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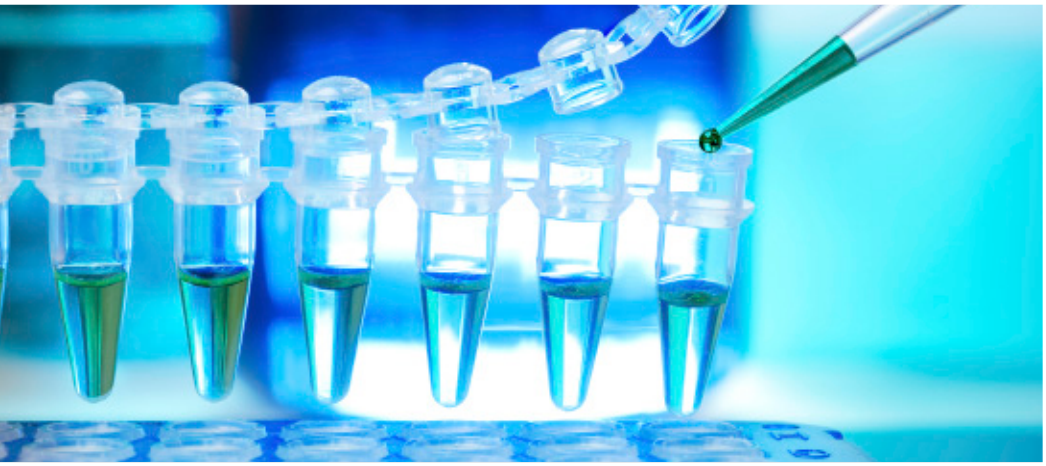
The Science of Drug Abuse & Addiction

May 2015

Report from the

Division of Clinical Neuroscience and Behavioral Research Review Work Group



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April 22, 2015

Nora D. Volkow, MD,
Director
National Institute on Drug Abuse
6001 Executive Boulevard
Bethesda, MD 20892

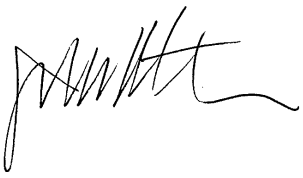
Dear Dr. Volkow:

It is my pleasure to transmit the report and recommendations of the NIDA Division of Clinical Neuroscience and Behavioral Research (DCNBR) Review Work Group. The report and recommendations reflect the unanimous view of the Work Group members, and we take full responsibility for the contents. We remain available to meet with you and/or members of your staff to discuss our findings and recommendations, if needed.

The Work Group was impressed with the devotion and accomplishments of the DCNBR leadership and staff. We present a vision for the future of translational neurobehavioral research on substance abuse and addiction; we note challenges and opportunities in the context of scientific advances and NIDA structure; we lay out a set of broad recommendations; and we discuss four major issues that may need to be addressed to implement the recommendations. Because these issues go beyond the scope, expertise, and authority of an external advisory group, we present these issues in terms of a set of options you may want to consider, with our preliminary thoughts on each option's advantages and disadvantages.

The members of the Work Group and I would like to thank Ericka Boone, Ph.D., for her support and guidance throughout the review process. We also thank the staff of SEI who supported our work: Susan Holbrook for meeting planning and other aspects of project administration, Patrice Pettinato for minutes of our early conference calls, and Robert Katt for technical writing and editing support in developing the final report. On behalf of the entire Work Group, I thank you for this opportunity to support NIDA's mission.

Sincerely,



John Rotrosen, MD

National Institute on Drug Abuse

Review of the Division of Clinical Neuroscience and Behavioral Research Portfolio and Activities

Report from the
Division of Clinical Neuroscience and Behavioral Research Review Work Group

May 2015

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EXECUTIVE SUMMARY

The Division of Clinical Neuroscience and Behavioral Research (DCNBR) was created over 10 years ago to provide a bidirectional translational program linking basic, preclinical, and applied research across the National Institute on Drug Abuse (NIDA). The mission of DCNBR is to utilize a translational approach, within a clinical research context, to promote the understanding of brain and behaviors in drug abuse and addiction. Key scientific areas used to advance this mission are clinical neuroscience, research on integrated neurobehavioral interventions, and developmental science (the science of how the brain and behaviors develop throughout the life span).

In November 2014, Nora Volkow, M.D., the Director of NIDA, convened a National Advisory Council on Drug Abuse Work Group to review the programs and activities of DCNBR, with the goal of providing recommendations to NIDA regarding the structure, function, and overall strategic directions of this Division. Recognizing that these scientific areas intersect and overlap with the mission of other NIDA Divisions,[1] NIDA leadership noted that options to strengthen these key areas and address opportunities and challenges might impact NIDA Divisions beyond DCNBR. The Work Group was encouraged to focus on how to best maximize the impact of clinical neuroscience, integrated neurobehavioral interventions research, and developmental research, without constraining its considerations to a narrow focus on DCNBR, *per se*.

The Work Group expressed a vision for the science in terms of a multidimensional neurobehavioral model of the etiology, progression, treatment, and outcomes of substance abuse and addiction. For the purposes of this report, the model is presented in terms of three dimensions: (1) the trajectory of stages in drug use and addiction, referred to here as the "addiction continuum; (2) The phases of brain and behavior development over the life span; and (3) the processes of brain and behavior considered as a nested set of spatial scales of biological function, from the genome/epigenome and molecular biology to cells, local circuits, distributed groups of circuits, organisms, and society. Each of these three dimensions includes a focus on individual differences, such as sex differences; other genetic and epigenetic factors; environmental interactions with individual experiences; and sociocultural factors.

The Work Group noted that recent rapid advances in genetics, molecular biology, the NIH BRAIN Initiative, precision medicine, Big Data, etc., create exceptional opportunities to expand translational neuroscience and neurobehavioral interventions in addictions. The Work Group views translational neuroscience and neurobehavioral interventions research to be central to NIDA's overall mission.

The Work Group considered the recent strengths and accomplishments of DCNBR and its three Branches: Clinical Neuroscience Branch (CNB), Behavioral and Integrative Treatment Branch (BITB), and Behavioral and Brain Development Branch (BBDB). It also identified specific challenges and opportunities that NIDA, in relation to the Division and its Branches, should address

[1] Throughout this report, the term "NIDA Divisions" includes DCNBR, Division of Epidemiology, Services and Prevention Research, Center for the Clinical Trials Network, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, Division of Basic Neuroscience and Behavioral Research, Division of Extramural Research and the AIDS Research Program.

to maximize the opportunities for the neurobehavioral model to be realized. In light of these strengths, challenges, and opportunities, the Work Group offers a set of recommendations for consideration by NIDA leadership:

1. Apply a multidimensional neurobehavioral model of substance abuse consisting of three dimensions: the addiction continuum, developmental phases, and levels of biological functional organization, including consideration of individual differences in each of these dimensions.
2. Ensure that the leaders of NIDA's Divisions and Branches have expertise not only in their own domains, but also a broad understanding of different aspects of addiction in general and a willingness to work closely with other units to accomplish goals in a creative manner. Currently, there are notable gaps in expertise in the areas of imaging, genetics/epigenetics, and imaging genetics, and in emerging advances in neurobehavioral interventions.
3. Strengthen functional integration and collaboration across and within NIDA Divisions, focusing on infusing the multidimensional neurobehavioral model, including the developmental framework, into all existing and new efforts.
4. Take advantage of the trans-NIH Adolescent Brain Cognitive Development (ABCD) Study to implement functional integration, with a focus on development, throughout NIDA and across other NIH Institutes and Centers.
5. Encourage multimodal integration of imaging studies of substance abuse and addiction across both human and animal studies.
6. Encourage data-sharing, repositories, and Big Data analytics.
7. Ensure that the research results of previously funded Requests for Applications are collated and reviewed to monitor their success and ensure that their results are integrated into future NIDA strategic plans and funding opportunity announcements.

Implementing these broad, function-oriented recommendations may require NIDA to re-examine its overall structure in the context of pragmatic and policy-based constraints and opportunities best understood by NIDA leadership. While such issues are critical to implementing the Work Group's vision and recommendations, resolving them entails expertise, authorities, and knowledge beyond the Work Group's purview. In particular, some options likely to be considered would affect NIDA Divisions outside DCNBR, as well as that Division and its Branches.

To aid NIDA leadership in making informed decisions, the report concludes with the Work Group's perspective on four major issues, potential options to address each issue, and advantages and disadvantages for each option. The options presented are intended to inform, but not to prescribe or circumscribe the ways NIDA leadership might address each issue. Similarly, the preliminary and partial set of advantages and disadvantages are offered as a starting point for deliberation, not a final tally.

Issue 1: What is the Best Home for NIDA Translational Neuroscience and Neurobehavioral Research?

Option 1.1: Preserve current DCNBR structure and strengthen the key areas for translational neurobehavioral research by re-engineering DCNBR; perhaps renaming it the Division of Translational Neuroscience and Neurobehavioral Research (DTNNR). Populate it

with leadership and staff having the skill sets required to bridge and integrate the key areas of clinical neuroscience, research on integrated neurobehavioral interventions, and developmental science.

Option 1.2: Merge DCNBR and the Division of Basic Neuroscience and Behavioral Research (DBNBR) to create a new DTNNR. Populate it with leadership and staff having the skill sets required to bridge and integrate the key areas of translational neuroscience and neurobehavioral research.

Issue 2: How Should NIDA Foster a Robust Neurobehavioral Interventions Program?

Option 2.1: Within the division housing translational neuroscience and neurobehavioral research (whether structured as described under Options 1.1 or 1.2), strategically strengthen and re-engineer BITB into a new Neurobehavioral Interventions Research Branch (NBIRB). Ensure that the Branch Chief has key leadership skills and fill vacant positions in line with the areas of responsibility of the re-engineered branch.

Option 2.2: Redistribute the current BITB portfolio. Retain neurobehavioral neuroscience and mechanistic research within a re-engineered NBIRB, but transfer neurobehavioral implementation and services research to the Division of Epidemiology Services, and Prevention Research (DESPR) and the Center for the Clinical Trials Network (CCTN). Ensure that the Branch Chief has key leadership skills and fill vacant positions in line with the areas of responsibility of the re-engineered branch.

Issue 3: What is the Best Way to Incorporate Developmental Science throughout NIDA?

Option 3.1: Establish an Office, Program, or Center for Developmental Research reporting directly to the NIDA Director or housed in the Division of Extramural Research (DER), and assign to it the responsibilities of coordinating developmental research across NIDA and administering the ABCD Study. For both functions, draw on scientific and content expertise from across NIDA (and to some extent from the other Collaborative Research on Addiction at NIH [CRAN] Institutes). Reassign the current BBDB portfolio to other Branches throughout NIDA as appropriate.

Option 3.2: Administer the ABCD Study from within the Office of the NIDA Director or DER, as in Option 3.1, but maintain a branch-level unit (BBDB or equivalent), either in the translational neuroscience division or elsewhere, to focus on a portfolio of developmental science.

Issue 4: How Should Genetics and Modern Molecular Biology Be Incorporated across NIDA's Organizational Structure?

Option 4.1: Create within the division housing translational neuroscience a new branch focused on genetics and molecular research in humans. This branch would manage genetics-related projects currently supported by other branches, including integrated neurobehavioral interventions research, medications development work, and imaging genetics. The human genetics portfolio would be shifted to this new branch.

Option 4.2: Instead of creating a new branch, as in Option 4.1, ensure that the division housing translational neuroscience has sufficient staff expertise in human genetics and molecular biology in key areas of clinical neuroscience, integrated neurobehavioral interventions, and developmental science. In addition to providing portfolio management for research grants with a major focus on human genetics, this staff expertise should provide

collaborative support for research with a human genetics component, but managed by others in the division and elsewhere in NIDA.

INTRODUCTION AND BACKGROUND

In November 2014, the Director of the National Institute on Drug Abuse (NIDA), Nora D. Volkow, M.D., convened a work group of the National Advisory Council on Drug Abuse to review the programs and directions of the NIDA Division of Clinical Neuroscience and Behavioral Research (DCNBR). The work group members, listed in Appendix A, included members of the National Advisory Council on Drug Abuse and other distinguished experts on clinical neuroscience and behavioral research related to drug abuse and addiction.

The mission of DCNBR is to utilize a translational approach, within a clinical research context, to improve health by advancing the understanding of brain and behavior in drug abuse and addiction, as well as the translation of basic research findings to applied clinical research and practice. This mission is pursued through programs of clinical research and research training within three Branches centered on neuroscience (the Clinical Neuroscience Branch, CNB), development (the Behavioral and Brain Development Branch, BBDB), and treatment (the Behavioral and Integrative Treatment Branch, BITB).

Charge to the DCNBR Review Work Group

The goal set for the DCNBR Review Work Group (hereafter, the Work Group) in Dr. Volkow's formal invitation to the members was, "to review research programs and activities of DCNBR in an effort to provide recommendations to NIDA regarding the structure, function, and overall strategic direction of this Division." During the initial Work Group telephone conference on November 21, 2014, Dr. Volkow expanded on this goal with the following points:

- The purpose of the review is to help identify scientific areas for expansion, strengthen the science supported by NIDA in clinical neuroscience and behavioral research, and identify opportunities for integrating priorities across the Institute.
- The Work Group should identify ways to integrate DCNBR's efforts with those of other NIDA Divisions,[2] as well as with other partners within and outside the National Institutes of Health (NIH).
    - The need to strengthen collaborative partnerships has become more salient with the adoption of the Collaborative Research on Addiction at NIH (CRAN) Initiative.
    - Other trans-NIH projects or initiatives relevant to clinical neuroscience and behavioral research at NIDA include the Adolescent Brain Cognitive Development (ABCD) Study, the NIH Blueprint for Neuroscience Research (Blueprint Initiative), and the Big Data to Knowledge (BD2K) Initiative.

[2] Throughout this report, the term "NIDA Divisions" includes DCNBR, Division of Epidemiology, Services and Prevention Research (DESPR), Center for the Clinical Trials Network (CCTN), Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMC), Division of Basic Neuroscience and Behavioral Research (DBNBR), and the AIDS Research Program (ARP).

  - The Pain Consortium is a cooperative effort among 19 NIH Institutes and Centers (ICs), the Fogarty International Center, and others, to enhance pain research and promote collaboration among researchers across the ICs that have programs and activities to address pain.
  - Program initiatives to enhance the diversity of the NIH-funded workforce include the following activities under the NIH Common Fund: Building Infrastructure Leading to Diversity (BUILD), National Research Mentoring Network (NRMN), and the Coordination and Evaluation Council (CEC).

- Dr. Volkow requested suggestions from the Work Group on how to improve the translation of emerging science from genetics and human behavior into clinical applications. For example, are there tools that could help with this translation? Is the science available to begin discussing the use of biomarkers in clinical applications, or is this question still too premature?

The Work Group discussed the scope of the review further with Dr. Volkow and NIDA Deputy Directory Wilson Compton, M.D., during the in-person meeting at NIDA in February. In the opening session, Dr. Volkow asked the Work Group to look at the science that has been and is being done within the DCNBR portfolio and determine if the science being done is likely to lead to the most important discoveries, taking advantage of the available resources, while not duplicating efforts. The task, she said, is to anticipate the directions for the most productive science. She also posed the questions, "Is the current organizational structure the best one for the science that is emerging?" "What structure would make the most sense for trends in the future?" She noted that integration across the NIDA Divisions has been a recurring issue raised in the series of Review Work Group reports, and the Institute's leadership is seeking to expand integration within NIDA and with other ICs.

After the February meeting, as the Work Group discussed and developed the content for this report, a question arose among Work Group members about the scope of the Work Group's recommendations. Specifically, should recommendations be limited to DCNBR and the Work Group's scientific and strategic vision for that Division, or should the Work Group also include identifying structural options (not necessarily recommendations) that might extend to or affect other parts of NIDA's structure outside DCNBR? In late February, this question was posed to the NIDA Deputy Director, who provided clarification along the following lines: The Work Group will not have fully reviewed all areas of NIDA, so it is not possible (and not the Work Group's responsibility) to explicate a full organizational shift for the Institute. However, identifying and highlighting the strengths and weaknesses of options that may involve other NIDA Divisions would be useful and appropriate. A key issue is how best to manage the key areas of neuroscience and other areas under DCNBR's purview in light of the important intersections and overlaps of those areas with work in other parts of NIDA. Advice on how to maximize the impact and strengths of clinical neuroscience, behavioral and integrated treatment research and development (for which the Work Group has proposed the term "integrated neurobehavioral interventions," as described below), and developmental research is more desirable than a narrow focus on DCNBR, *per se*.

The Work Group has taken to heart all of the above guidance. This report has been structured to fulfill the charge as explicated, based on the joint expertise and understanding of the Work Group's members.

- The second section of the report presents the Work Group's vision for future evidence-based, neurobehavioral interventions, informed by the etiology of substance abuse and addiction, the rapidly evolving state of neuroscience in many relevant areas, and the sociocultural context of substance abuse and addiction. For brevity, we have adopted the term "translational neuroscience and neurobehavioral research" to encompass three key scientific areas: clinical neuroscience, research on integrated neurobehavioral interventions, and the developmental science relevant to understanding and intervening in substance abuse and addiction.
- The third section applies this vision to the past and present work of DCNBR, highlighting significant strengths and accomplishments important to the vision, as well as challenges and opportunities important to address.
- The fourth section is a succinct list of recommendations that the Work Group sees as essential for strengthening translational neuroscience and neurobehavioral research, not only in DCNBR, but across all of NIDA.
- The final section presents four issues that the Work Group views as critical for implementing the preceding recommendations. Options for each issue, with the Work Group's thoughts on the advantages and disadvantages of each, are offered for consideration by NIDA leadership.

The Work Group's Review Process

In the course of conducting its review and preparing this report, the Work Group participated in 1 in-person meeting and 12 telephone conferences (telecons). Three telecons, including the initial conference in November described above, occurred prior to the 3-day in-person meeting on February 4-6. 2015.

The February meeting began with the session, described above, at which Dr. Volkow discussed further the charge to the Work Group and some Work Group questions about potential approaches that had arisen during the pre-meeting telecons. The Work Group then heard presentations from the DCNBR director, Dr. Joseph Frascella, the Branch Chiefs of the three DCNBR Branches, and the DCNBR Deputy Director, who discussed the Pain and Analgesia Program. (The meeting agenda is in Appendix B.) The final presentation on the first day and most of the presentations on the second day allowed the Work Group to hear from and have discussions with the Directors of the other NIDA Divisions and Offices. These presentations and the subsequent discussions focused on programmatic intersections and work activity interactions of the presenting Division or Office with DCNBR and its Branches. The Work Group also had the opportunity for a discussion with the previous BITB Branch Chief. On the morning of the third day, the Work Group met with the NIDA Director and Deputy Director. There were executive sessions reserved for Work Group discussions on each of the 3 days.

Eight telecons were conducted after the in-person meeting, roughly weekly, from February 11 through April 8, 2015. Drafts for each section of the report were developed, discussed, revised,

and refined through the group discussions during these telecons and a continual flow of emails among Work Group members and staff. The final report presented here represents a consensus view of all Work Group members.

The Work Group commends the DCNBR leadership and staff for the effort put into preparing for and participating in the in-person meeting and for their support from the first teleconference through the in-person meeting. They summarized Division programs and activities for the Work Group, both in the Review Notebook distributed to Work Group members before the February in-person meeting and in the presentations at that meeting. The Review Notebook included summaries and outcomes of special efforts initiated by Division staff. Also of note, the Review Notebook was assembled at a time when DCNBR was burdened with unprecedented staff vacancies, and the Work Group appreciates the efforts made to ensure it received information for the review.

A VISION FOR THE FUTURE: EVIDENCE-BASED NEUROBEHAVIORAL INTERVENTIONS INFORMED BY ETIOLOGY, NEUROSCIENCE, AND SOCIOCULTURAL CONTEXT

DCNBR Roles and Responsibilities in the NIDA Mission

The Work Group recognizes that, "NIDA's mission is to lead the Nation in bringing the power of science to bear on drug abuse and addiction. This charge has two critical components. The first is the strategic support and conduct of research across a broad range of disciplines. The second is ensuring the rapid and effective dissemination and use of the results of that research to significantly improve prevention and treatment and to inform policy as it relates to drug abuse and addiction."[3]

The strategic support and conduct of research across a broad range of disciplines starts with seeking, finding, and disseminating fundamental knowledge, gained from basic research, about human addiction and animal models of addiction. This includes research on the full range of biological, genetic, and environmental factors that play a role in the addiction continuum at every phase of development and at every scale of biological to societal organization and function.

Within the context of NIDA's mission, DCNBR's mission has been formally defined as follows:[4]

> The mission of the Division of Clinical Neuroscience and Behavioral Research is to utilize a translational approach, within a clinical research context, to improve health by advancing our understanding of brain and behavior in drug abuse and addiction. This mission is pursued through programs of clinical research and research training within three branches centered on neuroscience, development, and treatment. A major focus of the Division is the support of science for the translation of basic findings to clinical research, as well as for the translation of the results of clinical investigations to applied research.

A Multidimensional Neurobehavioral Model of Substance Abuse and Addiction

To review DCNBR's mission, the Work Group found it useful to frame a vision suited to the mission of DCNBR and to draw on that vision in its findings and recommendations. Central to this vision is a multidimensional neurobehavioral model of the etiology, progression, treatment, and outcomes of substance abuse and addiction. The intervention focus of this vision is on prevention, mitigation, and treatment. It acknowledges that complex neurobiological and behavioral trajectories characterize the transition from exposure to initial use to dependence, withdrawal, recovery, and relapse (the "addiction continuum") and that these trajectories involve multiple neural circuits with distinct roles in each of these processes. These trajectories are influenced by age-related differences

[3] Mission definition from the NIDA website: http://www.drugabuse.gov/about-nida.
[4] Mission definition from the DCNBR website: http://www.drugabuse.gov/about-nida/organization/divisions/division-clinical-neuroscience-behavioral-research-dcnbr.

in the functional states of these neural circuits and by sociocultural factors that also vary with age. In addition, other individual-difference factors modify addiction trajectories, and these factors can arise from genetic or environmental origins. Finally, the consequences of addiction, both neurobiological and behavioral, modify subsequent cycles of the addiction continuum. Thus, the goal must be to develop precisely targeted interventions appropriate for the addiction stage, the neurodevelopmental phase of the individual, and available knowledge of other relevant individual-difference factors.

NIDA leadership should ensure that current and newly recruited staff throughout the Institute share this vision and embrace it. The greatest threat to success appears to be a structure that at times focuses on specific elements of the model to the exclusion of other critical elements. The Work Group strongly recommend that all NIDA Divisions attend to critical behavioral aspects of addiction, the specific underlying neurobiological mechanisms (as manifested in humans and in model systems), important neurodevelopmental parameters, and other relevant genetic and cultural differences as they are brought to bear on developing maximally effective preventative and treatment interventions.

The Work Group identified three dimensions of the model, along with the role of individual differences as they affect those dimensions, as particularly relevant to its review of DCNBR.

Dimension 1: The Addiction Continuum

The Work Group notes that addiction comprises several stages of use, all of which serve as possible targets for intervention. These targets include risk factors predating drug use, exposure, initiation of use, repeated use and evolving dependence, difficulty stopping, withdrawal symptomatology, motivation for treatment, treatment effectiveness, abstinence (or reduction of harmful use), relapse, and recovery. This trajectory (the addiction continuum) and the most effective interventions may depend critically on the developmental phase (see Dimension 2).

Drugs have different actions on the brain depending on the stage of drug use and the stage of development. Drugs may strengthen or weaken connections within and between brain regions, and they may affect molecular pathways. Some substances may have neurotoxic effects that influence development or neurobehavioral function. These effects may depend on the phase of brain development, on the level(s) of biological function affected, and on other important individual differences in risk. Neurotoxicity and neurobehavioral consequences of drug use contribute to the enormous costs of drug abuse to society.

Drug use may affect the progression of development and cause permanent alterations in development. For example, prenatal or perinatal exposure to drugs presents one important target of intervention, and use of drugs in childhood or adolescence, which may have critical consequences for brain development and behavior, is a second important target.

Later in the addiction cycle, relapse to drug use, perhaps the greatest challenge to the drug addiction field, is another key clinical target for intervention development. Relapse can occur immediately after cessation or months or even years later; likelihood to relapse is exacerbated by stress, by co-existing psychiatric disorders, by powerful memories and learned associations, and by multiple other factors. The processes involved in relapse and recovery are arguably among the least well understood aspects of addiction.

Dimension 2: Developmental Phase

Understanding the addiction continuum *across the lifespan* is critical to understanding the process by which drugs change the brain and behavior. Consideration of neurodevelopment should inform and shape interventions tailored to the individual. Interventions should be contextualized to suit different phases of human development through childhood, adolescence, adulthood, and senescence. Whereas most interventions to date are modeled on an adult brain, the Work Group believes the science argues for interventions that target the developmental phases across the lifespan.

It is important to adapt intervention approaches to the timetable of behavioral and brain changes across development. Developmental stage is important for identifying therapeutic targets, guiding interventions by developmental phase, and informing prevention strategies that modify the environment to promote lasting beneficial effects. Identifying windows of maximum developmental change and those where the environment may have strong influences on brain and behavior may enhance intervention effectiveness. Understanding how these sensitive windows shift or constrict with substance exposure and use, or how these windows may be expanded at different points in development (childhood, adolescence, young and older adulthood) will guide the timing and type of intervention for the individual.

Dimension 3: Biological Functional Organization

Organisms arise from a complex set of interactions between their genome-epigenome and their environment. Drug misuse and addiction can be conceptualized as an organism's failure to adapt effectively to its environment. These adaptation failures can occur at different levels of biological organization, including multiple spatiotemporal scales of brain function. Alterations in neural circuitry may occur as an immediate adaptation, whereas alterations in genome-epigenome, molecular machinery, and cellular function may represent adaptation failures on a longer time scale.

Brain processes can be viewed as biological functions occurring on a nested set of spatial scales. For example, the genome/epigenome is nested within cells (neural and glial) that in turn are nested in neural groups that constitute local circuits. Local circuits participate in interconnected groups distributed across the brain. Individual organisms and social organization occur at still wider spatial and temporal scales of relevant biological functioning. Dense sampling of one scale of brain function can yield information on processes at the other scales. The scale of distributed neural groups can be sampled using imaging modalities, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Multicellular recording techniques can be used to sample local circuits or neural groups composed of excitatory and inhibitory synapses and axonal and dendro-dendritic circuits. The individual cell, with its intracellular signaling and surface receptors, can be characterized by measures of local field potential and sequences of action potentials.

The Role of Individual Differences

Individual differences are present at every stage in the addiction continuum (Dimension 1), every developmental phase (Dimension 2), and every scale of biological organization (Dimension 3), where they act as sources of variance on response and outcomes in these dimensions. They include sex differences and gender identification; genetic variations lifetime environmental interactions, including sociocultural factors; and epigenetic changes in neural cell genomes. These sources of variance must be understood and taken into account to optimize interventions.

In principle, interventions need to be targeted not only to an individual's age, but also to his or her sex and other individual characteristics. This approach will require bridging discoveries across molecular, circuit, and behavioral levels in the DBNBR portfolio with discoveries in humans in the DCNBR portfolio, in order to enhance the capacity—in conjunction with the Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMC), the Division of Epidemiology, Services and Prevention Research (DESPR), and the Center for the Clinical Trials Network (CCTN)—to develop, target, and scale up interventions across the addiction continuum and by developmental phase. In short, pursuing the vision represented in this model will require increasing integration of research across NIDA's Divisions.

Complementarity of Neurophysiological and Behavioral Components in Integrated Interventions

Innovative technologies in genetics, psychopharmacology, neurostimulation, and brain imaging are providing a new understanding of brain circuitry and function and opening possibilities for a new era of interventions for substance use disorders. Potential interventions enhance synaptic plasticity in preclinical studies, reopening windows that might permit therapeutic change. Approaches include a variety of medications; electrical and magnetic stimulation, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS); and targeted gene transfer, such as designer receptors exclusively activated by designer drugs (DREADDs). These approaches also afford the opportunity to accelerate normalization of brain function and research into the neurobiology of successful abstinence and recovery.

These approaches offer windows of opportunity by enhancing neuroplasticity and circuit function, but alone, they may not change drug-seeking and drug-taking behaviors. Persistent changes in behavior will likely require using approaches such as these to induce plasticity alongside behavioral interventions to retrain the brain. Precise and intense retraining is likely to be needed to effectively "rewire" a brain affected by substance abuse and restore previously lost capacity, either by normalizing affected brain circuits or enabling other brain circuits to take over compromised functions. If this paradigm is supported by further studies and clinical trials, the implication is that the most effective interventions of the future will ***combine*** neurophysiologic ***and*** behavioral interventions. Understanding how these windows of therapeutic change may be expanded at different phases in development may protect and prolong the capacity of the brain physically, emotionally, cognitively, and socially, yielding optimal outcomes. NIDA is leading NIH efforts in this area, and a continued strong focus on translational neuroscience and neurobehavioral interventions is essential and likely to be pivotal in translating the fruits of basic and clinical science into novel and effective interventions.

Applying the Neurodevelopmental Addiction Model to NIDA Research

The Work Group considered how NIDA might implement a translational, neurodevelopmental model of addiction. The goal would be to integrate and coordinate human and animal research, with a focus on all stages of drug use (i.e., initiation through recovery), at different stages of development (i.e., from childhood through senescence), and across biological scales (i.e., molecular to organism to societal). The Work Group thought that it is essential to foster bidirectional communication to bridge clinical and preclinical research efforts. Clinical research should identify clinical intervention targets and preclinical research should attempt to model these. Similarly, preclinical research should identify potential mechanisms and processes for intervention, as well as molecular targets, which should then rapidly be tested in humans. We note that human

and animal studies that use directly comparable outcome measures and testing conditions offer an especially powerful translational opportunity. There is also potential for translational research in the areas of prevention and treatment, including relapse prevention. Finally, the developmental perspective (as exemplified by the ABCD Study) can also be effectively modeled in animal studies. As part of this aim, a key integrative interface between clinical and preclinical studies is provided by human laboratory studies, including those with healthy volunteers. These goals can be achieved ***only*** with close and effective interactions among NIDA's Divisions and Branches.

Although the Work Group is not recommending a specific organizational structure to implement the vision outlined above, we note that the success of any future structure will depend on the energy, expertise, initiative, and cooperation of NIDA staff. In particular, we identified a need for additional staff with expertise in development science (especially adolescent development, given the ABCD Study's focus), neurobehavioral intervention neuroscience, imaging, genetics, mobile technology, and Big Data analytic methods.

DCNBR STRENGTHS, ACCOMPLISHMENTS, CHALLENGES, AND OPPORTUNITIES

Strengths and Accomplishments

The past decade has witnessed advances in addiction neuroscience, pathophysiology, and pharmacologic and behavioral interventions that have outpaced or rivaled those achieved for any other brain disease. No small part of the credit for this is owed to work that DCNBR has led and funded and to NIDA leadership. DCNBR was established in 2004, early in Dr. Volkow's tenure as NIDA Director, to play a central and critical role in the overall organization of NIDA, focusing on the development, clinical neuroscience, and treatment pillars of NIDA's basic science, prevention, and treatment mission. DCNBR builds on preclinical research ongoing in DBNBR, and it develops interventions often tested and brought to scale in DESPR and NIDA's Clinical Trials Network (CTN). The Work Group felt that DCNBR has an outstanding portfolio of research and training projects and fulfills many of its administrative roles in an exemplary manner. It encourages NIDA to continue to build on this legacy and to strengthen its portfolios in translational neuroscience and neurobehavioral interventions research to capitalize on breakthroughs in basic and clinical science and on other opportunities to advance the field.

Recent DCNBR strengths and accomplishments that the Work Group views as particularly relevant to the vision developed in the previous section include the following:

- Among the notable achievements of DCNBR are the formation of the Centers of Excellence for Pain Education; the exploration of new strategies in the Translationally Oriented Approaches, Devices, and Strategies initiative; the initiative to build developmental research training capacity; and the initiative to examine consequences of substance exposure and use on the developing brain (which the Work Group views as a valuable predecessor-contributor to the ABCD Study).
- Strategic directions identified by DCNBR leadership and staff that align well with the Work Group's vision include: (1) harmonizing procedures used in animal models with human approaches more closely linked to clinical applications, (2) better understanding the role of genetics and epigenetics, (3) aggregating imaging data across studies and laboratories, and (4) pursuing opportunities afforded by emerging capabilities in eHealth, mHealth, and Big Data information analytics. At the Division and Branch levels, the Work Group found strong recognition of the importance of individual differences at every stage of the addiction continuum, the need for progress in prevention, and the need for basic neuroscience to understand processes by which drugs change the brain and behavior. DCNBR staff recognized the importance of harmonizing basic and clinical research and translating basic science findings into effective interventions. The Work Group agrees and urges further strengthening of these translational goals.
- The Work Group found that DCNBR leadership and staff appreciate and clearly communicate the importance of understanding the addiction continuum, especially as it intersects with different stages of development, and of understanding the process of recovery from substance abuse and addiction.

- The Work Group notes the success of research funded by the BITB, which has informed new science-based treatments and has emphasized potential behavioral and neural mechanisms for substance abuse treatment. These successes include, in the past 10 years, bringing several interventions from small efficacy trials to adoption in state and national systems; identifying effective interventions that reduce smoking in pregnant women, with demonstrated benefits on their infants' health; interventions aimed at improving cognitive control and harnessing brain plasticity to affect basic cognitive processes associated with addiction (working memory, attentional bias, decision-making); and utilizing the power of technology (web-based, mobile-device applications) to develop effective, low-cost, interventions that can be implemented at multiple points in the health care system. Moreover, while development of novel medications has been a high NIDA priority, NIDA-funded research has consistently demonstrated that treatment adherence and outcomes are greatly enhanced when medications are combined with effective behavioral interventions. This Branch has been and will continue to be the face of NIDA to the clinical community, Congress, and taxpayers; thus, it must be preserved and strengthened.
- BITB is currently supporting multiple innovative translational strategies that are likely to greatly enhance our understanding of the neurobiology of successful abstinence, as well as how effective treatments achieve their effects. These include, for example, systematic evaluation of direct stimulation approaches (TMS), as well as pairing validated interventions with pre- and post-treatment neuroimaging and real-time fMRI to better understand neural effects of effective interventions. These strategies highlight the benefits of BITB's linkage with the CNB.
- The neuroimaging research supported by CNB has played and will continue to play an important role in filling translational gaps in intervention development. Too often, clinical trials fail when translating preclinical animal findings directly into human trials without appreciation for how the circuitry implicated is conserved across species. Human imaging provides this translational step. A strategic need in the future is the capacity to identify, optimize, and evaluate neurobiological processes disrupted in addiction that can be assessed in animals and humans. This work could reveal when such measures are similar or dissimilar between preclinical species and humans and yield new targets for treatment. Thus, human imaging studies focused on translational neuroscience could foster and guide the translation of research results from animals to humans, with this translational work serving as a basis for selecting preclinical treatment/intervention candidates for further development and clinical testing.
- The BBDB has been an important counter to the tendency for human developmental neuroscience to become fragmented across NIDA Divisions and programs. The Branch has maintained a focus on the impact of toxic prenatal exposure on development and the consequences of substance abuse on children and families. These are programs and vital interests that can be lost in the larger program on adult addiction. Also, in recent years, BBDB has addressed gaps in human developmental neuroscience—for example, with its support of the Pediatric Imaging Neurocognition and Genetics (PING) Data Repository.

DCNBR Challenges and Opportunities

Although excellent work is being done in DCNBR, there are also gaps in the Division's expertise and in coordination and communication among its Branches and with other NIDA Divisions.

1. The Work Group notes the loss of imaging expertise within CNB, particularly the loss of developmental imaging expertise with the recent departure of Jim Bjork. Given the importance of human imaging, particularly developmental imaging with the signature ABCD Study, this scientific expertise will be needed.

2. Human genetics is not sufficiently covered in DCNBR at present, including genetics of basic human behavior related to substance abuse, human imaging genetics, and addiction-related statistical genetics. The Work Group felt that this is an important gap in DCNBR because the science of human genetics has implications for research at every level, from basic neuroscience to treatment responses. Genetics, like lifespan neurodevelopmental science, should be integral to any NIDA Branch or Division, not siloed in a specific Branch or Division.

3. Although BITB has had an enormous impact on the field of addiction treatment, the Branch is currently experiencing significant problems that the Work Group views as urgently in need of attention:

    a. The significant attrition of BITB leadership and staff, including, notably, the departure of Lisa Onken to the National Institute on Aging, poses a critical risk for its portfolio of external research, which is widely viewed in the research community as a key strength of NIDA. Restaffing BITB to a level adequate to support the Branch's important research portfolio is urgent and imperative.

    b. Restaffing of the Branch should be coordinated with re-engineering it to encompass the full range of current and emerging neurobehavioral interventions and to integrate BITB research with translational neuroscience research supported by other Branches and Divisions (e.g., genetics, imaging, developmental science).

    c. As expressed in the Work Group's vision for the complementarity of neural and behavioral interventions, both pharmacotherapies and neurophysiological intervention can open windows of opportunity for behavioral intervention. Likewise, behavioral interventions can play an important role in improving adherence to somatic treatment. Staffing to support this essential role will require expertise in pharmacology and medication implementation, adherence, and refinement.

    d. BITB should also have closer ties with DPMC. BITB and DPMC research should be complementary, to ensure that the breadth of pharmacotherapies and behavioral research and testing is represented in NIDA's portfolio.

4. BBDB is isolated from other Branches within DCNBR and from other NIDA Divisions and Branches, including the signature NIDA initiative, the ABCD Study. Elsewhere in this report, the Work Group has noted that the theme of developmental stages should be emphasized across NIDA to address the different stages of neural development.

5. There is a gap in translating between human and animal levels of investigation. Across biomedicine, clinical trials fail due to directly translating from preclinical animal work to candidate human treatments without examining the similarities and differences in neurocircuitry, genetics, and behavior across species. Although DCNBR is positioned to use human imaging, behavioral, and genetic studies to fill this translational gap, there is little evidence of such work within the Division or within other NIDA units.

6. As exemplified by the neuroeconomics revolution in behavioral theory, there is growing recognition in the field that a clearer understanding of the granularity of behavior is needed. An initiative is needed to provide a shared taxonomy of evidence-based "elements of behavior." This effort was identified by the Work Group as a key need in the field and one that could represent a major contribution to the science of addiction and human behavior. It cuts across the portfolios of DCNBR and presents a major opportunity for NIDA to be at the forefront in this area of inquiry.

7. The level of DCNBR collaboration and dialogue with other NIDA Divisions must be strengthened. For example, DCNBR expertise and investigators could contribute more to medications development, including DPMC medications work. DCNBR could also interact more with CCTN and DESPR; the former could scale up and test new interventions in real-world effectiveness trials, and the latter could evaluate impacts on services and costs. Increased formal interactions with DBNBR could contribute to filling translational gaps from animal models to humans, advancing therapeutics more rapidly. There is a need for mechanisms to foster collaboration and for structures that will better permit these interactions.

RECOMMENDATIONS FOR STRENGTHENING TRANSLATIONAL NEUROSCIENCE AND NEUROBEHAVIORAL RESEARCH

In light of the above assessment of DCNBR in the context of the Work Group's vision for the functional areas central to the Division's mission, and with particular attention to the challenges and opportunities highlighted in the previous section, the Work Group offers the following recommendations for consideration by NIDA leadership.

1. Apply a multidimensional neurobehavioral model of substance abuse consisting of three dimensions: the addiction continuum, developmental phases, and levels of biological functional organization, including consideration of individual differences in each of these dimensions.

2. Ensure that the leaders of NIDA's Divisions and Branches have expertise not only in their own domain, but also a broad understanding of different aspects of addiction in general and a willingness to work closely with other units to accomplish goals in a creative manner. Currently, there are notable gaps in expertise in the areas of imaging, genetics/epigenetics, and imaging genetics and in emerging advances in neurobehavioral interventions.
   - Leaders of NIDA Divisions should meet regularly to coordinate and integrate their goals and portfolios. They should share a common vision of the Institute, recognizing the overarching goals noted in recommendation 1, above.
   - It is essential that Division and Branch leadership exhibit a willingness to work together across organizational units to integrate the complex neurobehavioral approaches to addiction.
   - Only with highly capable, visionary leadership and staff will the goals of the Institute be accomplished, and the Work Group strongly recommends a search for additional, energetic leadership and staff to continue to foster clinical research at NIDA.
   - Clearly there is a need to build and sustain a robust program of neurobehavioral intervention research.

3. Strengthen functional integration and collaboration across and within NIDA Divisions, focusing on infusing the multidimensional neurobehavioral model, including the developmental framework, into all existing and new efforts.
   - Given staffing/funding constraints, this recommendation may require reassignment and sharing of staff across Branches and Divisions, along with reassignment of program oversight responsibilities.
   - Emphasize funding mechanisms that translate and integrate work across NIDA Divisions, such as use of the combined R21/R33 mechanism applied to facilitating transition from one species or type of work to another (e.g., animal to human, preclinical human to clinical).

4. Take advantage of the trans-NIH ABCD Study to implement functional integration, with a focus on development, throughout NIDA and across other NIH ICs.

5. Encourage multimodal integration of imaging studies of substance abuse and addiction across both humans and animal studies.

6. Encourage data-sharing, repositories, and Big Data analytics.

7. Ensure that the research results of previously funded Requests for Applications (RFAs) are collated and reviewed to monitor their success and ensure that their results are integrated into future NIDA strategic plans and funding opportunity announcements.

ISSUES AND OPTIONS FOR TRANSLATIONAL NEUROSCIENCE AND NEUROBEHAVIORAL RESEARCH

Introduction

The previous section presented the Work Group's recommendations for supporting and strengthening three key scientific areas essential to the vision presented earlier in the report: clinical neuroscience, research on integrated neurobehavioral interventions, and developmental science. Implementing these broad, function-oriented recommendations will require resolving tactical issues in the context of NIDA's current structure and in light of pragmatic and policy-based constraints and opportunities best understood by the Institute's senior leadership. The Work Group has wrestled with the following four implementation issues in particular:

1. Where should these three key areas of translational neuroscience and neurobehavioral research be housed within the Division and Branch structure of NIDA?

2. How should NIDA foster a robust neurobehavioral interventions program to fulfill the vision presented above?

3. How should developmental science be incorporated in NIDA's organizational structure to achieve this vision, particularly in light of the importance of the ABCD Study as a "beacon" for this developmental science?

4. How to strengthen the focus on human genetics in translational neuroscience and foster collaboration between NIDA's human genetics portfolio and the three key areas of clinical neuroscience, research on integrated neurobehavioral interventions, and developmental science?

The Work Group agreed that these issues are critical to implementing the vision and recommendations, but also agreed that decisions on them are beyond the expertise of its members, beyond the purview of an external advisory group, and appropriate for the senior leadership of the Institute to decide. Therefore, in this section, we discuss a selection of options that NIDA leadership may consider for each issue. For each option, we offer a preliminary and partial set of advantages and disadvantages that seem relevant from the Work Group's perspective. The options presented are intended to inform, but not to prescribe or circumscribe the ways NIDA leadership might address each issue. Similarly, the advantages and disadvantages are offered as a starting point for deliberation, not a final tally.

While the Work Group did not conduct a thorough review of areas of NIDA outside DCNBR, it encourages NIDA leadership to identify an overall structure that will build on existing strengths and emerging opportunities in clinical neuroscience, research on integrated neurobehavioral interventions, and developmental research that fosters further functional integration across the Institute. The Work Group considered the following factors that complicate resolution of this issue. (1) The key functional areas intersect and overlap with work in other NIDA Divisions. (2) NIDA leadership told the Work Group that a current management objective is to bring the ratio of staff-to-budget in line with NIH norms. Also, given anticipated budget constraints, trade-offs may be needed between maintaining or adding staff and maintaining the funding level for

extramural research. Where an option calls for strengthening leadership and staff for a functional area, the Work Group understands that NIDA leaders may decide to redeploy staff resources as an alternative to recruiting for new hires. (3) In the Work Group's estimation, collaboration across the Institute (that is, effective functional integration within NIDA) remains less than optimal, despite recent initiatives and improvements.

Issue 1: What is the Best Home for NIDA Translational Neuroscience and Neurobehavioral Research?

Option 1.1: Preserve current DCNBR structure and strengthen the key areas for translational neurobehavioral research by re-engineering DCNBR, perhaps renaming it the Division of Translational Neuroscience and Neurobehavioral Research (DTNNR). Populate it with leadership and staff having the skill sets required to bridge and integrate the key areas of clinical neuroscience, research on integrated neurobehavioral interventions, and developmental science.

Advantages:

- This option preserves the integrity of the DCNBR mission, while allowing NIDA leadership to strengthen and redirect structures and functions within the Division to implement the recommendations in the previous section of this report.
- Optimization of the coordination and integration of the key functional areas probably would be easier with all three areas in one Division.
- Re-engineering DCNBR would allow for staffing focused on the expertise and skill sets needed for the key functional areas.

Disadvantages:

- Unlike Option 1.2, this option does not reduce overall staffing by decreasing Division management and administration positions.
- Although this option may enable closer coordination across the functional areas within the Division, it does not in itself foster functional integration at the interfaces with other NIDA Divisions and entities (e.g., DBNBR, DESPR, CCTN, etc.).
- Providing adequate leadership and staffing for a division re-engineered from DCNBR to focus on translational neuroscience and neurobehavioral research will require staffing above the level of Branch staffing currently in DCNBR. Difficult choices will be needed among the options of recruiting for vacant positions, reassigning current staff to new areas/responsibilities, and reassigning staff now in other Divisions.

Option 1.2: Merge DCNBR and DBNBR to create a new DTNNR. Populate it with leadership and staff having the skill sets required to bridge and integrate the key areas of translational neuroscience and neurobehavioral research.

Advantages:

- A merged division would enable better coordination of translational (i.e., T1, bench-to-bedside) neurobehavioral neuroscience research and translation of this neurobehavioral research to integrated interventions development.

- Combining the Divisions would help to eliminate the silos between basic (animal) and clinical (human) research that have been barriers to collaboration and translational work.
- A combined division would bring human and clinical studies into closer alignment with genetics research.
- A merger would reduce the number of NIDA Divisions, permit efficiencies, and free up existing staff to support existing and new initiatives.

Disadvantages:

- Merging these Divisions would be detrimental to clinical research if the clinical neuroscience and interventions research portfolios are competing for the same funds with basic science initiatives.
- Merging the two Divisions into one may be disruptive to the many functions and relationships that are already working well in DBNBR. For example, would new leadership be considered for such a Division (see Issue 2), and would that disrupt what appears to be a healthy and well-performing Division focused on animal studies and human genetic analysis?
- Merging DCNBR with DBNBR to become part of a new translational Division may marginalize human imaging, behavioral, and genetic studies.

Issue 2: How Should NIDA Foster a Robust Neurobehavioral Interventions Program?

Option 2.1: Within the Division housing translational neuroscience and neurobehavioral research (whether structured as under Options 1.1 or 1.2), strategically strengthen and re-engineer BITB into a new Neurobehavioral Interventions Research Branch (NBIRB). Ensure that the Branch Chief has key leadership skills and fill vacant positions in line with the areas of responsibility of the re-engineered Branch.

Advantages

- Critical leadership and staffing vacancies would be filled.
- Current behavioral therapies development and implementation research would be retained within a single Branch and focused on carrying out the vision articulated in this report.
- Co-locating NBIRB within a Division focused on translational neuroscience and neurobehavioral research co-locates the neuroscience-related aspects of neurobehavioral interventions with clinical neuroscience.
- Co-locating NBIRB within a Division focused on translational neuroscience and neurobehavioral research would enable NIDA to capitalize on new opportunities to translate findings from neuroscience into neurobehavioral interventions.
- A cohesive NBIRB would preserve and strengthen neurobehavioral interventions research at a time when integrated interventions need to be developed for primary care settings.

Disadvantages

- If, in response to Issue 1, a translational neuroscience division were formed by combining DCNBR and DBNBR, there may not be adequate focus on translating results of basic

research (both animal studies and clinical neuroscience) into the requisite next steps of research on and development of integrated neurobehavioral interventions.

Option 2.2: Redistribute the current BITB portfolio. Retain neurobehavioral neuroscience and mechanistic research within a re-engineered NBIRB, but transfer neurobehavioral implementation and services research to DESPR and CCTN. Ensure that the Branch Chief has key leadership skills and fill vacant positions in line with the areas of responsibility of the re-engineered branch.

Advantages

- Critical leadership and staffing vacancies would be filled.
- Preserves and retains a strong emphasis on neurobehavioral research.
- Co-locates the neuroscience aspects of neurobehavioral interventions with clinical neuroscience (and possibly with basic neuroscience and genetics) programs.
- Co-locates implementation and services aspects of neurobehavioral interventions with epidemiology, services, and prevention programs and affords the opportunity to take advantage of DESPR and CCTN infrastructure to bring interventions research to scale and conduct effectiveness studies in real-world settings, including primary care.

Disadvantages

- Distribution of the BITB portfolio might make it more difficult to recruit visionary new leadership.
- Breaking up the portfolio, with the resulting disruptions, is likely to weaken, rather than strengthen, this highly successful and crucial NIDA unit.
- Some critical neurobehavioral research could get lost or reduced in priority in the transfer.
- Separates neurobehavioral interventions neuroscience from implementation and services programs.
- Separates interventions and treatments from preclinical studies and clinical neuroscience, risking missed opportunities for likely synergy in these areas and diminishing the importance of neurobiologically informed treatments.

Issue 3: What is the Best Way to Incorporate Developmental Science throughout NIDA?

Option 3.1: Establish an Office, Program, or Center for Developmental Research reporting directly to the NIDA Director or housed in DER, and assign to it the responsibilities of coordinating developmental research across NIDA and administering the ABCD Study. For both functions, draw on scientific and content expertise from across NIDA (and to some extent from the other CRAN Institutes). Reassign the current BBDB portfolio to other Branches throughout NIDA, as appropriate.

Under this option, the Work Group anticipates that much of the existing BBDB portfolio would be assigned to CNB (e.g., developmental neuroscience), some would be assigned to a new NBIRB or to

whatever Branch oversees intervention research and development (e.g., developmental interventions), and some to DESPR (e.g., developmental epidemiology).

Advantages

- Establishing a NIDA organizational entity focused on developmental research would increase the visibility of and establish a high priority for this area.
- A designated leader for developmental research can coordinate expertise from across NIDA (and CRAN Institutes).
- A designated entity for developmental research would allow NIDA to co-locate management of the ABCD Study and coordination of NIDA's overall developmental research portfolio.

Disadvantages

- This entity for developmental research may lack leverage over the developmental research portfolio throughout NIDA, as funding (other than for the ABCD Study) would be distributed through other Divisions and Branches. Unlike the Office of AIDS Research, this entity would lack the leverage of overseeing designated NIH funding (except for the ABCD Study).

Option 3.2: Administer the ABCD Study from within the Office of the NIDA Director or DER, as in Option 3.1, but maintain a Branch-level unit (BBDB or equivalent), either in the translational neuroscience Division or elsewhere, to focus on a portfolio of developmental science.

Advantages

- Preserves BBDB structure, leadership, and staffing and retains a cohesive umbrella to manage NIDA's important developmental research portfolio (with the exception of the ABCD Study).

Disadvantages

- Establishing a Branch for a limited portfolio in developmental science could lead to yet another "stove-piped" isolation of that portfolio from the functionally related work being managed by other Branches, whether in the same Division or in other NIDA Divisions. The relevance of developmental issues in programs of other units could be deemphasized. Thus, an unintended consequence could be increased functional isolation, rather than functional integration.

Issue 4: How Should Genetics and Modern Molecular Biology Be Incorporated across NIDA's Organizational Structure?

Option 4.1: Create within the Division housing translational neuroscience a new Branch focused on genetics and molecular research in humans. This Branch would manage genetics-related projects currently supported by other Branches, including integrated neurobehavioral interventions research, medications development work, and imaging genetics. The human genetics portfolio would be shifted to this new Branch.

Advantages:

- A new Branch focused on human genetics and molecular research would strengthen clinical neuroscience. Strong connections between this new Branch and CNB and BITB would enhance translational exchanges between human genetics and molecular biology and clinical neuroscience and treatment research.

Disadvantages

- Creating a new Branch might be disruptive to existing structures and portfolios.
- Establishing a Branch could lead to yet another "stove-piped" isolation of the portfolio managed by that Branch from the functionally related work being managed by other Branches in the same division or elsewhere in NIDA. An unintended consequence could be functional isolation, rather than functional integration.

Option 4.2: Instead of creating a new Branch, as in Option 4.1, ensure that the Division housing translational neuroscience has sufficient staff expertise in human genetics and molecular biology in key areas of clinical neuroscience, integrated neurobehavioral interventions, and developmental science. In addition to providing portfolio management for research grants with a major focus on human genetics, this staff expertise should provide collaborative support for research with a human genetics component, but managed by others in the Division and elsewhere in NIDA.

Advantages:

- This staff expertise would strengthen the Division's capability to manage and guide research across all three key areas in which human genetics is a component of the study design.
- Not defining a specific Branch for human genetics and molecular research, but ensuring that expertise in these fields is available where needed, could support functional integration across areas, both within the translational neuroscience division and across division boundaries.

Disadvantages

- Historically, applying a "matrix management" approach to extend staff expertise across Division/Branch lines has been fraught with difficulties and has had limited success.

APPENDIX A: DCNBR REVIEW WORK GROUP

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APPENDIX B: MEETING AGENDA, FEBRUARY 2015

Day 1, Wednesday, February 4, 2015

2:00 pm–6:00 pm	**EXECUTIVE SESSION**
2:00 pm–2:10 pm	Welcome and Overview of the Work Group Charge *Nora D. Volkow, M.D., Director, National Institute on Drug Abuse*
2:10 pm–2:20 pm	Opening Remarks, Work Group Introductions *John Rotrosen, M.D., Work Group Chair, New York University School of Medicine*
2:20 pm–2:45 pm	Overview of Division of Clinical Neuroscience & Behavioral Research *Joseph Frascella, Ph.D., Director*
2:45 pm–3:15 pm	Clinical Neuroscience Branch (CNB) *Steven Grant, Ph.D., Branch Chief*
3:15 pm–3:45 pm	Behavioral & Integrative Treatment Branch (BITB) *Will Aklin, Ph.D., Acting Branch Chief*
3:45 pm–4:10 pm	Discussion with Previous BITB Branch Chief *Lisa Onken, Ph.D., National Institute on Aging*
4:10 pm–4:20 pm	BREAK
4:20 pm–4:50 pm	Behavioral & Brain Development Research (BBDR) *Cheryl Anne Boyce, Ph.D., Branch Chief*
4:50 pm–5:10 pm	Pain and Analgesia Program *David Thomas, Ph.D., Deputy Director, DCNBR*
5:10 pm–5:30 pm	Women & Sex/Gender Differences Research Program *Cora Lee Wetherington, Ph.D., Program Coordinator*
5:30 pm–6:00 pm	Brief Work Group Discussion
6:00 pm	ADJOURN

Day 2, Thursday, February 5, 2015

8:00 am–5:00 pm	**EXECUTIVE SESSION**
8:00 am–8:15 am	Recap of Day 1 *John Rotrosen, M.D., Work Group Chair*
8:15 am–8:30 am	Brief Work Group Discussion
8:30 am–9:00 am	Division of Basic Neurosciences & Behavioral Research (DBNBR) *Joni Rutter, Ph.D., Director*

9:00 am–9:30 am	Center for Clinical Trials Network (CCTN) *Betty Tai, Ph.D., Director*

Day 2, continued

9:30 am–10:00 am	Welcome and Work Group Discussion
10:00 am–10:30 am	Division of Epidemiology, Services, & Prevention Research (DESPR) *Redonna Chandler, Ph.D., Acting Director*
10:30 am–11:00 am	AIDS Research Program (ARP) *Jacques Normand, Ph.D., Director*
11:00 am–11:30 pm	Division of Extramural Research (DER) *Susan Weiss, Ph.D., Director*
12:00 pm–1:30 pm	Working Lunch
1:30 pm–2:00 pm	Office of Diversity and Health Disparities (ODHD) *Albert Avila, Ph.D., Director*
2:00 pm–2:30 pm	Intramural Research Program (IRP) *Antonello Bonci, M.D., Director*
2:30 pm–3:00 pm	Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMC) *Phil Skolnick, Ph.D., D.Sc. (hon.), Director*
3:00 pm–3:15 pm	BREAK
3:15 pm–5:00 pm	Work Group Discussion • Work Group recommendations • Next steps • Work Group timeline and assignments • Additional Work Group information needs
5:00 pm	ADJOURN

Day 3, Friday, February 6, 2015

8:30 am–1:00 pm	**EXECUTIVE SESSION** *Work Group Discussions from Day 2, Continued*
1:00 pm	ADJOURN