The future of cognitive neurorehabilitation

In this chapter we will attempt to set out the opportunities and challenges facing the development of an integrated science of cognitive neurorehabilitation, in the context of the impressive range of clinical, methodological and theoretical advances outlined in the previous chapters. We will begin by considering a possible working definition of cognitive neurorehabilitation. This may at first sight seem to be strange – defining the concept in the last chapter of a book on the subject. Neurorehabilitation is such a bewilderingly varied enterprise, however, and in such an early stage of development, that we believe it to have been better to set out the table first of the rich diversity of the field, and in that context try to hew out a possible working definition. We leave it to the readers to assess the usefulness of this definition, which underpins the rest of the chapter, in its attempt to assess the future of cognitive neurorehabilitation.

Definition

Cognitive neurorehabilitation can be defined in terms of the following elements:
- Structured, planned experience;
- derived from an understanding of brain function;
- which ameliorates dysfunctional cognitive and brain function;
- and improves everyday life function.

For the purposes of this chapter, we will define successful cognitive neurorehabilitation as follows:

Structured, planned experience derived from an understanding of brain function which ameliorates dysfunctional cognitive and brain processes caused by disease or injury and improves everyday life function.

By this definition, cognitive neurorehabilitation is a subset of what might be considered the more broadly defined field of general rehabilitation. General rehabilitation may focus on goals that do not attempt to change brain function – for instance on altering family processes to facilitate better adjustment and improved quality of life, eliminating socially constructed barriers that hinder participation such as inaccessible buildings, transportation, or leisure activities, or providing assistive technologies. While these activities may change brain function as a result of experience, altering brain function is not usually the stated goal, as is the case for cognitive neurorehabilitation.

Furthermore, principles derived from cognitive neurorehabilitation (attending, learning, practice, goal-setting) may be necessary to help people – even individuals without brain-damage or cognitive loss – achieve general rehabilitation goals. For instance cognitive demands must be addressed when learning to use a wheelchair, achieving standing balance, acquiring skilled use of a prosthetic device or implementing strategies for independence in everyday life.

We will return to our definition later in this chapter, after a brief assessment of the progress that has been made creating a science of cognitive neurorehabilitation over the last few decades.
An assessment

- Cognitive neurorehabilitation increasingly calls on theoretical, methodological and practical advances made in neuroscience, cognitive neuroscience, pharmacology, medical imaging and other related fields, cognitive neurorehabilitation is now the province of a community of researchers and clinicians covering the full breadth of the translational continuum. Particular areas where progress can be highlighted include those outlined below.

Brain imaging

The availability of a variety of clinical imaging tools that can be used to monitor the extent and location of brain tissue disruption resulting from injury or disease, including restoration of blood flow and metabolism, increasingly allows treatment to be based on the underlying neurological nature and cause of dysfunction. Diagnostic scans should accompany patients and guide treatment from the initial clinical episode through neurorehabilitation.

The use of functional brain imaging in evaluating possible mechanisms of recovery of function, and more rarely, in evaluating the effects of therapy, is a major advance. Functional brain imaging need not, or indeed should not, replace the use of robust behavioral outcome measurements in the clinical rehabilitation setting but imaging can and should be used to develop and validate interventions. Functional brain imaging is likely to play its most important role in the research setting or in the study of small patient groups, aiding the development of neurorehabilitation methods more closely tied to theoretical models of cognitive function.

Multilevel integration

A major challenge for the future of cognitive neurorehabilitation is integrating across the behavioral and cognitive changes observed in recovery and neurorehabilitation with the underlying neural systems, cellular and molecular alterations resulting from neurological insults. Such integration is a major scientific challenge, as attempts at integration across levels of analysis are in their infancy even within basic neuroscience. One goal for the future of cognitive neurorehabilitation could be a
more explicit attempt at a multilevel description of interventional approaches (see Stickland, Weiss and Kolb, Chapter 22, this volume). It occurs to us that the science of cognitive neurorehabilitation, precisely because it requires serious attempts at such integration, could actually lead the field of neuro-science in this effort. The ability to design successful cognitive neurorehabilitation strategies is, to some degree, the ultimate test that theories and models of nervous system function, particularly the dynamic nature of its organization, function and response to experience, are correct.

The science of complex systems provides the theoretical and mathematical tools needed for taking a multilevel approach to the study of neuro-rehabilitation. Gene expression, cellular functions, neural circuits, functional networks, and behavioral outputs are linked such that changes at any one level can alter functional characteristics at many other levels (see Chapter 2 by Dixon, Garrett and Bäckman and Chapter 10 by Corbetta, in this volume). For example, it is possible to affect brain function and the resulting behavioral readouts by using pharmacologic interventions whose mechanisms of action are to alter neurotransmitter actions at the synapse. The converse is also true – altering behavior can affect neurotransmitter function, gene expression, cellular properties and so on. A more sophisticated understanding of such interlevel dynamics should be a fundamental component of a mature science of cognitive neurorehabilitation.

A multilevel systems approach also provides a way to rationally incorporate findings from animal research. To some extent, animal research has both contributed to, and hindered, cognitive neurorehabilitation research. Species similarities and differences must be carefully catalogued. The current controversy over whether or not neocortical neurogenesis occurs in human brain is one example of how extrapolation from animal models to humans must be done carefully lest animal results mislead efforts to design neurorehabilitation strategies. Most often, animal research is too far removed from patient needs to provide clinically useful findings immediately. The similarity of genetic background, environmental experiences and rigidly controlled experimental protocols stand in stark contrast to the variability characterizing human patients in a clinic. How might animal research contribute meaningfully to a science of cognitive neurorehabilitation? Animal models can be used for evaluating how interventions and perturbations at one level of analysis, for example the molecular (e.g., pharmacological), affect neural systems, cognitive function and behavior. Too often, causal relationships have been assumed and offered as explanations without the required evidence. Perturbations at the circuit or network level may or may not result in changes at the functional level. Similarly, interventions aimed at altering neuronal properties may very well have their intended effect at the level of the neuron but may or may not alter the behavioral output of a circuit or a network. Rather than being assumed, a deeper understanding of these relationships requires empirical study. Studies with animal models, where invasive procedures can be used, may make it possible to identify and validate noninvasive imaging biomarkers or behavioral outcome markers amenable to use with human subjects that are diagnostic or predictive of neural change and recovery. What are needed are animal models that are more reflective and predictive of human neurological dysfunction and recovery.

The challenge for the future is to build the required translational linkages (we will turn to this topic again later in the chapter). Carefully designed animal studies can play an important role in advancing the science of cognitive neurorehabilitation, particularly in the development of small-scale neurorehabilitation research studies whereby the animal studies are a component of converging evidence models. Results from diverse experimental systems, including findings from animal models and computational models, when integrated with data acquired from human subjects, could achieve a goal of extracting principles of brain function that, in turn, can be used to develop research studies with patient populations and, ultimately, clinical trials.

- Understanding how attentional demands interact with function.
The need for a science of cognitive neurorehabilitation

It is possible that impairment of brain function resulting in cognitive impairments (CI) may be one of the most common and disabling categories of health problem in the world today. While no comprehensive review of the prevalence of cognitive deficits has been carried out, this conclusion has support from the range of diseases and injuries that impair brain function. For example, aging: 16–24% of the aging population have mild cognitive impairment and dementia; schizophrenia: 85% of schizophrenics with impaired memory; traumatic brain injury (virtually all with CI); stroke (high prevalence of CI); substance and alcohol abuse (significant levels of CI); diabetes (significant levels of CI); multiple sclerosis (high levels of CI); depression (significant levels of CI).

This is an enormous health, social and personal burden, and cognitive neurorehabilitation may be indicated for all, or at least a majority, of these conditions. Yet the investment in research and services for cognitive neurorehabilitation does not reflect the size of the problem. Why is this?

Without an effort to develop a research-based, clinically relevant science, the delivery of cognitive neurorehabilitation and the development of new research-based clinical interventions are likely to persist as somewhat marginal endeavors against the backdrop of the enormous investment made in providing patients with acute medical services. It is important that those committed to cognitive neurorehabilitation explicitly ask why it is we are willing to invest so heavily in acute medical care and so sparingly in the neurorehabilitation needed to make good on that investment. Altering the future course for cognitive neurorehabilitation requires that there be an international effort to demonstrate that the field is rooted in and grows strongly from clear models of brain and mental functioning, with links from the cognitive to the molecular level informing both research and practice. If the research progress on new models of nervous system structure-function relationships made over the last 20 years continues, or hopefully quickens its pace over the next two decades, we can be cautiously optimistic that our vision for the future will happen. Achieving our scientifically optimistic projections is, of course, subject to economic realities. All healthcare delivery systems are going to become increasingly financially challenged (a) by the increased demands of aging populations and (b) by the development of new and very expensive therapies for a range of diseases and injuries arising from molecular medicine, nanobiology and the medical devices industry. Treatments and therapies that cannot demonstrate efficacy will not survive in the healthcare marketplace.

We do not believe that a true economics of health-care inherently values technology-based or molecular/cellular-based treatments over ostensibly less glamorous behaviorally based treatments, but we do believe the development of validated outcome measurements that could be used to demonstrate effectiveness across the entire spectrum of interventional approaches must become a priority for cognitive neurorehabilitation. Effective cognitive neurorehabilitation programs, allowing individuals with cognitive impairments and/or their caregivers to resume participation in important life activities will figure substantially in medical and social economic analysis. Over time, it is likely that pharmacological and technical interventions will also be held to rigorous standards and also be required to demonstrate efficacy in terms of real world functional outcomes. A true complex systems approach to healthcare may, in fact, lead to more rather than fewer behavioral interventions. It is not controversial to state that our eventual efforts to make good on the promissory notes currently offered by the development of “smart” prosthetics, cellular transplantation and nanotechnology will rely on the ability to retrain neural function and provide correct experiences in optimal learning environments via the science of cognitive neurorehabilitation.

Improving neural function through the use of pharmaceutical interventions designed to alter neurotransmitter and neuromodulator actions will also
most likely require pairing with behaviorally based neurorehabilitation interventions to achieve the desired goals. The widening use of cognitive therapy for the treatment of individuals diagnosed with depression provides a good illustration. Research shows that cognitive, behavioral-based treatments can, for certain subgroups, be as effective or even more effective than pharmacologic treatments. Combining cognitive therapy with the use of pharmacologic agents may offer another alternative approach for some patients. These conclusions have been arrived at after a number of trials of a consistently applied, protocol-based therapy, which in turn grew out of a broad base of basic research characterizing cognitive mechanisms of depression and its recovery. Cognitive therapy treatments for depression are now widely accepted and used in relatively standardized ways worldwide. The standardization of the therapy is important. Standardization not only makes it possible to assess efficacy, it allows for continuous improvement and refinement. New theoretically motivated, testable hypotheses can be generated, new protocols can be developed, and better outcome measures can be field-tested. Cognitive therapy for depression stands in marked contrast to the rather fragmented way many interventions in cognitive neurorehabilitation are conceived, implemented and evaluated.

Building a true science of cognitive neurorehabilitation could also serve as a model for how to accomplish the much sought-after biomedical “translational research.” How is it possible to create a continuum balancing the tenets of research (often focused on identifying the differences among groups) with the needs of clinicians faced with the responsibility for delivery care to individual patients? At the moment, cognitive neurorehabilitation services are designed to address an individual patient’s needs but the interventions have often been devised in isolation of current neuroscience and cognitive neuroscience research. The neurorehabilitation protocols often arise from the desire of well-intentioned and caring therapists to provide something to desperate patients seeking treatment. Often, the therapist providing the therapy is also responsible for monitoring the patient’s progress, making objective evaluation difficult. Evaluating efficacy is further confounded by using the same tasks for both the training paradigms and the outcome measurement. Conversely, researchers are often not particularly interested in developing treatments but rather in pursuing projects that may yield scientifically interesting results. Effects achieved in the research setting may be statistically significant on highly selected subjects. Validating effects, scaling up studies for large clinical trials, and developing protocols amenable to clinical settings offers researchers few academic rewards. Unfortunately, too often the magnitude of the effect seen in a controlled research setting is small and may not be sufficiently robust to withstand the variability introduced in real-world clinical environments where neither the skill of the therapist nor patient individuality is controllable. Efficiency could be gained if the science of cognitive neurorehabilitation can establish a shared language that facilitates two-way communication between academic research centers and the non-academic clinics where much of patient services are provided.

We are proposing that in the “translational continuum” for cognitive neurorehabilitation cognitive neuroscience itself a multidisciplinary endeavor represents the basic science much as basic biomedical research is the foundation of medicine. Clinicians might question the need for a science of cognitive neurorehabilitation based on an understanding of brain function. A convincing argument could be put forward that cognitive neurorehabilitation might be best served by a highly individualized, idiosyncratic approach (see Chapter 7 by Cicerone in this volume). Wilson and Kapur’s chapter (Chapter 30, this volume) presents practical, empirically tested interventions derived from a performance perspective that relies very little on basic science research. However, we think cognitive neuroscience research could make real contributions in determining why a particular intervention is effective, which aspects of an intervention are essential for the desired effect.
and for which patients the treatment is indicated. It is important to know how treatment effects could be maximized, what the proper dose-response relationship is, and how to structure the learning environment so that behaviorally based strategies become less effortful and more automatic over time. We believe we can get better at matching training strategies to patients using an understanding of both the anatomical and functional deficit. It may seem counterintuitive – but it is likely a scientifically motivated approach to cognitive neurorehabilitation will result in more, rather than less, personalized care.

Examples of a cognitive neuroscience approach to cognitive neurorehabilitation

- Cognitive neurorehabilitation methods should be instantiated in detailed protocols, with or without assistive technologies, which allow for replication of evaluation studies.
- There should be at least some theoretically articulated and empirically supported model underlying the intervention.
- Effective cognitive neurorehabilitation should be able to demonstrate changes both in cognitive function and in brain function as measured by one or more imaging or associated methods.
- Cognitive neurorehabilitation should be able to demonstrate effects in the everyday life of the individual.
- There are very few examples of cognitive neurorehabilitation which meet these criteria: constraint-induced therapy may be one of the few.

Constraint-induced therapy (CIT; see Chapter 23, this volume, by Morris and Taub) is based on years of research carried out by Edward Taub and colleagues. It focuses on loss of motor function, which is of course a complex, cognitive-controlled process. Taub’s initiating model proposed that injury to a limb results in neural shock and initial depression of function, leading to a learned non-use of that limb even when movements could potentially be made. Taub demonstrated, first in a nonhuman primate model and later with human subjects, that learned non-use can be overcome. In cases where there is a minimum of residual function, restricting movement of the intact limb can induce use of the deafferented limb.

Constraint-induced therapy occupies a special importance in the development of cognitive neurorehabilitation. In addition to its theoretical grounding in neuroscientific principles, the therapy design is articulated into a coherent and replicable protocol which allows for a degree of assessment and replication notably lacking in a landscape littered with protocols of uncertain efficacy. The fact that CIT has been evaluated in over 400 patients (see Chapter 23) worldwide in multicenter clinical trials is a mark of the maturity and critical importance of this milestone in neurorehabilitation. The theoretical principles, the feedback from clinical use, and validated outcomes provide a blueprint that should encourage the design and testing of new interventions extending the CIT approach.

Perhaps one of the important lessons learned from CIT derives from its somewhat counterintuitive nature – stopping patients from doing something that may interfere with, or inhibit, behavioral recovery. One of us (IR) remembers clearly attending a workshop by the advocate of an internationally used physiotherapy method where it was categorically stated that rehabilitation of hemiplegia must be “symmetrically based,” namely with repeated bilateral movements – if necessary with the hemiplegic arm lifted by the unimpaired arm – being an essential component of treatment. While of course this may be a valid approach under some conditions (Staines et al., 2000), it is clearly not a panacea to be advocated in a blanket fashion. Similarly, the belief that interventions cannot be assessed until after natural recovery has plateaued needs to be empirically investigated. Intuition-based treatment is an understandable consequence of having a practice-led rather than a research-led culture of developing therapies, and cognitive neurorehabilitation is still beset by this type of approach, though this is changing slowly.
Nevertheless, if one considers the costs – to the patient in terms of time, effort and discomfort devoted to a significantly suboptimal treatment – and to the health provider in terms of precious and expensive therapist time – then the dangers of not developing a strong scientific base for therapies can not be justified. We need to know to whom which treatment should be delivered, when, and how intensively for how long. The functional organization of the nervous system and the principles of recovery and plasticity should guide cognitive neurorehabilitation.

There are other examples of relatively nonintuitive methods of neurorehabilitation. As we have seen in Chapter 26 by Singh-Curry and Husain, a wide range of such methods have arisen out of largely theoretically derived cognitive neuroscience research into spatial neglect. Schindler et al. (2002), for instance, showed that applying a standard electromechanical vibrator to the left neck muscles of patients while they engage in visual search exercises produces marked and enduring clinical and real-life benefits. This treatment arose out of basic research into the brain mechanisms of sensory integration and higher level perception. Neglect patients were studied because of what their damaged brains revealed about the functional architecture of the intact brain. Neck vibration was used purely because of its known effects on the body's normal coordinate frame of reference according to which sensory inputs and motor outputs are integrated. In neglect, not only is this egocentric reference frame biased to the right, but also the neck vibration can temporarily correct this imbalance. What we see in the Schindler et al. (2002) paper is that, when combined with systematic visual search training, and when systematically applied for 15 treatment sessions over 3 weeks, temporary effects become long lasting and hence therapeutically important.

An important difference between CIT and neck vibration treatment for neglect is that the latter has not been subject to the same number of replications, and does not, to our knowledge, have brain-imaging data to indicate at least partial mechanisms for recovery. Are there ways in which standardization and dissemination of candidate protocols could be fostered? We believe that CIT provides an excellent model for other types of cognitive neurorehabilitation: if standardized protocols based on good theoretical models are developed, then opportunities for replication and multicenter trials will multiply, along with the funding and credibility for the field that will inevitably follow. As mentioned above, a major challenge for the field is how to facilitate the development of such protocols and to channel resources in such a way that critical mass of basic and evaluative research is attained.

One possibility is that the institutionalization of an accreditation or regulatory system such as exists for medical devices and pharmaceuticals be devised for cognitive neurorehabilitation methods. Given how small the field of cognitive neurorehabilitation is, and the adaptability of most interventions to a variety of care-delivery systems, an international effort may be the best approach. Even the most cursory glance at the reviews of evidence for the effectiveness of cognitive neurorehabilitation presented in Part V will reveal that there are very few candidate neurorehabilitation methods that would meet most likely sets of criteria. What might some of the elements of a list of such criteria look like? Let us return to the definition of cognitive neurorehabilitation given at the beginning of the chapter: Structured, planned experience derived from an understanding of brain function which ameliorates dysfunctional cognitive and brain processes caused by disease or injury and improves everyday life function.

A possible set of criteria for an acceptable science of cognitive neurorehabilitation might be captured in this definition, as follows:

(a) **Structured, planned experience.** Implicit in this element of the definition is that cognitive neurorehabilitation methods should be instantiated in detailed protocols with or without assistive technologies, that allow for replication and evaluation studies.

(b) **Derived from an understanding of brain function.** This element implies that there should be
at least some theoretically articulated and empirically supported model underlying the intervention;
(c) ... which ameliorates dysfunctional cognitive and brain processes. Implicit in this part of the
definition is that effective cognitive neurorehabilitation should be able to demonstrate
changes both in cognitive function and in brain function as measured by one or more
imaging or associated methods (MRI, fMRI, PET, ERP, MEG, EEG, TMS);
(d) and improves everyday life function. Cognitive
neurorehabilitation should be able to demonstra-
ate effects in the everyday life of the
individual.
A further criterion may be added to this defini-
tion, namely that methods should be tested in large
multicentered phase III clinical trials (without the
array of participant inclusion and selection criteria
often seen in small trials). Finally, treatment deliv-
ery and outcome assessment must be independent
of one another.
As can be seen from the chapters in this book,
there are very few studies of cognitive neurorehab-
ilitation that meet all of these criteria, though pro-
gress has been made over the last few decades. One
study of cognitive training with normal elderly
serves as an example of a theoretically motivated
approach, strongly based on cognitive and neuro-
sience research (Stuss et al., 2007). Healthy sub-
jects experiencing age-related cognitive declines
showed meaningful changes in everyday perfor-
ance as rated both by the participating subject and
by caregivers. Future studies with this protocol
should identify possible mechanisms of improve-
ment through imaging measures and they must
also determine whether the findings are robust
even to hold up in the clinical trials arena with
individuals experiencing cognitive decline as a
result of injury or disease. If the next phase of pre-
clinical research is promising the protocol needs to
be shaped for a multicenter, double-blinded, ran-
omised, controlled clinical trial. Ultimately, of
course, the real goal is to have a finding robust
enough to be useful in everyday clinical practice.
These are the examples of the sorts of challenges
facing all cognitive neurorehabilitation protocols if
research is truly going to be translated into wide-
spread clinical practice.
If, as we believe, anatomical and functional brain
imaging is to be important to the future evaluation
of cognitive neurorehabilitation, then there are a
number of important factors that may bear on the
future of cognitive neurorehabilitation, in particular
raised in Chapter 10 by Corbetta.
Among other things, Corbetta reviews evidence
that better language production recovery in aphasic
disorders is associated with an apparent reactiva-
tion of left hemisphere language systems, while less
optimal recovery is associated with right hemi-
sphere activations. Furthermore, it appears that
in some cases, inhibitory rTMS applied at the
chronic stage to right hemisphere frontal regions
produces some limited but persistent gains of nam-
ing in patients with severe aphasia. In contrast,
however, with respect to speech comprehension,
Corbetta shows that right hemisphere activity
alone may also lead to good outcome, possibly due
to a more bilateral representation of comprehen-
sion mechanisms.
This implies that our indices of brain imaging will
have to become more sophisticated and theoretici-
ally informed. More is not necessarily better, and
successful neurorehabilitation may be indexed as
much by certain decreases in brain activation as by
increases. This is particularly true when the extent
of diaschisis in certain types of lesion is observed –
for instance in the case of unilateral neglect follow-
ing right hemisphere stroke – where widespread
suppression of blood flow is observed even in cer-
tain distant regions of the brain. Corbetta raises the
intriguing possibility that activity spreads in sensory
and motor systems differently, with a lesion to the
former blocking a “spreading” activation to widely
distributed networks of areas. In contrast, lesions to
motor areas may operate quite differently because –
he speculates – motor signals may require greater
focusing onto the appropriate response mecha-
nism, which may involve the inhibition of other
response areas. Lesions to motor areas may
therefore lead to a decrement of inhibition and a consequent over-activation of motor areas. Corbetta argues that the principal mechanism for recovery is reorganization of widely distributed neural networks, and cognitive neurorehabilitation has yet to take on board this complexity in its models of treatment.

Cognitive neurorehabilitation has yet to be considered in the light of new technologies for altering brain function such as deep brain stimulation, repetitive transcranial magnetic stimulation, or neural transplantation and related procedures. There can be no doubt that the precision and neuroanatomical specificity of these methods will present bracing challenges to the science underpinning cognitive neurorehabilitation. An important area of research will be how useful they are in restoring meaningful function useful to patients in their everyday lives. But it is early days, and it is most likely that technological approaches and behavioral approaches will continue to be tested, refined and evaluated. There equally can be no doubt that if cognitive neurorehabilitation rises to these challenges, then its potential – both alone and in combination with these emerging therapies – for improving the lot of the tens of millions of people worldwide suffering from impaired brain function will be very high indeed.

Practical recommendations for the future of cognitive neurorehabilitation

(1) Establish an international clinical trials network so that promising neurorehabilitation interventions tested in research laboratories and on small groups of patients can quickly be scaled up for trials on large numbers of patients in diverse environments.

(2) Develop a mechanism whereby clinical outcome information is made readily available to researchers so that a continuous improvement communication loop is created.

(3) Create convenient and readily accessible training and professional development tools for clinicians.

(4) Establish a shared repository of validated outcome measurements that can be easily applied in the clinical setting but are ecologically valid and reflective of real world improvements.

(5) Develop diagnostic tests guiding the selection of potential therapies.

Summary: some questions for the future science of cognitive neurorehabilitation

The authors of this chapter are optimistic that the vision for the future of the science of cognitive neurorehabilitation can be realized. We acknowledge that there are elements missing, and even that there may be visions departing significantly from the one suggested. We find it unlikely, however, that a scientific approach to cognitive neurorehabilitation grounded in an understanding of brain function, cognitive science and behavior challenged by a serious commitment to improving everyday performance will not succeed. In summary, we leave you with some questions we believe the science of cognitive neurorehabilitation can answer in the near term and when it does, the impact on patient care will be measurable.

(1) What are the neural, cognitive, behavioral and environmental factors that contribute to the observed disconnect between an individual's cognitive function as measured with neuropsychological tools and their observed performance in everyday life? (See Chapter 14 by Dawson and Winocur.) Understanding this disconnect will reveal important interactions among these different levels and the ways by which each contributes to everyday performance.

(2) In what ways do alterations in cognitive function impact behavioral performance in the short and near term? What is the impact of altered behaviors on the functioning of cognitive systems? In other words, what are the feedforward and feedback links between cognition and behavior? It might be worth knowing if the inability of an individual to engage in certain behaviors could further "decondition" cognitive
functions. For example, how might the effects of early brain injury manifest throughout an individual's lifespan? Similarly, how might brain injuries acquired in mid-life interact with natural aging processes?

(3) Could understanding the dynamic interplay whereby neural and cognitive dysfunction reduce an individual's capacity for altering/reacting to/ modifying his or her environment hold promise for the treatment and cognitive neurorehabilitation of certain neuropsychiatric diseases?

(4) How can we successfully exploit combinations of pharmacologic, technical and behavioral interventions? The appeal of engineered smart prosthetics and cellular replacement therapies will be difficult to fulfill unless we know much more about how computations are performed and actions represented by neural circuits. Pursuing the development of highly technical or cell-replacement treatments will command significant financial investments. In the absence of a science of cognitive neurorehabilitation as envisioned in this chapter, such enterprises may become little more than intellectual exercises.

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