Part III

Developmental Disorders, Alternative Approaches, and Emerging Technologies

Introduction

The final goal of this volume is to provide perspectives on multiple special topics ranging from therapeutic drug use to enhance cognition in children, emerging technologies, pharmacological disruption of maladaptive memory, and nonpharmacological approaches to cognitive enhancement. Although the range of special topics is not all-inclusive, they serve to ignite awareness of special populations that may benefit from cognitive enhancement or, in some cases, disruption and to inspire scientists to embrace innovative technologies and approaches in their quests for cognitive enhancement in neuropsychiatric and neurological disorders.

Chapter 11 (Vahabzadeh, Landino, Finger, Carlezon, and McDougle) details much of the relevant progress in the field of autism research. Autism spectrum disorder has come to the forefront in a major way over the past 10 years at least in part due to enhanced diagnosis and public awareness. A complex behavioral disorder, autism, is likely the result of numerous environmental and genetic factors—some, albeit few, are known. Of the many attributes associated with patients with autism, foremost is a deficit in social cognition. Social cognition can be enhanced by oxytocin and modulated by glutamatergic tone, and both neural systems have been studied preclinically and clinically with select pharmacological tools. Another field of focus is neuroinflammation as it may be a contributing factor to the etiology of autism. Together, learning more about the networks that control communication will be critical to understanding autism and developing potential medicines for this disorder, particularly in the area of social cognition.

Chapter 12 (Fernandez and Reeves) discusses many of the recent advances in Down syndrome research. It is quite clear that the clinical phenotypes, although overlapping somewhat, are quite variable. This is due in part to the diverse number of brain regions affected in the disorder, resulting in divergent effects on various cognitive domains in individuals with Down syndrome. The effects of the triplication of human chromosome 21 are certainly not limited to those in the

central nervous system. These people often present with disorders such as hypothyroidism and congenital heart disease, and are predisposed to early aging in general. Thus, multiple biochemical and physiologic networks are altered. The expression of the various phenotypes is likely related to dysregulation of GABAergic networks, apolipoprotein E, or the processing of amyloid peptides. All these lead to certain difficulties for the conduct of clinical research studies, and thus, clinical trial design for studies with people having Down syndrome requires unique attention.

Chapter 13 (Taylor and Torregrossa) outlines the disorders of maladaptive memory and how a range of pharmaceutical agents can weaken the strength of these memories if used in conjunction with techniques that target memory reconsolidation. Disorders range from post-traumatic stress disorder to disorders of addiction, schizophrenia, and mood. Several categories of drugs have been investigated since the pioneering work showing that inhibition of protein synthesis at the time of memory reactivation can disrupt its reconsolidation and weaken its strength. The most well-studied drugs in both animal and human subjects include beta-adrenergic receptor antagonists and glucocorticoid antagonists. Preclinical research is currently discovering the relevant intracellular signaling pathways involved in memory reconsolidation, potentially giving rise to new and improved targets for treating disorders of maladaptive memory (e.g., inhibitors of PKA, ERK, mTOR, GSK3, NFkB, and histone acetylation). Parallel to the discovery of new compounds is the need to unveil the optimal reactivation conditions for reconsolidation manipulations of newer as well as older (remote) memories.

Chapter 14 (Kelly) describes the use and benefits of incorporating nonpharmacological cognitive enhancers that involve lifestyle interventions. In particular, aerobic exercise and environmental enrichment have strong empirical support, with proven efficacy in humans and in animal models. For example, in healthy humans, aerobic exercise can improve learning, response inhibition, and working memory. In the elderly, exercise has neuroprotective effects and reduces the incidence of cognitive impairment and dementia. People with depression benefit as well. Most research with environmental enrichment has been conducted in animals, and though it naturally varies to a degree in how it is implemented in people vs. animals, most investigators agree that cognitive stimulation and social stimulation offer an enriching experience in childhood through adulthood. Computerized training programs are a relatively recently developed source of targeted cognitive stimulation. Positive effects have been reported in the elderly and in Parkinson's disease patients. However, the persistence of enhancement and the transfer of the learned skills to real-life situations have not yet been demonstrated.

Chapter 15 (Kondabolu, Kowalski, Roberts, and Han) focuses on two emerging technologies that can impact, in a rather precise manner, brain networks. These are optogenetics and deep brain stimulation. Optogenetics is a revolutionary technology that allows one to control or modulate highly specific neural circuits. As it has been introduced only recently, it is still primarily in a research phase now, and clinical applications, although approachable, have not yet been realized. In practice

for much longer than optogenetics, deep brain stimulation has shown therapeutic efficacy in disorders such as Parkinson's disease and depression. Although not specifically designed for cognition enhancement, the use of these technologies should allow the field to assess brain circuits that impact specific domains of cognition.

Chapter 16 (Kantak and Wettstein) provides closing thoughts for this volume on cognitive enhancement. The status of cognitive enhancement is first summarized to suggest the availability of therapeutics for improving attention and dementia, but that more research is needed to develop effective therapeutics for improving these and other cognitive domains. The advances that have been made in translational models of cognitive enhancement and in the neurobiology of learning and memory are major achievements from the past 20 years, and these achievements will help speed the availability of cognitive-enhancing (or disrupting) therapeutics for neuropsychiatric and neurological disorders. The availability of such therapeutics raises several ethical questions regarding cognitive enhancement or its disruption. Should cognitive enhancers be available for everyone, or should they be limited to special or medically defined populations? Who will be the gatekeepers dictating how and when cognitive enhancement is permissible? Scientific questions also persist, particularly the question of whether cognitive enhancement is better achieved via pharmacological vs. nonpharmacological means. There is a need to develop rational policies for the use of cognitive enhancers.