ENABLING DISCOVERY, DEVELOPMENT, AND TRANSLATION OF TREATMENTS FOR COGNITIVE DYSFUNCTION IN DEPRESSION

WORKSHOP SUMMARY

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Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

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

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

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1

Introduction and Overview[1]

Major depressive disorder (MDD) is recognized worldwide as a major cause of disability, morbidity, and mortality. According to the World Health Organization's (WHO's) *The Global Burden of Disease: 2004 Update*, unipolar depressive disorders affect more than 150 million people around the world and represent the leading cause of "years lost due to disability" among both men and women and across low-, middle-, and high-income countries (WHO, 2008). In the United States alone, nearly 8 percent of persons over the age of 12 report current depression (Pratt and Brody, 2014).

The direct and indirect costs of MDD are correspondingly alarming. In 2010, the economic burden in the United States was estimated to be more than $210.5 billion, about half of that due to workplace costs generated by absenteeism and reduced productivity (Greenberg et al., 2015). This figure represented an increase of more than 20 percent in the 5 years between 2005 and 2010. Perhaps most troubling is the fact that depression often goes untreated or undertreated. The WHO World Mental Health Surveys showed that even in the United States, only about one-third of patients receive treatment in the first year of the disease, and face a median delay of 4 years before treatment is provided (Wang et al., 2007).

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

MDD has long been defined primarily as a mood disorder.[2] However, more recently people have begun to recognize effects on cognition as a major contributor to the disablement that accompanies depression and to consider this an underrecognized treatment target for depression.

WORKSHOP OBJECTIVES

On February 24, 2015, the Institute of Medicine's (IOM's) Forum on Neuroscience and Nervous Disorders convened key stakeholders at a workshop in Washington, DC, to explore how best to enable the discovery, development, and translation of treatments for cognitive dysfunction in depression, including a focus on the regulatory path forward (see Box 1-1).

BOX 1-1
Statement of Task

An ad hoc committee will plan and conduct a 1-day workshop to explore opportunities and challenges related to discovery, development, and translation of treatments for cognitive dysfunction in depression. The workshop will bring together key stakeholders to explore the discovery, development and regulatory path for new treatments addressing this aspect of depression.

Presentations and discussion will be designed to

- Examine opportunities to facilitate new target and validation strategies aimed at reinvigorating the development of treatments that address cognition, an undertreated aspect of depression.
- Discuss how lessons from the translational aspects of cognitive dysfunction in other disorders could apply to depression.
- Highlight gaps and limitations of current tools for assessing cognitive dysfunction in depression in clinical trials, and consider how improvements in cognition could relate to functional outcomes.
- Explore potential regulatory challenges, such as recognition of cognitive dysfunction in depression as a public health need, and opportunities for treatments.

[2]According to the criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (the DSM) (American Psychiatric Association, 2013), MDD is characterized by the presence of symptoms of depressed mood and/or anhedonia (loss of interest in pleasurable activities) as well as other symptoms, including "diminished ability to think or concentrate, or indecisiveness" and "psychomotor retardation," which impairs one's ability to function. The DSM criteria require that these symptoms persist for at least 2 weeks and that they are not attributable to normal grief, substance use, or another psychiatric or medical disorder.

Thomas Insel, director of the National Institute of Mental Health (NIMH), noted that while a broad range of treatments have been developed to treat depression, resistance to treatment is widespread and residual symptoms, particularly in the cognitive domain, often lead to incomplete recovery. Indeed, only approximately 45 percent of patients achieve remission (Simon, 2000), and those who do frequently relapse (Rush et al., 2006). As discussed in more detail later in this summary, among patients who fulfill traditional criteria for response or remission of depression, many continue to have subjective complaints that contribute to impaired function, such as the ability to return to work. Clinical and epidemiologic evidence suggests that cognitive dysfunction represents an underestimated dimension of depression that may, in part, explain patients' inadequate response to treatment. Yet questions remain regarding the relationship between depression and cognitive dysfunction as well as how to assess cognitive dysfunction in depressed patients. Moreover, currently available pharmacologic treatments for depression may fail to address or even worsen the cognitive aspects of this crippling disease.

Pharmaceutical companies have begun to take an interest in developing drugs that target cognition in depression, said Thomas Laughren, director of Laughren Psychopharm Consulting, LLC, and formerly director of the Division of Psychiatry Products in the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA). Until recently, Laughren said that FDA had not been convinced of the value of targeting cognitive impairment in depression separately from other symptoms of depression, but he believes that a careful review of the data has altered that perception, and that the agency is now ready to take a new look at the issue.

ORGANIZATION OF REPORT

The following report summarizes the presentations from expert speakers and discussions among workshop participants. Chapter 2 provides the backdrop against which these discussions were framed, that is, how we define cognitive impairment in depression, its prevalence and impact on function, and neurobiological mechanisms and targets for intervention. Chapter 3 explores the state of the science in pharmacologic and nonpharmacologic treatment development. Chapter 4 discusses the challenges related to developing successful treatments for cognitive im-

pairment in depression. Chapter 5 presents regulatory challenges from the perspective of both regulators and clinical researchers. Finally, Chapter 6 discusses lessons learned from the schizophrenia field, which has grappled with many of the same issues. References are in Appendix A, the workshop agenda is in Appendix B, and the list of registered participants is in Appendix C.

TOPICS HIGHLIGHTED DURING PRESENTATIONS AND DISCUSSIONS[3]

Cognition is an appropriate target for treatment of depression, said many participants throughout the workshop. They discussed a number of challenges to achieving broader acceptance of this concept within the larger community and transforming this paradigm into effective treatments. The challenges and potential opportunities to address them identified by individual participants are listed here and expanded on in the succeeding chapters:

- **Defining cognitive impairment in depression:** The lack of a consensus definition of cognitive impairment in depression may hinder diagnosis and treatment development, said several participants. Despite increased recognition of the importance of cognitive dysfunction in depression, a precise definition of the disorder remains elusive. Both cold and hot cognition[4] appear to be affected, leading to reduced function, and it seems important to separately consider cognitive biases and cognitive deficits.[5] Several participants, including regulators, noted that the lack of a consensus on the cognitive domains leads to methodologic differ-

[3]The following list highlights topics discussed throughout this workshop, but should not be construed as reflecting a consensus of workshop participants or any endorsement by the Institute of Medicine or the Forum on Neuroscience and Nervous System Disorders.

[4]Cold cognition refers to information processing that is independent of emotion, while hot cognition refers to constructs that are affected by emotional state. Although these terms are not universally used, they were used throughout the workshop and therefore in this summary.

[5]Cognitive biases include distorted information processing and increased attention to negative stimuli; cognitive deficits include impairments in attention, short-term memory, and executive functioning (Murrough et al., 2011).

ences in studies that obscure the reasons for different results and impedes the regulatory path forward.

- **Understanding the neurobiology of cognitive impairment:** An incomplete understanding of the neurobiology underlying cognitive impairment in depression appears to be impeding the development of new treatments, noted some participants. Ongoing research to define the brain circuits affected in depression could help to explain the suboptimal effectiveness of current treatments and identify potential targets for novel treatments.
- **Targeting cognition to improve treatment efficacy:** Targeting cognition in depression could improve the efficacy of treatment for depression, suggested several participants. They said the reason for the high rate of treatment resistance in depression may relate to the failure of treatments to target cognition, yet no new drugs have been approved by FDA for the treatment of cognitive impairment in depression. Although cognition has been assessed in many treatment studies, the effects on cognition have been nominal. Furthermore, most studies have looked only at cold cognition, yet some participants said hot cognition may be the more important target.
- **Using holistic approaches and combining treatments:** These approaches appear promising, said some participants. After discussing a range of pharmacologic and nonpharmacologic treatment approaches, including neurostimulation and cognitive remediation, several participants concluded that effective treatment will require combinations of drugs and other treatments that target multiple neurobiological mechanisms and cognitive domains and that ensure good functional outcomes in the workplace and home environments.
- **Improving early diagnosis and early treatment:** Earlier diagnosis of depression and early effective treatment could improve response to treatment, emphasized some participants, noting that delayed treatment leads to poorer response to antidepressant therapy and more frequent relapses. Tools are needed to enable earlier detection as well as to predict the response to treatment.
- **Developing biomarkers:** Biomarkers would be valuable, and cognition potentially could be used as a surrogate biomarker, said a few participants. These biomarkers include genetic, neuroimaging, cognitive, and other physiologic measures, and could not only enable earlier identification of persons with depression,

but also improve the efficiency of clinical trials by identifying appropriate candidates for trials and by providing indicators of target engagement and treatment response.

- **Using experimental model approaches:** Experimental model approaches can be helpful for screening and predicting the effects of antidepressant treatments on cognition, said some participants. For example, early changes in emotional processing (hot cognition) are seen with antidepressant drug treatments, and this is predictive of later therapeutic response. Modeling the disease process in humans may provide answers to questions about the neurobiologic effects of a treatment early in the drug development process, before billions of dollars have been spent on a treatment that ultimately fails to show efficacy. One experimental model discussed at the workshop is already being used by pharmaceutical companies to screen candidate treatments.
- **Heterogeneity and stratifying study participants:** Heterogeneity presents challenges in developing treatments, and stratifying study participants into subgroups can be beneficial although it limits generalizability, noted various workshop participants. Patients with depression constitute a diverse group in terms of both symptomatology and response to treatment, and these aspects also vary with gender and across the lifespan. Moreover, heterogeneity has a huge impact on clinical trials, creating "noise" that obscures treatment benefits. Several participants discussed different approaches to stratification of study participants into subgroups that could provide clearer answers in trials and enable the identification of interventions appropriate for different subgroups.
- **Addressing pseudo-specificity:** Pseudo-specificity may be a major roadblock to the design of clinical trials and regulatory approval, recognized many participants. In order for a treatment to be approved for cognitive dysfunction in depression, regulators likely will ask for data showing that the drug works only or better in patients with depression-related cognitive impairment as opposed to cognitive impairment in general or depression in the absence of cognitive impairment.
- **Employing novel trial designs:** Novel trial designs could be useful, said some participants. They suggested a number of modifications to existing trial designs, as well as innovative new designs such as adaptive trials, which could address some unique

concerns raised by targeting cognition in depression, expedite drug development, and increase the likelihood of success. Several participants also emphasized the need for patient engagement and real-world studies that take a holistic approach.

- **Improving assessment tools:** Improved tools to assess cognition in patients with depression would be useful, some participants said. A number of batteries are available for testing cognition in patients with depression, yet not all test the same domains or employ the same neuropsychological tests. Several participants acknowledged both the advantages and disadvantages of a standardized battery, using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery as a point of reference. Other major issues discussed with regard to assessment were the use of objective versus subjective and cognitive versus functional measures. As mentioned by some participants from regulatory agencies, clinical meaningfulness is paramount. In other disease conditions such as Alzheimer's disease and schizophrenia, regulators have required demonstration of efficacy on a co-primary endpoint, such as a functional or global measure. Whether a similar requirement would be made for cognitive impairment in depression remains to be determined.
- **Embracing innovative technologies:** These technologies could help to improve assessment and could also be used in treatment, said some participants. Examples include a number of innovative technologies, such as tracking tools available on smartphones and in-home devices that could provide continuous functional measures of disease progression across all stages of disease and with a high degree of clinical meaningfulness.
- **Enhancing clarity in the regulatory pathway:** Clarity in the regulatory pathway for approval of treatments would be beneficial, noted some participants. No treatment targeting cognitive impairment in depression has yet received regulatory approval. Regulators participating in the conference expressed willingness and flexibility with regard to many aspects of trial design and encouraged investigators to meet with them early in the process of developing their trials.
- **Learning from the MATRICS program:** Many lessons can be learned from the MATRICS program, said some participants who had worked on the MATRICS initiative, which was designed to address the roadblocks to developing treatments for

cognition in schizophrenia. By heeding the lessons learned from MATRICS, they expressed the hope that they could avoid some of these roadblocks; however, few participants appeared inclined to support a MATRICS-like process to advance development of treatments for cognitive dysfunction in depression.

In his concluding remarks, Insel said he was initially skeptical that there was a need for new cognitive interventions and cognitive measures for depression. However, he said the proceedings had convinced him that even cognitive interventions that have been available for some time may not be adequate to address the cognitive concerns of patients with depression. He also expressed concern about how little is actually known about the current set of interventions, noting that the meta-analyses that have been published are "underwhelming" and limited by issues of heterogeneity. However, he noted that there are many directions for further exploration and potential opportunities to improve the treatment of cognitive dysfunction in depression, as mentioned above and described in more details in subsequent chapters.

2

The Burden of Cognitive Dysfunction in Depression

Highlights

- Cognitive dysfunction in depression occurs as both cognitive biases and deficits (Nierenberg).
- There are impairments in both hot and cold cognitive processes in depression (Sahakian).
- Depression represents a disorder of brain circuits; a better understanding of the neurobiological underpinnings of cognitive dysfunction in depression could point the way to improved treatments (several workshop participants).

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

Cognitive dysfunction in depression has been relatively overlooked by clinicians, academic researchers, and industry, said Andrew Nierenberg, who holds the Thomas P. Hackett, M.D., Endowed Chair in Psychiatry at Massachusetts General Hospital. However, there is now increased recognition that cognitive dysfunction in depression occurs as both cognitive biases, such as distorted information processing and increased attention to negative stimuli, and cognitive deficits, such as impairments in attention, short-term memory, and executive functioning (Murrough et al., 2011). The consequence of these cognitive impairments, said Nierenberg, is that in the presence of emotionally laden negative thoughts, the person with depression lacks the cognitive flexibility to regulate mood. He or she becomes "stuck in a rut" (Holtzheimer and Mayberg, 2011).

COGNITIVE DYSFUNCTION: A CORE ELEMENT OF DEPRESSION

Cognitive dysfunction affects both cold (i.e., emotion-independent) and hot (i.e., emotion-laden) cognition, said Barbara Sahakian, professor of clinical neuropsychology at the University of Cambridge and the Medical Research Council/Wellcome Trust Behavioral and Clinical Neuroscience Institute (Roiser and Sahakian, 2013). The sustained attention and planning needed for arranging a meeting or formulating a business plan, for example, requires intact cold cognitive processes; depressed patients show consistent impairments in these domains (Clark et al., 2009). Hot cognition, in contrast, involves thinking patterns that are influenced by emotions, such as the negatively biased responses that are common in depression and decision making when there is a conflict between risk and reward. Indecisiveness, one of the DSM-recognized criteria for depression, represents dysfunction in both cold and hot cognitive processes.

Importantly, cognitive dysfunction impacts both functionality and psychosocial functioning, which contribute to poor outcome and high relapse rates (Bortolato et al., 2014). For example, in a study of 48 patients hospitalized with a diagnosis of MDD, nearly 60 percent remained functionally disabled 6 months after hospitalization despite significant improvement in depressive symptoms (Jaeger et al., 2006). According to Sahakian, persisting deficits in information processing, memory, and verbal fluency predict poor academic, occupational, and daily functioning in MDD and are among the most debilitating problems for patients (Lee et al., 2012). These cognitive deficits result in poor workplace functionality and elevated costs due to absenteeism and reduced productivity. Indeed, the indirect costs related to workplace issues are the major contributor to the economic burden imposed by MDD (Fineberg et al., 2013; Greenberg et al., 2015; Olesen et al., 2012).

Various components of cognition can be measured objectively with multiple neuropsychological tests. Sahakian coinvented the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992), which tests multiple aspects of mental functioning using nonverbal approaches. These and other cognitive tests show that patients with depression have moderate deficits in spatial working memory as well as problems in other forms of executive function, attention, and memory. In addition, remitted patients continue to show problems in executive functioning and attention.

NEUROBIOLOGY OF COGNITIVE IMPAIRMENT IN DEPRESSION

Depression, like other mental disorders, represents a disorder of brain circuits (Insel et al., 2010), and the suboptimal effectiveness of currently available treatment likely reflects an incomplete understanding of the neurobiology of depression and, in particular, its neurobiological relationship to cognitive dysfunction, according to several workshop participants.

In 1986, Garrett Alexander and colleagues described five parallel and partially segregated loops that link the cortex to the basal ganglia (Alexander et al., 1986; Lawrence et al., 1998). Sahakian said the cold cognitive loop has to do with planning and problem solving, whereas the hot affective loop links emotional brain areas with the orbitofrontal cortex (see Figure 2-1).

Using functional magnetic resonance imaging (fMRI), characteristic patterns of brain activation in depressed patients have been identified. Catherine Harmer, professor of cognitive neuroscience at the University of Oxford, said depressed patients show increased activation in task-positive networks (networks that are activated in response to attention-demanding tasks) in areas such as the dorsolateral prefrontal cortex (DLPFC), which is involved in attention-demanding tasks such as spatial working memory tasks (Fitzgerald et al., 2008; Harvey et al., 2005; Matsuo et al., 2007; Walter et al., 2007), and reduced deactivation in a network called the default-mode network (DMN), which is involved in reflective thinking (Norbury et al., 2014; Rose et al., 2006). According to Harmer, in depressed patients task-positive networks go into overdrive while, at the same time, patients find it difficult to switch off the DMN, which may contribute to rumination. Modulating these circuits are neurotransmitters such as dopamine, noradrenaline, and serotonin, said Sahakian.

One phenomenon observed in patients with MDD, as well as in those with subclinical depression and even healthy controls with genetic variants linked to an increased risk for depression, is the tendency to have "catastrophic reactions to errors," said Diego Pizzagalli, professor of psychiatry at Harvard Medical School (Elliott et al., 1997; Holmes and Pizzagalli, 2008a; Holmes et al., 2010; Pizzagalli et al., 2006). What this means is that after a mistake is made even on a relatively simple neuropsychological task, performance is significantly impaired, said Pizzagalli.

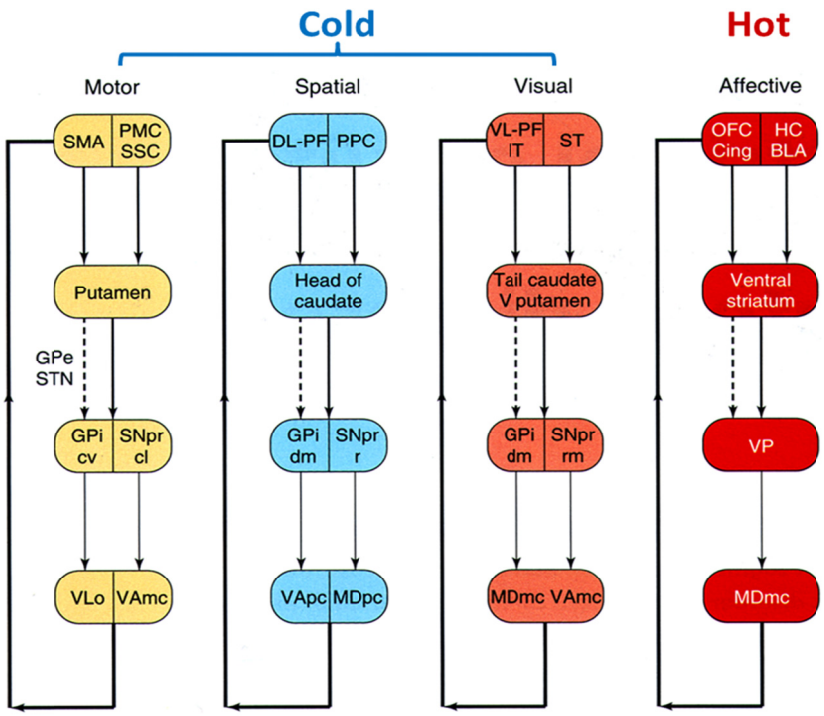

FIGURE 2-1 Cold and hot cognitive cortico-striatal circuits in the human brain. NOTE: BLA, basolateral amygdala; Cing, anterior cingulate; cl, caudo-lateral; cv, caudo-ventral; DL-PF, dorsolateral prefrontal cortex; dm, dorsomedial; GPe, external segment of globus pallidus; GPi, internal segment of the globus pallidus; HC, hippocampus; IT, inferior temporal cortex; mc, magnocellularis; MD, mediodorsal thalamus; o, pars oralis; OFC, orbitofrontal cortex; pc, parvocellularis; PMC, premotor cortex; PPC, posterior parietal cortex; r, rostral; rm, rostromedial; SMA, supplementary motor area; SNpr, substantia nigra, pars reticulata; SSC, somatosensory cortex; ST, superior temporal gyrus; STN, subthalamic nucleus; V putamen, ventral putamen; VA, ventral anterior thalamus; VLo, ventrolateral thalamus; VL-PF, ventrolateral prefrontal cortex; VP, ventral pallidum SOURCE: Adapted from Lawrence et al. (1998, fig. 1). Presented by Barbara Sahakian at the IOM Workshop on Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression, February 24, 2015.

Neurobiologically, this can be explained by a combination of dysfunctions: over-recruitment of regions of the brain necessary for responding quickly and automatically to emotionally salient cues (e.g., the rostral anterior cingulate cortex, or rostral anterior cingulate cortex [ACC]) coupled with an inability to recruit the brain region responsible for regulating emotion (e.g., the left DLPFC) (Holmes and Pizzagalli, 2008b). In addition, there may be increased coupling between the rostral ACC and the amygdala, leading to an inability to cope with the task and excessive rumination, said Pizzagalli (2011).

DEFINING COGNITIVE IMPAIRMENT IN DEPRESSION

Given the importance of cognitive impairment in depression, several workshop participants called for an expansion of the diagnostic criteria for MDD in the DSM-5, particularly to include symptoms that capture hot cognition, which is important in depression. Of the nine diagnostic criteria currently listed, only one, "diminished ability to think or concentrate or indecisiveness," clearly represents a cognitive issue (American Psychiatric Association, 2013). Several participants noted, however, that research on hot cognition is sparse, and called for additional research to clarify the underlying biology of cognitive impairment in depression, in particular hot cognition.

3

State of the Science: Treatment Development

Highlights

- Cognition should be a target for treatment in depression (Sahakian).
- Studies of the effectiveness of pharmacologic treatment of depression have failed to show consistent benefits for cognition, in part because of variability in trial design and assessments (Keefe).
- Pharmacological treatment of depression has only small beneficial effects on certain aspects of cognition, such as verbal and visual memory, and may even worsen others such as processing speed (Keefe).
- Innovative pharmacotherapy approaches may improve therapy for cognitive dysfunction in depression (Harmer, Sahakian).
- Non-invasive neuromodulation has shown some effectiveness for the treatment of depression, but effects on cognition are unclear (Etkin, Pizzagalli).
- Very few studies have assessed the effects of psychotherapy, cognitive behavior therapy, or cognitive remediation on cognition in depression (Bowie, Pizzagalli).
- Effective treatment of cognitive dysfunction in depression will likely require a multimodal approach and stratification of patients to enable more individualized therapy (Areán, Bowie, Pizzagalli, Sahakian).

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

As outlined earlier, depression is associated with neuropsychological dysfunction across multiple domains, including executive function, attention, memory, and psychomotor speed. Although there are many approaches to target cognition in depression—including both pharmacological and nonpharmacological approaches—developing new treatments has proved challenging. Amit Etkin, assistant professor of psychiatry and behavioral sciences at Stanford University, framed the challenges with three key questions:

1. Does treating depression improve cognition?
2. How do we know if cognition is improved?
3. What would a cognition-improving treatment target look like?

PHARMACOLOGICAL TREATMENT

Antidepressant medications developed in the 1950s have been largely supplanted by second generation antidepressants that modulate the monoamine neurotransmitter system by increasing the availability of serotonin, norepinephrine, and dopamine. However, even these newer drugs have limited efficacy, with only modest superiority over placebo in most clinical trials (Undurraga and Baldessarini, 2012). Moreover, no drugs have been approved by FDA or the European Medicines Agency (EMA) for the treatment of cognitive impairment in MDD, although many clinical studies of antidepressants have included cognitive endpoints and have shown either improvements in cognition or treatment-associated cognitive impairment as an adverse event (Keefe et al., 2014). Because mood symptoms and cognition track with one another in patients with depression, particularly during treatment, it has proved challenging to design studies that assess cognition independently from changes in mood, said Richard Keefe, professor of psychiatry and behavioral sciences at Duke University. These challenges relate to selection of the appropriate study design, patient population, and assessment tools, as well as the method of data analysis. Keefe discussed a meta-analysis of the literature that he and his colleagues conducted to assess the effects of antidepressant monotherapy and augmentation therapy (i.e., adding a second drug to existing antidepressant therapy) on cognition (Keefe et al., 2014). Forty-three studies were included in this analysis, yet they varied in terms of the study design (e.g., placebo controlled versus active comparator versus open label), study participants, sample size in the individual study, study duration,

agents tested, and primary and secondary outcomes. Most of these studies had cognition as a primary outcome, although some had it as a secondary outcome or safety report. Most studies also assessed cognitive function in the presence of mild to severe depressive symptoms, which made it difficult to determine whether treatment directly affected cognition or if effects were secondary to changes in mood. Furthermore, the studies used a wide variety of tests across multiple domains, including processing speed, psychomotor function, attention, verbal learning and memory, verbal fluency, visuospatial awareness, and executive function. The categorization of an individual test to a domain varied from study to study, said Keefe, reflecting the lack of consensus across the field. All of this variability made it challenging to compare studies, he said.

Most of the studies demonstrated at least some statistically significant cognitive benefit, particularly in the domains of verbal memory, working memory, and processing speed. However, the effects were small, and for only 12 percent of the cognitive measures did the analyses favor active treatment over placebo; 4 percent percent favored placebo. One question Keefe asked is whether these results exceed "the file drawer problem," by which investigators tend to publish positive results, but not negative results. He noted that all cognitive tests were included in the analysis, with no attempt to support a specific hypothesis, such as that certain domains would be affected more than others. Nor was the question of clinical meaningfulness addressed in this analysis. Nonetheless, some tentative trends emerged: Monotherapy resulted in slight improvements in verbal memory, while augmentation therapy resulted in improvements in visual memory, verbal memory, processing speed, executive function, and cognitive control.

Keefe also noted that all of these studies looked only at cold cognition because the literature on hot cognition is new and sparse. However, it may be that hitting hot cognition is necessary to improve cognition as well as to alleviate depressive symptoms and experiences. He also mentioned another study of lisdexamfetamine, which included self-reports and informant reports as well as a cognitive battery as outcome measures. Interestingly, in this study, the computerized battery did not demonstrate significant improvement with the active compound compared to placebo, although both self- and informant reports did (Madhoo et al., 2014).

With regard to determining whether a drug affects cognition directly or indirectly, Keefe described a recent study comparing vortioxetine and duloxetine using both objective and subjective assessments: the digit

symbol substitution test (DSST) to measure a direct effect on cognition, the Montgomery-Åsberg Depression Rating Scale (MADRS) to assess improvement in depressive symptoms that could directly affect cognition, and improvement on a functional capacity measure, the University of California, San Diego (UCSD), performance-based skills assessment (UPSA). Both drugs improve cognition, as has been demonstrated in other trials, but path analysis in this trial indicated that vortioxetine does so through a direct effect of the treatment, whereas the cognitive improvement from duloxetine is mediated by a consequence of improvements in depressive symptoms (Katona et al., 2012; Mahableshwarkar et al., 2015; Raskin et al., 2007).

Keefe concluded that no firm conclusions can be drawn about the effects of antidepressants on cognition using pharmacotherapy. Although tentative trends toward cognitive improvements from both monotherapy and augmentation therapy emerged, the studies were limited by a high degree of variability in study design, numbers of patients enrolled, duration of treatment, outcome measures, and heterogeneity among patients (e.g., comorbidities and the severity of depression). He further noted that while antidepressants may have very small beneficial effects on some aspects of cognition such as verbal and visual memory, they may worsen others, such as processing speed. These effects may be limited only to certain subgroups of patients, he added.

Barbara Sahakian and others called for innovation in the development of new treatments. For example, cognitive-enhancing drugs represent a class of drugs that may be beneficial in patients with depression. Modafanil, a putative cognitive-enhancing drug, has been shown to enhance working memory and task-related motivation in healthy volunteers, and emotional processing (hot cognition) in patients with first episode psychosis, according to Sahakian (Muller et al., 2013; Scoriels et al., 2012). A meta-analysis demonstrated that as an augmentation therapy, modafanil improved overall depression scores, remission rates, and fatigue symptoms (Goss et al., 2013). Sahakian commented that the multimodal drug vortioxetine has been reported to improve performance on tests of cold cognition (McIntyre et al., 2014). Sahakian also advocated for further research on the use of fast-acting antidepressants, such as ketamine, a glutamate NMDA receptor agonist that induces synaptogenesis (Duman and Aghajanian, 2012). Indeed, studies suggest that a single dose of intravenous ketamine significantly improves symptoms of depression within 2 hours (Zarate et al., 2006). Other novel drugs are also in development. For example, Catherine Harmer is using experimental

medicine approaches (discussed in Chapter 4) in studies with Eli Lilly on the development of a nociceptin receptor agonist for the treatment of depression.

NON-INVASIVE NEUROMODULATION

Based on findings discussed earlier about the neurobiological basis of cognitive dysfunction in depression, a variety of nonpharmacologic treatments are being considered as potential treatments, including transcranial magnetic stimulation (TMS), especially repetitive TMS (rTMS); transcranial direct current stimulation (tDCS); psychotherapy; and cognitive remediation.

Neuromodulation with rTMS or tDCS provides a non-invasive way to stimulate regions of the brain that function abnormally in depressed patients. However, although many studies have demonstrated effectiveness in treating depression, their effects on cognition remain unclear. TMS delivers stimulation via a coil placed over the DLPFC. Etkin said TMS appears to normalize connectivity between brain networks involved in cognition and emotional regulation, that is, the left DLPFC and the DMN, although the specific targets within these networks have yet to be elucidated (Liston et al., 2014). Neuromodulation with tDCS uses a different approach, applying a very low-intensity direct current over the scalp between two electrodes, which generates a current flow that can elicit cortical excitability changes (Demirtas-Tatlidede et al., 2013; Nitsche et al., 2003). Again, the neurophysiologic response to this excitation is unclear, although some studies have suggested that it may modulate synaptic plasticity (Marquez-Ruiz et al., 2012).

Diego Pizzagalli discussed many studies of TMS. In one review of 16 randomized, sham-controlled studies, only 3 showed beneficial effects on executive function (Tortella et al., 2014). In another review of 13 sham-controlled studies, 5 showed significant differences in measures of cognitive function (Demirtas-Tatlidede et al., 2013). While methodological differences between the studies may account for these varying results, another possibility is that sham TMS itself produces an effect, or that very strong placebo effects mask the effectiveness of the approach, said Pizzagalli. Sham-controlled studies of tDCS have produced somewhat more promising results in terms of beneficial effects on some domains of cognitive function, such as working memory and attention (Demirtas-Tatlidede et al., 2013; Mondino et al., 2014; Tortella et al., 2014).

Another factor may help to explain the variable results using neurostimulation, said Etkin. Nearly all data available on rTMS for depression targets the left DLPFC with high-frequency stimulation; however, the literature supporting this as the best target in depression is weak. The field has settled on this target without, for example, rigorously testing whether left or right DLPFC high frequency rTMS is better. For post-traumatic stress disorder (PTSD), most rTMS studies have targeted the right side, and some of these studies have shown cognitive improvement, he said. He also noted that other brain regions, such as the basal forebrain or the amygdala, might also be interesting targets; however, tools to reach those targets are not available.

PSYCHOTHERAPY AND COGNITIVE REMEDIATION

Very few studies have tested the effects of psychotherapy or cognitive behavioral therapy on cognition in depression, said Pizzagalli. One study he cited found that a combination of psychodynamic therapy plus fluoxetine was superior to either one alone (Bastos et al., 2013). A new type of treatment called metacognitive therapy, which targets perseverative thinking and includes an attentional training component, has shown some promise in improving spatial working memory and executive functioning in patients with depression. However, there were substantial individual differences among the 48 subjects tested, and changes in cognition did not correlate with changes in mood symptoms (Groves et al., 2015).

Another approach, cognitive remediation, has proved to be both efficacious and effective in treating schizophrenia, yet has been applied infrequently and with mixed results for the treatment of depression, according to Christopher Bowie, clinical psychologist and associate professor at Queen's University in Kingston, Ontario, Canada (McGurk et al., 2007). Cognitive activation—such as the computerized drill and practice puzzles and games popularized by Lumosity and other companies—represents only one pillar of cognitive remediation. The other two pillars are strategic monitoring, which involves helping people to identify the strategies they use to solve problems, and generalization, often referred to as bridging, which aims to help people envision or practice how they would use their improved cognitive skills in an everyday environment. Bowie said that for people with depression, strategic monitoring and generalization represent perhaps the most important aspects of cognitive

remediation because patients lose their incentive to participate if they are unable to see benefits in their everyday lives (see Figure 3-1).

Early studies of cognitive remediation in depression have, for the most part, failed to address all three pillars, but have involved computerized cognitive training in small, minimally controlled studies. Although patients saw improvements in cognitive measures, everyday behaviors remained relatively unchanged (Alvarez et al., 2008; Elgamal et al., 2007; Meusel et al., 2013; Morimoto et al., 2014; Naismith et al., 2010). Bowie's group conducted a study that used all three pillars of cognitive remediation in a group of patients with treatment-resistant depression.

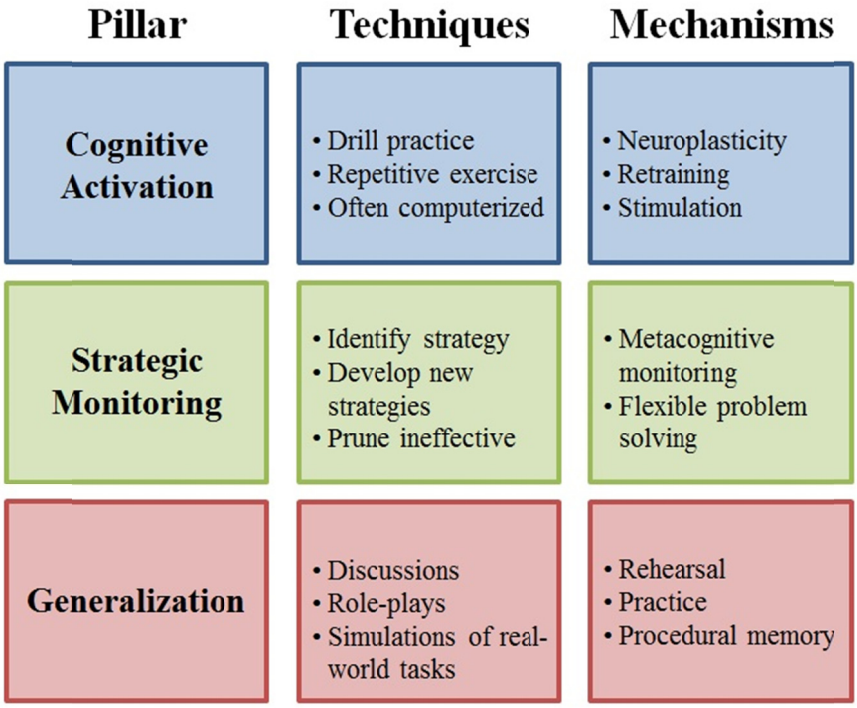

FIGURE 3-1 The three pillars of cognitive remediation.
SOURCE: Presented by Christopher Bowie at the IOM Workshop on Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression, February 24, 2015.

Following 90-minute sessions that included computer-based exercises and working with a therapist for 10 weeks, patients were given homework: two 20-minute online sessions per day with the same computerized

tasks they had done with the therapist as well as taking notes about their strategies for using cognitive skills in their everyday life (Bowie et al., 2013). Large effects were observed on cognitive tests for learning and memory, attention, and information-processing speed, but not for executive function, and there were no improvements in self-rated everyday behavior. These results prompted the researchers to explore how to focus cognitive remediation approaches on acquisition of everyday skills and behaviors and how to help people understand how to use new-found abilities in everyday life.

In response to the lack of improvements in self-rated behavior seen in these studies, Bowie and colleagues developed an "Action-Based Cognitive Remediation Program," which takes a holistic behavioral therapy approach. The program aims to help patients develop and prune strategies so they can use their cognitive skills optimally to solve problems. It teaches skills procedurally using a computer-based cognitive training program and then immediately puts those skills to use in simulated real-world environments. Participants showed robust and durable improvements in verbal memory, verbal fluency, and functional capacity, said Bowie, as well as statistically significant increases in the number of people working 3 to 6 months post-treatment, and less job stress among those who were already working.

COMBINING AND PERSONALIZING THERAPIES

The choice of optimal treatment for an individual patient varies depending on a number of factors, many of which have yet to be clearly defined. Sahakian said cognitive treatments are important for top-down control, while pharmacologic interventions are important for treating negative affective bias and reinstating positive attitudes (Roiser et al., 2012). Multiple treatments may be needed, including use of pharmacologic treatments to put people into the right state so they can learn and change the way they are thinking using cognitive-behavioral approaches. Such approaches also may enable patients to identify when their mood is being dysregulated. Bowie agreed that combination treatments may be needed to synergistically improve both cognition and function. He also suggested that the different treatments may have variable levels of effectiveness at different stages of disease. For example, those with depression but very mild cognitive impairment may respond differently to a treatment than the typical population recruited into research studies.

Identifying people with certain neural abnormalities is another approach to personalizing treatment, said Pizzagalli. For example, individuals who have difficulty switching off the DMN and engaging task-positive networks might benefit from neurostimulation or cognitive remediation. Prescreening and stratifying patients may be the way forward to deal with the problem of heterogeneity, he said. However, stratifying patients into different subgroups based on symptomatology, neurobiology, and biomarkers remains a substantial challenge. Etkin concurred, adding that while many participants supported the idea of subtyping, it points to the need for many more targets and tools to match subgroups to mechanisms to interventions.

Patricia Areán, then professor of psychiatry at the University of California, San Francisco, School of Medicine, suggested that cognitive responses to treatment may help identify subgroups of depression as well as appropriate therapeutic approaches. For example, behavioral problem-solving approaches may be particularly efficacious in patients with depression and executive dysfunction.

4

Challenges and Potential Solutions to Enable Development of Successful Treatments

Highlights

- Early detection and early effective treatment may prevent depression from becoming chronic, debilitating, and relapsing (Sahakian).
- Experimental medicine models that enable modeling the disease process in humans may provide efficacy signals early in the development of new treatments (Harmer).
- Stratification of patients into narrow groups for clinical trials of cognition in depression may improve the efficiency of the trial and help address pseudo-specificity, but may also limit generalizability (Fava, Keefe, Laughren).
- Cognitive assessments are widely used to assess the effects of treatment on cognition, yet functional measures may provide more clinically meaningful measures (Harvey).
- Subjective and objective measures of cognition both have value in assessing treatment effects, yet both also have disadvantages and often do not correlate with one another (Areán, Fava, Harvey).
- Brain changes across the lifespan must be taken into account when selecting assessment tools for clinical studies (Areán).
- Innovative technologies, such as those using smartphones, have the potential to provide continuous assessments of mood and cognition and could also be useful in treatment decisions (Areán).

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

Several workshop participants outlined challenges and potential solutions that would enhance studies of cognitive improvement in depression. Progress will require clarification of definitions and consideration of a variety of design and assessment strategies, all of which impact the ability of a trial to demonstrate effectiveness in a reasonable time frame and with a manageable number of participants, said several participants. As mentioned by Barbara Sahakian and others, depression studies are further constrained by the fact that, because most patients with depression are treated by primary care physicians, tools for the trials need to be simple enough to be used in the primary care setting.

EARLY DETECTION AND TREATMENT AND THE IMPORTANCE OF BIOMARKERS

Cognitive dysfunction is present even in the first episode of MDD, and persists even after other symptoms of depression have abated (Bora et al., 2013; Trivedi and Greer, 2014). In addition, untreated depression leads to poorer response to treatment with antidepressant medications, a lower rate of remission, a higher risk of chronicity, and a higher number of recurrences, according to a systematic review and meta-analysis of studies by Lucio Ghio and colleagues that looked at the relationship between the duration of untreated depression and clinical outcomes (Ghio et al., 2014). What this means, said Sahakian, is that early detection and early effective treatment may prevent depression from becoming debilitating, chronic, and relapsing.

Tools needed to achieve early detection and predict response to treatment include a range of biomarkers, including genetic, neuroimaging, cognitive, and other physiologic measures (Insel et al., 2013). For example, studies from Ian Goodyer's and Sahakian's group have shown that elevated morning cortisol levels in adolescent boys signal an elevated risk of MDD, and that a genetic marker associated with serotonin (5-HTTLPR) as well as early exposure to childhood adversity predict deficits in cognitive and emotional processing in adolescents (Owens et al., 2012, 2014). These markers can be measured objectively and easily, said Sahakian, offering the means to detect individuals at risk of developing depression 1 year later.

Neuropsychological tests may also be useful to detect early signs of depression or predict response to treatment. Amit Etkin described the International Study to Predict Optimized Treatment in Depression (iSPOT-D), in

which 1,008 unmedicated patients were randomized to treatment with one of three common antidepressants over an 8-week period and followed with a broad cognitive battery. The aim of the study was to determine whether performance on a standardized test battery of cognitive and emotional function was predictive of remission or response to treatment. The battery included tests of psychomotor function, decision speed, verbal memory, working memory, cognitive flexibility, attention, response inhibition, information processing speed, executive function, emotion identification reaction time, and emotion bias reaction time. The study showed that a subgroup of depressed patients that could be discriminated based on cognitive test performance had poorer treatment outcomes, suggesting that a composite biomarker based on the antidepressant outcome and test performance could be used to predict treatment outcome (Etkin et al., 2014). Another study by Walsh and colleagues suggested that tests of working memory, such as the n-back verbal memory task, may predict clinical outcome (Walsh et al., 2007).

EXPERIMENTAL MEDICINE MODELS

Lack of efficacy is the main reason for drug development failures (Hay et al., 2014) yet the current phased approach to drug development means that efficacy is typically not assessed until a relatively late stage of development, after substantial resources have been invested (Kola and Landis, 2004). Novel candidate treatments are often screened for efficacy using preclinical animal models, but these models have low predictive validity, according to Catherine Harmer. She proposed using an experimental medicine approach, which models the disease process in humans by testing how various parameters (e.g., different experimental compounds, dosing, etc.) impact how individuals suffering from MDD perform on neurocognitive tests. This approach aims to provide answers to key questions early in development.

Drug development for depression has largely been built on the success of selective serotonin reuptake inhibitors (SSRIs) and thus has led to a generation of similar drugs that focus on serotonin. More recently, therapeutic delay, or the delayed onset of antidepressant drug action, prompted the search for neurobiological correlates that are expressed in a delayed manner, such as changes in plasticity. A third approach, advocated by Harmer, is to assess the effects of antidepressants on neural and psychological processes that are important in the early stages of depression; for

example, the effects of drugs on negative biases in emotional processing, or hot cognition. Indeed, studies show that early antidepressant drug treatment can affect hot cognitive bias even before patients notice improvements in mood, suggesting that antidepressants may work not directly as mood enhancers, but indirectly by changing the way information is processed (Harmer et al., 2009; Roiser and Sahakian, 2013).

Harmer showed data from her studies in patients with depression on their ability to pick up on happy facial cues (Harmer et al., 2009). In comparison to healthy controls, depressed patients find it much more difficult to perform this task; however, after just one dose of the noradrenergic reuptake inhibitor reboxetine, patients show an improved ability to recognize happy facial expressions. They do not feel any better and are no less depressed, said Harmer, but these early changes in emotional processing suggest they are already processing emotional cues in a more positive way, which would be expected to have therapeutic benefit over time. Moreover, these findings suggest this type of model might be used to screen new treatments early in the development process. Further investigation showed that the model met a number of key criteria that allow it to be used for this purpose:

1. The model is sensitive to a range of established antidepressants with different neurochemical actions.
2. Early effects predict treatment response.
3. The model can discriminate between ineffective and effective agents.
4. It is sensitive to novel mechanisms of action.
5. It can be used to generate hypotheses, calculate dosing information, or identify subgroups useful for randomized clinical trials.
6. It can be used in healthy people as well as in depressed patients (Harmer et al., 2009; Pringle et al., 2013; Roiser and Sahakian, 2013; Shiroma et al., 2014).

This marker is now being used by five pharmaceutical companies to explore new candidate treatments for depression and anxiety at an early stage of development, said Harmer. For example, in a collaboration with Eli Lilly and Company on the development of a new drug with a novel mechanism of action that showed good results in preclinical animal models, Harmer and colleagues showed that the emotional processing response at 1 week not only provided an early marker of likely efficacy, but also predicted a subgroup of responders.

Harmer said it also may be possible to use these same kinds of models to understand and predict mechanisms of action on cold cognitive targets such as memory, executive function, and depression. The CANTAB, for example, has been used extensively to understand the impact of drug treatment on cognition and the mechanisms behind drug efficacy, and to identify which patient groups are most likely to benefit from specific drugs (Turner et al., 2003, 2004a,b).

The n-back task is one specific test used to assess visual working memory in both healthy and clinical populations, said Harmer. As mentioned earlier, depressed patients find it hard to switch off the default-mode network, but have increased activation in the task-positive network. Indeed, using the n-back test, investigators showed that depressed patients exhibited the characteristic hyperactivity of task-positive circuits, and that treatment with fluoxetine failed to normalize this overactivity (Walsh et al., 2007). This suggested that the n-back test might be useful as an experimental model to separate out mood and cognitive effects of novel antidepressants on cognition. To test this hypothesis, Harmer said that she and her colleagues used the n-back test in combination with fMRI in patients randomized to receive vortioxetine or placebo for 10 days. Vortioxetine is a novel, multimodal antidepressant that has been shown to have positive effects on cognition in depression (Katona et al., 2012; McIntyre et al., 2014). In both healthy controls and depressed patients in remission, vortioxetine treatment improved both subjective and objective measures of cognition and resulted in decreased neural activity across the brain regions that are affected in depression, that is, a reduced activation of the DLPFC and increased deactivation of parts of the DMN. The fact that these effects were seen in healthy people demonstrates the usefulness of this approach in early-stage drug development, said Harmer. However, she noted that more sensitive tasks may be needed to demonstrate cognitive improvements in individuals who are cognitively healthy.

TRIAL DESIGN

A variety of study designs may be used in evaluating treatments aimed at improving cognition in patients with depression. Three specific types—adjunctive, acute-phase, and switching—were mentioned frequently during the workshop. The choice of design affects the duration and size of the study as well as inclusion and exclusion criteria. Other

important trial design decisions involve the choice of control, that is, active comparator, placebo, or both, and the study population.

Design Type

Adjunctive approaches, where a second treatment is added to an existing treatment regimen, may be particularly useful to address cognitive impairment in depression because cognitive symptoms frequently remain even after mood has improved in response to treatment with an antidepressant, said Tiffany Farchione, deputy director, Division of Psychiatry Products at FDA. A concern from the regulators' perspective is whether the second drug improves depression overall or specifically targets cognition. Thomas Laughren referenced the lisdexamfetamine trial as an example in which patients improved on both the cognitive measure and the MADRS when lisdex (in comparison to placebo) was added. However, a more careful look at scores on MADRS items suggested that the drug was specifically targeting cognition. Laughren suggested that this design represents one way of addressing concerns regarding pseudo-specificity, which is discussed in more detail in Chapters 5 and 6.

Acute-phase designs target the acute phase of the illness. Such designs might incorporate three arms with two different treatments (active control and investigational agent) as well as a placebo arm, and could enable targeting of both depression and cognitive impairment, while also addressing the concern of pseudo-specificity. Although both treatments might show antidepressant effects, if the investigational agent but not the active control also improves cognition, this could be taken as evidence that the agent specifically targets cognition. The vortioxetine study (CONNECT) is an example of this approach. The CONNECT study compared vortioxetine and duloxetine, both active agents, against a placebo with results demonstrating that both treatments significantly improved depressive symptoms based on the MADRS scale, but only vortioxetine was found to be efficacious in improving cognitive function in depressive patients (Mahableshwarkar et al., 2015).

Switching designs, in which patients in a residual phase of depression or remission are randomized to continue on one antidepressant or switch to a second drug that is thought to improve cognition might also be useful, said Laughren; however, he said he is not aware of anyone using this design in depression studies.

Controls

The use of an active comparator versus placebo as the control represents another important design consideration. According to Farchione, the agency has a strong preference for an active comparator, typically another antidepressant.

Study Population

Depression is a heterogeneous condition, affecting people across the lifespan and varying in terms of symptomatology and response to treatment. Because not all patients with depression have cognitive impairment, enrichment for those who do makes sense for trials aimed at improving cognition in depression, Fava said. Beyond selecting individuals with cognitive impairment, other population decisions include whether to include untreated patients, those who have responded to treatment and remitted, or those who have responded but have residual cognitive symptoms. Each choice has advantages and disadvantages, depending on the trial being conducted. For example, for a trial of an augmentation therapy, enrichment with patients who have residual cognitive symptoms may make the most sense.

Stratifying patients into narrow groups for clinical trials may, in addition to improving the efficiency of the trial, help deal with pseudospecificity, said Richard Keefe. For example, a recent study of lisdexamfetamine enriched the study population by selecting patients with remitted depression and no attention deficit hyperactivity disorder (ADHD) in order to remove the confounding effects of ADHD on measures of attention (Madhoo et al., 2014). Fava, however, said a simpler design would be to start with remitted MDD patients. While enrichment may be deemed necessary to ensure that a trial is able to demonstrate a treatment effect, selecting more narrow groups for clinical trials also has a downside in terms of the generalizability of the results. To illustrate this point, Laughren described a meta-analysis of placebo-controlled antidepressant trials conducted by FDA, in which out of nearly 100,000 patients in the analysis, there were only 8 suicides. This suggests that suicidal patients were excluded from most controlled trials, despite the fact that suicidality is a significant issue in depression (Stone et al., 2009).

Enrichment may be achieved using either objective or subjective measures, each of which has advantages and disadvantages. This is discussed in more detail in the section on assessment.

Future Directions in Study Design and Content

Keefe suggested a number of changes to study design that could increase the field's likelihood of identifying an efficacious drug. These changes include using study designs and statistical methods that maximize test validity and minimize confounding factors, assessing treatment effects on specific domains of cognitive function. Other changes in design that were mentioned by several participants included assessing changes over time rather than only at baseline and end of study, and identifying signals that can be assessed in 1 week or 48 hours to enable faster trials, particularly in Phases I and II. Adaptive approaches such as those used in the I-SPY2 TRIAL for breast cancer therapies might also be useful for testing treatments for cognitive impairment in depression, said Thomas Insel (Barker et al., 2009). This approach uses a clustered randomized design to match experimental therapies with the appropriate patients, using interim outcomes to adapt the trial as it progresses.

Keefe also called for an increased number of larger-scale, longer-term, placebo-controlled studies, as well as further research to overcome the substantial methodological limitations of prior investigations and a more systematic examination of the cognitive effects of pharmacotherapy in MDD, similar to what is under way in schizophrenia. More studies are also needed to optimize the use of neurostimulation and psychotherapy as treatments for cognition in depression, said Diego Pizzagalli. One fundamental question that needs answering, he said, is whether improvements in cognition are mediated directly or indirectly by improvements in symptoms of depression. Pizzagalli also called for studies that demonstrate target engagement with specific interventions.

A number of other suggestions emerged related to the concept of stratifying participants to deal with heterogeneity. Rather than using depression as the target, Insel suggested that stratification could enable development of a "purer culture" of participants with a specific problem than can be addressed with drugs, devices, or psychotherapy. Pizzagalli suggested using neural navigation to identify people who might disproportionately benefit from various interventions based on neural function and dysfunction. Patricia Areán suggested not looking at cognitive impairment as an outcome, but as a way of identifying "flavors" of depression. For example, there is some evidence that certain interventions are particularly effective on those who have a depressive disorder and executive dysfunction, However, Etkin noted that while many participants expressed support for the idea of subtyping, tools are needed to show whether a treatment

effect is a subgroup effect or a general effect. Matching mechanism to intervention would be helpful in clarifying the reasons for a treatment effect or lack of effect.

ASSESSMENT

Assessment of cognition and function can be accomplished using both objective measures that are performance based, as well as subjective observational, self-reported, and informant-reported measures. Whatever the approach, the requirements are essentially the same: validity, adequate psychometric properties, practicality, and tolerability, said Philip Harvey, professor of psychiatry and behavioral sciences at the University of Miami Miller School of Medicine. The measure must also be sensitive to treatment effects and clinically meaningful, a point that was raised by several participants, including regulators. Yet while these general requirements are the same across studies and across disease conditions, the components of individual tests may vary.

Cognition Versus Function

Naturally, cognitive measures are widely used in studies to assess the effects of a treatment on cognition, but the need to find measures that are clinically meaningful to patients has prompted many investigators to consider functional measures as an alternative or adjunct. Harvey and colleagues conducted a study of clinically stable patients with schizophrenia, schizoaffective disorder, bipolar disorder, and depression, using a battery of neuropsychological tests assessing eight cold cognitive domains. The study showed that cognitive performance profiles were similar across all four groups, although there were quantitative differences, with schizophrenia patients exhibiting more severe cognitive impairment (Harvey et al., 2015; Reichenberg et al., 2009). However, functional impairments vary substantially among these different groups. Many patients with schizophrenia have never held down a job, for example, while patients with MDD typically have experienced greater lifetime achievement not only in employment, but in social activities and education as well. Harvey suggested that in patients with depression who were previously functional but became unable to resume productive activities, one possible functional outcome measure for MDD trials might be returning to work or resuming other activities.

Objective Versus Subjective

Objective measures have the advantage of norms that are relatively devoid of bias; however, norms are population based and do not reflect premorbid performance levels. In contrast, subjective, self-reported measures are able to capture perception of change from premorbid levels; however, a patient's perception may be affected by cognitive appraisal, self-esteem, depression, and anxiety. Linking either objective or subjective measures to functional change may be one way to ensure that the results are clinically meaningful, said Fava (see Figure 4-1).

A recent meta-analysis of studies using objective measures of impaired cognition in depression showed that several tests—including the Stroop task, Trail Making Test B (TMT-B), and n-back—show robust impairments in depression (Snyder, 2013). Fava and colleagues have taken a different approach to assessing components of cognition such as attention and memory, developing a subjective self-rated scale called the Cognitive and Physical Functioning Questionnaire (CPFQ) (Fava et al., 2009). The CPFQ asks simple questions such as "How has your ability to find words been over the past month?" to which patients respond using a 6-point Likert scale ranging from "greater than normal" to "totally absent." The CPFQ has demonstrated internal consistency, high test-retest reliability, and sensitivity to change with treatment, and has been used in a number of studies from Fava's group. In addition, it has shown that even people who respond to treatment continue to report impairments in attention, memory, word finding, and mental acuity (Fava et al., 2006, 2009).

Fava and colleagues have also used the CPFQ to explore how heterogeneity of depression affects cognition. Correlating CPFQ results with data from the Harvard National Depression Screening Day Scale (HANDS), they found that the residual symptoms of cognitive impairment by self-report hold no association with the core symptoms of MDD (Pedrelli et al., 2010).

Fava's team has also looked at the overlap between objective (DSST, TMT-B, Cognitive Reflection Test [CRT], one-back) and subjective (CPFQ) measures of cognitive impairment using data from a clinical trial of vortioxetine. These studies have not yet been published, but suggest there is only partial overlap between subjective and objective measures. However, subjective impairment correlated with greater severity of depression

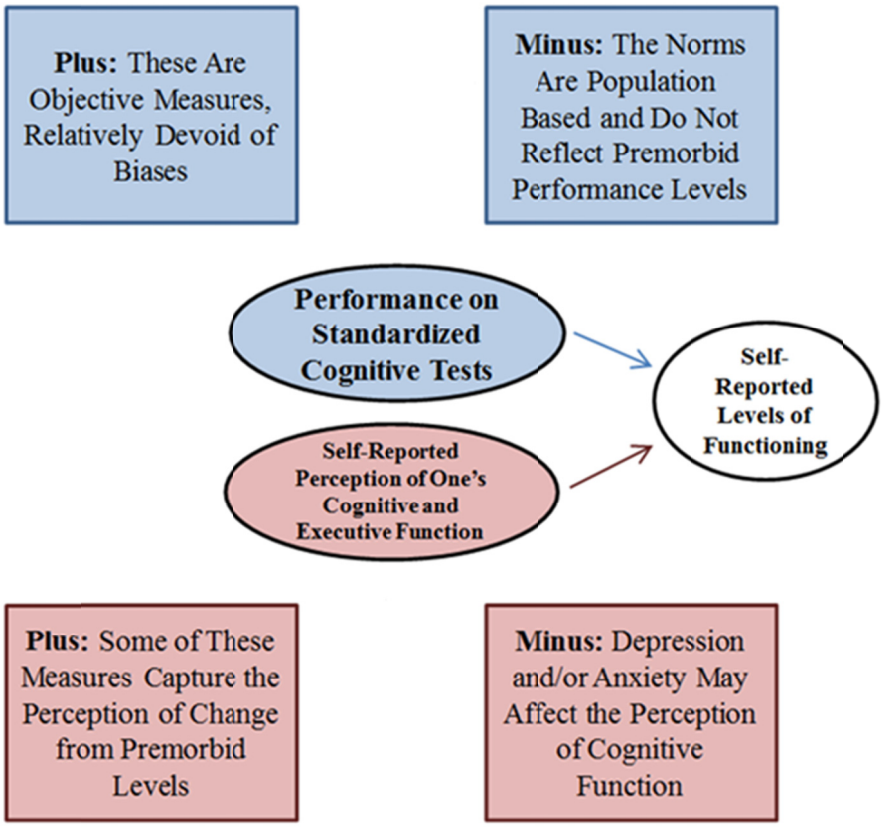

FIGURE 4-1 Objective versus subjective measures of cognition.
SOURCE: Presented by Maurizio Fava at the IOM Workshop on Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression, February 24, 2015.

and greater functional impairment, whereas objective impairment correlated only with functional impairment, but not severity. In the lisdexamfetamine study mentioned earlier, both self- and informant-reported measures showed significant improvement, but a computerized cognitive test battery did not (Madhoo et al., 2014). Fava and colleagues concluded that both subjective and objective measures have value, and that regardless of the measure, the functional impairment drives the outcome.

Harvey's group has been experimenting with interview-based strategies aimed at assessing cognition and function in both patients and informants. When using such measures, the difference between patient and informant reports appears to be especially important. For example, in a recent study of patients with schizophrenia, the single best predictor of everyday disability was the size of the discrepancy between the patient's assessment of his or her cognition and the clinician's impression, with patients tending to significantly overestimate their own cognitive function (Gould et al., 2015). Harvey concluded that patients' impressions of the severity of their disturbance was affected by their mood, and not correlated with objective measures.

Several participants expressed concern about the use of self-report measures because of concerns about the effects of mood or the patient's lack of insight or awareness about their condition. In a study of 30 patients with bipolar depression, patients' self-report of their functioning or the severity of their disturbance was uncorrelated with any objective performance-based measures, suggesting that mood or other factors may markedly influence patients' self-assessment (Harvey et al., 2015). However, Areán noted that while subjective measures may not be useful as standalone assessments, they can be useful as initial indicators that something is wrong. Moreover, she and Harvey added that in depression, even so-called objective measures are affected by amotivation and anhedonia, and that this can confound the results.

Co-Primary Measures

Harvey noted that in both Alzheimer's disease and schizophrenia trials, regulators have asked for co-primary measures in addition to cognitive performance, and both performance-based and interview-based measures have been used to determine functional capacity. Co-primary measures are thought to increase the face validity of the trial, resulting in better acceptance by consumers and clinicians, according to Michael Green, professor-in-residence in the Department of Psychiatry and Biobehavioral Sciences at the University of California, Los Angeles, Geffen School of Medicine and Co-Principal Investigator of the MATRICS project. The MATRICS-CT (Co-Primary Translation) initiative conducted a Validation of Intermediate Measures (VIM) study to assess various potential co-primary measures (Green et al., 2011). This study determined that the UPSA correlated well with the MATRICS

Consensus Cognitive Battery (MCCB) as the primary outcome measure, while self-reported measures did not.

In another study of patients with schizophrenia, a blinded clinician interview-based assessment (the Schizophrenia Cognition Rating Scale, or SCoRS) correlated with neuropsychological test performance as well as real-world functioning, but self-reported cognitive performance did not (Keefe et al., 2006). The SCoRS also demonstrated sensitivity to treatment effects, said Harvey. However, interviews with the patient but not the informant did not correlate, indicating that sensitivity to treatment effects is not necessarily linked to the questions that are asked, but rather who provides the answers. These data suggest that both clinician interview-based and performance-based assessments of cognition and function correlate with neuropsychological tests, and thus that they are essentially interchangeable.

Harvey described another study, again in schizophrenia, that assessed the independence of benefit from cognitive remediation and skills training with the UPSA, MCCB, and a clinician-based assessment of function, the Specific Level of Functioning Scale (SLOF). Cognitive remediation alone improved only neuropsychological test (MCCB) scores, while skills training alone improved only everyday outcome (UPSA) scores; only the combined therapy improved scores on all three tests. What this suggests, said Harvey, is that if a drug or treatment has a meaningful effect size, changes in everyday outcome could be used as a measure. Indeed, the UPSA has been widely used for conditions other than schizophrenia and bipolar disorder. In support of this view, in a study of patients with both schizophrenia and bipolar disorder, the UPSA scores were shown to correlate with independence in residential functioning (Mausbach et al., 2010).

Harvey concluded that validated performance-based measures of functional capacity that are related to everyday outcomes are optimal for assessing treatment outcomes.

Assessment Across the Lifespan

Given the brain changes that occur across the lifespan, Areán emphasized the need to take into account lifespan issues when doing assessments. In particular, children and older adults exhibit somewhat different symptoms and may respond differently to medication and behavioral interventions than do those in the middle years, yet these populations are difficult to recruit for studies and, as a result, existing longitudinal stud-

ies and clinical trials may not fully represent the full spectrum of people with depression and other mood disorders.

Areán also explored issues important to consumers. Interestingly, the treatment outcomes important to children and older adults with depression align, although they are applied in different contexts. For instance, both groups express concern about sleep, social contact, and the ability to concentrate and focus. Researchers have been historically interested in testing cognitive domains such as executive function, attentional bias and reward, motivation, and valuation, all of which affect everyday function and social contact. However, assessment in both children and older adults brings with it certain challenges. Both groups are notoriously poor reporters of their own mood, said Areán, and children may have a hard time naming what they are experiencing. In addition, assessment can be particularly burdensome in these groups: in children because of distraction and in elders because of fatigue. Another important consideration for children is the context in which an assessment is done; for example, teachers may report different behavior from parents. Some objective functional measures may be particularly useful in these populations, said Areán. For example, in older adults, driving performance is directly related to the degree of cognitive impairment, and in children school performance may be directly related to the degree of cognitive and emotional impairment. So combined assessments of behavior, cognition, and mood may be the most valid assessments of treatment effectiveness.

Innovative Tools for Assessment

Many participants spoke of the need to embrace innovation for the assessment and treatment of cognitive impairment in depression. Assessment can benefit from increased use of technology, ranging from the development of touchscreen computerized tests of hot cognition with domains including emotional processing, social cognition, motivation, and reward to the use of ubiquitous computing tools. These new tools have the potential not only to increase the accuracy of assessment, but may improve engagement and provide more meaningful data, said Areán. She also mentioned the need to look at outcomes other than mood and cognition that may be more salient to people's concerns.

Areán has been working with a number of innovative technologies designed to assess mood across the lifespan. One of these, Ginger.io, runs passively in the background on a smartphone, assessing activity, sleep patterns, and social connectedness in real time across many days or

weeks. The tool can also push surveys to participants about various issues such as mood and medication compliance. Tools such as this one have been used in treatment studies to collect data unobtrusively about changes in daily mobility and function that reflect changes in mood and that may be predictive of outcome.

Cognitive Health Corporation is using a variety of computer platforms and technologies to assess changes in mood and cognition by looking at eye movement, eye tracking, facial expressions, activity, coordination, manual dexterity, fine-motor dexterity, and voice data. In designing these tools, developers have been cognizant of the need not only to accurately assess cognition, but also to engage patients in the activity through games and provide outcome measures that are meaningful to patients. Many of these tools offer an additional advantage in that they can be adapted to individual performance at baseline or as the trial progresses, analyzing data in real time and optimizing information from previous trials. This improves accuracy and lessens the amount of time required for testing.

Areán described a study she is currently running to test whether mobile apps can improve mood, concentration, and motivation in people with depression. The BRIGHTEN study (brightenstudy.com), funded by an R34 grant from NIMH, recruited nearly 1,700 volunteers in only 6 months, with a broad age and geographical representation. They are now collecting cognitive, mood, and activity data on these participants.

Sahakian suggested that in combination with deep "in-clinic" profiling of cognition, frequent assessments using in-home or mobile computing technologies (such as CANTAB mobile[1]) could provide combined cognitive, behavioral, and functional assessments that are more individualized and clinically meaningful to patients (see Figure 4-2). Sahakian thought that some nonverbal tests would have the advantage of being culture-free, not dependent on language, and less affected by language level. Sahakian also pointed out that computerized tests have the advantage of being objective, less affected by tester bias, and could more accurately measure speed of response. These assessments could also be combined with data from biomarker, neuroimaging, genetic, and other physiologic studies for a much richer understanding of cognitive impairment in depression. Sahakian also suggested that games on iPads or

[1]See http://www.cambridgecognition.com/healthcare/cantabmobile (accessed June 17, 2015).

smartphones may be useful in reducing attentional bias or anhedonia and increasing motivation (Sahakian et al., in press).

As an example of a potential model for this type of approach, Sahakian discussed the National Institute for Health Research (NIHR) and the Medical Research Council jointly-funded feasibility study for intensive phenotyping of 24 preclinical Alzheimer's disease patients. The study, which involves industry collaboration, aims to identify biomarkers that change over periods of months, rather than years. It will use an extensive range of magnetic resonance imaging and cognitive testing, along with additional clinical testing and biomarkers, at multiple frequent intervals over the course of three months. The goal is that these biomarkers could be used in a range of follow-on trials.[2]

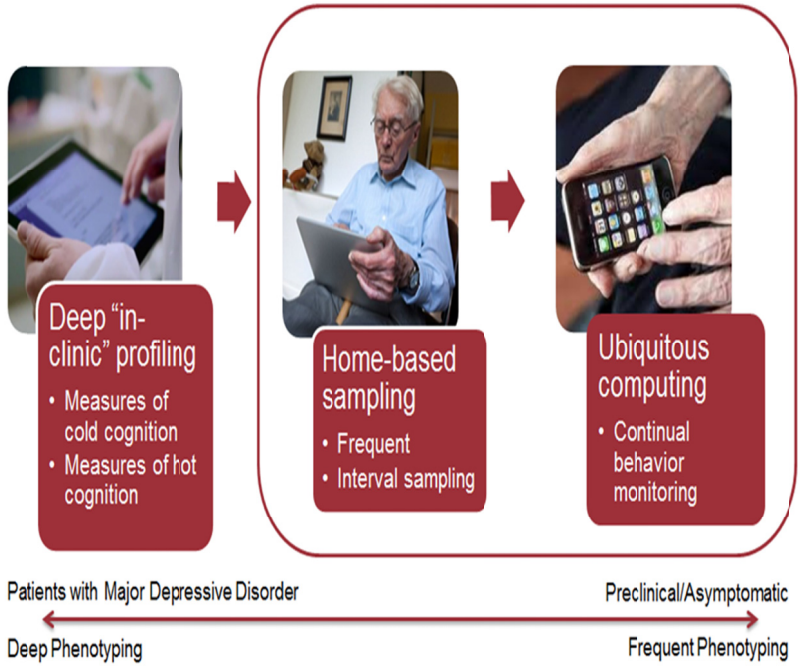

FIGURE 4-2 In-depth assessment of cognition in depression and frequent monitoring of changes in severity.
SOURCE: Barbara Sahakian presentation, February 24, 2015.

[2]See http://www.mrc.ac.uk/research/facilities/dementias-platform-uk (accessed June 17, 2015).

Innovation may also be useful in terms of recruiting and retaining patients for clinical trials. For example, the social media website company PatientsLikeMe (www.patientslikeme.com) has enrolled tens of thousands of people with mood disorders and is now interested in adding cognitive assessment to their tool box, according to Insel. Many of the patients who enroll provide consent to be contacted again for upcoming studies.

Future Directions in Assessment

In addition to the need to embrace innovation, a major issue that arose during workshop discussions was the need for alignment on appropriate assessments to use in clinical trials. Two approaches to assessment that seemed diametrically opposed emerged: (1) homing in on what is important to patients, or (2) focusing on mechanisms. Etkin suggested that the challenge is to think about mechanisms from an explanatory perspective that translates work across the field into a set of common data elements, and determine how to measure these elements and why we should care about them.

A question frequently asked throughout the day was whether a MATRICS-like process is needed to gain consensus on an assessment battery. Pizzagalli noted that the lack of a common battery such as MATRICS makes the integration of findings challenging. This view was supported by William Potter, senior advisor in the Office of the Director of NIMH. Potter suggested that pooling data from different sources, which would require agreeing on a common core of measures, might expedite the process of reaching a better understanding. Madhukar Trivedi, Betty Jo Hay Distinguished Chair in Mental Health at University of Texas Southwestern Medical School, suggested aligning on four to seven measures that would capture the important aspects of the illness, then developing metrics that would represent a meaningful change in these measures.

However, several participants shied away from the MATRICS-like approach. For example, Fava favored deemphasizing a specific set of measures in favor of looking at specific measures based on the mechanism of action of a particular drug, and combining that with a functional measure. Several other speakers and audience participants also expressed concern that a MATRICS-like approach could stifle innovation.

In the absence of a MATRICS-like approach, Laughren asked how the field would be able to gain more clarity about a pathway forward,

which he said is needed to give drug companies confidence to enter this space. Insel replied that although we may not need a MATRICS battery, we might want to develop a set of standard measures that can be integrated across multiple studies to allow larger datasets to be compared.

Laughren asked if we need a cognitive assessment at all, or whether we should go straight to a functional measure. While some participants favored this approach, Trivedi raised the concern that such an approach would not assess what a molecule is actually doing in the brain. He argued that something more proximal to brain changes is important because so many factors (work, social life, etc.) influence functional measures. Areán added that regardless of intervening variables, what matters to patients is whether something makes them feel better and leads to better functioning. However, she and others agreed that it remains important to know the mechanism of how a treatment works. For example, said Fava, if statins were discovered simply because they improved morbidity and mortality, we might not have known about their effects on cholesterol and inflammation.

5

Regulatory Issues

Highlights

- Regulators urged sponsors to consult with them early in the development process to get feedback on study design (Farchione, Peña).
- Assessments used in a clinical trial will need to demonstrate outcomes that are clinically meaningful to patients (Farchione).
- The regulatory pathway for neurostimulation and neurodiagnostic devices includes evaluation of risks and benefits (Peña).
- In evaluating a potential treatment for cognitive dysfunction in depression, drug regulators will likely require evidence that drug effects are not pseudo-specific, and may also require co-primary endpoints (Farchione, Laughren).

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

Regulatory agencies have one central goal: to ensure the safety and effectiveness of a variety of medical products, including both drugs and devices. With regard to products targeting cognitive impairment in depression, regulatory approval of any product has yet to be achieved. According to Thomas Laughren, the time is right for the pharmaceutical industry to address cognitive impairment in depression. He said the field seems ready to coalesce around the notion that cognitive impairment in depression represents a critical unmet medical need and a legitimate target for treatment development, as described in earlier chapters. From the

perspective of regulatory agencies, he presented several important questions that the field and individual sponsors will need to address to move forward:

- What domains of cognitive impairment should be targeted?
- What assessments are optimal?
- What populations should be studied?
- What study designs are optimal?
- Assuming a successful drug development program, what claims can be supported?
- What is the clinical significance of any demonstrated drug effect?

WORKING WITH REGULATORS: FDA AND EMA

While the job of sponsors is to put their best case forward to regulatory agencies and back it up with data, the job of the regulators is to evaluate the evidence, identify data gaps, and ensure that the claims made by the sponsor are supported by the data, said Tiffany Farchione. The burden is on the sponsor to make the case for the target population and possible enrichment strategies; the scientific rationale for targeting specific domains and using adjunctive versus monotherapy; the trial design (e.g., active comparator versus placebo controlled); the type of assessments that will provide the best measure of efficacy; how to quantify improvement; and what constitutes a clinical meaningful change. Farchione urged sponsors to consult with the agency as early as the study design stage to get feedback on aspects of a trial that will come under regulatory scrutiny.

In the United States, FDA also handles regulation of neurologic medical devices, such as the neurostimulation devices discussed earlier as well as neurodiagnostic devices, through the Office of Device Evaluation at the Center for Devices and Radiological Health (CDRH). Carlos Peña, director of neurological and physical medicine devices, said the regulatory path for devices includes evaluating risks and benefits. Medical devices are classified into three classes, with level of risk and regulatory control increasing from levels I to III. For neurodiagnostics, the diagnostic capability may be one of several factors that determine the level of regulatory oversight. Neurotherapeutics require attention to some of the same issues that are required for drugs: validated outcome assessments, clearly defined parameters for what constitutes a clinically meaningful

change, and a strong focus on patient needs. Peña pointed to a number of Guidance Documents available on the FDA website that delineate the path toward regulatory approval and, like Farchione, he urged sponsors to consult with the agency at the earliest stages of development.

The approach to regulatory approval in Europe largely mirrors that in the United States, albeit with different regulations, according to Maria Isaac, senior scientific officer at the EMA. As in the United States, the European depression guidelines do not identify cognition as a primary therapeutic target in depression. Isaac noted that the EMA works closely with FDA, exchanging views and sharing expertise in order to optimize and facilitate global development. Sponsors can seek parallel FDA–EMA qualification advice and hold joint discussions with the two agencies; however, each agency will issue separate responses to sponsors' questions.

STUDY POPULATION AND ASSESSMENT

With regard to defining the target population, several workshop participants identified that the challenge for sponsors is to sort out the specific population that should be targeted for treatment development programs and decide whether to target cognition broadly or whether to home in on a particular domain that may be impaired in a specific subgroup. As described earlier, many cognitive domains may be impaired in people with depression, and different subgroups may have different impairments that may require different treatments. According to Laughren, regulatory agencies have already accepted targeting specific domains or subgroups of other DSM-defined syndromes, so he does not see this as an insurmountable hurdle.

With regard to assessments, arguments can be made for both subjective and objective measures, said Farchione. While the agency has not endorsed or rejected any specific cognitive assessments for MDD, they have indicated that patient-reported outcomes are important to define a change that is meaningful to patients. Farchione said assessment issues would most likely be taken up by FDA's Study Endpoints and Labeling Development (SEALD) Team, which has the psychometric and statistical expertise to evaluate the appropriateness of a measure for a specific trial.

PSEUDO-SPECIFICITY

Farchione said that although FDA operated for many years under the general assumption that cognitive dysfunction in depression was pseudo-specific, that is, if depression improved cognition would improve as well, the opinion of FDA regarding approval of drugs for depression is evolving. New data have now paved the way for FDA to consider cognition a legitimate target for treatment in depression.

Laughren, however, said he still views pseudo-specificity as a primary regulatory challenge. If a company wants to target a specific subgroup or symptom, regulators will likely ask for a demonstration that the drug works only or better in that subgroup or on that symptom. Unless data indicate that the drug is unique in some way to the specific subgroup or symptom, the agency may be unwilling to accept a narrow focus. Laughren used the example of schizophrenia. Over the past decade, accumulating data have led to acceptance across the field that cognitive impairment is a well-established aspect of schizophrenia. To address the pseudo-specificity concern, he said investigators also had to make a strong case that even when positive symptoms of psychosis are successfully treated, many patients continue to have prominent cognitive impairment, and that cognitive impairment has a different time course than other symptoms. These data have led regulatory agencies to endorse cognitive impairment in schizophrenia as a legitimate target. Regulators have also endorsed other narrow targets for drug development such as agitation in schizophrenia and bipolar disease, indicating that they are willing to accept a narrow target if the data support it. To overcome regulators' concerns about pseudo-specificity in trials of agents targeting cognitive dysfunction in depression, Laughren suggested that different clinical trial designs, such as adjunctive, acute-phase, and switching designs (see Chapter 4), may also provide the necessary data.

Laughren opined that several aspects of depression, including cognitive impairment, might be considered by regulatory agencies as targets for intervention. Other potential narrower targets in depression might be irritability, fatigue, and apathy. What is needed, he said, is a better understanding of the biological underpinnings of the target. To address pseudo-specificity, he said, investigators need to show that even when mood and other symptoms of depression are successfully treated, cognitive impairment persists and interferes with the ability to function. This might be achieved by demonstrating a residual phase of depression or by

making the case for subtypes of depression in which certain symptoms predominate, resulting in poorer treatment response.

CO-PRIMARY ENDPOINTS

Another regulatory issue that emerged with regard to cognitive impairment in schizophrenia was the need for a co-primary endpoint. The basis for this concern, said Laughren, is that even if the primary endpoint shows a benefit on a fairly abstract cognitive measure, such as word recall, the clinical relevance to a patient may be unclear. For both schizophrenia and Alzheimer's disease, regulators want to see improvement on a functional or global measure as well. Whether a similar requirement would be made for cognitive impairment in depression has yet to be determined. The question is further complicated by the possibility that a sponsor might have reason to believe a drug works on a particular domain of cognition, and therefore could make the case of using a single measure as the primary endpoint. Another complication is that an antidepressant drug potentially could worsen certain aspects of cognition, such as speed of processing, while improving other aspects such as negative bias. These issues make the choice of endpoints extremely complex, said Laughren.

FUTURE DIRECTIONS

Diego Pizzagalli asked whether regulators might consider a neurophysiologic change as a primary outcome with a functional improvement as the co-primary. Laughren broadened the question to ask, at what point will our understanding of behavior at a biological level allow the abandonment of artificial DSM categories and move instead to look at actual domains of function? Moreover, he suggested that if investigators were able to identify the specific brain circuits involved in a cognitive domain such as working memory, and if data showed similar impairments by a biological marker such as fMRI across different diseases such as depression and schizophrenia, it might be possible to get a broad claim for a treatment that improved that measure. However, he acknowledged that the field is nowhere near that at this point. Farchione added that even in the absence of that clear neurobiological understanding, a clinically meaningful change in a domain such as working memory, along with a functional improvement across two or three different disorders, could

provide a legitimate claim for a more general indication. The key, said Farchione, is having sufficient data to prove that an improvement is generalizable across multiple disease conditions.

6

Lessons Learned from the Schizophrenia Field

Highlights

- As in depression, cognitive impairment is a core feature of schizophrenia. Lessons learned from the schizophrenia field thus have relevance for the treatment of cognitive dysfunction in depression (Green, Harvey).
- Many of the same strategies for assessing cognition and function in schizophrenia can be used successfully in depression, although patients differ considerably from a functional standpoint (Harvey).
- Several workshop participants identified concerns about developing a composite cognitive battery for cognition in depression similar to that developed through a consensus process for schizophrenia (Fava, Keefe, Sahakian).

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

As in depression, cognitive impairment is a core feature of schizophrenia and a predictor of poor functional outcome (Green, 1996; Heinrichs and Zakzanis, 1998). According to Philip Harvey, much of what we know about cognition in schizophrenia may apply to studies of cognition in depression, particularly as the field grapples with issues of assessment. Just as cognitive assessments needed to be tailored for use in schizophrenia, they need to also be tailored for mood disorders, said Harvey.

The schizophrenia field tackled the issue of assessment as part of the MATRICS initiative, which was established by NIMH in 2003 in response to the recognition that antipsychotic medications for schizophrenia do not improve cognition. Michael Green said the initiative was undertaken to address the bottlenecks that had slowed the development of treatments targeting cognition in schizophrenia, namely (1) a lack of consensus regarding cognitive targets, (2) lack of widely accepted endpoints, (3) ambiguity regarding the optimal designs for clinical studies, and (4) an unclear path to FDA approval and labeling.

While the steps undertaken by MATRICS to address these challenges may offer lessons for the depression field, some workshop participants expressed concerns about strictly following the MATRICS model. For example, the initiative developed a consensus cognitive battery (the MCCB) using the RAND panel method, which included input from individuals from academia, NIMH, industry, FDA, and consumers (Buchanan et al., 2005). However, several workshop participants, including Maurizio Fava, suggested that the depression field may not yet be ready to reach consensus on outcome assessments.

PSEUDO-SPECIFICITY

One of the first challenges encountered by the MATRICS team was the problem of pseudo-specificity or, for a drug treatment, an artificially narrow claim of a drug effect, Green said. As mentioned in the previous chapter, for the treatment of cognitive dysfunction in depression, pseudo-specificity is likely to be a major regulatory concern and design challenge, several workshop participants said. For example, regulators are likely to reject a claim that a drug improves cognition in depression if it actually works in general for cognition, or if depressive mood is driving poor cognition. Similarly, if cognitive impairment in schizophrenia is driven by some other feature of the illness, such as psychosis, an antipsychotic treatment would be considered pseudo-specific for cognition in schizophrenia. Pseudo-specificity was discussed in more detail in Chapter 5.

MATRICS addressed this challenge by presenting data showing that the pattern of neuropsychological cognitive deficit scores in schizophrenia differs from the pattern in Alzheimer's disease, that is, cognition in schizophrenia was not pseudo-specific. They later reached consensus that to isolate a change in cognitive function from a change in other clinical

features, studies should restrict symptom severity in subjects prior to randomization and select clinically stable patients (Buchanan et al., 2005).

ASSESSMENT TOOLS

Harvey said studies of schizophrenia may help to inform efforts to assess cognition and function in depression. Indeed, Harvey cited the conclusions of a bipolar consensus group that cold cognition can be assessed with the same strategies in schizophrenia and bipolar disorder, and a study by Harvey and colleagues showed that cold cognitive domains were similar in both schizophrenia and depressed patients who were stabilized after a first episode of their illness (Harvey et al., 2015; Reichenberg et al., 2009). However, these patients differed considerably from a functional standpoint, said Harvey.

Also, as mentioned in Chapter 4, many studies of tools for assessing cognition in depression compared patients with schizophrenia to those with mood disorders, using a combination of subjective and objective measures aimed at both cognition and everyday function. One of the most common objective tests used in these studies is the MCCB. In developing this tool, MATRICS employed a multistep process (see Figure 6-1), which began by identifying the relevant cognitive domains to be tested, selecting the criteria for appropriate tests of those domains, soliciting nominations for tests, narrowing the number of tests to six or fewer per domain, creating a database and evaluating the tests using the criteria defined earlier, selecting two to five tests per domain for the "beta" battery, conducting a psychometric study with this battery, finalizing the battery, and then co-norming the tests of a community sample.

According to Green, selecting the criteria for test selection and collecting the data to evaluate the tests proved to be problematic in that it required an inherent trade-off between balancing the need for data from existing studies and the desire to find novel but more sensitive tests that might provide more power for clinical trials. To address these challenges, a separate initiative, CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia), was launched to move the field beyond standard tasks to those that reflect the state of the art in cognitive neuroscience.

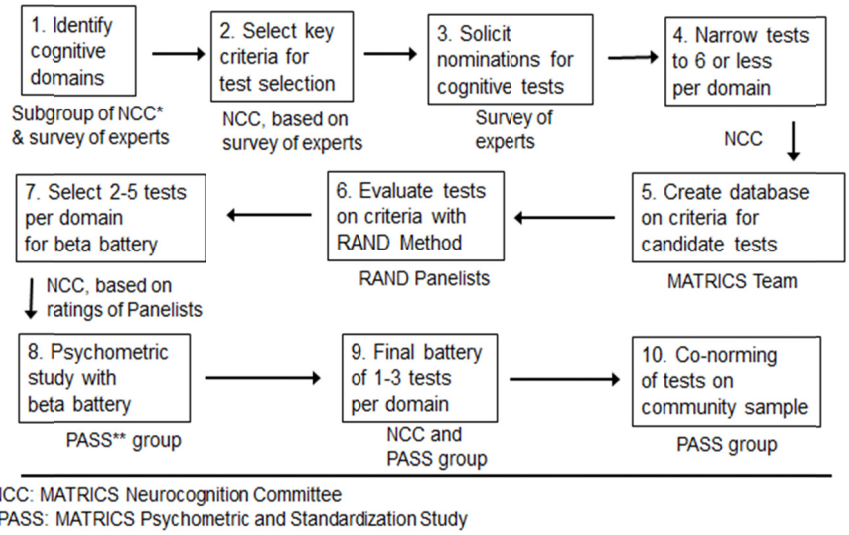

FIGURE 6-1 Steps to MATRICS Consensus Cognitive Battery.
SOURCE: Adapted from Green et al. (2004, fig. 1). Presented by Michael Green at the IOM Workshop on Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression, February 24, 2015.

MCCB, which emerged from the MATRICS initiative, included 7 domains and 10 tests (see Box 6-1). Following development of the battery, the team addressed challenges related to copyright, intellectual property, publication and distribution of the battery, and eventually starting a non-profit company to publish the battery. This enabled the test publishing companies that own the rights to individual tests to distribute the battery.

An unexpected roadblock that emerged was FDA's insistence on a co-primary measure that was functionally meaningful (Buchanan et al., 2005). Green thought that FDA might be inclined to take a similar stance with regard to cognition in depression. The need for a co-primary measure in schizophrenia trials led to the launch of another initiative, MATRICS-CT.

Workshop participants discussed whether the field should apply the MATRICS approach to building an assessment tool to measure cognitive impairment in depression. Several participants made arguments against taking such an approach. Barbara Sahakian, for example, said that it is important to utilize neuropsychological tests that are not only sensitive to

BOX 6-1
MATRICS Consensus Cognitive Battery (MCCB)

- Speed of processing—category fluency, Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding, trail making A
- Attention/vigilance—continuous performance test (identical pairs version)
- Working memory—Maryland letter number span, Wechsler Memory Scale (WMS) spatial span
- Verbal learning—Hopkins verbal learning test
- Visual learning—brief visuospatial memory test
- Reasoning and problem solving—Neuropsychological Assessment Battery (NAB) Mazes
- Social cognition—Mayer-Salovey-Caruso Emotional Intelligence Test) (MSCEIT) Managing Emotions

SOURCE: Green presentation, February 24, 2015.

cognitive dysfunction in depression, but also demonstrably sensitive to change. This sensitivity to change will be important for assessing the efficacy of treatments for cognitive dysfunction in depression. She emphasized it was essential to not stifle progress in the field. Richard Keefe suggested that for depression clinical trials, the focus should be more on cognitive neuroscience processes or practicality for use in trials, yet he noted that none of the elegant and exquisite neuropsychological tests derived from the CNTRICS program have yet been used in a Phase II clinical trial. Green commented that the perspective of both academics and clinical trialists will be needed to settle the question of which tests are suitable for evaluating cognitive dysfunction in depression in multi-site clinical trials.

With regard to practicality, Catherine Harmer mentioned that if a battery were to be constructed, it would need to be deployable through general practitioners rather than psychiatrists in order to conduct clinical trials data in a more heterogeneous group of patients. Similarly to the MCCB, for international clinical studies it would also need to be translated into multiple languages, and norms would need to be established that account for variants in age, gender, culture, language, etc. According to Green, the MCCB is now available in more than 20 languages. He said that by starting with an international focus, some of the substantial translation challenges that MATRICS faced might have been avoided; however, he also

noted that multisite clinical trials pose additional challenges in terms of detecting a signal.

A

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B

Workshop Agenda

Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression: A Workshop

February 24, 2015

National Academy of Sciences
2101 Constitution Avenue, Room 120
Washington, DC 20418

Background: It is increasingly recognized that many patients, while fulfilling traditional criteria for response or remission of depression, continue to have subjective complaints and have difficulties returning to their previous level of function (e.g., returning to work). Increasing clinical and epidemiologic evidence suggests that cognitive dysfunction is an underestimated dimension of depression. Such dysfunction could, in part, explain patients' poor response and/or poor functional outcomes. Currently available pharmacological treatments appear to only address cognitive dysfunction in depression in a limited way, and some treatments may even worsen cognition in some patients. Moreover, there is a lack of alignment in the scientific field on the best way to assess cognitive dysfunction and whether this dimension is congruent with, or independent from, mood symptoms. There is also an opportunity in this domain to look beyond the classical definition of major depressive disorder and consider approaches involving neurocircuitry and precision medicine. The goal of the workshop is to bring together key stakeholders to explore ways of speeding improvement of the discovery, development, and regulatory path for new treatments addressing this aspect of depression.

Meeting Objectives:

- Examine opportunities to facilitate new target and validation strategies aimed at reinvigorating the development of treatments that address cognition, an undertreated aspect of depression.
- Discuss how lessons from the translational aspects of cognitive dysfunction in other disorders could apply to depression.
- Highlight gaps and limitations of current tools for assessing cognitive dysfunction in depression in clinical trials, and consider how improvements in cognition could relate to functional outcomes.
- Explore potential regulatory challenges, such as recognition of cognitive dysfunction in depression as a public health need and opportunities for treatments.

8:30 a.m. Opening Remarks

THOMAS INSEL, *Workshop Co-Chair*
Director
National Institute of Mental Health

THOMAS LAUGHREN, *Workshop Co-Chair*
Director
Laughren Psychopharm Consulting, LLC

SESSION I: BACKGROUND AND OVERVIEW

Session Objectives: Provide an overview of the unmet medical need of cognitive dysfunction in depression. Discuss lessons learned from developing treatments for cognitive dysfunction in schizophrenia. Examine opportunities to facilitate new target and validation strategies aimed at reinvigorating the development of treatments that address cognition.

8:40 a.m. Opening Remarks

ANDREW NIERENBERG, *Session Moderator*
Thomas P. Hackett, M.D., Endowed Chair in Psychiatry
Massachusetts General Hospital

8:45 a.m. Cognitive Dysfunction in Depression: The Need for Discovery, Development, and Translation in This Domain *(20 min talk + 10 min discussion)*

BARBARA SAHAKIAN
Professor of Psychiatry
Cambridge University

9:15 a.m. Experimental Design and Approaches: Opportunities to Facilitate New Target and Validation Strategies for Cognitive Dysfunction in Depression *(20 min talk + 10 min discussion)*

CATHERINE HARMER
Professor of Cognitive Neuroscience
University of Oxford

9:45 a.m. Lessons Learned from Cognitive Dysfunction in Schizophrenia *(20 min talk + 10 min discussion)*

MICHAEL GREEN
Professor-in-Residence
Department of Psychiatry and Biobehavioral Sciences
Geffen School of Medicine, University of California, Los Angeles

10:15 a.m. BREAK

SESSION II: STATE OF THE SCIENCE FOR TREATING COGNITIVE DYSFUNCTION IN DEPRESSION

Session Objectives: Examine the current state of the science for treating cognitive dysfunction in depression, including what aspects of this dysfunction can be treated with medications, cognitive behavioral therapy, devices, and other treatment modalities. Identify promising future directions.

10:30 a.m. Opening Remarks

AMIT ETKIN, *Session Moderator*
Assistant Professor of Psychiatry and Behavioral Sciences
Stanford University

10:35 a.m. Effects of Non-Pharmacological Treatments on Cognition in Depression

DIEGO PIZZAGALLI
Professor of Psychiatry
Harvard Medical School

10:50 a.m. Effects of Pharmacological Treatments on Cognition in Depression

RICHARD KEEFE
Professor of Psychiatry and Behavioral Sciences
Duke University

11:05 a.m. Effects of Cognitive Remediation on Cognition in Depression

CHRISTOPHER BOWIE *(by videoconference)*
Clinical Psychologist and Associate Professor
Queen's University

11:20 a.m. Discussion Among Panelists and Workshop Participants

12:00 p.m. LUNCH

SESSION III: DESIGN AND ASSESSMENT CHALLENGES

Session Objectives: Examine opportunities and challenges in studying and assessing treatments for cognitive dysfunction in depression, including combination therapies. Highlight gaps and limitations of current tools for diagnosing and evaluating depression in clinical trials, and consider how the indexes could be expanded to include indexes of cognitive functioning.

Discuss how improved cognition can be measured in short trials and the potential role of proxy measures. Consider acute versus residual treatment.

12:45 p.m. Opening Remarks

MADHUKAR TRIVEDI, *Session Moderator*
Betty Jo Hay Distinguished Chair in Mental Health
University of Texas Southwestern Medical Center

12:50 p.m. Design

MAURIZIO FAVA
Director, Clinical Research Program
Massachusetts General Hospital

1:05 p.m. Assessment

PHILIP HARVEY
Professor of Psychiatry and Behavioral Sciences
University of Miami Miller School of Medicine

1:20 p.m. Lifespan Issues

PATRICIA AREÁN
Professor of Psychiatry
University of California, San Francisco, School of Medicine

1:35 p.m. Discussion Among Panelists and Workshop Participants

2:15 p.m. BREAK

SESSION IV: REGULATORY CHALLENGES AND POTENTIAL SOLUTIONS

Session Objectives: Explore potential regulatory challenges, such as recognition of cognitive dysfunction in depression as a public health need and opportunities for treatments. Examine methods for evaluating cognitive dysfunction in depression. Discuss the evidentiary base that would be needed for approval of treatments for cognitive dysfunction in depression, including combination treatments.

2:30 p.m. Opening Remarks

THOMAS LAUGHREN, *Session Moderator*
Director
Laughren Psychopharm Consulting, LLC

2:35 p.m. Food and Drug Administration Perspective: Drugs

TIFFANY FARCHIONE
Acting Deputy Director
Division of Psychiatry Products
Food and Drug Administration

2:45 p.m. Food and Drug Administration Perspective: Devices

CARLOS PEÑA
Director, Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

2:55 p.m. European Medicines Agency Perspective

MARIA ISAAC *(by videoconference)*
Senior Scientific Officer
European Medicines Agency

3:05 p.m. Addressing Regulatory Challenges

THOMAS LAUGHREN
Director
Laughren Psychopharm Consulting, LLC

3:20 p.m. Discussion Among Panelists and Workshop Participants

4:00 p.m. BREAK

SESSION V: MOVING FORWARD

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

4:15 p.m. Panel Discussion

ANDREW NIERENBERG
Thomas P. Hackett, M.D., Endowed Chair in Psychiatry
Massachusetts General Hospital

AMIT ETKIN
Assistant Professor of Psychiatry and Behavioral Sciences
Stanford University

MADHUKAR TRIVEDI
Betty Jo Hay Distinguished Chair in Mental Health
University of Texas Southwestern Medical Center

THOMAS LAUGHREN
Director
Laughren Psychopharm Consulting, LLC

4:40 p.m. Discussion Among Panelists and Workshop Participants

5:15 p.m. Final Comments

THOMAS INSEL, *Workshop Co-Chair*
Director
National Institute of Mental Health

THOMAS LAUGHREN, *Workshop Co-Chair*
Director
Laughren Psychopharm Consulting, LLC

5:30 p.m. ADJOURN WORKSHOP

C

Registered Attendees

Patricia Areán
University of California, San Francisco

Deanna Barch
Washington University of St. Louis

Chanel Barnes
Common Health ACTION

Mitchell Belgin
Washington Square Integrative Psychiatry

Eva Bøge
H. Lundbeck A/S

Silvana Borges
Food and Drug Administration

Lizbet Boroughs
American Psychiatric Association

Christopher Bowie
Queen's University

Linda Brady
National Institute of Mental Health

Stephen Brannan
Takeda Pharmaceuticals International, Inc.

Daniel Burch
Pharmaceutical Product Development

June Cai
Walter Reed National Military Medical Center

Rosa Canet-Aviles
Foundation for the National Institutes of Health

C. Thomas Caskey
Baylor College of Medicine

Allen Egon Cholakian
IRDF Project
Harvard/Columbia

Michael Christensen
H. Lundbeck A/S

Bruce Cuthbert
National Institute of Mental Health

Nicholas DeMartinis
Pfizer Inc.

Kristin D'Onofrio
Takeda Pharmaceuticals International, Inc.

Martin Duenas
Leidos

Amit Etkin
Stanford University

Jennifer Evans
National Institutes of Health

Tiffany Farchione
Food and Drug Administration

Maurizio Fava
Massachusetts General Hospital

Rebecca Fitch
Department of Education/Office for Civil Rights

Scott Fogerty
Epistem

Mark Gorman
Member of the Public

Michael Green
University of California, Los Angeles

Catherine Harmer
University of Oxford

Philip Harvey
University of Miami Miller School of Medicine

Renee Heese
Pfizer Inc.

Mi Hillefors
National Institute of Mental Health

Thomas Insel
National Institute of Mental Health

William Jacobson
Takeda Development Center Americas

Judith Jaeger
CognitionMetrics, LLC

Charles Jeck
Physician

Peter Kaskan
National Institute of Mental Health

Gary Kay
Cognitive Research Corporation

Richard Keefe
Duke University Medical Center

Noam Keren
National Academy of Sciences

Inhwa Kim
American Association for the Advancement of Science
Center for Science, Technology, and Security Policy

Lawrence Klusman
Walter Reed National Military Medical Center

Manasi Kumar
University of Nairobi/University College London

Ian Laquian
Takeda Pharmaceuticals

Thomas Laughren
Laughren Psychopharm Consulting, LLC

Alan Leshner
American Association for the Advancement of Science (Emeritus)

Sheldon Levin
University of California, San Francisco

Elin Lof
H. Lundbeck A/S

Søren Lophaven
Lundbeck, LLC

Glenn Mannheim
Food and Drug Administration

Daniel Mathews
Lundbeck, LLC

Shelly Menolascino
Shelly Menolascino, M.D., LLC

Nivedita Mohanty
National Science Foundation

Randall Morrison
Janssen Research & Development

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Joseph Palumbo
Mitsubishi Tanabe Pharma Development America Inc.

Atul Pande
Tal Medical

Jonathon Parker
Takeda Pharmaceuticals

Vanessa Perez
Takeda Pharmaceuticals

Diego Pizzagalli
Harvard Medical School & McLean Hospital

Jorge Quiroz
Roche

Juan Ruiz
Nestlé Health Science-Pamlab

Judith Rumsey
National Institute of Mental Health

Barbara Sahakian
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Joanna Sambor
Takeda Pharmaceuticals

Sara Sarkey
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Eugenia Schenecker
George Washington University

Dana Schloesser
Office of Behavioral and Social Sciences Research

Mary Smith
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Cole Werble
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Jerry Yang
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Teresa Yang
Takeda Pharmaceuticals

Jing Zhang
Food and Drug
Administration

Stevin Zorn
Lundbeck Research USA