Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia II: Developing Imaging Biomarkers to Enhance Treatment Development for Schizophrenia and Related Disorders

Cameron S. Carter, Deanna M. Barch, Edward Bullmore, James Breiling, Robert W. Buchanan, Pamela Butler, Jonathan D. Cohen, Mark Geyer, Randy Gollub, Michael F. Green, Judith Jaeger, John H. Krystal, Holly Moore, Keith Nuechterlein, Trevor Robbins, Steven Silverstein, Edward E. Smith, Milton Strauss, and Til Wykes

The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative, funded by an R13 from the National Institute of Mental Health, seeks to enhance translational research in treatment development for impaired cognition in schizophrenia by developing tools from cognitive neuroscience into useful measures of treatment effects on behavior and brain function. An initial series of meetings focused on the selection of a new set of tasks from cognitive neuroscience for the measurement of treatment effects on specific cognitive and neural systems. Subsequent validation and optimization studies are underway and a subset of validated measures with well-characterized psychometric properties will be generally available in 2011. This article describes results of the first meeting of the second phase of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, which seeks to develop imaging biomarkers and improved animal models to enhance translational research. In this meeting, we considered issues related to the use of methods such as functional magnetic resonance imaging, electroencephalography, magnetoencephalography, and transcranial magnetic simulation as biomarkers for treatment development. We explored the biological nature of the signals measured by each method, their validity and reliability as measures of cognition-related neural activity, potential confounds related to drug effects on the signal of interest, and conceptual, methodological, and pragmatic issues related to their use in preclinical, first into human, and multicenter phase II and III studies. This overview article describes the background and goals of the meeting together with a summary of the major issues discussed in more detail in the accompanying articles appearing in this issue of *Biological Psychiatry*.

Key Words: Biomarker, CNTRICS, cognition, schizophrenia, treatment

Impaired cognition in schizophrenia is a core feature of the illness, present at the onset and persistent throughout the life span. Despite substantial progress in understanding the neurobiology of cognitive and emotional processing and of its perturbations in the brains of individuals with schizophrenia, limited progress has been made to date in developing effective therapies for this disabling aspect of the illness. Developing such therapies is one of the major challenges to biomedicine in the 21st century.

A major obstacle to translating progress in basic neurobiology into targeted treatments for cognition is that there are significant discrepancies between the tools and constructs used to measure cognition across different levels of analysis during the treatment development process. An optimal mechanism for translational research (Figure 1) involves a vertically integrated set of projects interacting across levels of analysis, applying a common conceptual framework, language, and set of experimental tools that allow basic science to inform clinical and ultimately therapeutic research. However, in the case of cognition in schizophrenia, there are significant questions regarding the degree to which 1) the behavioral measures frequently used to assess cognition in clinical trials map onto the cognitive constructs validated in basic human and cognitive neuroscience studies; 2) we have available biomarkers that can allow us to assess neural function during cognitive processing in clinical trials; and 3) the animal models traditionally used to screen pharmacological treatment candidates are valid homologues to the cognitive deficits that are the target of treatments. In part, these concerns arise because the present tools that are used to measure the effects of drugs in clinical trials bear insufficient relationship to those that are used in the clinical imaging and electrophysiological studies or even the animal studies that have refined our understanding of the nature of cognitive deficits in schizophrenia.

The goal of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) process is to enhance and accelerate the process of developing treatments for impaired cognition in schizophrenia. To accomplish this goal, an initial series of three meetings were held that sought to develop a consensus based set of cognitive mechanisms to be targeted for

From the Department of Psychiatry (CSC), University of California at Davis, Sacramento, California; Departments of Psychology and Psychiatry (DMB), Washington University in St. Louis, St. Louis, Missouri; Department of Psychiatry (EB, TR), University of Cambridge and GlaxoSmithKline, Cambridge, United Kingdom; National Institute of Mental Health (JB), Bethesda, Maryland; Department of Psychiatry (RWB), Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland; Department of Psychiatry (PB), New York State University, New York, New York; Department of Psychology (JDC), Princeton University, Princeton, New Jersey; Department of Psychiatry (MG), University of California at San Diego, San Diego, California; Department of Psychiatry (RG), Massachusetts General Hospital, Boston, Massachusetts; Department of Psychiatry (MFG), Semel Institute at University of California Los Angeles, Los Angeles, California; VA Greater Los Angeles Healthcare System (MFG), Los Angeles, California; AstraZeneca (JJ), Wilmington, Delaware; Department of Psychiatry (JHK), Yale University School of Medicine, New Haven, Connecticut; Department of Psychiatry (HM, EES), Columbia University, New York, New York; Department of Psychiatry (KN), University of California Los Angeles, Los Angeles, California; Department of Psychiatry (SS), University of Medicine and Dentistry of New Jersey, Newark, New Jersey; Department of Psychiatry (MS), University of New Mexico, Albuquerque, New Mexico; Institute of Psychiatry (TW), King's College London, London, United Kingdom.

Address correspondence to Cameron S. Carter, M.D., University of California at Davis, UC Davis Imaging Research Center, 4701 X Street, Sacramento, CA 95816; E-mail: cameron.carter@ucdmc.ucdavis.edu.

Received Nov 3, 2010; revised Jan 9, 2011; accepted Jan 11, 2011.

0006-3223/$36.00
doi:10.1016/j.biopsych.2011.01.041

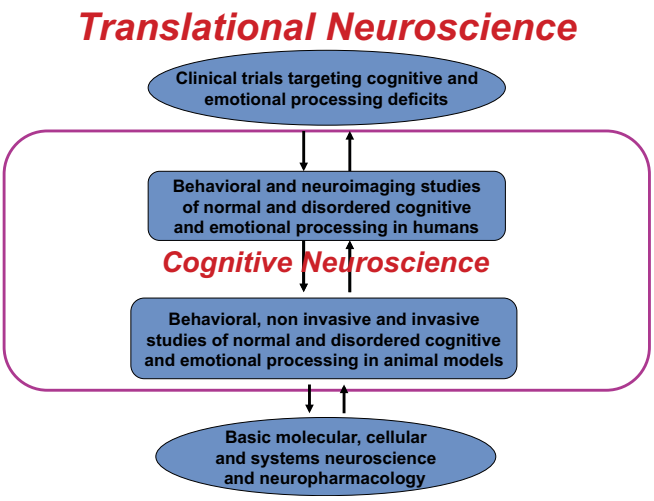

Figure 1. Vertically integrated translational research process for targeted treatment development. Under optimal conditions, there is a common set of concepts, a common language, and a common set of tools informing the transfer of information across levels in a bi-directional manner, such that more clinically related observations can inform work occurring at a more basic level and more basic knowledge leading to targeted treatment development. A basic tenet of Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia is that cognitive neuroscience can provide these tools and constructs and serve as a translational bridge to enhance the progress of efforts to develop treatments for impaired cognitive and emotional processing in schizophrenia.

treatment development, a set of principles to guide the optimization of experimental cognitive paradigms for implementation in treatment development studies, and a set of candidate tasks that could be refined and optimized for use in treatment studies. The results of these meetings have been published in this and other journals and have led to subsequent National Institute of Mental Health funded projects presently underway to produce useful translations of paradigms that have construct validity for measuring specific cognitive processes that are impaired in schizophrenia, have robust psychometric properties (e.g., absence of floor and ceiling effects, internal and test-retest reliability), and are practical for administration in treatment development settings. The specific measures recommended for translation are summarized in Barch *et al.* (1) and described in detail, along with the criteria used to identify them described in a series of related articles in the special issue of *Schizophrenia Bulletin*. These details, together with the slides of the presentations at each of the meetings and downloadable versions of a subset of the tasks, may also be found on the CNTRICS website (http://cntrics.ucdavis.edu).

With support from a National Institute of Mental Health funded conference grant, CNTRICS has now begun a second phase of work, with the goal of further enhancing the translation of tools from basic cognitive neuroscience into the treatment development processes. The focus of this second set of meetings and associated online surveys is twofold. The first is to facilitate the development of imaging biomarkers for use in human studies. The second is to facilitate the development of optimized animal model systems that can potentially have stronger predictive value than many current animal paradigms for beneficial effects of novel treatments on cognition in schizophrenia and related disorders. In this issue of *Biological Psychiatry*, we describe the first of this second series of CNTRICS meetings, in which we addressed conceptual and methodological issues involved in developing imaging biomarkers, as well as transcranial magnetic stimulation (TMS) related physiological measures that can be combined with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) for development of effective treatments for impaired cognition in schizophrenia and related disorders.

Biomarkers and Their Potential Utility in the Treatment Development Process

A biomarker is a characteristic that is measured objectively as an index of a pathogenic process or a response to treatment. We would argue that in evaluating the utility of a biomarker, the issues are similar to those involving the development of cognitive measures such as those considered during the first phase of CNTRICS discussed above (which can of themselves serve as biomarker measures). These issues are 1) validity, the degree to which a measure reflects the neural substrates of particular cognitive mechanisms; and 2) reliability, the measurement properties of the measure. A third issue relevant to use in treatment development involves practicalities of administration and this can be a major issue for imaging biomarkers depending upon the imaging technology involved. A fourth issue is relationship between functional brain measures and symptoms and measures of functioning.

With the development and widespread use of noninvasive imaging methodologies such as fMRI, EEG, and magnetoencephalography (MEG), the notion of using functional imaging based measures as markers of altered neural activity associated with cognitive and emotional processing in schizophrenia, and its modulation as a function of intervention, has obvious appeal. Pharmacological fMRI, for example, has become its own field, and it has become widely used as a tool to investigate the mechanisms by which central nervous system acting drugs exert their effects in the brain (2,3). Indeed, the potential utility of imaging biomarkers seems quite self-evident. Using methods that have been well worked out in basic cognitive and affective neuroscience leverages over 50 years of progress in these fields and in related areas of neurobiology and neuropharmacology. This approach allows us to conceptualize and measure the target of an intervention as a discrete neural system supporting the impaired cognitive and emotional processes that we seek to remediate, bypassing the obvious limitations imposed on treatment studies that seek to impact categorically based diagnoses that may actually be highly heterogeneous neurobiologically (4).

There are a number of different ways in which imaging biomarker measures may be used in the treatment development process, with the purpose to which they are put potentially differing as a function of the phase of development. For example, in phase I clinical studies, the use of imaging biomarkers may provide initial evidence for pharmacodynamic effects in the neural systems being targeted to achieve cognitive remediation. In doing so, it may be possible to establish proof of mechanism of action in the human brain. For example, based upon recent pharmacological and fMRI data from both animal models and humans, it has been hypothesized that a final common pathway for stimulant effects in the brain is mediated by changes in the functional state of the locus coeruleus norepinephrine system (5,6).

A related strategy is the use of imaging markers in the context of normal volunteer models of cognitive impairment—for example, sleep deprivation or acute nicotine withdrawal in chronic smokers. Drugs that can mitigate the brain functional changes associated with cognitive impairment in these and other phase I models of neuropsychiatric disorders might be more likely to succeed therapeutically in later studies involving patients. Another potential application in early clinical studies will be to evaluate pharmacoki-

netic-pharmacodynamic relationships. In this context, one might explore the relationship between drug plasma levels or brain receptor occupancy determined with positron-emission tomography or single-photon emission computed tomography and its effects on brain function as measured by fMRI or EEG/event-related potentials (ERPs). In general, the early clinical use of fMRI or EEG/ERPs to support evaluation of the dose-response properties of centrally acting drugs and to inform rational dose selection is a potentially important area of future application of imaging biomarkers.

It was also noted that the opportunity to measure brain function in animal models using fMRI provided a new opportunity for a translational bridge between preclinical and clinical phases of drug development, which might help to reduce the high levels of attrition often ascribed to the poor predictive utility of traditional animal models of cognitive impairment and other psychiatric syndromes. In later (e.g., phase II) stages of the treatment development process, pharmaco-imaging measures might be used to predict treatment effects on cognition before the onset of measurable changes in behavioral task performance. They might also be used to predict individual differences in response to a specific treatment within the context of a personalized medicine approach.

The potential of fMRI markers to predict treatment response would naturally be of particular interest in the development of centrally acting drugs that were expected to require several weeks or months of treatment to demonstrate clinical benefits by more established outcome measures or end points. For example, one can imagine using imaging biomarkers in future clinical trials to screen patients for a brain functional profile that is likely to predict a good therapeutic response to disease-modifying treatment of neurodegenerative disorders. Such imaging-based strategies for sample enrichment might be expected to reduce the cost and improve that statistical power of clinical studies, while also limiting the unnecessary treatment of patients unlikely to derive much therapeutic benefit from the drug.

Overall, the greatest value of imaging to the process of commercial drug development is likely to reside in its capacity to reduce the inherent risks of progressing a drug from preclinical through early clinical and proof-of-concept studies to large and expensive late-stage clinical trials. Despite the potential appeal and opportunities for neuroscientifically based risk mitigation described above, the use of noninvasive imaging biomarkers in treatment development has been limited (though growing) to date.

The cautious approach taken by the pharmaceutical industry and others to the use of imaging biomarkers is arguably based upon a number of fundamental conceptual and methodological concerns, which were the focus of the meeting described in this issue. Thus, we started work on addressing these concerns before the meeting by identifying the criteria the field felt were most important in selecting useful imaging biomarkers.

The Development of Criteria to Evaluate the Utility of Different Imaging Biomarker Methods

As with our efforts to identify valid cognitive constructs in the first series of CNTRICS meetings, the CNTRICS Executive Committee developed an initial list of potential criteria for evaluating the utility of different imaging biomarkers for use in cognition-enhancing treatment development and evaluation (Table 1). Like our prior surveys and meetings, we felt it important to involve as many individuals as possible in the process, as the Food and Drug Administration and the National Institute of Mental Health are more likely to benefit from the consensus views of a large group than the opinions of only a small subset of the field. We used a web-based survey to ask individuals from a wide range of expertise domains to rank the criteria in terms of their relevance for deciding whether to use an imaging biomarker in the treatment development and evaluation process. These domains of expertise included over 200 individuals from academia and industry (pharmaceutical, biotech, and cognitive testing) and from the basic and clinical sciences whose research focus was on measuring of brain function during cognitive and affective processing, as well as individuals with experience in clinical trials of medications and cognitive rehabilitation in schizophrenia. We used several methods to generate the list of individuals asked to participate in the survey, including: 1) the names of those individuals that were involved in the prior CNTRICS meetings; 2) individuals serving on the editorial boards of basic and clinical psychopharmacology, cognitive science, cognitive neuroscience, neuroimaging, and schizophrenia related journals; and 3) individuals from as many small and large industry organizations as could be identified by the CNTRICS Steering Committee.

We asked these individuals to rank each potential criterion on a 5-point scale, ranging from 0 (not important) to 4 (very essential). A total of 121 individuals completed this survey, and Table 1 shows the results for the total sample, as well as separately for those

Table 1. Importance Ratings of Initial Criteria for Evaluating Imaging Biomarkers

Potential Criteria	Total (n = 121) Mean/Mode/SD	Academics (n = 107) Mean/Mode/SD	Industry (n = 14) Mean/Mode/SD
Demonstrated Sensitivity to Manipulations of Cognitive/Affective Processing	3.49/4.0/.85 (1)	3.49/4.0/.87 (1)	3.46/4.0/.66 (2)
Test-Retest Reliability	3.38/4.0/.78 (2)	3.33/4.0/.80 (2)	3.77/4.0/.44 (1)
Clear Quality Assurance Protocols	3.25/3.0/.84 (3)	3.22/4.0/.87 (3)	3.46/4.0/.66 (2)
Patient Tolerance	3.15/3.0/.75 (4)	3.15/3.0/.76 (4)	3.15/3.0/.69 (6)
Standardization of Administration Protocols	2.93/3.0/.92 (5)	2.89/3.0/.94 (5)	3.15/3.0/.80 (6)
Standardization of Analysis Protocols	2.85/3.0/.95 (6)	2.80/3.0/.97 (6)	3.23/3.0/.60 (5)
Directness of Interpretation (e.g., known source of signals, etc.)	2.82/3.0/.80 (7)	2.83/3.0/.82 (7)	2.77/3.0/.60 (10)
Ability to Assess Both Cortical and Subcortical Signals	2.70/3.0/1.03 (8)	2.68/2.0/1.07 (8)	2.84/3.0/.55 (9)
Demonstrated Sensitivity to Pharmacological Manipulations	2.68/2.0/1.08 (9)	2.57/2.0/1.06 (10)	3.46/4.0/.66 (2)
Practicality and Ease of Use	2.66/3.0/.81 (10)	2.65/3.0/.83 (9)	2.69/3.0/.63 (12)
Feasibility of Application in Multicenter Trials	2.54/2.0/1.01 (11)	2.52/2.0/1.04 (11)	2.69/3.0/.85 (12)
Easy Accessibility	2.50/2.0/.91 (12)	2.48/2.0/.92 (12)	2.62/2.0/.87 (14)
Temporal Resolution	2.38/2.0/.86 (13)	2.32/2.0/.84 (13)	2.85/3.0/.90 (8)
Openness to Pharmacological Confounds	2.31/2.0/1.08 (14)	2.25/2.0/1.11 (15)	2.77/3.0/.73 (10)
Spatial Resolution	2.31/2.0/.84 (15)	2.27/2.0/.86 (14)	2.54/3.0/.78 (15)

Note: 0 = not important; 1 = somewhat helpful; 2 = very helpful but not essential; 3 = somewhat essential; 4 = very essential.
SD, standard deviation.

Table 2. Feasibility Ratings for Different Biomarker Imaging Methods

Potential Biomarker Imaging Method	Mostly Negative Findings	Mixed Findings	Mostly Positive Findings	Has Not Been Studied Sufficiently to Judge	I Do Not Have Sufficient Knowledge to Answer
Functional Magnetic Resonance Imaging	0%	21.6%	58%	8%	12.5%
Event Related Potentials	1.1%	20.7%	31.5%	15.2%	31.5%
Electroencephalography	2.4%	37.6%	20%	12.9%	27.1%
Magnetoencephalography	0%	12.8%	11.6%	25.6%	50%
Near Infrared Spectroscopy	0%	4.1%	1.7%	29.4%	62.4%
Transcranial Magnetic Stimulation	5.9%	7.1%	11.8%	28.2%	47.1%
Receptor Based Cognitive Imaging	1%	21.4%	29.8%	17.9%	29.8%
Structural Imaging	21%	23.5%	22.2%	16%	17.3%

Note: 0 = not important; 1 = somewhat helpful; 2 = very helpful but not essential; 3 = somewhat essential; 4 = very essential.

individuals from academia and industry. As can be seen in Table 1, academic and industry participants rated many of the same criteria highly, including conceptual and validity criteria such as demonstrated sensitivity to manipulations of cognitive/affective processing and directness of interpretation, and methodological criteria such as test-retest reliability, clear quality assurance protocols, patient tolerance, and standardization of administration and analysis protocols. However, one interesting divergence was that the industry respondents rated demonstrated sensitivity to pharmacological manipulations more highly than academic respondents. This may reflect the more exclusive focus of industry respondents on pharmacological approaches to cognitive enhancement, while the academic respondents included those who also use behavioral interventions to modify cognition. Sensitivity to treatment effects is, however, a critical property for any biomarker measure that will inform treatment development.

Initial Evaluation of Alternative Potential Imaging Biomarker Methods

We then asked respondents to evaluate a range of potential imaging biomarkers on the feasibility of their use in cognition enhancing clinical trials, using the types of criteria outlined in Table 1 to make these evaluations. Specifically, the respondents were asked the question, "How would you evaluate the evidence that this method is useful for assessing neural responses to procognitive manipulations?" for each of the following methods: fMRI, ERPs, MEG, EEG, near infrared spectroscopy, TMS, receptor based cognitive imaging, and structural imaging. The response scale was "mostly negative findings," "mixed findings," and "mostly positive findings," with options for participants to note that the methods had not yet been studied sufficiently or they themselves did not have sufficient knowledge. The percentage of individuals choosing each option for each method is shown in Table 2. As can be seen, respondents were most familiar with fMRI and had the most positive evaluation of this method as having utility as an imaging biomarker in studies of cognition enhancing agents in schizophrenia. Respondents also gave relatively high ratings to ERPs and receptor based cognitive imaging. In contrast, it is clear that many participants did not feel that structural imaging had much utility in this context, which makes sense given the likely slow time course of pharmacological influences on brain structural characteristics likely to influence cognitive function. Respondents were less familiar with many of the other methods (e.g., MEG, near infrared spectroscopy, TMS) and felt that more work was needed to evaluate the utility of the methods as imaging biomarkers in cognition treatment studies in schizophrenia.

Summary of First CNTRICS II Imaging Biomarkers Meeting

In the following three articles, the background talks and discussions that occurred at the meeting are summarized. The meeting was organized to provide overview talks by experts in a range of potential imaging biomarker measures. These experts were asked to generate talks that would provide information to address the types of criteria outlined above, as well as other concerns or issues using imaging biomarkers in treatment studies. These concerns include a desire to clearly understand the physiological basis of the signal we measure with different potential biomarker methods and in particular how these signals are related to neural activity and to potential pathophysiological mechanisms. These issues are discussed in depth for EEG and MEG in the article by Luck *et al.* (7), for TMS in the article by Pasqual-Leone *et al.* (8), and for fMRI in the article by Barch and Mathalon (9) A second concern also addressed by Barch and Mathalon (9), which has led to caution in the interpretation of fMRI effects of cognition enhancing drugs, is the potential direct effects of drugs on the coupling between neural activity and our signal of interest, for example, drugs that may have direct effects on the hemodynamic response underlying the blood oxygenation level-dependent signal in fMRI or on the coupling between metabolism and blood flow. A third concern that has limited the application of imaging biomarkers in treatment studies is the question of the reliability of different methods and how reliability can be better measured and optimized. Poor internal and test-retest reliability of a measure that may otherwise be sensitive to a treatment effect in the brain can substantially reduce the power of a study and lead to a false-negative result (10). By contrast, poor methodology with a lack of statistical rigor and correction for multiple comparisons can lead to false-positive results. Concerns about these issues have led to caution in using measures such as fMRI to guide critical go/no-go decisions during the costly and risky process of bringing a potential treatment for preclinical to clinical trials.

Data related to the reliability of fMRI are discussed in the Barch and Mathalon article (10), which also discusses how generalizability theory may be applied to provide informative data on the reliability of candidate imaging biomarkers using fMRI. In general, these articles suggest that there is a growing body of data that supports the reliability of fMRI based biomarkers for treatment development studies and that there is a robust methodology for evaluating specific measures. At the same time, these articles point to important pathways for further improving assessment and optimization of the reliability of imaging biomarker measures, as well as for addressing additional practical concerns associated with factors such as cross-site implementation. Less work has been done in these areas (e.g.,

reliability) for EEG and MEG, as discussed in the article by Luck *et al.* (7). However, a future research and method development agenda as laid out in the Luck *et al.* (7) article should provide a roadmap for the future development of these measures as biomarkers.

Beyond the above-mentioned conceptual, interpretive, and measurement issues, there are substantial practical ones that will have an impact on the development and application of imaging biomarkers on treatment development. During the course of the conference described in this issue, we sought to address the unique challenges of using each method in multisite studies and how these can be overcome. Electroencephalography clearly has an advantage with regard to portability when compared with MEG and fMRI. By contrast, the widespread availability of fMRI and the necessary tools for data analysis and the increasing knowledge of the relevant calibration methods to obtain scanner harmonization do make this an increasingly feasible approach for use in multicenter studies. There are a number of notable examples of such studies that are underway at this time.

Finally, it was noted that the above pragmatic issues varied considerably according to the phase of treatment development. For example, first-in-human studies tend to be small in scale and conducted in a single site so that issues related to multiple sites and the calibration and harmonization of instruments do not apply in this context. However, studies conducted by contract research organizations with no expertise in functional imaging or cognitive neuroscience are likely to be poor candidates for the use of imaging biomarkers even if the instrumentation is available, as substantial technical expertise in data acquisition is needed to ensure successful collection of meaningful data using these methods.

Imaging biomarkers are likely to play an increasing role in the treatment development process, especially when treatment targets consist of identifiable cognitive and neural systems that can be engaged reliably by valid cognitive tasks. Our understanding of the underlying neural processes and their relationship to drug effects has grown substantially and a growing body of experience and data support the feasibility as well as the utility of using these measures. The articles in this issue of *Biological Psychiatry* provide a detailed review of the state of the field and as such should help to guide our future research agenda as we work toward optimizing specific biomarker measures to enhance translational research and accelerate our progress toward developing effective therapies for impaired cognitive and emotional processing in schizophrenia and related disorders. In the coming months, CNTRICS will conduct a second imaging biomarkers meeting to identify specific measures for further development and optimization. Each of these recommended imaging biomarker paradigms will require additional validation and optimization for patient administration in treatment development settings, as well as quantification of their measurement properties. The insights and principles described in the articles in this issue will help to guide this process.

Dr. Krystal acknowledges support from US Department of Veterans Affairs Alcohol Research Center, National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, West Haven, Connecticut, and Clinical and Translational Science Awards Grant Number UL1 RR024139 from the National Center for Research Resources, a component of the National Institutes of Health, and National Institutes of Health Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of National Center for Research Resources or National Institutes of Health.

Dr. Carter has served as a consultant for Pfizer, Roche, Lilly, Merck, and Servier and has received research funding from GlaxoSmithKline.

Dr. Barch has received grants from the Allon and Novartis.

Dr. Buchanan is on Advisory Boards of Abbott, Astellas, AstraZeneca, Merck, Pfizer, Roche, Solvay Pharmaceuticals Incorporated, and Wyeth; a consultant for Abbott, Cypress Bioscience, GlaxoSmithKline, Sanofi-Aventis, Schering-Plough, and Takeda; and a Data and Safety Monitoring Board member for Pfizer, Cephalon, and Otsuka.

Dr. Bullmore is an employee of the University of Cambridge (.5 full-time equivalent) and GlaxoSmithKline (.5 full-time equivalent); a stockholder in GlaxoSmithKline and the Brain Resource Company; and has received financial compensation resulting from a license agreement between Cambridge Enterprise Limited, University of Cambridge, and Cypress Bioscience, Incorporated.

Dr. Geyer has received contract research support from Intracellular Therapeutics, Incorporated, and compensation from Acadia, Addex, Amylin, Cerca Insights, Johnson & Johnson, Medivation, Merck, Omeros, Sepracor, Takeda, Teva, and Wyeth-Ayerst and holds an equity interest in San Diego Instruments.

Dr. Green has served as a consultant for Abbott Laboratories, Cypress, Dainippon Sumitomo Pharma, Lundbeck, Otsuka, Sanofi-Aventis, Takeda, and Teva, and served as a speaker for Janssen Cilag and Sunovion.

Dr. Jaeger is an employee of AstraZeneca Pharmaceuticals and owns stock in AstraZeneca Pharmaceuticals.

Dr. Krystal is a consultant for Aisling Capital, LLC; AstraZeneca Pharmaceuticals; Brintnall & Nicolini, Incorporated; Easton Associates; Gilead Sciences, Incorporated; GlaxoSmithKline; Janssen Pharmaceuticals; Lundbeck Research USA; Medivation, Incorporated; Merz Pharmaceuticals; MK Medical Communications; Naurex, Incorporated; Pfizer Pharmaceuticals; F. Hoffmann-La Roche Ltd.; SK Holdings Company, Ltd.; Takeda Industries; Teva Pharmaceutical Industries, Ltd.; and Transcept Pharmaceuticals and on the scientific advisory board of Abbott Laboratories, Bristol-Myers Squibb, Eli Lilly and Company, and Lohocla Research Corporation. Dr. Krystal also has exercisable warrant options for Tetragenex Pharmaceuticals (value less than $150). Research support to Department of Veterans Affairs for Janssen Research Foundation (provided drug and some study support to the Department of Veterans Affairs); derives income greater than $10,000 as the Editor of Biological Psychiatry; Board Of Directors for Coalition for Translational Research in Alcohol and Substance Use Disorders; President Elect of the American College of Neuropsychopharmacology (12-2010); on the Editorial Board of the Shanghai Archives of Psychiatry; and has the following patents and inventions: 1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. Patent #: 5,447,948. September 5, 1995; 2) Dr. Krystal is a co-inventor with Dr. Gerard Sanacora on a filed patent application by Yale University related to targeting the glutamatergic system for the treatment of neuropsychiatric disorders (PCTWO06108055A1); and 3) Intranasal Administration of Ketamine to Treat Depression (pending).

Dr. Neuchterlein has received research funding from Ortho-McNeil Janssen Scientific Affairs (the new name for Janssen, LP) and served as a consultant to Merck.

Dr. Robbins has stock options in Cambridge Cognition; serves as a consultant for Cambridge Cognition, Pfizer, Eli Lilly, GlaxoSmithKline, Wyeth, and Allon Therapeutics; and has received research Grants from Pfizer, GlaxoSmithKline, Lundbeck, and Eli Lilly.

Dr. Silverstein has received research funding from Pfizer and AstraZeneca.

All other authors reported no biomedical financial interests or potential conflicts of interest.

1. Barch DM, Carter CS, Arnsten A, Buchanan RW, Cohen JD, Geyer M, *et al.* (2009): Selecting paradigms from cognitive neuroscience for translation

into use in clinical trials: Proceedings of the third CNTRICS meeting. *Schizophr Bull* 35:109–114.
2. Minzenberg M, Carter CS (2007): The quest for developing new treatments from imaging techniques: Promises, problems and future potential *Expert Opin Drugs Discov* 2:1029–1033.
3. Matthews PM, Honey GD, Bullmore ET (2006): Applications of fMRI in translational medicine and clinical practice. *Nat Rev Neurosci* 7:732–744.
4. Insel TR, Cuthbert BN (2009): Endophenotypes: Bridging genomic complexity and disorder heterogeneity. *Biol Psychiatry* 66:988–989.
5. Aston-Jones G, Gold JI (2009): How we say no: Norepinephrine, inferior frontal gyrus, and response inhibition. *Biol Psychiatry* 65:548–549.
6. Minzenberg MJ, Watrous AJ, Yoon JH, Ursu S, Carter CS (2008): Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. *Science* 322:1700–1702.
7. Luck SJ, Mathalon DH, O'Donnell BF, Hämäläinen MS, Spencer KM, Javitt DC, Uhlhaas PJ (2011): A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. *Biol Psychiatry* 70:xxx–xxx.
8. McClintock SM, Freitas C, Oberman L, Lisanby SH, Pascual-Leone A (2011): Transcranial magnetic stimulation: A neuroscientific probe of cortical function in schizophrenia. *Biol Psychiatry* 70:xxx–xxx.
9. Barch DM, Mathalon DH (2011): Using brain imaging measures in studies of procognitive pharmacologic agents in schizophrenia: Psychometric and quality assurance considerations. *Biol Psychiatry* 70:xxx–xxx.
10. Barch DM, Carter CS (2008): Measurement issues in the use of cognitive neuroscience tasks in drug development for impaired cognition in schizophrenia: A report of the second consensus building conference of the CNTRICS initiative. *Schizophr Bull* 34:613–618.