spike-triggered stimulation gained by a weighting rule. (c) Artificial Hebbian or BCM learning rule, comparing the relative spike timing of two units to decide if and at what frequency to stimulate one of the units. (d) Multiple neurons coupled to each other via artificial synapses in a neural network. (e) Connections routed through a neural circuit model or ectopic neural tissue.

of neurons to each other in a customized manner fit to promote neurorehabilitation. One could envision several connection rules beyond spike-triggered stimulation, such as weighting the assignment or by interpolating a time sensitive Hebbian plasticity rule (Fig. 2b). This plasticity could be scaled up with multiple input and output neurons coupled to artificial, modifiable synapses (Fig. 2c).

Given the sheer magnitude of connectivity disruption found in conditions such as Alzheimer's disease or cerebral palsy, it might not be anatomically feasible to implant a sufficient number of electrode or optical array pairs even if it were technologically possible. Hence purely biological approaches, in which engineered bioartificial nerves, crafted into a kind of ectopic white matter, might be necessary to link diverse cortical and subcortical areas [69,112]. Microsurgical techniques are already practiced to promote nerve regeneration along sheaths in the periphery [151], the outstanding question would be whether these could be adapted to create white matter bundles placed atop the cortical mantle or running within the ventricular system to link multiple brain regions.

4.7. Expanding the neural substrate

Whether the purpose of paired arrays is to re-instate lost connectivity or induce new connectivity, the procedure generally follows the principle of recording in one area being used as a trigger to stimulate another area. The paradigm entails a fascinating opportunity: instead of reconnecting a cortical area to another cortical area within the patient's brain directly, what about routing the signals through an artificial model of cortex? If this were possible then in addition to reconstituting pathways, one could provide patients with additional neural substrate. Just as areas of the brain may be damaged and become unusable due to stroke, injury or degenerative conditions, so too there might be the possibility to add new virtual or ectopic cortex to compensate for lost tissue. Recordings of units throughout the brain could be fed into a software model, or into actual ectopic neural tissue, and then activity from this model or neural tissue would be used to drive stimulation back into the patient's brain (Fig. 2e).

Initially, such additional cortex may exist as computational models in software programs in an external computer interlinked to the patient through wireless connections. Eventually however, software could be rendered as neuromorphic very-large-scale-integrated (VLSI) microchips. Bidirectional recording-stimulating devices in the brain could be coupled – through wireless telemetry, high-bandwidth fiber optics [138], or bioengineered vitronerves [69,112] – to chips or ectopic neural tissues implanted in the chest or peritoneum to restore lost function.

The fundamental hypothesis of such a project is that if the brain were given access to new cortical and subcortical "real estate" in time it would take over this real estate and use it in a behaviorally useful and measurable manner. This hypothesis is based on phenomena well documented in the basic neuroscience literature. Animals in which retinal projections are redirected neonatally to auditory thalamus develop visually responsive cells in auditory thalamus and cortex, even developing retinotopic maps in auditory cortex [164]. In addition to animal models, early work in direct brain–computer interfaces in paralyzed humans suggests that human neocortex can take over representation of novel outputs such as computer cursors, in effect adding 'cursor cortex' to the traditional motor homunculus [72].

If the perceptual modality of a given neocortical region is guided to a significant extent by extrinsic inputs, could artificial cortex be made to follow the same rules? Could real cortex be rewired by extrinsic inputs which derived from artificial neural circuitry? The columnar organization of neocortex, the ubiquitous features of the synaptic connectivity of circuits within these columns, and basic thalamocortical architecture, are features that have been widely studied *in vitro* and modeled using computer simulation [29,58,91,101]. One can imagine a child with a degenerative condition implanted with multiple microelectrode arrays throughout the cortical mantle. These arrays could be reciprocally coupled to an artificial counterpart cortex such that even as the child's real cortex degenerated, the artificial cortex, which over time had become tightly interlinked and entrained to the child's normal neural pro-

cessing, would provide additional processing as a compensatory mechanism [134].

Subcortical structures such as the basal ganglia and hippocampus have been rendered in computational models or have been fabricated as VLSI microchips [4,12,117]. Approaches have also been developed to characterize closed-loop neural-computer systems such that the behavior of living neural tissue can be reduced to sets of equations; the equations in turn can be rendered in VLSI hardware [121]. Given a patient implanted with pairs of electrode arrays, one could track the interactions between neurons in the system and build a dynamical model such that if a target area in between the areas were removed, a VLSI module would take its place. Multiple areas could be duplicated such that a person with neurological abnormalities could have several auxiliary artificial neural modules, each in turn coupled to each other to form what one might consider a second brain.

By directly coupling the surviving brain tissue to computer models of lost or damaged nuclei, certain behaviors might be restored. In a patient with working memory and executive planning difficulties due to frontal cortex damage from traumatic brain injury or tumor resection, arrays in parietal cortex, the amygdala and remaining basal ganglia could be coupled to a firmware implementation of a prefrontal cortex-basal ganglia working memory model [54]. If the model can learn on its own to control itself in a strategic, task-appropriate manner, it might be possible to re-instate some of these behaviors to the impaired patient. Likewise hardware implementations of minimal spiking networks that self-organize into a number of groups that exceeds the number of neurons in the system might serve as an ideal extracerebral buffer for patients with memory impairment [12,40,61,74,81].

In patients with disease processes that have a somewhat predictable time course, such as degenerative conditions like ALS or MS, arrays could be implanted before cortex was compromised giving clinicians the opportunity to map out a patient's connectivity before it is lost. Anatomical MRI, including diffusion-tensor imaging of white fiber tracts, could be co-registered to maps based on known human white fiber anatomical connections. This could be coupled to functional connectivity maps derived by coherence analyses of cortico-corticopotentials recorded by subdural grids and by fMRI time series data run through wavelet algorithms [1,94,109].

Given the remarkable degree of plasticity intrinsic to mammalian brains, it may be possible to create entirely new somatosensory modalities and motor output effectors to restore and augment cognition. Comparative neuroanatomy reveals how different species develop multiple somatotopic maps in cortex, while studies show not only how premature auditory cortex in a rat can take on visual functions [164], but how additional barrel fields can be added to the somatosensory cortex of animals bred to have supernumerary whiskers [24,167]. These empirical studies reveal principles by which artificial extensions might be constructed and interfaced to a patient's brain. In addition to restoring lost function, such extensions might provide humans with sensory organs that already exist in other animals (e.g., electroreception of the *Ornithorhynchidae*) in order to grant patients novel compensatory techniques.

Audition, somatic sensation and vision all involve transduction organs (organ of Corti, skin receptors, retina), relay nuclei in the thalamus (MGN, VM, LGN), and primary cortices (A1, S1, V1). Could one map abstract data on to its own relay nucleus and primary cortex to create artificial thalamocortical modules that facilitate database creation or internet searches in patients with memory or executive impairment? Just as vibrissae movements are tightly coupled to gestalt sensory processing in rodents, novel somatomotor systems could enable a patient to perceive, navigate through and 'whisk' abstract data. Whether implemented in software or actual neural

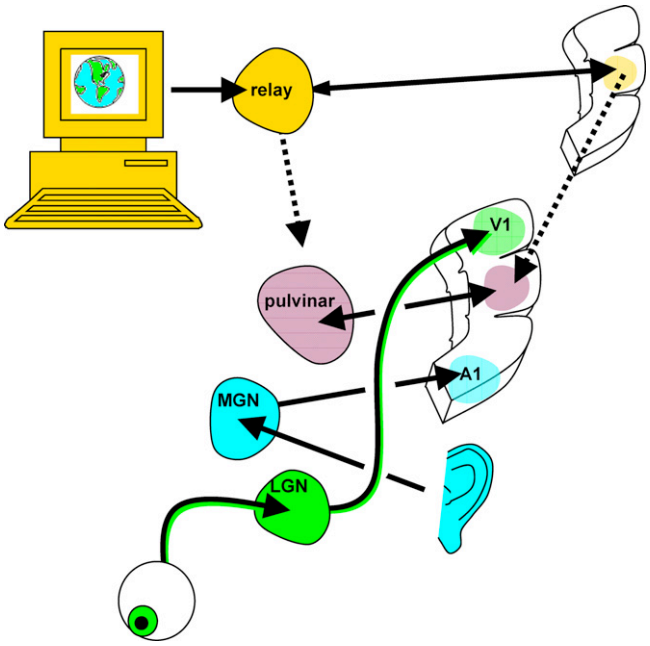

Fig. 3. A hypothetical computer thalamocortical 'organ' to represent and process web browser, relational database or other computer-based data. The artificial relay and primary cortices send their outputs to the real pulvinar nucleus and association cortex of the patient.

tissue, novel organs could be connected to frontal or parietal integrative areas of a patient's brain. Multimodal neurons in the parietal cortex and the thalamic pulvinar nuclei are known to coordinate cortical ensembles across multiple areas [140]. Hence the layer V output of an artificial primary cortex could be used to stimulate electrodes chronically implanted in layer IV of patient's association cortex, and layer VI of the artificial primary cortex to stimulate cells in the patient's pulvinar nucleus of the thalamus (Fig. 3). Bidirectional interfaces could facilitate the integration of an artificial thalamocortical module into global brain processing states such as wakefulness, REM and slow-wave sleep (i.e., the artificial module would 'dream' along with the patient's brain).

4.8. Ectopic neural modules

In addition to artificial neural circuits rendered in silicon, it may also be possible to grow living ectopic cortex, basal ganglia nuclei, hippocampus and other structures. Neural models rendered in VLSI or nanotechnologies are limited because these media often suffer considerable cross-talk and cannot meet the wiring requirements intrinsic to real neural tissue [21]. Ectopic neural modules could exist as extracorporeal, *in vitro* systems bidirectionally linked, by means of telemetry or percutaneous connectors, to arrays implanted in a patient's brain. Alternately these modules could be encapsulated versions of the *in vitro* systems or bioengineered into self-contained organ-like structures such that they could be implanted within a patient's body and connected to arrays in the brain by means of electrical leads, optical fibers, or vitronerves [112,138].

Neuron-chip interfaces could be built to perform processing as an *in vitro* computational module. *In vitro* neuron-silicon circuit hybrid devices have been studied extensively [176,121]. Complex networks of neurons can be cultured *in vitro* and kept alive and physiologically active for years at a time. Multiple distinct spatiotemporal oscillatory patterns emerge spontaneously in these chronic neural cultures [160,161,166]. Populations of neurons

attached to a multi-electrode array can be connected to tissue-engineered axons that are free to integrate with a host nerve stump upon transplantation [69,112]. Human stem cells can be coaxed to grow into neurons growing on a multi-electrode array. Such living neural networks are capable of reproducing distinct activity patterns in response to digital patterns presented by means of stimulation through a subset of the electrodes [113]. Given that well organized spatiotemporally coherent responses to specific sensorimotor activities are a marker of normal cognition [87], *in vitro* systems could function as a novel substrate for sensorimotor and hence cognitive processing in patients with neurological impairment.

Using neural cultures or organotypic slices grown *in vitro* atop multi-electrode arrays pose numerous challenges, not the least of which is the internal wiring that emerges spontaneously in tissue culture. Compared to circuits within the brain, cultures (dissociated, roller tube, or organotypic) develop numerous abnormal connections, including autapses, and consequently give rise to abnormal bursting behavior [21]. One way to dampen or extinguish such abnormal bursting is to adjust the coupling strengths between a culture and hardware. This technique of purposely inducing the "amplitude death" regime of coupled oscillators has been implemented in tissue–computer systems [108]. One might also prevent interictal-spike-like phenomenon by washing cultures with neurotransmitters that would have come from subcortical efferents to block potassium conductances; however, a more elegant and better studied approach is to use co-cultures. Such co-cultures incorporate tissue or slice-circuits from multiple cortical regions or subcortical nuclei. Septo-hippocampal co-cultures spontaneously display oscillatory synaptic activity at theta frequencies; the muscarinic receptors in the hippocampal portion of such co-cultures are activated by acetylcholine released by septal afferents [35]. Beyond functional connections made within an explant, one can create connections between explants in so called 'mega' co-cultures. These mega-cultures, comprising organotypic slices from multiple brain areas, have been found to give rise to slow-wave sleep-like oscillatory activity akin to that observed in the actual brain [6].

Advances in bioengineering imply that these *in vitro* systems could be encapsulated as an implanted medical device, or be made completely of biological components. Cells can be isolated from tissue biopsies from patients and used to engineer functional organs or novel chip-tissue hybrids. Autologous bladders tissue-engineered from patients' own cells were recently implanted back into those patients to restore bladder function [5]. Human bioartificial muscles (HBAMs) are tissue-engineered constructs that are made by suspending human muscle cells in a collagen gel, casting them in a silicone mold containing end attachment sites, and allowing the cells to differentiate for 8–16 days [116]. Derived from cells of a patient, the autologous construct can then be implanted into the patient without provoking an immune response.

Such tissue-engineering approaches have been extended beyond bladder and skeletal muscle to include neural tissue. By using gravity-enforced self-assembly of embryonic fibroblast and dorsal root ganglion mouse cells in hanging drops, scientists have been able to create three-dimensional cell cultures which form ganglia-like microtissues that include sensory neurons and myelinating Schwann cells [71]. Neural stem cells acquired from biopsy of the olfactory epithelium or the ependymal lining may be cultured and grown on a patterned culture media to recreate functional neural circuits. Recent work has shown it is possible to biopsy the human olfactory epithelium and culture neural progenitors *in vitro* [50]. Neural progenitors derived from human olfactory epithelium may also be coaxed to form neurospheres which in turn can lead to autologous transplantation where minimal donor material can be isolated and expanded *ex vivo* [92]. The potential to create self-assembled scaffold-free multicellular neural tissue, combined with the fact that pluripotent neural progenitor cells can be isolated from human olfactory epithelium, implies that thalamocortical, hippocampal and other ectopic neural modules could be created from a child or adult's own cells and implanted and interface with his or her brain to restore or augment function that was compromised due to disease or injury. These ectopic neural modules could incorporate vascular elements to ensure that this new organ or tissue could be vascularized once implanted into the abdomen or other parts of the body. If the patient's brain could take over this new cortical real estate, then these new extracranial neural tissue structures could potentially improve movement, communication, affect regulation, memory and cognition (Fig. 4). Ectopic, engineered neural tissue implanted in the abdominal fat pad or elsewhere in the body could escape degenerative conditions that are related to being in proximity of the neurotoxic milieu within the brain; certain theories on the pathophysiology of Alzheimer's disease imply a gradient-based effect such that a second, ectopic hippocampus implanted in the abdomen and interfaced to the brain via fiber optic high-bandwidth links, would be spared such neurotoxicity and not undergo the severe plaque buildup and degenerative sequelae of Alzheimer's [57].

For patients who must undergo unilateral hippocampectomy in order to remove a seizure focus or tumor, one could attempt to reconstitute function in the following manner: recordings from the ipsilateral entorhinal cortex would be used to specifically stimulate granule cells in the dentate gyrus of an organotypic hippocampal slice grown on a multi-electrode or multi-optic array. Recordings in turn from CA1 pyramidal neurons or subiculum in the slice would be used to drive stimulation back into the intact entorhinal cortex of the patient [21]. If the contralateral hippocampus were spared, then recordings from the CA3 neurons in the culture could be used to stimulate electrodes placed in the CA3 region of the contralateral hippocampus (to create an artificial associational commissural pathway). Given that a single slice culture would be unlikely to be able to serve as an equivalent for an entire *in situ* hippocampus, banks of parallel slice cultures or three-dimensional cultures could be used. Indeed, hippocampus-like organoids could be bioengineered using collagen matrices and appropriate primordial cells to give rise to non-neural components such as glia and microvasculature. Likewise, rather than completely removing an epileptogenic temporal lobe from a patient, it could be completely severed *in situ* (hence preventing seizure spread via gray or white matter, but retaining vascular supply), but be buffered on either side with multiple arrays that could re-instate connectivity and yet monitor, and hence prevent, the spread of ictal activity.

Just as human muscle cells have been expanded *in vitro* and then transfected to overexpress therapeutically beneficial proteins, so too a patient's neural progenitor cells could be similarly isolated, expanded *ex vivo*, transgenically modified, integrated into a circuit, and implanted [17]. By being autologous, such neural modules are less likely to induce an immune inflammatory reaction. By conducting the transfection *ex vivo*, the systemic transfection risks associated with the use of viruses could be altogether circumvented.

4.9. Internal neural assistant

The culmination of the assistive software and implantable techniques described thus far would be a streamlined, continuously available internal assistant that could function as a central gateway to frequently used software such as calendars and email, and to a self-monitoring system that helped a person avoid simplified and stereotyped behaviors as part of ongoing rehabilitation. To better mimic silent thought, instead of typing or speaking queries aloud,

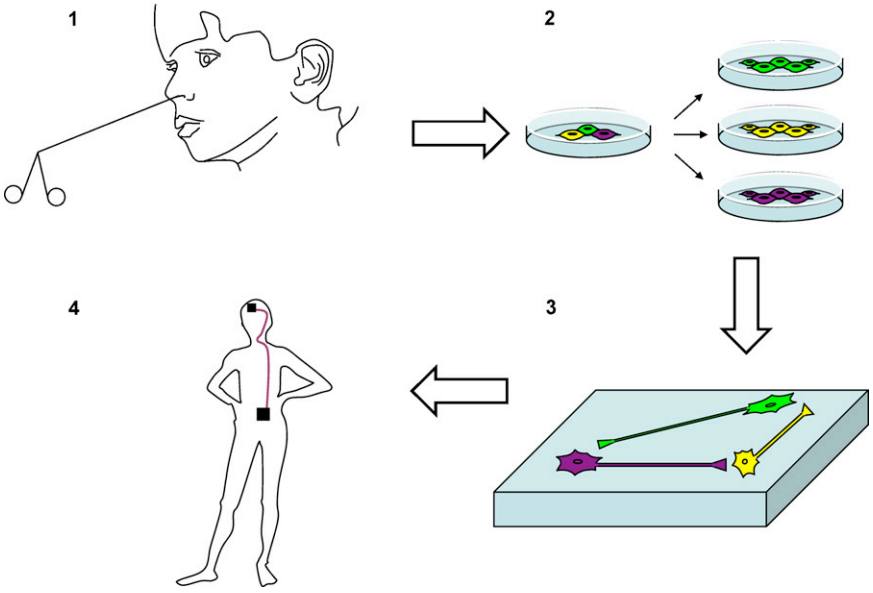

Fig. 4. Autologous ectopic neural tissue to restore cognitive function lost to brain injury, congenital anomalies, or degenerative conditions. (1) The olfactory epithelium is biopsied. (2) Neural progenitor cells are isolated and cell lines are created by addition of growth factors. In addition, cells may be genetically modify to express novel proteins, such as photo-sensitive channelrhodopsin. (3) Cell types are cultured upon a bidirectional silicon chip. Neurons may be placed directly on the gate oxide of transistors or on conductive disk electrodes. The cell assembly may be structured in three dimensions and seeded with vascular progenitors to ensure vascularization. (4) The ectopic neural tissue assembly is implanted chronically into the patient. The ectopic tissue is bidirectionally linked to one or more sensor-stimulator devices implanted in the brain by means of ultra-high-bandwidth fiber optic conduits.

a user could use imagined gestures or vocalizations via a neuromotor prosthetic interface [136]. Replies could be delivered through an external speaker, or via stimulation of cortex to increase synaptic strength to distributed neural ensembles representing memories associated with those sensory precepts. Animal data suggests that cues delivered via direct microstimulation might be more salient than external auditory stimuli [107]; inasmuch as the ability to avoid distractors is a key element of working memory, such 'pure' stimuli might be better encoded and recalled in patients with cognitive impairment.

By modulating anterior cingulate cortex activity associated with the conscious perception of effort, an internal neural assistant could relax the patient when the artificial system was sustaining a memory [102]. Assured that a given item was properly stored, a patient might be spared conscious effort to better use their remaining cognitive resources to deal with other tasks at hand. Given the presence of an individual's oscillatory pattern signifying that an item has been successfully encoded, a device might modulate circuits related to motivation to signal the person that they need not keep devoting effort and time to encoding that item and could move on to others.

Just as primary motor and sensory cortices contain topographical maps of the body, ectopic neural modules could be created to contain maps of the cortical mantle itself (Fig. 5). A meta-map might facilitate neurofeedback by providing a patient with a novel manner to perceive the power spectral and coherence properties of their own brain activity. Such metacortex might provide another layer of redundant connectivity between areas that could compensate for loss of medial temporal lobe hubs or white fiber degeneration.

5. Unique features of neurocognitive prosthetics

The selection, implantation and rehabilitation strategy to be used with neurocognitive prosthetics will need to be customized to each patient to a degree not encountered in other medical devices. This stems partially from the complexity of the neural substrate of cognition, and partially from the heterogeneous effects of particular lesions or injuries on human cognition. While most medical devices are generally tested and approved in a "one size fits all" paradigm, a more flexible strategy may be required to restore higher cognitive functions. Although most humans share nearly identical gross neuroanatomical structures, the fine structure of the brain is profoundly affected by experience and development.

The two most well known medical devices that interface with the nervous system, cochlear implants and deep brain stimulators, rely on focusing the delivery of energy to the same anatomically defined brain regions in patients with a given condition. Higher cognitive functions however are not so easily mapped in a one-to-one basis between behavior and anatomical locus. While specific structures are essential for certain cognitive functions (e.g., prefrontal cortex for executive planning, the hippocampus for memory), over-

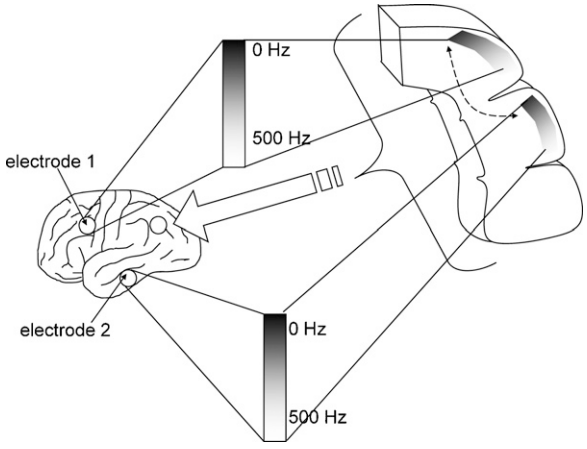

Fig. 5. The electrical activity captured by electrodes implanted above and within the brain are mapped on to artificial cortex. The layers V and VI outputs of the metacortex stream back to both association area (as shown) as well as to primary A1, V1, S1.

all cognition relies on the coordinated activity of widely distributed neural networks.

The development of the techniques and devices discussed in this review will continue to occur under the rubric of traditional clinical investigational trials. Withal, rather than having techniques or devices that are designed to narrowly treat one defined behavior, it appears more likely that the clinicians of the future will instead have a toolbox of technique and device components. Though the manner in which FDA monitors safety of neurocognitive prosthetics will be the same as for other devices, the determination of efficacy constitutes an extraordinary challenge. A new medical discipline may need to evolve in which neurologists, neurosurgeons, and neuropsychologists develop specialized expertise in evaluating what behavioral, non-invasive and implantable device based strategies should be used.

Though the various techniques in this review were discussed separately, many techniques may bring fruit only when combined. It may be that the cognitive enhancement abilities of neurofeedback and rTMS are synergistic. Likewise virtual reality could be integrated with tDCS to help children with stroke re-acclimate to a classroom or study new material. The choice of techniques, parameters and the details of their combinations could be tailored to a person's particular neuroanatomy, pathology, age, educational level, social context and rehabilitation goals.

Though the primary goal of neurocognitive prosthetics is to restore cognition and make quantifiable improvements in daily life, this clinical mission goes hand in hand with a basic science mission of understanding the basis of cognition itself. As with any newly developing therapy, the line between basic science and clinical application will be blurred: there will be a continuous exchange of ideas and discovery between basic scientists and clinicians. The possibility of tracking the unit activity of hundreds of individual neurons simultaneously, and to likewise have the ability to inject signals back in to specific brain regions, would provide an unprecedented scientific opportunity. Patients participating in clinical trials designed to assess the safety and clinical utility of such devices might also elect to participate in additional, concurrent trials conducted in collaboration with basic science colleagues.

6. Conclusion

Ongoing developments in non-invasive techniques and behavioral training promise to provide future clinicians with a greater selection of options to help restore cognition in adults and children with neurological disease and injury. Recent rapid developments in devices that can be chronically implanted in to the brain, coupled with burgeoning knowledge of the neurophysiology of higher cognitive function, imply that the time has come to develop and test a new generation of implantable neurocognitive brain–computer interfaces. For tens of thousands of children and adults disabled with a range of diseases and injuries to their brain, treatment options to ameliorate or cure their conditions are limited or nonexistent. The development of neurocognitive prosthetics might represent a new way forward to address this urgent need and give these individuals the possibility of life with greater enrichment and independence.

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