The New Frontier

Neuroscience Advancements and Their Impact on Nonprofit Behavioral Health Care Providers

Laudan Aron

Carl Zimmer

Patrice Heinz,
Contributing Editor

ALLIANCE
For Children & Families
The Ultimate Agency Advantage

THE ROBERT WOOD JOHNSON FOUNDATION®

Contents

Preface

Advancements in biotechnology, bioengineering, neuroscience, genetics and other medical specialties have dramatically altered the way people are diagnosed and treated for injury or disease. These advancements promise to continue at unprecedented rates of discovery. Along the way, bioethicists, philosophers, politicians, medical practitioners and other professionals will debate the numerous and very complex ethical, financial and service delivery issues inherent in each new development.

While discussion has already begun on these issues within the medical field, very little attention has been given to the potential for these advancements to impact a parallel field: nonprofit behavioral health services. These providers – many operating under traditional social service models – provide a multitude of services aligned to medicine, including mental health and substance abuse counseling.

This report, funded by the Robert Wood Johnson Foundation, is the first effort of a multi-year project that focuses on exploring how advancements in neuroscience will impact the abilities of nonprofit human service providers to organize and deliver behavioral health services in the future. Two questions framed the paper's development and organization:

> *What neuroscience diagnostic and treatment advancements have occurred which are likely to impact nonprofit human service providers?* Three areas were targeted for this examination: pharmaceutical, surgical and biomedical.
>
> *What is likely to change in response to these advancements?* Capacities of nonprofits explored in this area included clinical, institutional/systemic and societal roles.

The answers to these questions will in turn, we expect, foster another set of critical questions for the nonprofit behavioral health care field: How will agencies create or set strategies for growth when rapidly emerging neuroscience advancements will demand the ability to react quickly to new opportunities? How will they capitalize new technological and neuroscientific functions required for behavioral health diagnostic and treatment strategies? Will the human services field undergo dramatic reorganization as smaller and less adept agencies go out of business and larger, more technically sophisticated agencies gain a greater share of the behavioral health market through partnerships with scientific or medical professions? What public policy strategies will be required to support the integration of neuroscience advancements with traditional social service behavioral health care models?

The Alliance for Children and Families is pleased to publish this pioneering analysis of the impact of neuroscience advancements on nonprofit behavioral health care. We hope the information presented here serves as a stimulus for a thoughtful and provocative discussion on the integration of neuroscience advancements with traditional social services. We are committed to remaining a leader in this important and timely dialogue.

Peter B. Goldberg
President and Chief Executive Officer

Acknowledgements

We would first and foremost like to thank the Pioneer Group of the Robert Wood Johnson Foundation for its recognition of the importance of this critical issue. Its understanding and vision of the role of nonprofits in behavioral health care stands as testament to its leadership in exploring the edges of emerging medical science. We would like in particular to thank Constance M. Pechura, Ph.D., Senior Program Officer at the Foundation, for the guidance, experience and wisdom she so graciously and willingly contributed to our efforts.

We are also grateful to the many individuals who contributed their time, experience and insights as we researched the intersection of neuroscience and behavioral health care, and strove to understand its implications for the nonprofit sector. Our appreciation goes most notably to:

Daniel G. Amen, M.D.
President and CEO of Amen Clinics, inc.

Martha J. Farah, Ph.D.
Professor, Department of Psychology, University of Pennsylvania

Laurie Flynn
former Executive Director of National Alliance for the Mentally Ill

Laurie R. Garduque, Ph.D.
Senior Program Officer, The John D. and Catherine T. MacArthur Foundation

Michael S. Gazzaniga, Ph.D.
Director, Center for Cognitive Neuroscience, Dartmouth College

David C. Guth
CEO and Co-Founder of Centerstone (TN)

Judy Illes, Ph.D.
Director, Program in Neuroethics, Center for Biomedical Ethics,
Stanford University School of Medicine

Lauren R. LeRoy, Ph.D.
President and CEO, Grantmakers in Health

Terri Moffitt, Ph.D.,
Professor, Department of Psychology, University of Wisconsin

John R. Weisz, Ph.D.
Judge Baker Children's Center, Harvard University

Finally, we would like to acknowledge the assistance of the leadership and staff from three Alliance members or affiliated agencies who served as resources for this report:

Louise Burgess
President and CEO, Family & Children's Service (TN)

Bill Martone
President and CEO and Emily McGrath,
Assistant Director of Program Evaluation, The Sycamores (CA)

C.T. O'Donnell
President and CEO, KidsPeace (PA)

About the Authors and Contributors

LAUDAN Y. ARON is a Senior Research Associate with the Urban Institute's Center on Labor, Human Services, and Population. She has over fifteen years of experience in social policy research and is noted for her work on homelessness, disability, employment and training, education, child welfare, child support, and family violence. She is the lead author of *Serving Children with Disabilities: A Systematic Look at the Programs* (Urban Institute Press 1996), and more recently, *Helping America's Homeless: Emergency Shelter or Affordable Housing?* (Urban Institute Press 2001). She has written three book chapters on rural homelessness, and is now working on a second book on childhood disability programs.

Her work has included national program evaluations, survey designs and analysis, and reviews of the literature for many federal agencies, including the Departments of Health and Human Services, Labor, Justice, Housing and Urban Development, and Education. Prior to joining the Urban Institute in 1992, Ms. Aron served as an Associate and later a Senior Associate in the economic analysis and evaluation practice area of Lewin-ICF.

Ms. Aron recently managed a project for the Social Security Administration to develop an initial design for the Mental Health Treatment Study, and has co-authored a paper for the Ticket to Work and Work Incentives Advisory Panel on promoting work among SSI/DI beneficiaries with serious mental illness. She is also currently conducting research on educational alternatives for vulnerable youth, and intimate partner violence and the "mail order bride" industry.

CARL ZIMMER, author, journalist and lecturer, writes about science for *The New York Times*, as well as for magazines including *The New York Times Magazine*, *National Geographic*, *Discover, Science*, *Newsweek*, and *Natural History*. His book reviews appear in *The New York Times Book Review, The Washington Book World, Newsday,* and *Scientific American*. From 1994 to 1999 he was a senior editor at *Discover*.

The *New York Times Book Review* calls Carl Zimmer "as fine a science essayist as we have." His first book, *At the Water's Edge* (1999) followed scientists as they tackled two of the most intriguing evolutionary puzzles of all: how fish walked ashore, and how whales returned to the sea. It was followed in 2000 by *Parasite Rex,* which explores the bizarre world of nature's most successful life forms. In 2001 he published *Evolution: The Triumph of An Idea*, the companion volume to a PBS television series. It was named one of the best science books of the year by both *Discover* and *New Scientist*. *Soul Made Flesh*, Zimmer's latest book, chronicles the dawn of neurology in the 1600s. The *Sunday Telegraph* calls it a "tour-de-force." It was named one of the 100 notable books of 2004 by the *New York Times Book Review* and was chosen as a 2004 Editor's Pick by Amazon.com.

His honors include the American Association for the Advancement of Science's 2004 Science Journalism Award, the Pan-American Health Organization Award for Excellence in International Health Reporting, the American Institute Biological Sciences Media Award, and the Everett Clark Award for science writing. In 2002 he was named a John Simon Guggenheim Memorial Foundation Fellow. He is also an associate fellow at Morse College, Yale University. Zimmer frequently lectures about science, and has appeared on numerous radio programs, including *Fresh Air* and *This American Life*.

DR. HAROLD DAVIS serves as Project Advisor to the Alliance's neuroscience project. He is President of HMD Consulting, LLC, providing insight and expertise on issues related to healthcare delivery in urban communities, health disparities impacting low-income groups, corporate healthcare delivery systems, business ethics, executive leadership, development and coaching, organizational and individual stress management, mentoring, corporate philanthropy, corporate diversity, multicultural marketing, and urban education initiatives. Prior to his retirement in January 2002 from Prudential Financial, Inc., Dr. Davis served as Senior Vice President and Chief Ethics Officer. Before becoming Senior Vice President and Chief Ethics Officer, Dr. Davis served as Vice President, Employee Health Services, Departmental Vice President and Chief Medical Director, Employee Health and Wellness. Before joining Prudential, Dr. Davis was Associate Medical Director at ITT Corporation (1977-1978) and Clinical Director at Mobil Oil Corporation (1978-1987).

Dr. Davis has served as a thirty-three year member of the Executive Board of Sponsors for Educational Opportunity, a New York City based scholastic assistance organization. He is currently chairman of the Strategic Planning Committee and member of the Board of Trustees and Governors of Cathedral Healthcare System, an Advisory Board Member of the National Eagles Leadership Institute, an Advisory Board Member for the Center for Disease Control (CDC) Committee on HIV and AIDS prevention; Chairman of the Community Advisory Board for the Institute for the Elimination of Health Disparities at the University of Medicine and Dentistry of New Jersey (UMDNJ), Award Committee Member for the American Business Ethics Award (ABEA), and Chairman of the National HOPE Award Committee. Dr. Davis is also a member of the Board of Directors for KidsPeace, a multi-state organization focused on serving children in crisis. In addition, Dr. Davis has served on several national and local committees dealing with the nation's HIV/AIDS epidemic, and with organizations focused on improving healthcare opportunities and outcomes for low-income communities.

Dr. Davis has a BA degree from Wesleyan University (1969) and an MD degree from Yale University Medical School (1974), where he was awarded the Litz prize for best medical student thesis on a psychosocial topic. He is the recipient of numerous awards and honors, including the Achievers Award in Industry from ITT Corporation and Prudential, Columbia University's Charles Drew Award, the National Eagle Leadership Institute's Award, the Corporate Citizenship award from Women in Support of the Million Man March, the G. Albert Shoemaker Award in Business Ethics from Penn State University, and the U.M.D.N.J Urban Scholars Program award.

Foreword

We stand witness today to neuroscientific discoveries that are increasing at exponential rates. But as exciting as these advancements in neurotechnology, neuropharmacology, and neurobiology are, we must acknowledge that they pose important organizational, educational, relationship, and ethical challenges for practitioners, funding sources, consumers, and other interested groups.

The challenges confronting nonprofit community-based behavioral health organizations in particular are daunting – and increasing in their complexity, scope, and composition. Demands for these organizations to be much more credible providers of service, with evidence that they are achieving verifiable results, represent the new business model. It is a model imperative to the successful integration of neuroscience advances with traditional social services. In the future, it will be results which determine the "winners" and "losers," both in the public's eye and the funders' priorities.

For organizations with adequate staff and available funding sources, the challenge of evidence-based practice will no doubt be viewed as an opportunity. For those with small operations and very limited funding, this new criterion of credibility quite possibly portends the demise of their organizations. As Laudan Aron, one of the authors of this report observes, many organizations are struggling just to survive in this environment of intense competition. They are not positioned in structure, funding, personnel composition or service sophistication to either establish evidence-based practices or incorporate the advancements being made in neuroscience. This, unfortunately, characterizes many community-based organizations: they view the lavish banquet table of plenty before them with frustration because they have not been invited to partake or they are ill prepared to feast.

To overcome these barriers, advocates on each side of the issue, both service providers and funding sources, must fashion new relationships and collaborations. These relationships must be built on a clear communication of expectations by funders and oversight agencies. Doing so will allow for optimal organizational mission, structure, operation, and outcomes on the part of service providers – and a greater guarantee that they will achieve credible and verifiable enhancements in mental health services.

The responsibility for providing credible performance and service does not sit solely on the shoulders of service providers. It must be shared by funders and oversight agencies that identify the problems to be addressed and participate in determining the outcomes that must be achieved. What is funded is what is serviced. Indeed, if the target is wrong, then all of the arrows expended, even if they hit the bull's eye, reflect a miss!

Research institutions themselves must also become partners in this new journey. They must enhance their functional scope and mandates by determining how they will disseminate their advances to the service-provider networks that actually interface with the clients who are the research targets. For too long the barriers between research and application have not been addressed or dismantled, leaving in its path wasted resources, societal discontent and dismay, and the ineffective application of behavioral science and health advancements. Its most dire consequence is lives lost to purposeful function.

Through this project, we encourage an open, dynamic, and useful conversation between all of the agencies committed to enhancing the behavioral health profile of our citizens. To achieve this end we will have to be brave, open, and honest in our deliberations with old and new colleagues. The challenges before us are great, but the opportunities to achieve a greater good are limitless. I welcome and encourage your involvement in our journey towards relationship and discovery.

Harold Davis, M.D.
Project Advisor

Introduction

The idea for this paper was germinated several years ago in a briefing report that the Alliance asked me to develop on the impact of emerging technologies on nonprofits. As a passionate hobbyist of medical science, I recognized and argued that it was more likely neuroscience, not the hard wires and software of new technologies, which stood to profoundly alter the future of nonprofit behavioral healthcare. The response from the Alliance was immediate and positive: examine it, include it.

In the four years since that briefing report was published we have borne witness to a steady, albeit hushed, revolution. Some of the Alliance's members have become actively engaged in applying neuroscience and biotechnology advancements in their practices, as this report details. Others have forged linkages with universities and researchers as a way to better understand and prepare for the formal integration of neuroscience into their traditional practices. A few have been approached by larger, better capitalized behavioral health organizations in takeover, merger or partnership attempts – we'll examine one of those agencies in a case study to be published later this year. But all have been touched in some way by neuroscience – through the pharmaceutical industry and its new drugs prescribed for many human service clients, the better understanding of the mind-body link within the psychology and psychiatric fields, or the emergence of evidence-based practice, driven by research and increasingly demanded by funders and reimbursement streams.

In their respective sections, authors Carl Zimmer and Laudan Aron define the specific neuroscience advancements most likely to impact nonprofits in the next decade (Zimmer), and the implications those advancements will stimulate (Aron). Their findings and assessments are remarkable for their depth, clarity and direction – it is one thing to grasp the concepts of emerging science; it is altogether another thing to communicate those concepts in a manner that is accessible and compelling. Indeed it was Carl Zimmer who, in a discussion on the impact of neuroscience developments on troubled youth, capsulized a critical issue for providers of nonprofit behavioral health care. "Society," he said, "views these kids as bad people. But science says they simply have 'bad' brains."

In his section discussing neuroscientific developments, Zimmer argues that much of the recent attention-grabbing neuroscience headlines (for example, stem cell research) will not have much impact on behavioral health care in the next decade. Instead, he winnows the magnitude of neuroscience advancements down to five critical areas that his research suggests will impact nonprofits in direct and/or significant ways: the emergence of more accurate diagnostic tools through genotyping and brain imaging; the use of electrical stimulation to treat behavioral health issues; the development of better drugs based on better neuroscientific understanding of brain-based disorders; the use of imaging technologies to establish and monitor treatment strategies for behavioral health care patients; and the combining of talk-based therapies with cognitive-enhancing drugs.

For her part, Aron posits that advances in neuroscience will accelerate the medicalization of behavioral health care, leading to further specialization of all behavioral health functions – assessment, treatment and post-treatment – and affecting both the types of services that are delivered to clients and the sequencing of those services. That said, she suggests that advancements in neuroscience will add to the understanding of the importance of healthy social and physical environments in life, and because of that, there will be additional support forthcoming for more and better early intervention and prevention efforts – including effective counseling and other psychosocial interventions. She presents a strong case that these advancements will require providers to be much more knowledgeable and "evidence-based" in their thinking (both for clinical and business reasons), to engage in more consumer education (and reeducation), and to quicken their shift from institutional- and facility-based delivery of behavioral health services to home- and community-based settings. Finally, she observes that advancements in neuroscience will require new institutional relationships and partnerships, including linkages between more traditional nonprofit social service agencies and psychiatric and medical-surgical hospitals or private diagnostic and screening centers with sophisticated imaging and other medical equipment.

The intersection of neuroscience, biotechnology and behavioral health described here is an extraordinary and astonishing accomplishment in our lifetime. Although not a definitive list, this paper suggests the complexity created by these advancements does indeed pose a number of critical programmatic, organizational, ethical, social and political challenges for the nonprofit behavioral health sector. And yet, as the report also suggests, there is magnificent opportunity – to embrace new approaches, new partners, new ways of thinking and doing business. We welcome you to the new frontier.

Patrice A. Heinz
Project Director & Contributing Editor

Advancements in Neuroscience

Carl Zimmer

Neuroscience research covers a vast range of topics from consciousness to neurochemistry. For providers of nonprofit behavioral health care, reports on recent advances in neuroscience can be perplexing. Will brain scans and new medications do away with more traditional diagnoses and therapies? Will stem cells provide the "cure" for mental illness or behavioral health issues? Or is it all so much hype, with no real relevance to the reality of nonprofit behavioral health care?

A survey of current neuroscience research suggests that the future will lie somewhere between these two extremes. Some current advances in neuroscience may change nonprofit behavioral health care in direct, dramatic ways. Other advances will likely have an impact that's not quite as direct but nonetheless still significant. And those advances underway in neuroscience research that are most effective at grabbing headlines? They will probably not have much effect on behavioral health care in the next several decades. What is clear is this: neuroscientists are revealing the ways in which trauma, depression, and other disorders leave tangible marks on the functioning of the brain. It is this broadening knowledge more than perhaps anything else that will change the way behavioral health care providers think about psychological disorders.

The Once and Future...Now

The advancements discussed in this paper – by no means a definitive accounting of the neuroscience revolution – offer nonprofit behavioral health care providers an opportunity to merge science with service. Our review suggests there are five advancements that hold the most immediate promise of having an important and direct impact on nonprofit behavioral health care:

- The identification of more accurate diagnoses using genotyping and brain imaging.
- The use of electrical stimulation (including surgically implanted devices and transcranial magnetic stimulation) as treatments for PTSD (post-traumatic stress disorder), depression, and other psychological disorders.
- Improved drugs developed on better neuroscientifically-based understanding of psychological disorders.
- The use of brain imaging to establish treatment strategies and monitor responses to those strategies.
- The integration of talk-based therapies with cognitive enhancing drugs.

To appreciate this range of impacts, we have organized this portion of our report into two general sections. In the first, "How the Brain Works – The View from 2005" we examine some of the key tools now used to probe the brain, such as neuroimaging and genetic studies. In the second section, "The Intersection of Neuroscience and Behavioral Health," we take a closer look at particular aspects of the brain that are especially relevant to behavioral health and consider how advances in neurosciences are likely to engage with traditional practices.

Neurons:

Neurons are exquisitely sophisticated cells *capable of receiving information, processing it, and then relaying it to another neuron by means of electrical impulses. The light from the sun, for example, enters your eye and is absorbed by receptors on the ends of neurons located in the retina. These receptors trigger an electrical impulse that travels down the length of the neuron. The neuron triggers an impulse in other neurons it makes contact with in the optic nerve, which relay the signals to the brain, ultimately producing your perception of the sun. The branches through which a neuron sends this signal are called axons. A single neuron may have a thousand or more axons, each communicating to a separate neuron.*

A small gap exists between an axon and another neuron, known as a synapse. When an impulse reaches the tip of an axon, it causes a number of compounds to be released into the synapse. These neurotransmitters can then be taken up by the next neuron. Depending on the combination and levels of these compounds, an electrical impulse may be triggered in the next neuron. Some neurons specialize in releasing neurotransmitters that can make it easier or harder for neighboring neurons to respond to an incoming signal. Because a single neuron may form synapses with dozens of axons, it may receive many incoming signals. It processes these signals in a process akin to a computer, and the combination of the signals determines the output it produces.

How the Brain Works: The View from 2005

Studying the Brain

The brain is made up of an estimated 100 billion neurons. They are organized into specialized networks that allow the brain to process information about the world (and about ourselves) with remarkable speed. These networks are relatively distinct from one another, but they are also linked together so that they can cooperate.

Neuroscientists use a range of techniques to learn how the many regions of the brain work. Neuroimaging, a method that allows neuroscientists to map diverse activity in the brain, has provided scientists with remarkable opportunities to explore not just the structure of the brain, but its networking functions and malfunctions as well. For many nonprofit behavioral health care providers, one of the most relevant advances in brain imaging has been the development of methods that allow for the safe and accurate imaging of children.

These methods have opened the door to a growing number of studies that are shedding light on how the human brain develops through childhood and revealing important differences between mature and immature brains.

Functional Magnetic Resonance Imaging (fMRI)

FMRI takes advantage of the fact that when certain molecules are exposed to an intense rotating magnetic field, they release radio waves. During an fMRI scan, this field is produced by a large doughnut shaped magnet. Subjects lie on a bed with their head surrounded by this magnet. As the magnet field moves around, molecules in the brain release radio waves. These signals are detected by the scanner and sent to a powerful computer where they can be analyzed. This analysis produces a series of "brain slices"— high-resolution two-dimensional maps of a set of brain layers. The brain slices can then be combined into a three-dimensional scan of the brain.

Once neuroscientists have acquired this high-resolution scan of the brain's anatomy, they can pinpoint regions of the brain that become active during different kinds of thought. This technique takes advantage of the fact that neurons must consume oxygen to generate energy whenever they receive a signal. As active regions consume oxygen, more oxygen-rich blood moves towards them. FMRI can detect this shift in regions as small as a cubic millimeter, the size of a peppercorn. In typical fMRI experiments, a complete scan of the brain can be completed every two seconds.

A single fMRI scan offers relatively little information, because many regions of the brain are active at any moment. One common method to extract information from fMRI is to compare scans from different experimental conditions. For example, neuroscientists have shown subjects a series of pictures, some of which are frightening (a pointed gun, for example) and others that are neutral (a door, for example). Both sets of pictures activated visual processing regions of the brain, as expected. But the frightening images on average trigger a stronger reaction from the amygdala, a region we will examine later.

Positron-Electron Tomography (PET)

In PET, subjects are injected with a radioactive tracer. As the tracer flows through the subject's bloodstream, some of it makes its way into the brain. Depending on the tracer used in a given study, it will accumulate in different parts of the brain. Some tracers will simply concentrate in parts of the brain that use a large amount of energy. A scanning device can then detect the emissions released by the tracers and create a map of their concentrations in the brain.

It can take several minutes for tracers to build up enough in the brain before a PET scan can be made. In this respect, PET is at a disadvantage to fMRI. But PET offers a number of other advantages. Scientists can produce tracers, for example, that bind only to receptors on the surface of neurons. They can even bind to a certain type of receptor that can accept a single neurotransmitter.

Other Neuroimaging Techniques

Most neuroimaging studies published today rely on fMRI or PET. But researchers are also investigating other means of scanning the brain. SPECT, or single-photon emission computed tomography, is similar to PET, detecting radioactive tracers injected in the body. Instead of detecting positrons and electrons, as in PET, SPECT detects gamma rays. Another method in development uses beams of near-infrared light to detect changes in oxygen levels in the brain. New imaging techniques promise to overcome the constraints of current neuroimaging methods, such as the bulky equipment of fMRI and the invasive injections of PET.

The Intersection of Neuroscience and Behavioral Health

Genes, Brains, and Behavior

Research on genes may someday lead to advances in treatment and diagnosis strategies used in nonprofit behavioral health care. Currently, scientists are still only beginning to decipher the role genes play in the development and function of the human brain. Many people think that DNA contains the brain's "blueprint," but the metaphor quickly collapses when you consider what is actually known about genes. Genes carry the code for proteins, but typically a protein must cooperate with many other proteins to perform even a simple function in the brain, such as growing an axon tip. Emotions, cognition and other high-level functions of the human brain—the functions that are most relevant to the work of nonprofit behavioral health care providers—each depend on a vast number of genes. Consequently, it appears that there is no single gene "for" depression, aggression, or any other condition.

Making matters even more complicated, the information carried in our DNA is only transformed into proteins when cells receive specific signals. The environment in which a brain develops—both in the mother's womb and during childhood—help determine which signals are received by neurons, and therefore help steer the brain towards its mature form.

While the interplay of genes and environment may be complex, that doesn't mean that neuroscientists have no way of studying it. Because we share an evolutionary heritage with other mammals, we inherit similar genes, making the study of laboratory animals valuable to the understanding of humans. Scientists have found that humans and other mammals respond in strikingly similar ways to stress, down to the hormones and neurotransmitters that are released in response. By breeding generations of animals, scientists can isolate individual genes that play a role in stress or other features of the brain. They can also expose lab animals to different experiences and environments to see how these factors interact with genes.

Of course, humans are not identical to monkeys or mice, and as a result animal models have certain limitations. Because many experiments on humans are unethical, scientists can only gather information about the roles of genes and environment indirectly. In recent years, scientists have made important strides in the methods they use to gather this information.

One way is to compare twins. All twins experience the same environment in their mothers' womb. But while identical twins (who have developed from a single egg) carry identical genes, fraternal twins (who develop from two separate eggs each fertilized by a separate sperm) only share 50% of their genes.

Scientists can look for genetic components to a condition by comparing its rate in identical and fraternal twins. If an identical twin has a condition with a strong genetic component, his or her twin will be likely to have it as well. If the condition has only a weak genetic component, the correlation between identical twins will be much lower—comparable to that found in fraternal twins.

These surveys have allowed geneticists to identify individual genes that may play a role in given conditions. The search for behavior-related genes has produced many failures and much frustration, but several promising candidate genes are now known. And neuroimaging promises to help bring the roles of these genes into sharper focus.

In the 1990s, for example, several teams of scientists found an association between a gene involved in transporting the neurotransmitter serotonin and levels of anxiety and neuroticism. The gene, called 5HTT, comes in short and long forms, and the short form was associated with higher levels of anxiety and neuroticism.

Other research suggested that this was a plausible link. A number of effective anti-anxiety drugs are known as selective serotonin reuptake inhibitors (SSRI). It has been proposed that by interfering with the return of serotonin inside neurons, these medications somehow relieve symptoms such as anxiety, although the precise mechanism has not been identified. Despite the plausibility of this link, however, later studies failed to replicate it.

A 2002 study by scientists at the National Institutes of Health suggests that this failure may be the result of conventional psychological measurements, which may not be able to detect a small but real correlation. The NIH team conducted fMRI studies on subjects to measure how strongly their amygdala responded to the sight of fearful faces. They found that people who carried one or two copies of the short version of the serotonin transporter gene had a stronger response than people who had two long copies of the gene. The correlation was much stronger than previous studies.

As we will see in later sections, understanding the interplay of genes and experience could improve diagnosis and treatment.

Insights about Psychological Disorders

Neuroscience research is generating new hypotheses about the origins of a number of psychological disorders.

Depression

Of all psychological disorders, no other condition has attracted more attention from neuroscientists than depression. While the biological dimensions of depression still pose many mysteries, researchers have made some important advances that will help in the diagnosis and treatment of this condition.

In the 1990s, scientists began scanning the brains of depressed subjects, using fMRI, PET, and other technologies. It became apparent that depression is associated with significant changes in the level of activation in certain regions of the brain. But the changes were not consistent. In some depressed people, the prefrontal cortex was less active than normal, while in other depressed people it was more active.

Recent research has begun to resolve this paradox. Scientists have begun looking not for isolated brain regions that become more or less active in depressed people, but for a network of regions that consistently display correlated differences. Scientists have also studied depressed people who benefit from medication or psychotherapy, comparing their brain activity before and after treatment. Finally, researchers have looked for differences between the brains of depressed patients who respond to different kinds of treatment, as well as to patients who do not respond to any of them.

These studies indicate that depression consistently affects the same "depression network," but that it affects it in different ways

continued on page 14…

Brain Architecture:
The Cerebral Cortex and the Limbic System

The brain can be divided into a set of relatively distinct regions. Two that are particularly relevant to nonprofit behavioral health care providers are the cerebral cortex and the limbic system. These regions carry out different functions, but they are intimately connected. Abnormal changes in these connections have been associated with a number of psychological disorders.

The Cerebral Cortex

The brain is covered with a series of layers known as the cerebral cortex. The cerebral cortex interprets the signals received by the brain and produces appropriate responses. Studies on individual neurons in the cerebral cortex of monkeys have allowed scientists to reconstruct the path that signals take through this region of the brain. Consider a monkey that has been trained to push a button when it sees a picture of a dog. Within 60 millisecond of seeing a picture of a dog, signals have already reached the visual cortex, a region in the back of the brain that processes visual information. Here the signal is projected into thirty different fields, each specialized for picking out certain features. Some are sensitive to edges, some to shading, some to corners. Signals spread from these visual fields across the rest of the monkey's cortex. In a region around its ears, known as the temporal cortex, these processed signals can be processed still further, allowing the recognition of more complicated features such as shapes and movement. The neurons in these regions participate in the recognition that a certain arrangement of light is a dog, as opposed to a cat.

By 100 milliseconds, the signals have moved from the temporal cortex to the front of the monkey's brain, just behind its forehead. This region, known as the prefrontal cortex, sorts through rules for action—such as see dog, press button. From the prefrontal cortex, the flow of information starts moving back towards the body. The region of the cerebral cortex at the top of the monkey's head contains a map-like representation of its body. The neurons corresponding to the monkey's hand begin firing, producing commands that can control its hand. Within 160 milliseconds these command signals are moving down the spinal cord. The monkey's finger presses the button only 180 milliseconds after the picture of the dog appeared.

The human cerebral cortex works much the same way as a monkey's. However, over the course of human evolution it has grown into a much more complex structure, capable of more complex thought. Several regions of the cerebral cortex make it possible for humans to understand and produce language, for example. Other regions are particularly important for reasoning. Other regions help us to infer the intentions and thoughts of other people, while other regions maintain our sense of self.

The Limbic System

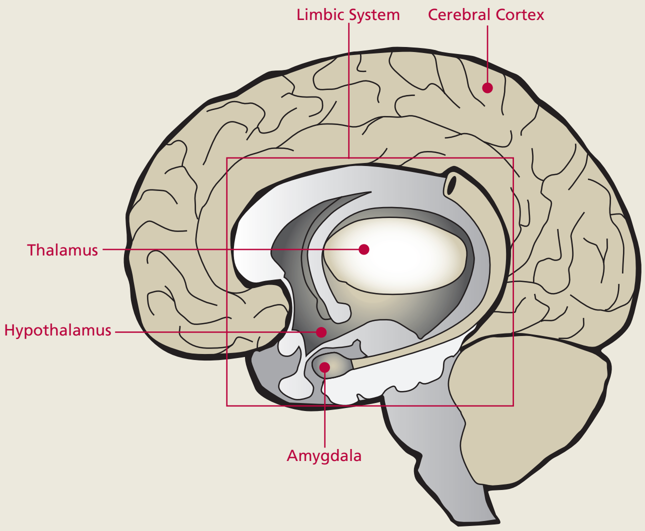
Buried beneath the cerebral cortex is a set of brain structures that are collectively known as the limbic region. These structures play a vital role in motivation, emotions, memory, and autonomic responses. The limbic region has been nicknamed "the reptile brain," in part because the structures it contains were present early in the evolution in vertebrates. But this nickname gives the misleading impression that the limbic system is distinct from the "higher" regions of the cerebral cortex. In fact, the limbic system has many connections to many parts of the cerebral cortex, and each region relies on the other for its proper function.

To understand how the human brain produces emotions, it's necessary to consider these cortico-limbic networks, rather than their isolated parts. This aspect of the brain is most relevant to nonprofit behavioral health care providers, and we will consider it in the following section.

The Feeling Brain

Emotions, moods, and motivation are essential features of the brain. Both for humans and animals, they produce behaviors that can mean the difference between life and death. Neuroscientists have made great strides in recent years in dissecting the networks that produce emotions, and their insights may have a large impact on nonprofit behavioral health care. That's because depression, conduct disorder, post-traumatic stress disorder, and many other psychological disorders are increasingly being recognized as the result of dysfunctional emotional networks in the brain.

Fear has an obvious role in survival. If you see a tree falling towards you, you immediately leap away without giving the action much thought, as your brain produces a fearful response without much conscious deliberation. Scientists have identified some key nodes in the "fear network" responsible for this response. One particularly important node is the amygdala, an almond-shaped cluster of neurons in the limbic region. One of the regions to which the amygdala is linked is the thalamus, a gateway for signals from the eyes and other senses. When emotionally charged stimuli enter the thalamus, they can then activate the amygdala. The amygdala may respond well before the cerebral cortex does. Neuroscientists have documented this quick response by showing subjects fear-provoking images, such as a pointed gun or a barking dog, for just a tenth of a second. In these experiments, the amygdala becomes active even though the subject is not aware of what he or she just saw.



By responding to signs of potential threat, the amygdala can help produce a rapid action in response. It does so by communicating with the hypothalamus, a small hormone-producing region of the limbic region. The hypothalamus releases a hormone called corticotrophin-releasing factor (CFR), which travels to the pituitary gland, located on the underside of the brain. In response to CFR, the pituitary gland releases adrenocorticotropic hormone (ACTH) into the bloodstream. This hormone then travels through the body until it reaches the adrenal glands (which sit on the kidneys). ACTH triggers the adrenal glands to release a third hormone, cortisol.

Cortisol spreads through the body, creating a wide range of rapid change, such as rapid breathing and increased heart rate. It even produces changes in the brain. In very short order, the amygdala can prepare a person to cope with a dangerous situation. After the crisis passes, the stress system allows the body to recover.

Some fearful reactions are hard-wired from birth. But other responses are learned. A person makes an association between an experience and a painful outcome with the help of another region of the brain known as the hippocampus. The hippocampus plays many different roles in the formation of memories, but one of its most important ones is helping to produce fear-provoking associations. These associations include not just the actual sources of pain, but the cues that reliably precede them.

For example, scientists have run experiments in which they give people mild electric shocks. If they turn on a light before applying the shock, the light will eventually produce a galvanic skin response—part of the stress response triggered by the amygdala. People who have suffered damage to the amygdala do not develop this response to the light.

While some cues produce a stress response, others have just the opposite effect on the brain. They are reliable indicators of a reward, and they produce a feeling of anticipation and expectation in the brain. The human brain is motivated to seek rewards by a set of neurons near the brain stem that produce a neurotransmitter called dopamine. These neurons extend throughout much of the brain, and when they produce dopamine, they can produce a dramatic change in the brain's functioning.

Like the amygdala and other regions associated with emotions, dopamine-producing neurons can be found in other animals. For a rat, a reward might be a tasty piece of food in a garbage can, and its cue might be the food's odor. The dopamine released in response to this sort of cue triggers widespread changes to the brain. It makes a rat more alert to new stimuli, and encourages the formation of new synapses between neurons. As a result, the rat can learn how to connect reliable cues to rewards.

This dopamine-based reward system is not fixed in the brain from birth. Instead, experience can modify it as an animal (or a person) learns to associate new cues with new rewards. If an animal encounters a reward unexpectedly, dopamine-producing neurons release much higher levels, priming the brain to recognize new cues. As the animal comes to recognize these new cues, the surge of dopamine arrives between the cue and the reward, and becomes smaller. Finally, once the association is fully discovered, the dopamine surge comes immediately after the cue.

Dopamine plays an essential role in every moment of a person's waking life. It is vital for our ability to carry out complex body movements, such as walking, and for the steady control of our muscles. The devastating motor disability that is caused by Parkinson's disease is caused by damage to the dopamine-producing system of the brain. Cocaine and a number of other drugs produce their high by triggering the release of enormous amounts of dopamine in the brain. This rush of dopamine can cause widespread changes to the brain, producing the symptoms of addiction.

One particularly important source of emotions is our relationships with other people, ranging from positive emotions such as happiness and love to negative emotions such as anger and sadness. Our "social brain" is also adapted to infer the emotions and intentions of others. Neuroscientists have identified "empathy networks" in the brain which are activated by emotionally charged perceptions of other people. The amygdala not only becomes active in response to fear-inducing danger, such as a falling tree, but also to faces expressing fear. When human subjects feel pain, a distinctive network becomes active in the brain. Seeing pictures of other people experiencing pain activates that same network.

The limbic region, which helps generate emotional responses, is intimately connected to several regions on the cerebral cortex. These connections allow the cerebral cortex to regulate emotional responses. In some cases, this regulation can be quite conscious. In one experiment, scientists had subjects watch pornography while scanning their brains with fMRI. Regions in the limbic region associated with sexual excitement became activated. The scientists then had the subjects consciously try to control their response. The scientists found that the limbic regions then became less active, while regions of the prefrontal cortex (known as the dorsolateral prefrontal cortex) became more active.

Emotional regulation is often not conscious, however. One region of the prefrontal cortex called the orbitofrontal cortex is believed to set the value we place on things. It receives information from many regions, including limbic regions and regions involved in memory. The orbitofrontal cortex then exerts a strong influence over the amygdala and other regions important for emotional responses. When we win at gambling, the orbitofrontal cortex is responsible for translating the size of our winnings into the size of our emotional response. Likewise, it is responsible for making the taste of chocolate pleasant at first bite—but then sickening after we've eaten too much.

… continued from page 11

in different individuals. According to studies at Emory University and the University of Toronto, this network includes regions of the brain in the limbic region, such as hippocampus, as well as regions in the prefrontal cortex such as the orbitofrontal cortex. All of these regions are known to be anatomically connected, and they all tend to show correlated changes in neuroimaging studies.

The Emory and Toronto researchers see depression as a disruption in the normal regulation of negative emotions. Depressed people tend to respond more strongly to negative experiences and words, perhaps because they summon up negative associations in their memory with their hippocampus. The orbitofrontal cortex is able to regulate these limbic responses, but in depressed patients it is less activated than in normal individuals.

In some cases of depression, individuals compensate for this dysregulation by activating other regions of the prefrontal cortex. These other regions of the prefrontal cortex have been associated with rumination. This hyperactivation of the prefrontal cortex may explain why some depressed patients become agitated, rather than experiencing the apathy of other depressed patients.

This difference in the depression network is reflected in how patients respond to treatments. In patients who respond to cognitive-behavioral therapy, the first changes occur in the prefrontal cortex. Gradually the changes spread to the limbic region and other areas deep within the brain. In contrast to this "top-down" pattern, patients who respond to medication show a "bottom-up" pattern, in which lower regions of the brain display changes in activity before the prefrontal cortex.

What causes the dysregulation seen in the depression network in the first place? Scientists have suspected that the 5HTT gene, discussed earlier, might play a role. But initially studies found only a weak correlation between variations in the gene and the incidence of depression. The correlation became much stronger, however, when researchers at the Institute of Psychiatry in London took experience into account.

The scientists studied 847 members of the Dunedin Multidisciplinary Health and Development Study in New Zealand. These individuals had been assessed at regular intervals through childhood. The researchers tested the subjects to see whether they had two copies of the short 5-HTT allele, two copies of the long 5-HTT allele, or one of each. They also reviewed the assessments for their subjects to see whether they had experienced a stressful life event.

The researchers found that carrying short or long alleles had a significant effect on whether stressful life events led to adult depression. Individuals with two long alleles did not have a higher probability of a major depressive episode if they experienced severe maltreatment as children. But, if they carried one copy of the short allele and experienced severe maltreatment as a child, probability of depression was significantly raised. Carrying two copies of the short allele raised it even further.

This particular study offers an important lesson about genetic studies of psychological disorders. If a child turned out to have two copies of the short 5-HTT allele, but did not experience severe maltreatment, he or she would not be destined to a life of depression. Only the interaction of genes and experience, of nature and nurture, produces the outcome.

Aggression

The overwhelming majority of people convicted of violent crimes show multiple psychopathological disorders. Discovering the biological underpinnings of these disorders may help reduce abnormally aggressive behavior. This search is a difficult one, in part because aggression is a symptom of a wide range of recognized disorders, ranging from schizophrenia to antisocial personality disorder to PTSD. It appears that many different brain dysfunctions can produce abnormal aggressive behavior.

Studies of animals such as mice and monkeys show that aggression is a normal component of behavior. Competition can produce aggression in normal animals, for example, whether for food or mates. Just as the limbic region can produce a rapid fear response, it can also quickly trigger aggressive behavior in response to a threat. Studies suggest that these aggressive responses can be inhibited by regions of the prefrontal cortex that recognize that an ambiguous situation does not in fact pose a threat. Abnormal aggression may result from weak activity in the prefrontal cortex, or unusually strong activity in the limbic region. Other studies suggest that violent behavior may normally be inhibited by the human brain's "empathy network." Perceiving suffering in others, according to this theory, prevents an individual from behaviors that would produce more suffering. If this empathy network is somehow damaged, it may become unable to regulate aggressive behavior. Studies have shown that violent psychopaths do not show the brain response seen in normal people when presented with pictures of sad faces.

Studies on the genetic roots of violent behavior in the past have been ambiguous. It's long been known that boys who are exposed to abuse at a young age are more likely to develop conduct disorder, antisocial personality symptoms, and even to become violent offenders. But maltreatment only increases the risk of later criminality by about 50%. Why should some boys who suffer serious abuse manage to avoid developing antisocial behaviors, while others do not?

A number of neuroscientists have suspected that genetic differences might be part of the answer, but until recently their evidence has been inconclusive. Much of their attention has been focused on a gene called MAOA, which produces an enzyme that breaks down neurotransmitters such as dopamine. Mice in which the MAOA gene is experimentally removed become more aggressive than normal mice. In humans, a rare genetic disorder can completely shut down production of the MAOA enzyme; a study of a Dutch family with this disorder found that like the mice, they also showed high levels of antisocial behavior.

This family may represent a rare extreme case of MAOA's effect on aggression. But other variations of the gene are common, and they are known to lead to low and high levels of the MAOA enzyme in the brain. Neuroscientists have looked for a correlation between these common variants and antisocial behavior, but for years their results were inconclusive.

The Institute of Psychiatry researchers described earlier in the section on depression have found that antisocial behavior can only be understood as an interplay of genes and experience. They genotyped over 1,000 individuals who had been assessed regularly throughout childhood and young adulthood. They recorded whether individuals had an MAOA allele that produced high levels of the enzyme or low levels. They then examined the records of the subjects to see whether there was evidence of maltreatment during childhood. Finally, they noted how the subjects scored on tests that assess conduct disorder, disposition towards violence, and antisocial personality disorder. They also noted whether the subjects were convicted for violent offenses.

The researchers found that high levels of antisocial behavior were strongly correlated with a combination of low levels of MAOA and severe maltreatment. Some 85% of subjects with both risk factors ended up displaying antisocial behavior. People with high levels of MAOA were far less likely to turn out this way. On its own, however, the low-MOAA allele does not automatically lead to antisocial behavior. In fact, people with the low MAOA allele who experienced no maltreatment as children were no more likely to become antisocial than those with a high MAOA allele.

Post-traumatic Stress Disorder

Neuroscientists are finding that post-traumatic stress disorder—which may be brought on by physical abuse, sexual abuse, or other traumas—is associated with significant changes to the brain. The brain, as we've seen, responds to stress with the release of hormones such as cortisol. While the stress response is useful in short bursts, stress that is extremely intense or sustained can be harmful. For example, the hippocampus, which helps regulate the stress response, can become damaged by cortisol. Neuroimaging has shown that the hippocampus of people suffering from PTSD tends to be reduced in volume. In one study of Vietnam veterans with PTSD, the loss ranged as high as 26%.

Since the hippocampus is important to both responding to stress and storing memories, PTSD may alter both of these functions. PTSD can also damage regions of the prefrontal cortex involved in regulating emotions. As a result, traumatic memories can trigger intense emotions that cannot be inhibited. At the same time, however, the damage to the hippocampus can cause difficulty retrieving other memories, much like the loss of memory that comes with old age. PTSD's effects on the prefrontal cortex can also interfere with the region's role in attention and cognition.

Diagnosis and Treatment

Diagnosis

When cardiologists examine a patient, they make quantitative biological measurements of the heart and arteries. This information helps cardiologists to make a diagnosis. Cardiologists can then use an algorithm to decide on the best treatment of the patient, taking into consideration these measurements, along with information about genetics, medical conditions, and other risk factors. Unfortunately, there is no such objective algorithm, based on biological measurements, available for psychological disorders. Without such algorithms it can be difficult to accurately diagnose psychological disorders. For instance, borderline personality disorder and PTSD may seem similar in observing the behavior of a person, but research now suggests that their underlying biology is quite distinct.

Neuroscientists however are optimistic that algorithms for psychological disorders may emerge in the future.

Consider the research described earlier on the neuroimaging of depression. The brain of a person diagnosed with depression tends to have a pattern of activation that is markedly different from a healthy person. It may therefore become possible in the future to diagnose depression with the aid of neuroimaging. What's particularly significant about this possibility is that neuroimaging has the potential to distinguish between different types of depression. Scientists have identified distinctive patterns of connectivity in the brains of depressed patients who later responded well to cognitive behavioral therapy, to medication, and to other treatments. Thus, neuroimaging not only can help with the diagnosis of depression but could also give an indication about what sort of treatment would be most likely to work in a given patient.

Diagnostic tests may also emerge from recent research on the expression of genes during psychological disorders. When genes become active in a cell, their DNA code is converted into a copy, called messenger RNA. Messenger RNAs are then ferried to cellular factories called ribosomes, where they become templates for building proteins. To study the genes that are active in cells, scientists split the cells open and extract the RNA. They then put the RNA in a microarray, a device that contains molecules that bind specific messenger RNA molecules. By identifying the messenger RNA molecules produced in a cell, scientists can discover which of its genes are active.

Given the changes in brain activity documented in psychological disorders, it would not be surprising to find a corresponding change in gene expression. Obviously, extracting neurons from the brain to document these changes is not a practical option. But a team of Israeli scientists recently decided to see whether post-traumatic stress disorder might produce distinctive changes to white blood cells. They were motivated by previous research that had shown significant changes in immune activity in response to stress and in PTSD. They took blood samples from individuals who were admitted to an emergency room after a traumatic experience such as a car accident. One month after the blood sample was taken, the researchers followed up with the subjects to test them for PTSD, and then repeated the test at four months. The researchers found that they could distinguish between people who developed PTSD from those who did not by their unique pattern of gene expression in their white blood cells (Segman 2005).

If this study can be replicated, it might offer a promising way to quickly and accurately diagnose people at risk of developing PTSD after a traumatic incident. Psychological assessments that are currently used do not do a very good job of predicting the long-term development of PTSD, possibly because they cannot distinguish its symptoms from transient responses to trauma. A person with gene expression patterns indicating a high risk of PTSD might then become a candidate for treatments for traumatic memories (see below).

Treatments

Electric Stimulation

As we've seen, some psychological disorders are associated with unusually high or low electrical activity in certain regions of the brain. Scientists are investigating a number of ways to alter this activity with pulses of electricity or magnetism.

Deep Implants

Electrodes surgically implanted in the brain can produce high-frequency electric impulses that can alter the signals produced by neighboring neurons. In the 1990s, people suffering from Parkinson's disease received electrodes implanted in the basal ganglia, a region of the brain that coordinates movements of the body. The implants altered the activity of the basal ganglia, leading to dramatic improvement in the control the patients had over their bodies.

Neuroscientists are now investigating how the same surgical techniques can be applied to other disorders of the brain, including psychological disorders. As discussed earlier in this report, scientists at the University of Toronto and Emory University had identified a network of brain regions that are affected by depression. They noted that one region was consistently overactive in depressed people, a part of the cerebral cortex known as the subgenual cingulate. This is also a region that becomes active in healthy individuals when they think about sad memories. In all patients who overcame depression, the subgenual cingulate became less active. One reason for the central importance of this region is its connection to many other regions in the depression network. Changes in activity in the subgenual cingulate can thus have a widespread effect.

The researchers hypothesized that electrodes implanted near the subgenual cingulate in depressed patients could reduce the activity of the region. If the subgenual cingulate was as important as they believed, the reduction of its activity might reduce the symptoms of depression. To test this hypothesis, the researchers selected six patients with severe depression that had not responded to medication, psychotherapy, or shock therapy. Surgeons implanted electrodes around the subgenual cingulate in each of the subjects.

All of the patients soon reported a sudden change, described as a sudden calmness or lightness by some. Four of the six patients experienced a striking and sustained remission that was sustained six months after the surgery. PET scans revealed changes in brain activity seen in depressed patients who had recovered with the help of medication.

If these results are replicated, they may herald a new chapter in the treatment of psychological disorders. As discussed earlier, other disorders such PTSD appear to produce distinctive changes in the normal patterns of brain networks. People who do not respond to psychotherapy or medication for these conditions may someday also benefit from deep brain stimulation.

Other Methods of Electrical Stimulation

Deep brain stimulation appears promising, but it does have the drawback of requiring surgery. But other noninvasive methods exist for altering the electrical activity of the brain. Electroconvulsive therapy (ECT) has been in use for decades. Early applications of ECT generated a great deal of controversy about side effects such as memory loss, but it is currently considered safe and effective. Only now are scientists beginning to understand how ECT affects the brain.

Transcranial magnetic stimulation (TMS) is another external means of altering electrical activity in the brain. Rather than applying electrical current to the scalp as in ECT, TMS produces a local magnetic field that interacts with the electric fields produced by neurons. Typically, TMS is administered with a small wand-shaped instrument held a few inches from a subject's head. Depending on where the instrument is positioned, it can alter the electric activity in a desired region of the brain. Typically, TMS shuts down electrical activity in a small region of the brain for a few minutes.

Some studies have found that TMS can improve symptoms in depression and PTSD. However, meta-analysis of these studies does not show a significant change. A number of research groups are studying TMS to learn how to make it more effective.

Medication

Over the past twenty years, medication has become increasingly common for the treatment of psychological disorders such as depression, PTSD, and other conditions commonly encountered by nonprofit behavioral health care providers. While these drugs have brought relief to many, they are not panaceas by any means. In many cases, they do not relieve symptoms. And as the recent controversy over suicide rates in teenagers taking antidepressants has shown, they may have serious side effects in a small portion of the population.

It is difficult to foresee what sort of medications will be available in twenty years, but some current trends offer some hints. In the past, trial-and-error experimentation has dominated the search for new antidepressants and other drugs for psychological disorders. Increasingly, scientists are trying to understand the underlying neurobiology of these disorders in order to target treatments more effectively. PTSD, for example, has been associated with damage to the hippocampus. That link has led some researchers to test drugs that have been found to foster neuron growth in the hippocampus or to alter its ability to take up neurotransmitters. In both cases, these medications have helped restore memory. Research on how traumatic memories are initially laid down in the brain has led to some speculations about blocking the encoding of traumatic events in long-term memory. A person who survived a terrorist attack might take a medication within a day that might stop the event from spiraling into full-blown PTSD. At the moment, however, this remains speculation.

Pharmacogenomics

Another important area of research is *pharmacogenomics*—the study of how different genotypes can influence the effectiveness and side-effects of psychiatric medications. There is good reason to believe, for example, that people with certain genotypes may not be able to metabolize certain medications properly and will therefore not benefit from taking them. Likewise, it is possible that certain genotypes may cause some individuals to suffer serious side-effects from certain medications while other genotypes do not pose this risk. If these links could be established, genotyping might become an important element in determining what sort of treatment is best for an individual patient.

While pharmacogenomics has received a great deal of press recently, it remains a very new field that has a long way to go before it influences how nonprofit behavioral health care providers plan treatments. Only a handful of correlations have been published, and in many cases other researchers have failed to replicate them. It is difficult to establish positive findings in part because the response to medications probably depends on many genes, rather than single ones. Since each of those genes exists as several alleles (variants), the potential number of combinations that have to be tested explodes exponentially. And as we've already seen, the influence of genes often depends on the environmental influences with which they interact. Nevertheless, pharmacogenomics is moving forward rapidly and in ten or twenty years may help usher in a new era of "personalized medicine."

Psychotherapy and Other "Non-medical" Treatments

While medication has become much more common for the treatment of psychological disorders, its increase does not spell the doom of psychotherapy. In fact, neuroscience research is helping to document how psychotherapy produces significant biological changes in the brain. As discussed earlier, for example, patients who respond positively to psychotherapy for depression show a distinctive "top-down" response in brain scans. Neuroimaging may help psychotherapists track the progress of their patients, and may also help determine which types of therapy are most effective for various conditions.

In many cases, medication and psychotherapy can be more effective in combination than either is on its own. A simple example would be a schizophrenic patient who cannot even have a rational conversation without medication. Some researchers are exploring how new insight from neuroscience may point to ways in which medication and psychotherapy can work more effectively together. For example, psychotherapy may act in some cases as "emotional learning." A patient with a phobia or PTSD may learn not to associate a particular cue with a feeling of fear. Decades of neurobiological research on learning indicate that it involves the formation of new connections between neurons and the severing of old connections. Experiments on animals have shown that certain drugs enhance this process, allowing animals to learn new tasks faster. In other experiments, animals "unlearned" fear by learning that a particular cue no longer predicted a painful shock. Giving the animals certain drugs speeded up this unlearning.

Inspired by these results, researchers recently used a similar approach on people undergoing behavioral exposure therapy to overcome acrophobia, a fear of heights. While undergoing the therapy, the subjects of the study took D-cycloserine, a cognitive enhancer. The researchers found that the drug significantly improved the therapy. After three months, 70% of subjects taking the drug felt much improved, compared to only 25% of subjects taking a placebo (Ressler 2004).

Finally, research on the genetics of psychological disorders provides support for traditional social work. This might seem surprising, given the traditional image of genes as "hard-wiring" behavior. But as described earlier in this report, the current consensus is that genes can only predispose people to antisocial behavior, depression, and other psychological disorders. The environment plays a powerful role in shaping a person's behavior. In a 2005 review, the Institute of Psychiatry (London) researchers who pioneered this research argue that it shows how important nurse home-visitation programs can be to the long-term well-being of children. Long term studies have shown that children who were abused did not have more conduct problems than non-abused children if they were in nurse home-visitation programs. (Eckenrode 2001) The Institute of Psychiatry team argues that these programs can be particularly effective for children at genetic risk of antisocial behavior (Jaffee 2005).

Stem Cells

It is impossible to pick up a newspaper these days and not come across a new story about the controversy over stem cell research. Many scientists argue that stem cells could provide revolutionary new treatments for a wide range of diseases, while others object to some of the research on moral grounds, because it requires the destruction of embryos. A look at the scientific evidence gathered so far suggests that perhaps in the distant future stem-cell derived treatments may have an impact on nonprofit behavioral health care, but the other treatments described in this report are likely to become a reality far sooner.

Stem cells are a special class of cells in the human body that can develop into a wide range of different tissues. The cells that develop in the first few days after an egg is fertilized are believed to have the capacity to give rise to any type of cell found in the adult body if they get the right set of signals. As the embryo develops, most cells begin to lose their flexibility. Neural stem cells, for example, can give rise to a wide range of neurons, but will not produce a muscle or liver cell on their own. In the body of an adult, the vast majority of cells have lost their ability to divide into new types. However, a few populations of cells still retain some flexibility. Most important for this discussion are the neural stem cells that survive in the adult brain.

The discovery of these stem cells in recent years has come as a big surprise to the scientific community. It was traditionally believed that neurons in the adult brain could no longer produce new neurons. But neural stem cells can continue to divide, adding new neurons to the brain even into old age. These neural stem cells can only be found in a few regions of the brain, including the hippocampus. The hippocampus's neural stem cells are responsible for the regrowth of neurons seen in people who recover from depression and other psychological disorders.

It is conceivable that one might be able to treat these disorders by surgically implanting stem cells in the hippocampus to encourage the growth of new neurons. Research on monkeys suggests it might even be possible to harvest some neural stem cells from a patient, culture them in a laboratory until they had produced a large number of stem cells, and then re-implant them in the hippocampus. Scientists have already begun experimenting with stem cells to treat Parkinson's disease, which kills dopamine-producing cells. As exciting as these developments are, no one has performed any stem cell experiments to directly test their potential to treat psychological disorders. Moreover, stem cell therapy would require invasive brain surgery. As a result, it is difficult to say when, if ever, stem cell therapy will affect nonprofit behavioral health care.

Monitoring Treatment

Medications such as SSRIs can take weeks to reduce the observable symptoms of depression and other psychological disorders. If a patient fails to respond to the medication or suffers adverse side effects, this long delay can cause serious problems. By recognizing these disorders as being based in the brain, however, it may be possible to do a much more effective job of monitoring treatments. In one promising study, researchers repeatedly scanned the brains of depressed people who were prescribed medications. After six weeks, some of the subjects enjoyed some relief from depressions while others did not respond. Looking back at their scans, the researchers observed significant changes in many of the patients who had responded positively within a week of starting to take the medication. The early changes took place in subcortical regions; only when cortical regions began to change weeks later did people begin to report feeling better. Similar results have been found in studies on psychotherapeutic treatment of depression. Neuroimaging may thus become a useful tool for monitoring patient response to treatment. Microarray tests of gene expression may also provide important cues to how the brain responds to treatment.

Summary

In summary, developments in neuroscience over the last several decades have laid the groundwork for a stronger integration of medicine, science and technology into the behavioral health services delivered by traditional social service agencies. Immediately available on the horizon for nonprofits are brain imaging technologies for use as diagnostic tools, treatment establishment and management protocols, and improved drugs to treat psychological disorders and enhance cognitive therapies. Behind those lie opportunities for neurosurgical intervention as treatments for behavioral health issues. Just over the horizon, but considered by many to be likely, research on genes will lead to further advances in treatment and diagnosis strategies used in nonprofit behavioral health care.

The Implications for Nonprofit Behavioral Health Care

Laudan Y. Aron

Advances in basic neuroscience are producing unprecedented opportunities to better understand and even redefine the pathophysiology of mental and addiction disorders and develop new interventions to treat these disorders. The new discoveries are challenging our ability to neatly sort brain-based disorders into either neurological or psychiatric conditions – in short, the mind-body distinction is blurring and it is blurring quickly.[1] As experts in the fields of neurology, psychiatry, and psychology question how their areas of expertise can and should relate to one another, an obvious question arises: what do all these developments mean for behavioral health service providers and consumers and their families? As new treatment options and even "cures" for brain-based conditions are discovered, refined, and subjected to clinical trials, how will the organization, delivery, and funding of behavioral healthcare change, and what might these changes mean for nonprofit behavioral health agencies operating now?

This section provides a preliminary look at how advances in neuroscience may affect the world of nonprofit behavioral health. Most of the advances are still in the early stages of basic scientific research, but there are strong pushes at the federal level to link basic findings to field practice; indeed a variety of emerging biotechnologies are already being used successfully in some clinical settings. For the most part, however, there has been little systematic thinking about how leaders, managers, and clinicians in nonprofit behavioral health agencies should prepare for these changes. How can agencies proactively position themselves to prepare for new treatments, services, or service system approaches that will be needed as neuroscience discoveries and technologies that are now "cutting edge" emerge into the mainstream over the next several decades? The advances present exciting challenges and opportunities for the field, but will also require careful planning and management.

It is important to keep in mind that the changes being unleashed by advances in neuroscience are not occurring in isolation. Many forces are already changing the landscape of the behavioral health industry and will set the stage for how well communities and individual agencies are able to meet the opportunities and challenges of the neuroscience revolution. These include an ongoing emphasis on quality and accountability through the use of managed care and disease management models; pressures to narrow the current gap between research and practice by implementing "evidence-based practices;" adopting sophisticated real-time clinical and financial management information systems through the use of electronic medical records and other cutting edge information technologies; encouraging the integration of behavioral health into primary care and other community-based settings such as schools, juvenile justice facilities, Head Start programs, etc.; and the general consolidation of the behavioral health industry into companies and agencies that are much larger, medically sophisticated, and more business-like in focus. The ability of individual nonprofit behavioral health agencies to respond to advances in neuroscience may very well depend on how well they are managing these current industry trends right now.

In this section, we examine the implications of these advances in three broad domains: clinical, institutional/systemic, and societal. Clinical implications include the impact of neuroscientific advances on the providers of care, consumers and their families, and the process and outcomes of behavioral healthcare. The institutional/systemic domain includes such factors as the organizational and administrative practices of service delivery, and the system of providers and institutions needed to meet demands for new types of care including how services and service structures are organized, financed, and regulated. Finally, the broader societal implications cover a variety of ethical issues that are likely to arise as neuroscientific advances move downstream from the laboratories of basic research scientists into clinical and community-based settings. A final section considers what steps nonprofit behavioral health providers might take to prepare for the changes that will come from the neuroscience revolution.

Clinical Implications of Neuroscience Advances

Groundbreaking findings in the neurosciences are being reported daily, but ultimately their real value for the field of behavioral health will need to be established through new treatments that are effective on behavioral grounds, treatments that improve the quality of life among individuals who have mental illness and addiction disorders. The path from basic scientific research (a discovery) to a

1 See, for example, SC Yudofsky and RE Hales, "Neuropsychiatry and the Future of Psychiatry and Neurology," American Journal of Psychiatry, 159:8, August 2002; JB Martin, "The Integration of Neurology, Psychiatry, and Neuroscience in the 21st Century," American Journal of Psychiatry, 159:5, May 2002; and ER Kandel, "Biology and the Future of Psychoanalysis: A New Intellectual Framework for Psychiatry Revisited," American Journal of Psychiatry, 156:4, April 1999.

treatment that works in a controlled research setting (an evidence-based practice), and finally to a treatment that works in routine practice settings (a practice-based evidence) is a long one, and behavioral health agencies have a very important role to play in this journey. Once the new treatments do penetrate the evidence base and start becoming "treatment as usual," they are likely to affect every aspect of current clinical practices in behavioral health agencies: from how clients are referred into treatment, to assessments, diagnosis, and treatment planning, to core treatment mechanisms, supportive services, and aftercare. Treatment inputs, including staffing, client characteristics, and service structure, are also likely to evolve. Depending on what treatments emerge (and when) and what services are reimbursed (and at what level), there may also be fundamental changes in the populations served by behavioral health agencies.

The new advances hold particular promise for diagnosing and treating youth with behavioral and emotional problems, post traumatic stress disorders, aggressive outbursts, sexual abuse, physical abuse, impulse control issues, and substance abuse problems. Traditional treatments for youth with these problems have been quite ineffective. Many behavioral health providers and other experts involved in serving this population describe the serious challenges they face when helping these youth, including increasing levels of acuity, greater shares of children with *multiple* psychiatric diagnoses and on *multiple* medications, and complications presented by underlying medical conditions (e.g., hyperthyroidism). Often the children have failed many other settings or systems (e.g., foster homes, group homes, attempts at medication management) before finally coming to a residential treatment center. But providers interviewed as part of this study have commented that many of the children are on psychiatric medications that are "not compatible with their biologies" and there is a lot of "educated guessing" when it comes to their treatment. They also describe "flying by the seat of our pants" when it comes to treating these youth, engaging in activities for which there is "no evidence," and candidly sharing that as an agency they are "thinking about survival, not about best treatments."

As our understanding of the neurobiological bases of behavioral health grows, individual clinicians and agencies will need to implement new practices and treatment paradigms. This process will involve many activities including assessing program, clinician and support staff readiness; developing knowledge about the new treatments; evaluating the degree of substantive change required to move from current practice to the new state of service delivery; examining various barriers to implementation; and identifying supports needed for the change process.

In addition to supporting basic science research, the National Institute of Mental Health (NIMH) has established among its

The Neurobiology of Adolescence

Our understanding of the neurobiology *of adolescence is leading to a greater recognition that many mental disorders (and concurrent changes in brain function) begin during this phase of development, and some practitioners are already incorporating this new way of thinking into their clinical practice. Neuropsychiatric approaches are being used to help with both diagnosis and treatment. One residential treatment center in California, The Sycamores, is using SPECT imaging to "add functional data to the clinical presentation" and thereby help psychiatrists make better informed decisions with respect to both diagnosis and treatment. Another residential treatment center dedicated to serving impulsively aggressive youth has developed the following criteria for determining if a child should be treated with neuropsychiatric interventions: having a normal range of intelligence; dangerous to self or others; recidivism; not benefiting from current treatment; impulse control issues; pathological aggression; and evidence of brain impairment.*[2] *They define "pathological aggression" as a pattern of aggressive behavior that occurs with little or no provocation, is unplanned and impulsive, and without either social or material gain. The behavior is also intense, destructive and repetitive, and is almost always caused by a* brain dysfunction. *Evidence of brain impairment, the last criterion listed earlier, includes any of the following: impulsivity (e.g., aggressive behavior that is impulsive rather than planned); poor planning skills (e.g., runaway with no plan, no money, nowhere to go); short attention span (e.g., attention too short for group therapy); laboratory evidence (e.g., abnormal CT scan, MRI, EEG); pathological aggression (e.g., violent behavior with no provocation, no gain); history of neurological disease (e.g., seizure disorder, encephalitis); neuropsychological tests abnormal (e.g., VIQ-PIQ > 30 points); repetitive rage behavior (e.g., requiring seclusion and restraint); toxic exposure in gestation (e.g., substance abuse by mother in pregnancy); and prior head injury with LOC (e.g., loss of consciousness – LOC > 1 hour).*

This same center, the Meridell Achievement Center, reports that neuropsychiatric treatments are yielding positive outcomes for 86 to 90 percent of impulsively aggressive adolescents in long-term residential centers.[3] *They define positive outcomes as no further violent episodes, no re-hospitalization, no runaways, no incarceration, and following an aftercare plan with continuation of school (or work) following discharge. Similar studies of outcomes following treatment in short term, acute settings are underway.*

2 See, for example, information posted on the website of the Meridell Achievement Center in Liberty Hill, Texas at https://www.meridell.com/neuro.shtml.

3 See website information of UHS Neurobehavioral Systems at https://www.ragebehavior.com/faq.htm.

highest priorities the translation of basic scientific discoveries into new interventions that will relieve the suffering of people with mental disorders and ensure that the new approaches are available to and used by diverse populations and in diverse settings. Building on the *Decade of the Brain*, NIMH is now launching the *Decade of Translation* with the goal of bringing recent discoveries from genomics, neuroscience, and behavioral science to new and more effective innovative behavioral and pharmacological treatments, and with an ultimate goal of preventing and even curing mental illness.[4] Individuals and agencies can and should take full advantage of the many efforts to disseminate new treatment approaches, and may even (as one Alliance member reported doing) proactively create "a research-friendly environment" so that other clinicians, researchers, and experts can study innovative new approaches within their agencies and with their clients (participation in research studies is discussed again later in this report). As new effective treatments become better known and more widely available, behavioral agencies will need to decide which treatments they will need to offer their clients (and how) and how far along the continuum of the medicalization of behavioral health they can and want to go. At the very least, clinicians should be trained in identifying those conditions for which innovative effective treatments are available (even if their own agency does not provide it) and directing their patients to other agencies or settings where they can learn more and seek new treatments if they choose.

Although clinical applications of advances in neuroscience are only beginning to penetrate treatment protocols (and the research base on which these protocols are usually based), there has been widespread recognition and concern about the existing gap between research and practice or "science and service" in the treatment of mental illness and addiction disorders. In 1998, the Institute of Medicine issued a major report entitled *Bridging the Gap Between Practice and Research: Forging Partnerships with Community-Based Drug and Alcohol Treatment*, and one year later the 1999 *Report of the Surgeon General on Mental Health*[5] reported that "a gap persists in the broad introduction and application of these [research-based] advances in services delivery to local communities, and many people with mental illness are being denied the most up-to-date and advanced forms of treatment."

Adopting evidence-based practices does not mean a wholesale

4 NIMH Strategic Plans and Priorities, http://www.nimh.nih.gov/strategic/strategicplanmenu.cfm?styleN=one

5 U.S. Department of Health and Human Services. Mental Health: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health, 1999.

Bridging Research & Practice

New strategies have been developed to bridge the gap between research and practice and to disseminate "state-of-the-art" treatment protocols. A variety of well-respected organizations and agencies are engaging in initiatives designed to disseminate evidence-based practices (i.e., clinical and administrative practices that have been proven to consistently produce specific, intended results). These include:

The American Psychiatric Association Practice Guidelines: http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

The federal Agency for Healthcare Research and Quality: http://www.ahrq.gov/clinic/index.html

The Cochrane Collaboration: http://www.cochrane.org

The National Evidence-Based Practices Project (Toolkit Project): http://www.mentalhealthpractices.org

The National Guideline Clearinghouse has diagnostic, assessment, and treatment guidelines: http://guideline.gov

The National Association of State Mental Health Program Directors (NASMHPD) Research Institute's rationale for establishing a Center for Evidence-Based Practices, Performance Measurement, and Quality Improvement: http://www.nri-inc.org/RationaleEBPCenterReview.pdf

The Human Services Research Institute website for evidence-based practices: http://tecathsri.org/knowledge.asp

The Centre for Evidence-Based Mental Health: http://www.cebmh.com/

The Technical Assistance Collaborative (TAC) and the American College of Mental Health Administration (ACMHA) have jointly developed a step-by-step manual for behavioral health providers entitled Turning Knowledge into Practice: A Manual for Behavioral Health Administrators and Practitioners About Understanding and Implementing Evidence-Based Practices (Fall 2003). This manual is available online at http://www.tacinc.org/index/viewPage.cfm?pageID=114 rejection of business as usual. There is a continuum between the worlds of practice and science, and both ends of this continuum can and should inform one another: practice needs to be informed by science, but science also need to be informed by practice—something that has come to be called "practice-based evidence." Because tightly controlled scientific studies are often not clinically representative, meaning the client populations, service providers, and clinical settings do not correspond to those found in real-world situations, evidence-based practices often need to be adjusted by the realities encountered in actual clinical settings. Still the word "evidence" underlies both the concepts of evidence-based practice and practice-based evidence, and evidence of outcomes is key to both. Adopting a strategy of practice-based evidence requires that agencies engage in systematic efforts to understand and monitor clinical outcomes of specific treatments as they are applied to specific sub-populations of interest.

It is also important to recognize that scientifically validated treatments do not exist for every condition, and that the level and quality of science available to support a given intervention varies from one intervention to another. The science base is also continually evolving, so one cannot simply adopt evidence-based practices and be done with it. Because of this, the real key is for provider systems and clinicians to adopt an ongoing philosophy of "evidence-based thinking." Doing this assures that one is at the forefront of existing science-based practice, and is well positioned to take advantage of neuroscientific advances as these too begin to be tested and penetrate the evidence-base on which state-of-the-art treatments are based. Of course adopting evidence-based practices—neuroscientific and others— has important advantages for individual behavioral health agencies: these include clinical, quality control, administrative, financial, and political reasons (see the Turning Knowledge into Practice manual referenced on page 21 for a fuller discussion of each of these advantages).

It is well known that susceptibility to certain mental and behavioral disorders is affected by social, cultural, and ethnic factors, and especially gender. These same factors influence response to treatment, access to behavioral healthcare, and resiliency to environmental influences on behavioral health. It is unclear how the new diagnostic and treatment approaches emerging from neuroscience will affect different sub-groups of people, but many observers have pointed to the importance of narrowing disparities between ethnic minorities and other underserved populations in their access to (and use of) high-quality treatment services, increasing the diversity of the populations studied, and broadening the diversity of behavioral health researchers and practitioners. Behavioral health agencies should keep these goals in mind as they make strategic decisions about their staffing, service structures, and other treatment inputs. Depending on how things play out, one can easily envision the new advancements giving large numbers of people from underserved populations access to high-quality behavioral health treatments for the first time in their lives (this is especially true if the treatments are shown to be more cost-effective than what has traditionally been offered); on the other hand, there is also the potential for a widening of the gap between those who do and do not have access to effective care for brain-based disorders: a neuropsychiatric well-being divide, similar to the "digital divide" created by the revolution in computer technology and information science.

In discussing the implications of advances in neuroscience for nonprofit behavioral health agencies and their clients, few observers are predicting the end of psychological or clinical counseling as we know it. Indeed, several people thought that the importance and effectiveness of more "traditional" psychosocial therapies and supports may *increase* as a result of our improved understanding of brain-based mental health and addiction disorders. One appropriate response to our new understanding of the brain, its plasticity and malleability, and its responsiveness to nurturing and environmental influences, would be a better recognition of the value of traditional psychosocial supports, especially among children and adolescents. As the National Academy of Science concluded in its report *From Neurons to Neighborhoods*:

> *Enormous potential exists at the intersection of child development research, neuroscience, and molecular and behavioral genetics to unlock some of the enduring mysteries about how biogenetic and environmental factors interact to influence developmental pathways. These include: (a) understanding how experience is incorporated into the developing nervous system and how the boundaries are determined that differentiate deprivation from sufficiency and sufficiency from enrichment; (b) understanding how biological processes, including neurochemical and neuroendocrine factors, interact with environmental influences to affect the development of complex behaviors, including self-regulatory capacities, prosocial or antisocial tendencies, planning and sustained attention, and adaptive responses to stress; (c) describing the dynamics of gene-environment interactions that underlie the development of behavior and contribute to differential susceptibility to risk and capacity for resilience; and (d) elucidating the mechanisms that underlie nonoptimal birth outcomes and developmental disabilities.*[6]

6 See pp 13-14 of National Research Council and Institute of Medicine (2000) From Neurons to Neighborhoods: The Science of Early Childhood Development. Committee on Integrating the Science of Early Childhood Development. Jack P. Shonkoff and Deborah A. Phillips, eds. Board on Children, Youth, and Families, Commission on Behavioral and Social Sciences and Education. Washington, D.C.: National Academy Press

Rather than the new neuroscientific technologies and pharmaceuticals displacing counseling and psychosocial supportive interventions, the technologies may very well help demonstrate how the brain can be retrained through psychotherapy and even supplement its effectiveness (e.g., with new medications). The new knowledge and technology may provide evidence in support of more and better investments of the public's resources in effective behavioral health interventions of all kinds (neurobiological and psychological) and at all points in the lifecycle (from early intervention and prevention early in life to treatments and cures later in life).

Another expert consulted for this project observed that as the complexity and technical sophistication of treatment options increase, there will be more need for education and advocacy of consumers and their families, as well as for high-quality psychosocial rehabilitation. Consumers are likely to need much more help understanding and navigating the array of treatment options (including privacy/legal issues, exercising informed choice, and providing informed consent). The relationship between behavioral health providers and consumers will also be affected by direct marketing of new technologies to consumers. Increasingly, consumers will be asking providers for a given pharmaceutical, genetic test, or brain image, and clinicians should be prepared to respond to these requests and deal with a lot of misinformation. Equally important will be the need for *post-treatment* management and recovery as home- and community-based supports replace institutional ones. Individuals and families who have been living with life-long behavioral illnesses will need a great deal of time and support to become fully-informed participants, select therapies that are well-matched to their individual needs, adhere to the therapies and manage medications reliably, and adjust to the new treatments and their effects. The human, supportive, and rehabilitative dimensions of recovery should not be undervalued, and may even be the key to the retention and success of some of the new therapeutic discoveries. Another head of a large behavioral health agency agreed with this general point, noting that advances in neurology "will not threaten services such as case management, coaching/mentoring, and continuum services for children." As an analogy, he commented that the great advances in orthopedic surgery and other procedures have not led to the demise of physical therapy. He did note, however, that the neuroscience advances in behavioral health may lead to changes in how clinical services are sequenced or ordered.

Institutional/Systemic Implications of Neuroscience Advances

The effects of advances in neuroscience for behavioral healthcare extend far beyond specific clinical approaches or treatments. In addition to the major trends reshaping the industry right now, discoveries in neuroscience are accelerating the medicalization of behavioral health as a field, and this will create a need for new professional skills, new technological equipment, new service delivery structures, and new cost reimbursement strategies. While these changes can occur within a single behavioral health agency, they are much more likely to be realized through new partnerships and institutional relationships, including linkages between traditional behavioral health agencies and other types of providers, such as psychiatric and medical-surgical hospitals, and even private diagnostic and screening centers with sophisticated imaging and other medical equipment.

Few of the behavioral health providers consulted for this project have started thinking about new institutional arrangements they may need as a result of neuroscientific advances. Many of them instead are focused on surviving in what is an increasingly competitive market, have merged with other agencies, or been approached with take-over offers. Even relatively large, well-managed behavioral health systems acknowledge they may not survive the competitive forces of the next five years, and will need to grow rapidly and demonstrate greater effectiveness and accountability to both consumers and payors. Smaller mom-and-pop agencies (even if they are among the oldest and have the trust and respect of the community) acknowledge feeling "light years behind" some of their counterpart agencies that have real-time clinical and financial management systems, are practicing "telepsychiatry," etc. These same agencies admit to not knowing how they can survive if they remain small, "mission-driven" organizations reliant on sliding-scale fee structures and community fundraisers to cover their operating costs.

In order to survive, most of these agencies will need to enter into new partnerships, not just with other behavioral health agencies but also with new types of service providers and institutions. Some of the partnerships to emerge, especially at the early stages of working with new professionals and new technologies, may be more serendipitous. One residential treatment center in California, the Sycamores, has started working with a private for-profit brain imaging center to do SPECT scans of children in residential treatment. Initially, the agency's use of SPECT began with just a small set of families with very proactive parents struggling to understand the behavioral problems of their children, but as the agency saw the benefits of incorporating this new information into their diagnostic and treatment planning they sought additional funds to make the scans available to more and more children. The agency also sought out funding from a local foundation to support a research project to study what difference adding scan information to the assessment had on outcomes for the children (the study has run into some problems but is ongoing).

Having flexible or dedicated funds to explore new and innovative technologies can be critical in an industry where reimbursement drives treatment offerings. Currently, public funding streams for behavioral health services (mainly state Medicaid agencies, but also state and county mental health and substance abuse authorities, and education, child welfare, and juvenile justice agencies) do not reimburse for sophisticated technologies except perhaps pharmaceuticals. When asked about new treatments to emerge from neuroscience research, behavioral health providers initially reacted by asking, "Who is going to pay for it and will it work for our population?" But later they conceded that most of what they do is driven by cost-benefit analyses, and "if there is good data supporting a given [new] intervention, then we can get funding for it." They also noted that monitoring an acutely chronically suicidal child 24 hours a day, seven days a week entails huge costs, so even if the new treatments are quite expensive, they may be more cost-effective than current treatment approaches.

A recent report from the American College of Mental Health Administration's (ACHMA) workgroup on financing results and value in behavioral health services puts financial structures front and center in the behavioral health industry:

> *The behavioral health field has learned much in the last 50 years about what it wants and needs, and how to get it by using financing mechanisms that provide the right incentives and avoid perverse ones. Above all, the field has learned that finances drive behavior. A statement of values, a strategic plan, research on evidence-based practices, and even regulatory efforts are critical, but they cannot overcome the reality* ***that what is paid for is what will be provided.*** *Frequently, what is paid for well or easily, or with a high reimbursement rate, will have more influence on which services are provided and in what manner they are provided than the professional standards or the non-financial actions of system leaders and stakeholders (emphasis added).*

The workgroup also identified many creative financing mechanisms behavioral health providers continue to create and test with different goals and objectives in mind. These include *risk corridors* to increase incentives to provide care; *risk-adjusted rates* to provide care to those most in need, and case rates to increase treatment flexibility and creativity for specific individuals and families. Other financing innovations are also being considered in the field: with *network financing*, funding streams are combined to purchase a continuum of care. Rather than subcontract with numerous programs to provide a fixed number of units of service in specific categorical areas, all elements of a system of care are part of a single purchase agreement that specifies performance targets, coordination and collaboration requirements, quality management expectations, and 24/7 coverage (this allows the purchaser to hold all subcontractors accountable, not only to the purchaser but to each other as well). The ACHMA acknowledges, however, that financing mechanisms alone cannot substitute for high quality treatment services. As they explain:

> *Because of the power of financing, behavioral health system leaders sometimes see a change in the financing mechanism as the chief method for effecting service delivery changes. While financing mechanisms can assist or impede the successful implementation of system values or purchasers' desires for beneficiaries, they cannot, in and of themselves, form the base of a high-quality, high-value system or a set of services. Systems do not change overnight—to achieve high-value services with the desired outcomes for the money spent, the process must have order and must be planned for over a period of time. Changing the financing mechanisms without articulating the desired outcomes or without being able to track those outcomes is likely to result in just different but still ineffective financial incentives, or in unintended consequences for services and service recipients.*[7]

Of course investments of public dollars are usually influenced by public perceptions of social welfare needs and especially the role of personal responsibility in the given problem. Personal responsibility has been found to be the single greatest correlate of the values driving decisions about resource allocation for mental health services.[8] Indeed Corrigan and Watson (2003) advise stakeholders to use advances in neuroscience to influence public thinking about mental illness and its causes:

> *Advocates need to help policy makers replace notions such as "people choose mental illness because of weak character" with more factual information such as "mental illness is caused by a personally uncontrollable brain disorder." In fact, one research study showed that research participants who were taught that people with mental illness are not responsible for their mental illness showed significant reductions in negative attitudes about and social distance toward mental illness. (p.4)*

8 PW Corrigan and AC Watson, "Factors That Explain How Policy Makers Distribute Resources to Mental Health Services," Psychiatric Services 54:501-507, April 2003.

7 See the American College of Mental Health Administration (ACHMA) Workgroup (2003) "Financing Results and Value in Behavioral Health Services," Administration and Policy in Mental Health, 31(2): 85-110, p.88.

As decision-makers and the public at large better understand the biological basis of many mental and addiction disorders, there may also be a greater willingness to support effective behavioral health intervention in other sectors connected to the social services field, including the criminal justice, education, housing, and child welfare systems. As the clinical benefits of neuroscientific advances become more widely available, these systems may well be expected to pay for effective interventions benefiting the populations they serve.

Societal Implications of Advances in Neuroscience

Advances in neuroscience will unleash a host of broader issues for society. A new term, "neuroethics," has even been coined to describe the variety of social and ethical issues that will emerge from both clinical neuroscience (neurology, psychiatry, psychopharmacology) and basic neuroscience (cognitive neuroscience, affective neuroscience). Along with "classical" bioethical matters such as safety issues, informed consent, and privacy, new technologies such as functional neuroimaging, psychopharmacology, brain implants, and brain-machine interfaces will give rise to new types of ethical questions. Neuroethics as a field is still in its infancy, but some of these new ethical questions are already being posed. As our ability to measure unconscious motivation to behave in certain ways improves, for example, what applications of "brainotyping" (analogous to genotyping) will be acceptable? Who can and should have access to such information and for what uses or purposes (e.g., brain-based lie detection, sexual preferences, racial attitudes, and mental health vulnerabilities and predispositions to violent crimes)? There is a growing body of evidence that brain imaging can be used to detect (rough measures of) various personality traits such as extroversion, neuroticism, risk-aversion, pessimism, persistence, and empathy. Who should have access to such brain-based information and under what circumstances? Many groups are potentially interested in such information: parents, schools, court systems, residential treatment programs, employers, and even the government. Once we decide on the legitimate uses (and users) of such information, how will it be protected from misuse and who will enforce these protections?

Neuropsychiatric illness and wellness occur along a continuum and most neuroscientific advances are being pursued to help people with *deficits* in the areas of attention, memory, and affect. But the same medications used for illness can (and are already being used to) improve the attention spans, memories, and moods of normal healthy people. Are enhancements of "normal" brain-states a legitimate use of neurocognitive medications and other technologies? The safety and side effects of neurocognitive enhancers must be studied with care, especially given the biological complexity and importance of the brain. But many social and even philosophical questions relating to enhancement must also be considered. Should neurocognitive enhancement become widespread, will individual adults, athletes, students, or job seekers who choose *not* to enhance be at a substantial disadvantage, thus introducing an element of coercion? Would outlawing or restricting the use of neurocognitive enhancement not also be coercive? Dr. Martha J. Farah of the University of Pennsylvania has also noted that widespread enhancement would redefine regular human behavior and runs the risk of "undermining the value and dignity of hard work, medicalizing human effort and pathologizing a normal attention span."[9] This in turn may lead to "diagnostic creep" whereby a behavior that was once thought to be within the range of what is considered "normal" is now seen as impaired and in need of a neurocognitive intervention.

Our increasing understanding of the physical causes of behavior is also beginning to challenge popular notions of free will and moral agency underlying the country's legal system. Evidence indicating neurological dysfunction is already being used in the penalty phase of criminal trials. It seems only natural that as our neuroscientific understanding of the brain grows, there will be a greater willingness to understand "bad" and even criminal behavior in terms of poor brain function. Exactly how this will impact our definition and operation of criminal justice is unclear. One positive outcome is that there may be less stigma attached to criminal behaviors that are brain-based; this in turn may lead to more treatment and rehabilitation and less chronic incarceration of people with serious mental illnesses. It is also very likely that courts and other justice and even social service agencies will increasingly mandate various neuropsychiatric interventions. Courts already mandate batterers, pedophiles, drug addicts, and others into various treatment programs (the vast majority of which are ineffective), so as new promising neuropsychiatric treatments become better known and available, there is every reason to expect courts to "order" such treatment. Our new understanding of the connections between the brain and behavior may also lead to changes in how we define things such as moral and legal responsibility and impaired consent. Even fundamental notions such as free will and personal identity may be reconsidered and redefined.

Finally, it is important to think about the social justice aspects of advances in neuroscience. The advances have the potential both to create and remedy serious social inequities, especially among groups who are already disenfranchised and/or experiencing discrimination: members of minority racial/ethnic groups, people with learning disabilities or mental illnesses, chronically homeless people, people who are repeatedly incarcerated, etc. Will access to neuro-

9 See discussions by Martha J. Farah, Director, Center for Cognitive Neuroscience at the University of Pennsylvania on the website of http://www.neuroethics.upenn.edu.

scientific interventions that can be used for treatment and/or enhancements be equally distributed, or will these technologies add to the existing divide separating those with and without money, power, and class privilege, and the "neurologically optimal" child-rearing environments these advantages often provide? Preferential treatment by public and private insurance providers of conditions and disabilities more common among advantaged groups should also be monitored with care.

It is unlikely that individual behavioral health clinicians (or even agencies) will need to grapple with many of the profound questions being raised by neuroethicists today. Most of these questions are likely to be played out at the national level, through the courts, federal policy, and even national media, as is currently the case with stem cell research and cloning. But individual behavioral health agencies and their staff will certainly be involved in adopting various clinical protocols, protecting the security and privacy of their administrative and clinical data, and ensuring that their clients are fully informed and protected. The latter will be especially challenging if the clients are children or individuals unable to make treatment decisions on their own behalf.

Role of Nonprofit Behavioral Health Care Providers

The neuroscience revolution and the new treatments it will yield present the nonprofit behavioral health world with very exciting opportunities. Taking advantage of these opportunities will require that behavioral health providers increase their knowledge and understanding of what the advances can and cannot do for their clients. This knowledge should be based on information from scientifically reliable and reputable sources and clinicians should be prepared to educate and respond to consumers who may be misinformed by overly simplistic media reports or by marketers of pharmaceuticals, genetic testing, and imaging centers. In addition to increasing their knowledge base, nonprofit behavior health providers will need to think strategically about what other service providers they should align themselves with (either collaboratively or through mergers) in order to offer their clients the best care possible. In some cases, they may simply decide to refer certain consumers with certain conditions to other providers in the community.

One promising way of increasing knowledge and changing agency practice is to create within one's agency a "research friendly" environment that attracts premier researchers and research institutions. Large-scale national clinical trials are often funded very generously (in the millions of dollars) and involve significant time and investments in professional development and clinician training, information technology such as clinical decision support systems (CDSSs), and other processes that engage multiple stakeholders and pave the way for changes in an organization's culture that are required before new treatment protocols can be accepted and adopted with fidelity. Often very careful procedures are put in place to ensure the informed consent and protection of all human subjects involved in the study.

Whether involved in clinical trials or not, to prepare for participation in the neuroscience revolution, nonprofit behavioral health agencies must commit themselves to rigorous outcomes collection and evaluation. By collecting high quality treatment and outcome data evaluating the effectiveness of their services and engaging in a process of continuous improvement, nonprofit behavioral health providers can demonstrate the effectiveness of their services to multiple stakeholders, and in the process, contribute to the emerging dialogue around the integration of neuroscience with nonprofit behavioral health care.

Summary

In summary, nonprofit providers interested in integrating recent neuroscientific developments into their behavioral health practices should:

- Become informed and knowledgeable on both the promises and limitations of the new advancements, relying on authentic scientific literature, and not popular media, for credible and objective information.
- Adopt evidence-based practice as the protocol for agency service delivery. Create a research friendly environment inside the agency by collecting high quality treatment and outcome data, linking the two, and acting on the findings
- Seek out collaboration opportunities with researchers in the neurosciences. Work to ensure diversity of both researchers and research participants in studies.
- Build strategic partnerships with a diversity of other service providers.
- Be prepared to respond to (and educate) consumers and their families about pharmaceuticals, genetic testing, and imaging centers they may have heard about through promotions and advertising.
- Facilitate the full participation of consumers and advocates in any decision-making related to the integration of neuroscience advances with behavioral health care.
- Seek flexible, unrestricted funding to underwrite the pursuit of new and innovative behavioral health treatments.

American College of Mental Health Administration (ACHMA) Workgroup (2003) "Financing Results and Value in Behavioral Health Services," *Administration and Policy in Mental Health*, 31(2): 85-110

Beck AT. The current state of cognitive therapy: a 40-year retrospective. Archives of General Psychiatry. 2005 Sep;62(9):953-9.

Bernal GM, Peterson DA. Neural stem cells as therapeutic agents for age-related brain repair. Aging Cell. 2004 Dec;3(6):345-51

Bremner JD. Long-term effects of childhood abuse on brain and neurobiology. Child and Adolescent Psychiatric Clinics of North America. 2003 Apr;12(2):271-92.

Bremner JD. Brain imaging in anxiety disorders Expert Review of Neurotherapeutics, Mar 2004, Vol. 4, No. 2, Pages 275-284

Bremner JD, Mletzko T, Welter S, Quinn S, Williams C, Brummer M, Siddiq S, Reed L, Heim CM, Nemeroff CB. Effects of phenytoin on memory, cognition and brain structure in post-traumatic stress disorder: a pilot study. Journal of Psychopharmacology. 2005 Mar;19(2):159-65.

Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. Science. 2002 Aug 2;297:851-4.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003 Jul 18;301(5631):386-9.

Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. American Journal of Psychiatry. 2004 Mar;161(3):515-24.

Corrigan PW and AC Watson (2003) "Factors That Explain How Policy Makers Distribute Resources to Mental Health Services," *Psychiatric Services,* 54:501-507.

Damsa C, Maris S, Pull CB New fields of research in posttraumatic stress disorder: brain imaging. Current Opinion in Psychiatry. 18(1):55-64, January 2005.

Daskalakis ZJ. Repetitive transcranial magnetic stimulation for the treatment of depression: to stimulate or not to stimulate? Journal of Psychiatry and Neuroscience. 2005 Mar;30(2):81-2.

Eckenrode J, Zielinski D, Smith E, Marcynyszyn LA, Henderson CR Jr, Kitzman H, Cole R, Powers J, Olds DL. Child maltreatment and the early onset of problem behaviors: can a program of nurse home visitation break the link? Development and Psychopathology. 2001 Fall;13(4):873-90.

Freyd JJ, Putnam FW, Lyon TD, Becker-Blease KA, Cheit RE, Siegel NB, Pezdek K. Psychology. The science of child sexual abuse. Science. 2005 Apr 22;308(5721):501.

Gazzaniga MS, Ivry RB, Mangun GR. *Cognitive Neuroscience: the Biology of the Mind*. 2nd ed. New York : Norton, 2002.

Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, Mayberg H. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Archives of General Psychiatry. 2004 Jan;61(1):34-41.

Goodman M, New A, Siever L. Trauma, genes, and the neurobiology of personality disorders. Annal of the New York Academy of Science. 2004 Dec;1032:104-16

Greenfield SA. Biotechnology, the brain and the future. Trends in Biotechnology. 2005 Jan;23(1):34-41

Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. Science. 2002 Jul 19;297(5580):400-3.

Hariri AR, Weinberger DR. Functional neuroimaging of genetic variation in serotonergic neurotransmission. Genes, Brain and Behavior. 2003 Dec;2(6):341-9

Hirshberg LM, Chiu S, Frazier JA. Emerging brain-based interventions for children and adolescents: overview and clinical perspective. Child and Adolescent Psychiatric Clinics of North America 2005 Jan;14(1):1-19

Hyde PS, K Falls, JA Morris, Jr., and SK Schoenwald, *Turning Knowledge Into Practice: A Manual for Behavioral Health Administrators and Practitioners About Understanding and Implementing Evidence-Based Practices*, The Technical Assistance Collaborative, Inc. (TAC) and the American College of Mental Health Administration (ACMHA), undated.

Institute of Medicine (1998) *Bridging The Gap Between Practice And Research: Forging Partnerships with Community-Based Drug and Alcohol Treatment,* Committee on Community-Based Drug Treatment , S Lamb, MR Greenlick, and D McCarty (eds.), Division of Neuroscience and Behavioral Health, Washington, DC: National Academy Press.

Jaffee SR, Caspi A, Moffitt TE, Dodge KA, Rutter M, Taylor A, Tully LA. Nature X nurture: genetic vulnerabilities interact with physical maltreatment to promote conduct problems. Development and Psychopathology 2005 Winter;17(1):67-84.

Kandel ER (1999) "Biology and the Future of Psychoanalysis: A New Intellectual Framework for Psychiatry Revisited," *American Journal of Psychiatry*, 156:4.

Kennedy SH, Evans KR, Kruger S, Mayberg HS, Meyer JH, McCann S, Arifuzzman AI, Houle S, Vaccarino FJ. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. The American Journal of Psychiatry. 2001 Jun;158(6):899-905.

Kelsoe JR. Genomics and the Human Genome Project: implications for psychiatry. International Review of Psychiatry. 2004 Nov;16(4):294-300.

Kim-Cohen J, Moffitt TE, Caspi A, Taylor A. Genetic and environmental processes in young children's resilience and vulnerability to socioeconomic deprivation. Child Development. 2004 May-Jun;75(3):651-68.

Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, Brockmoller J. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Molecular Psychiatry. 2004 May;9(5):442-73.

Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. Journal of Affective Disorders. 2005 Sep;88(1):79-86

Martin JB (2002) "The Integration of Neurology, Psychiatry, and Neuroscience in the 21st Century," *American Journal of Psychiatry*, 159:5.

Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. British Medical Bulletin 2003;65:193-207

Mayberg HS. Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging Clinics of North America. 2003 Nov;13(4):805-15

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. Neuron. 2005 Mar 3;45(5):651-60.

McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clinical Neurophysiology. 2004 Jun;115(6):1239-48

National Research Council and Institute of Medicine (2000) *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Committee on Integrating the Science of Early Childhood Development, JP Shonkoff and DA Phillips (eds.), Board on Children, Youth, and Families, Commission on Behavioral and Social Sciences and Education. Washington, D.C.: National Academy Press.

Nnadi CU, Goldberg JF, Malhotra AK. Genetics and psychopharmacology: prospects for individualized treatment. Essential Psychopharmacology. 2005;6(4):193-208

Olds DL, Kitzman H, Cole R, Robinson J, Sidora K, Luckey DW, Henderson CR Jr, Hanks C, Bondy J, Holmberg J. Effects of nurse home-visiting on maternal life course and child development: age 6 follow-up results of a randomized trial. Pediatrics. 2004 Dec;114(6):1550-9.

Paus T. Mapping brain maturation and cognitive development during adolescence. Trends in Cognitive Sciences. 2005 Feb;9(2):60-8

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nature Neuroscience. 2005 Jun; 8(6):828-34.

Purves D, Augustine GJ, Fitzpatrick D, Katz LC, Lamantia A-S, McNamara, Williams SM. Dale Purves. *Neuroscience*, Second Edition, Sunderland, Mass.: Sinauer 2001. Copyright © 2001 by Sinauer Associates, Inc.

Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, Hodges L, Davis M. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Archives of General Psychiatry. 2004 Nov;61 (11):1136-44.

Segman RH, Shefi N, Goltser-Dubner T, Friedman N, Kaminski N, Shalev, A Y. Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors. Molecular Psychiatry 2005 10:500-513

Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, Rafi-Tari S. Limbic-frontal circuitry in major depression: a path modeling metanalysis. NeuroImage. 2004 May; 22(1):409-18.

Serretti A, Artioli P, Quartesan R. Pharmacogenetics in the treatment of depression: pharmacodynamic studies. Pharmacogenetic and Genomics. 2005 Feb;15(2):61-

Sterzer P, Stadler C, Krebs A, Kleinschmidt A, Poustka F. Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. Biological Psychiatry. 2005 Jan 1;57(1):7-15.

Strome EM, Clark CM, Zis AP, Doudet DJ. Electroconvulsive shock decreases binding to 5-HT2 receptors in nonhuman primates: an in vivo positron emission tomography study with [18F]. Biological Psychiatry. 2005 May 1;57(9):1004-10.

U.S. Department of Health and Human Services (1999) *Mental Health: A Report of the Surgeon General*. Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health.

Varley CK, Smith CJ. Anxiety disorders in the child and teen. Pediatric Clinics of North America. 2003 Oct;50(5):1107-38.

Weber DA, Reynolds CR. Clinical perspectives on neurobiological effects of psychological trauma. Neuropsychology Review. 2004 Jun;14(2):115-29

Wong ML, Licinio J. From monoamines to genomic targets: a paradigm shift for drug discovery in depression. Nature Reviews. Drug Discovery.. 2004 Feb;3(2):136-51.

Yudofsky SC and RE Hales (2002) “Neuropsychiatry and the Future of Psychiatry and Neurology,” *American Journal of Psychiatry*, 159:8.