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Functional Magnetic Resonance Imaging (fMRI): An Invaluable Tool in Translational Neuroscience

Lori A. Whitten

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About the Author

Lori A. Whitten, PhD, is a science writer in the Knowledge Translation and Strategic Communication group in RTI International's Social, Statistical, and Environmental Sciences unit.

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RTI International
3040 Cornwallis Road
PO Box 12194
Research Triangle Park, NC
27709-2194 USA

Tel: +1.919.541.6000
Fax: +1.919.541.5985
E-mail: rtipress@rti.org
Web site: www.rti.org

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Functional Magnetic Resonance Imaging (fMRI): An Invaluable Tool in Translational Neuroscience

Lori A. Whitten

Abstract

The sophisticated methods of neuroscience—including molecular genetics, structural and functional neuroimaging, animal models, and experimental tasks that approximate real-world behaviors in human research—have yielded important insights about typical functioning and neurobehavioral disorders. Translational neuroscience endeavors to use this knowledge to improve the human condition by developing and improving interventions for these disorders. This paper reviews the literature on the contribution of functional magnetic resonance imaging (fMRI) and two related techniques, resting-state fMRI (rs-fMRI) and real-time fMRI (rt-fMRI), to the diagnosis and treatment of behavioral problems and psychiatric disorders. It also explains how incorporating neuroscience principles and techniques into research on the prevention of substance misuse and antisocial behavior may spur advances and innovations in this important area. This article argues that fMRI's potential contribution to these prevention efforts has yet to be fully realized, explores new ways in which the technique could be adapted to that end, highlights some of the work by researchers in the vanguard of this effort, and notes limitations of fMRI and ethical concerns the technique raises.

Contents

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Neuroimaging: A Major Driver of Neuroscience Research

Introduction

What is the final frontier of human exploration? Some, particularly neuroscientists, might answer that it is the human brain—"inner space" rather than outer space. During the 40 years since men walked on the moon, scientists have accumulated a tremendous wealth of knowledge about the brain, its functions, its relationship with behavior, and its underlying role in neurological and psychiatric diseases. Researchers trained in many different disciplines—including physiology, psychology, pharmacology, molecular biology, psychiatry, and neurology—work in neuroscience through a common passion to determine how the brain and nervous system work. No function or behavior appears too complex for neuroscience to tackle—from how children learn language (Kuhl, 2010) to the memory systems that preserve our experiences and knowledge (Squire, 2009)—and advances continue at a breathtaking pace.

As in all areas of biomedical research, a crucial challenge for neuroscientists is to translate the knowledge derived from scientific inquiry into practical tools or programs that improve people's lives. Translational neuroscientists strive to develop interventions for neurological and psychiatric disorders based on the latest brain and behavior research. By understanding how brain structure and function are influenced by genes, environmental factors, and their interactions, translational neuroscientists strive to alleviate the individual and societal impact of neurobehavioral disorders.

A great deal of translational neuroscience resources and efforts are dedicated to developing new pharmacotherapies to treat debilitating neurological and psychiatric disorders (e.g., dementia, neurodegenerative diseases, autism, schizophrenia, and depression). Other neuroscientists aim to translate research on brain and behavior into non-pharmacological treatments for psychiatric and neurobehavioral disorders (e.g., behavioral or cognitive therapies). Increasingly, biological factors and their reciprocal interaction with the environment are incorporated into work on prevention and intervention for a wide range of behavioral problems (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008; Cicchetti & Gunnar, 2008; van Goozen & Fairchild, 2008; Blair & Diamond, 2008; Fishbein & Tarter, 2009). Such work is based on the well-established neuroscience principle of brain plasticity—that is, the brain can change with experience and environmental influences.

Functional neuroimaging techniques—various types of scans that visualize brain activity—offer a powerful set of tools for observing experience-related changes. With functional neuroimaging, researchers can look at the brain's response to a particular input, such as a cognitive stimulus, a contextual setting or, in the clinical realm, a change in response to an intervention. For example, functional neuroimaging has examined the neural impact of peer observation on teens' risky decisions and accidents during simulated driving (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011) and of a regimen of cognitive-behavioral therapy for depression (Fu et al., 2008).

Findings from functional neuroimaging studies have great potential to contribute to the diagnosis, treatment, and prevention of behavioral problems and psychiatric disorders. The prevention field, however, has underutilized this knowledge. Researchers can help overcome this research-to-practice gap by translating knowledge from neuroscience to the science and practice of prevention. Brain science can help generate solutions and provide a foundation for a non-political, non-rhetoric-based dialog on these problems. To illustrate this, a brief description is provided on widely used techniques in functional magnetic resonance imaging (fMRI)—including resting-state fMRI (rs-fMRI) and real-time fMRI (rt-fMRI)—and how they are contributing to translational efforts in the treatment of neurobehavioral problems. The potential contributions of fMRI to prevention of neurobehavioral problems are then summarized. To highlight the potential of this technology in prevention research, the use of fMRI by RTI's Transdisciplinary Science and Translational Prevention Program, which focuses on substance misuse and related problems (e.g., aggression,

violence), is reviewed in this paper. Finally, fMRI's limitations and ethical issues regarding its use are discussed in the context of neuroimaging in research on neurobehavioral disorders.

A Brain With a View: Functional Neuroimaging

Functional neuroimaging includes a variety of techniques that examine how the brain is working—typically, to relate a change in activity in a particular region with specific task performances, experiences, or behaviors. Some methods record electrical currents or magnetic fields as a measure of activity in the brain areas just underneath the skull. Other techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), examine changes in glucose utilization or blood flow, from which researchers infer neural activity (Raichle & Mintun, 2006).

The fMRI technique, which emerged in the early 1990s, offered significant advances over other methods of studying brain function. For example, the widely available scanning technique visualizes activity in all areas of the brain, not just those close to the surface. Unlike PET, it does not rely on radiation or a radiolabeled tracer. Without requiring any injection, it measures altered oxygenation and deoxygenation of hemoglobin as brain blood flow shifts to activated regions, a process that takes from 1 to 5 seconds. An increased local ratio of oxyhemoglobin to deoxyhemoglobin is a marker of activity, called blood-oxygen-level-dependent (BOLD), and fMRI scanners record images of this signal over time (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Heeger & Ress, 2002). By applying high-powered computing and statistical analyses, researchers use the BOLD signal to infer changes in neuronal activity with high spatial resolution in a particular brain region (Glover, 2011).

What accounts for the dominance of the fMRI technique in research to understand the relationship between mind and body? Both the technical advantages mentioned above and the successful blending of brain scanning with relevant behavioral paradigms play important roles (Raichle, 2009a). The development of stereotaxic brain atlases for standardization, the capability to average multiple brain scans, and the development of powerful statistical analyses have helped enable fMRI to produce physiological measures relevant to behavior and mental processes.

Early in its development, fMRI research was strengthened by the involvement of behavioral scientists—particularly cognitive psychologists familiar with tasks that tapped into mental states (e.g., discriminating stimuli, recognition memory, and verbal processing). The field was thus founded on established experimental paradigms. These behavioral scientists were also familiar with techniques to control for practice, fluctuating attention, and other important factors. The technical advantages of fMRI and well-established behavioral tasks provide researchers with a unique tool to visualize what is happening in the brain as participants experience and respond to a wide range of stimuli or tasks.

Event-Related (Task-Based) fMRI

Scans taken while subjects are engaged in a task can enable researchers to link the activity of neural structures with a particular function, experience, or behavior. Building on behavioral studies, psychometrics, and other fields—and often working in interdisciplinary teams—researchers have been creative in designing fMRI tasks and protocols that bear on real-world thoughts and behaviors (Spiers & Maguire, 2007). The imaging technique has provided new information about uniquely human emotions (Takahashi et al., 2009) and has had practical implications regarding typical cognitive function (Houdé, Rossi, Lubin, & Joliot, 2010; Arsalidou & Taylor, 2011; Kim, 2011) and responses to people and social experiences (Dosch, Loenneker, Bucher, Martin, & Klaver, 2010; Swain, 2008; Chein et al., 2011; Sebastian et al., 2011).

Resting-State (rs-fMRI)

More recently, the neuroimaging field has recognized that the brain not only responds to events but is constantly active—consuming most of its energy at rest rather than during goal-directed tasks (Raichle, 2010). Communication between interconnected structures is continuous, although individual circuits

may be more or less active at various times. Marcus Raichle laid the evidentiary groundwork for rs-fMRI. He showed that when individuals appear to be doing nothing—as in, for example, the control condition of a task-based fMRI experiment in which participants stare at a mark in the center of a screen—interconnected brain circuits remain active in synchronized patterns, which he named the default-mode network (Raichle et al., 2001; Raichle & Snyder, 2007). This constant communication reflects many highly coherent functional networks and reveals the brain's functional organization (Raichle, 2009b; Deco, Jirsa, & McIntosh, 2011).

Research on the default-mode network has yielded insights on brain development. For example, de Bie and colleagues (2012) found that children aged 5 to 8 have sensory and motor networks with robust, adult-like functional organization but demonstrate immature characteristics in circuits related to higher-order cognitive functions. Similarly, Power and colleagues (2010) noted that the organizational characteristics of brain networks are present during childhood but undergo significant refinement with maturation. Results from rs-fMRI are complementary to those from structural neuroimaging—techniques that visualize the brain's structures and the fiber tract connections between them (Damoiseaux & Greicius, 2009)—and critical in advancing the understanding of neural network development (Supekar et al., 2010).

Studies that apply rs-fMRI to healthy adult volunteers are helping researchers test hypotheses about particular functional networks (Taylor, Seminowicz, & Davis, 2009), sub-networks (Vogel, Power, Petersen, & Schlaggar, 2010), and the impact of specific activities (e.g., mindfulness meditation) on the brain's intrinsic connectivity (Kilpatrick et al., 2011). Collaborative efforts to pool rs-fMRI brain scans into publicly accessible databases help overcome the problem of small-sample studies. Two ongoing efforts—the grassroots 1,000 Functional Connectomes Project (Biswal et al., 2010; http://www.nih.gov/news/health/jul2009/ninds-15.htm) and a government-initiated effort, the Human Connectome Project, which also includes genetic, behavioral, and structural imaging data, will further increase knowledge about the brain's intrinsic connections (http://www.humanconnectomeproject.org/).

Real-Time (rt-fMRI)

Instantaneous analyses of fMRI data yield a real-time view of neural responses. Combining such technology with well-established neurofeedback techniques offers a powerful tool, called real-time fMRI, to teach people to control their brain activity (deCharms, 2007). Proponents of rt-fMRI argue that it can increase a person's awareness of brain function, permitting him or her to change their thoughts or emotions (deCharms, 2008). (Preliminary evidence from rt-fMRI studies among healthy volunteers is described in the next section). This tool for teaching people to control activity in a specific brain region has therapeutic potential for pain modulation (deCharms et al., 2005) and perhaps as a component of treatment for behavioral and emotional problems (deCharms, 2008; Linden & Fallgatter, 2009).

Neuroimaging: A New Driver of Translational Neuroscience

Since the 1970s, when structural neuroimaging demonstrated that people with schizophrenia have enlarged cerebral ventricles, some psychiatrists have encouraged incorporation of such techniques into their field (Linden, 2012). With the advent of biological psychiatry, functional neuroimaging research on behavioral problems exploded. Although functional neuroimaging has not yielded clinically relevant biomarkers for mental disorders, current studies lay the groundwork for its eventual use in the diagnosis, treatment, and prevention of behavioral problems and psychiatric disorders (Linden, 2012; Bigos & Weinberger, 2010; Loth, Carvalho, & Schumann 2011; Hasler & Northoff, 2011). Powerful functional neuroimaging tools are helping researchers understand the origins of mental disorders and the mechanisms of effective treatments—both pharmacological and behavioral (Linden, 2012; Carter et al., 2011).

fMRI as a Tool in the Diagnosis and Treatment of Neurobehavioral Problems

Of all the neuroimaging techniques, fMRI is thought to have the greatest potential to change psychiatric practice. When combined with other techniques, particularly structural neuroimaging, fMRI can help

identify the pathophysiology underlying psychiatric disorders (Linden & Fallgatter, 2009). Much of this research compared brain activity patterns of patient populations with those of healthy controls.

Highly prevalent disorders, including depression, anxiety, and attention-deficit hyperactivity (Rigucci, Serafini, Pompili, Kotzalidis, & Tatarelli, 2010; Robinson & Shergill, 2011; Casey, Ruberry, et al., 2011; Wilens & Spencer, 2010) are being studied in this manner. Pediatric psychiatry increasingly uses fMRI to uncover the development of disorders (Pavuluri & Sweeney, 2008; Hulvershorn, Cullen, & Anand, 2011).

Descriptions of the pathology underlying neurobehavioral disorders based on structural and functional neuroimaging provide vital, objective data to improve psychiatric diagnoses. fMRI has the potential to provide biological indicators of disease, or biomarkers—critical for diagnosis in other fields of medicine—to psychiatry, although a great deal of work remains for this potential to be fully realized (Malhi & Lagopoulos, 2008; Linden & Fallgatter, 2009). Such neural markers would not replace symptom-based diagnosis and behavioral assessments in psychiatry, but they would augment clinical decision making (Linden & Fallgatter, 2009).

Task-Based fMRI

Using task-based fMRI, researchers have identified specific differences in brain response between healthy and psychiatric populations. These differences may serve as neural markers to identify underlying pathology and, ultimately, aid diagnosis. The process of identifying the emotion represented on others' faces, for example, not only guides how individuals interact with others but also may serve to gauge the presence of a mood disorder. To map areas of the brain involved in this important function, researchers have applied meta-analysis to many functional neuroimaging studies investigating how healthy volunteers process the emotions faces display—for example, identifying responses to happy, fearful, and sad faces (Fusar-Poli et al., 2009; Sabatinelli et al., 2011). Such mapping of the typical neural response is critical for interpreting aberrant brain activity observed among patient populations.

For example, depressed people who have not undergone treatment show heightened responses in the amygdala (a brain structure involved in fear and anxiety) in response to emotional facial expressions (Peluso et al., 2009; Fu et al., 2008; Victor, Furey, Fromm, Ohman, & Drevets, 2010), although results are not always consistent (Townsend et al., 2010). With confirmatory research, such neural responses may ultimately comprise an fMRI diagnostic for depression. Current diagnostic methods are characterized by a great deal of overlap within disorders, and fMRI may contribute to better specification of disease subtypes (Linden, 2012). It may be the case that subtypes of disorders are characterized by different patterns of brain activity despite similar categorization according to behavioral diagnostics.

In addition to their potential to improve diagnostic classification, neural markers may help predict and track therapeutic responses. Various studies have found that stronger pre-treatment activity in some brain areas (particularly the anterior cingulate cortex) are good predictors of clinical response to cognitive-behavioral therapy (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fu et al., 2008) and treatment for depression (Victor et al., 2010). Such predictors may help clinicians tailor behavioral treatment or determine which patients are likely to require particular combinations of therapies. Investigators are studying many other task-based brain activity patterns that may serve as neural signatures to predict treatment response among people with depression (Siegle, Carter, & Thase, 2006; Masten et al., 2011; Forbes et al., 2010; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011) and other disorders (Bryant et al., 2008).

By directly assessing improvement in brain functions with particular relevance to the disorder, psychiatrists may be able to use task-based fMRI to track progress in treatment. Indeed, such functional neuroimaging has shown that behavioral treatments change brain activity (Beauregard, 2009; Porto et al., 2009; Linden, 2006). Task-based fMRI also has revealed the neural impact of medications. For example, Rubia and colleagues (2011) found that boys with attention-deficit hyperactivity disorder (ADHD) showed

diminished activity in brain regions involved in monitoring one's own performance of a task. A single dose of methylphenidate normalized this activity.

Resting-State fMRI

Once researchers realized that rs-fMRI can highlight functionally linked brain regions, they began to explore the concept that resting-state connectivity might differ between psychiatric and healthy populations. As with specific neural markers revealed by task-based fMRI, scans for functional connectivity also have the potential to become a biomarker of disease (Greicius, 2008), and researchers have shown dysfunction in the default-mode network in several psychiatric and neurological disorders (for reviews see Broyd et al., 2009; Zhang & Raichle, 2010).

Among people with depression, for example, brain networks related to cognitive control, emotion, and the default-mode showed a greater functional connectivity to the bilateral dorsal medial prefrontal cortex region—an area the researchers call the dorsal nexus (Sheline, Price, Yan, & Mintun, 2010)—than in people who were not depressed. Heightened connectivity in this area, newly linked with depression, may explain how the cognitive and affective symptoms of the disorder co-occur and feed off each other.

Similarly, functional connectivity studies have identified some important neural network communication deficits that researchers may eventually translate into diagnostic tools and treatments for neurological disorders (Hampel, Prvulovic, Teipel, & Bokde, 2011; Yang et al., 2011). In people with mild cognitive impairment, for example, connectivity between the hippocampus—a brain structure central to memory—and cortical areas of the memory network was diminished and correlated with cognitive deterioration over a 3-year period (Wang et al., 2011). The initial rs-fMRI scan revealed some compensatory increased connectivity between the hippocampus and other areas of the brain, but some of this connectivity was lost as the disease progressed (Wang et al., 2011).

Combining rs-fMRI and structural MRI, these researchers found that disrupted connectivity in the dorsolateral prefrontal cortex, which is part of multiple neural circuits, was correlated with several measures of cognitive impairment. Moreover, patterns of neural deterioration indicated by structural MRI were generally consistent with rs-fMRI results (Liang, Wang, Yang, Jia, & Li, 2011). Such results highlight how rs-fMRI is providing knowledge about the etiology of brain disorders that will be useful to future diagnostic and treatment efforts.

As with task-based fMRI, rs-fMRI has the potential to gauge therapeutic response and predict treatment outcome. Goveas and colleagues (2011) found that patients with mild Alzheimer's disease showed reduced connectivity in hippocampal neural networks compared with healthy age-matched controls. After 3 months of treatment with the medication donepezil, cognitive improvement correlated with enhanced network connectivity in specific regions—suggesting that rs-fMRI results may predict response to this treatment.

A preliminary study by Negishi and colleagues (2011) found that epilepsy patients who had recurrent seizures were more likely to have functional connectivity distributed across the two hemispheres of the brain. The authors suggested that preoperative rs-fMRI scans, with particular attention to laterality of brain activity, might add to well-established predictors of surgery outcome.

The rs-fMRI technique is helping researchers better understand other complex behaviors, laying groundwork for early identification of impairments and intervention-related improvements. For example, Koyama and colleagues (2011) used rs-fMRI to overcome a long-standing challenge in reading research. Because rs-fMRI requires no tasks, it was unnecessary to develop equivalent tasks across different age groups. The rs-fMRI study demonstrated that reading competency, both among children and adults, is associated with stronger resting-state functional connectivity among motor regions and language and speech regions. It was also associated with a shift from the default network to enhanced activity in brain areas that process visual representations of words and language sounds (Koyama et al., 2011).

Real-Time Neurofeedback

Currently, most rt-fMRI neurofeedback studies involve small samples of healthy volunteers. Investigators identify a local neural area of interest related to a particular function (e.g., reacting to positive and negative emotional stimuli) and provide a means for subjects to monitor their own brain activity in that region (for example, a thermometer image, for which "temperatures" reflect strength of the fMRI signal relative to baseline). Participants then practice controlling activity in the target area using their own strategies or one suggested by the experimenters, alternating with rest periods (Caria et al., 2012).

With a relatively brief training period (typically, under 30 minutes), and only when subjects receive feedback from the target area (rather than from a non-related comparison region), participants have controlled activity in brain regions that process pain (deCharms et al., 2005), emotion (Caria et al., 2010; Johnston et al, 2010), speech (Rota et al., 2011), and complex thoughts (McCaig et al., 2011). More important, voluntary control of local brain activity alters function and experience—reducing pain (deCharms et al., 2005), increasing negative ratings of aversive emotional stimuli (Caria et al., 2010), and improving identification of the particular emotional conveyed by tone of speech (Rota et al., 2009; Rota et al., 2011). Teaching participants to control neural responses in a localized region is also a non-invasive means to manipulate brain activity so researchers can examine the effects on behavior and perhaps draw causal inferences about function (Caria, Sitaram, & Birbaumer, 2012).

Advances in the technology, processing, and training protocols that underlie rt-fMRI neurofeedback are occurring at a rapid pace. For example, researchers recently reported a new technique that reduces signal noise and enhances regional specificity, enabling them to create movies that reveal brain dynamics (Magland, Tjoa, & Childress, 2011). Such advances significantly improve the outlook for translational applications—including performance enhancement, rehabilitation, and therapy (Laconte, 2011).

Ongoing research in rt-fMRI is highly relevant to translation in many areas. For example, Yoo and colleagues (2011) used real-time monitoring of the parahippocampal cortex—a brain area required to form memories of scenes—to study learning and memory. Although in the early stages, such work may lead to ways to identify when individuals are most prepared to learn, based on brain responses. Similarly, other work using this technique is directed at controlling motor cortex activity, with the aim of improving rehabilitation regimens after brain injury (Berman, Horovitz, Venkataraman, & Hallett, 2011).

Some rt-fMRI studies have examined participants' ability to control emotion areas in the brain, and this work has particular relevance for therapeutic applications. For example, Hamilton and colleagues (2011) focused on the subgenual anterior cingulate cortex, which is linked with emotion generation; hyperactivity in this structure is implicated in depression and other affective disorders. With rt-fMRI neurofeedback training, healthy women learned to dampen activity in this structure (Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011). Although these results are preliminary and the study did not involve a clinical population, the findings raise the intriguing possibility that neurofeedback could contribute to behavioral or cognitive therapies for depression.

Other studies have demonstrated that subjects receiving rt-fMRI neurofeedback can voluntarily regulate the insula and amygdala, other brain regions that are important to emotion (Johnston, Boehm, Healy, Goebel, & Linden, 2010; Caria et al., 2007). In a major development in rt-fMRI neurofeedback research, McCaig and colleagues (2011) recently demonstrated that healthy volunteers can control activity of the rostrolateral area of the anterior prefrontal cortex—a region linked with awareness of one's own behavior. The team found that subjects could learn to control this area, which is critical to complex functions and seems to monitor and coordinate thoughts. The demonstration that rt-fMRI neurofeedback can help people control areas that regulate higher-order functions suggests the technique's potential in cognitive remediation and other translational applications.

Importance of Integrating fMRI With Other Approaches

A major strength of neuroscience is its interdisciplinary nature and its wide range of experimental methods. Translating neuroscience research results into practical solutions requires integration of research approaches. The combination of fMRI findings with those based on other techniques is particularly helpful in translational efforts.

Structural Neuroimaging

As suggested earlier, structural neuroimaging with MRI is helping to map the extensive system of neural networks—called the human connectome—in the healthy brain, the developing brain, the aging brain, and the diseased brain (Sporns, 2011). Diffusion tensor imaging (DTI) techniques outline the neural fiber pathways connecting different regions of the brain and can detect how these change with maturation, experience, or disease (Johansen-Berg & Rushworth, 2009; Thomason & Thompson, 2011).

Positron Emission Tomography (PET) Imaging

Hariri (2009) points out that fMRI research provides complementary information to PET scans, which use radiolabeled tracers to visualize the activity of specific neurotransmitter systems. Examples of this synergy can be found in studies on impulsivity and the ability to delay of gratification, traits that vary among individuals from an early age. Variation within the normal range correlates with positive adult outcomes—for instance, the ability to delay gratification at age 4 is associated with greater competence as an adult (Mischel, Shoda, & Rodriguez, 1989; Mischel et al., 2011). In the extreme, impulsivity and problems delaying gratification increase vulnerability to addictive disorders (Bickel et al., 2007). Basic neuroscience research indicates that such individual variation, which is influenced by both genetics and neurobiology, strongly relates to part of the brain's reward pathway called the ventral striatum (VS). fMRI studies find that strength of activation in the VS during reward-related tasks correlates with these characteristics. PET scanning studies have consistently demonstrated that the neurotransmitter dopamine modulates such neural responses.

Imaging Genetics

The combination of two powerful tools—genetics and neuroimaging—offers a significant advancement in translational research. In this approach, researchers use fMRI (or some other type of neuroimaging such as PET) to compare the neural activity of participants with different genotypes. They usually focus on a gene known to encode a specific neurochemical, transporter, enzyme, or receptor (or receptor subunit) in the brain that prior research has linked to a behavior. Imaging genetics has yielded insights into how genes may influence different neurobiological responses, particularly those that bear on neurobehavioral disorders, including aggression and depression. Such studies add value by pointing to specific mechanisms whereby genes influence brain function to affect behavior; behavior, in turn, then alters neurobiology and gene expression (Bigos & Weinberger, 2010; Loth, Carvalho, & Schumann, 2011).

Genetic studies combined with the neuroimaging studies mentioned above have identified genetic variants associated with individual differences in impulsivity and delay of gratification (Hariri, 2009). Applying those tools to a different problem, Eisenberger, Way, and colleagues (2007) found that persons with a genetic variant (the low-expression allele for the monoamine oxidase-A gene [MAO-A]) previously linked with aggression both reported more aggressive characteristics and responded to social exclusion with an exceptionally intense neural response in the dorsal anterior cingulate cortex, an area of the brain that processes emotional experiences.

In other imaging research, investigators found that heightened amygdala response during the processing of negative emotional stimuli was exaggerated in healthy children who carry a genetic variant linked with depression—the short allele for the serotonin transporter gene (5-HTTLPR) (Fortier et al., 2010). Interestingly, Schardt and colleagues (2010) found that women who carry that allele could reduce amygdala reactivity to pictures that evoked fear or disgust through purposefully detaching themselves from these emotions—a finding that highlights the malleability of neural responses and power of

immediate experience on the brain. Although a great deal of imaging genetics focuses on brain structures, researchers are now beginning to examine how gene expression patterns influence the functional connectivity of neural networks (Thomason, Yoo, Glover, & Gotlib, 2009).

Psychophysiological Monitoring

The interaction between brain and body has long been a subject of inquiry—first in philosophy, then in psychology, and now in neuroscience. The brain-body connection and its strong relationship with emotion and health makes this an important issue in translational neuroscience. Just as the brain influences what happens in the rest of the body, bodily responses can convey information about internal states back to the brain. Therefore, a powerful approach in translational neuroscience combines fMRI with the measurement of bodily responses, for example, skin conductance, heart rate, and levels of the stress hormone cortisol in saliva. Some researchers have noted that individuals who are emotionally resilient are able to reduce stress-related physiological responses through neural regulation and that others can improve this ability through training in mindfulness meditation (Davidson, 2004).

In the study of emotional information processing, psychophysiological monitoring during affective or stressful laboratory tasks offers complementary findings to fMRI (Critchley, 2009). This combination has shed light on the biological influences of health-promoting environmental variables, such as social support and psychosocial resources. For example, Eisenberger, Taylor, and colleagues (2007) found that healthy volunteers who regularly interacted with supportive others had diminished activity in emotional areas of the brain in response to a stressful social exclusion task, and the reduced neural activity was responsible for attenuated cortisol levels.

Similarly, Taylor and colleagues (2008) found that individuals with psychosocial resources—including self-esteem, purpose in life, a sense of mastery, and optimism—responded to threat with smaller increases in amygdala activity than those with fewer resources. Lower amygdala activity resulted in lower cortisol levels among these individuals. Researchers are now combining rs-fMRI with psychophysiological monitoring to examine how stress reactivity, for example, alters functionally connected brain networks (Thomason, Hamilton, & Gotlib, 2011).

By concomitantly using fMRI and other techniques, researchers are obtaining a fuller picture of the neurobiology of complex behaviors. Functional neuroimaging helps describe neurobiological mechanisms underlying individual differences in brain circuit function, neurochemical signaling pathways, and behavioral traits. The findings provide valuable information about neuropsychiatric diseases and neurobehavioral disorders. Through the identification of neural markers of disorder and descriptions of how they interact with environmental factors, this research will guide the development of more effective and individually tailored treatments and preventive interventions.

Translational Neuroscience and Prevention: Substance Misuse and Antisocial Behavior

Most of the translational interest in neuroscience and functional neuroimaging focuses on diagnosis and treatment of neurobehavioral disorders rather than prevention and intervention with individuals at risk. The current prevention and intervention paradigm for neurobehavioral problems generally acknowledges the importance of both biological and environmental factors—and their interaction. Despite this recognition, most prevention and intervention efforts to address substance misuse and antisocial behavior remain focused on environmental factors and have not incorporated the rich research findings from neuroscience.

Decades of neuroscience research indicates that biology plays an important role in the etiology of psychiatric and neurobehavioral disorders. As discussed below, environmental factors often exert an impact on biology—for example, by shaping neural circuits during development. Therefore, researchers have argued that prevention efforts must incorporate neurobiological methods (Beauchaine et al., 2008; Fishbein & Tarter, 2009; Cicchetti & Gunnar, 2008; van Goozen & Fairchild, 2008; Blair & Diamond, 2008).

A critical methodological implication is that randomized trials of prevention interventions must incorporate biological measures to help identify the processes underlying vulnerability to neurobehavioral problems. From such fundamental knowledge, researchers may determine the mechanisms of behavior change and determine the extent to which neural plasticity can be promoted (Beauchaine et al., 2008; Cicchetti & Gunnar, 2008).

Periods of development characterized by significant neurobiological changes and plasticity—particularly the pre-school years and early childhood—present prime opportunities for intervention because the brain is optimally responsive to environment and experience at this time. fMRI techniques may make it possible to determine how the brain is changed by preventive interventions.

The Complex Etiology of Substance Misuse and Antisocial Behavior

Many interacting risk factors increase the likelihood of substance misuse and antisocial behavior. Genes indirectly influence behavior through their impact on the brain's structure, neurotransmitter levels, and the functioning of neural circuits (Hariri, 2009; Stiles & Jernigan, 2010). Environmental factors influence gene expression, thereby altering the pattern of protein production (e.g., neurochemicals, receptors, and enzymes) in the brain. A key line of inquiry in neuroscience is to determine how inherited and environmental factors interact over time to shape the many neural networks that underlie particular behaviors and neurobehavioral disorders (Stiles, 2011).

Of course, individual- and family-level environmental factors—including poverty, stress, maltreatment, witnessing domestic violence, neglect, parent substance abuse, and prenatal drug exposure—play a strong role in increasing the risk for substance misuse and antisocial behavior. Environmental factors can influence neurobiology by, for example, shaping the development of neural circuits and neurochemistry (Lupien, McEwen, Gunnar, & Heim, 2009; Hackman, Farah, & Meaney, 2010; Gianaros & Manuck, 2010). The cumulative effect influences neurobehavioral predispositions (e.g., attention deficit, novelty seeking) during childhood and adolescence, thereby shifting the developmental pathway toward a higher likelihood of problem behaviors.

Prenatal exposure to drugs, including alcohol, tobacco, and illicit drugs (Salisbury, Ponder, Padbury, & Lester, 2009), is a common example of a factor that significantly influences many brain circuits and increases the propensity for high-risk neurobehavioral characteristics (e.g., problems with inhibition and attention, enhanced stress reactivity). Many individuals who experience prenatal exposure to drugs also suffer early-life adversity, and Fisher and colleagues (2011) found that each of these risk factors has unique negative influences on development. Prenatal drug exposure predicted problems with difficulty controlling socially undesirable or restricted behavior during early childhood and into adolescence. These difficulties indirectly influenced problems with executive function (Fisher et al., 2011). Early adversity independently and directly predicted difficulties with executive functions—a critical set of neurocognitive abilities needed to reach goals including memory, attention, planning, and inhibiting inappropriate responses. (The importance of executive functions in risk for behavioral problems is discussed in more detail below.)

Increased risk for behavior problems results from not only biologically influenced neural characteristics but also caregiver relationships—particularly inconsistent and harsh discipline during early life, lack of warmth, and low levels of spontaneous teaching behaviors (Dodge & Pettit, 2003). Researchers are now testing how growing up with maltreatment or a violent environment may alter a person's neurotransmitter function, stress response, and brain circuits involved in learning, attention, and emotional regulation (Loman & Gunnar, 2010). There is support for the idea that such stress during childhood sensitizes individuals to subsequent stressors (Andersen & Teicher, 2009).

The physiological basis for increased sensitivity to stress may be long-lasting functional and structural neurobiological changes associated with childhood maltreatment, particularly reduced volume of the hippocampus, a brain structure involved in mood and stress regulation. When researchers statistically

controlled for trait anxiety, depression level, age, intelligence, education, or more recent stressful life events, the neurobiological characteristics observed among adults who were maltreated as children were strikingly similar to those of adults with depression and posttraumatic stress disorder (PTSD) (Dannlowski et al., 2012). fMRI indicated that the extent of maltreatment was associated with exaggerated activity of the amygdala as participants viewed threat-related faces. Moreover, structural neuroimaging revealed that individuals with greater levels of maltreatment showed less gray matter volume in the hippocampus, insula, orbitofrontal cortex, anterior cingulate gyrus, and caudate (Dannlowski et al., 2012). Some researchers propose that such neural adaptations may promote survival in a violent environment but become maladaptive in other contexts (Mead, Beauchaine, & Shannon, 2010).

Living in a community with concentrated poverty, violence, low social cohesion, lack of safety, and physical disorder also increases risk for these problems and can interact with individual-level characteristics. For example, maltreatment during childhood increases the likelihood of later problem drinking, especially when individuals have grown up in neighborhoods characterized by physical disorder and chaos (Keyes et al., 2012). Broader environmental factors shape neurobiology further and have a negative effect on individuals' neurocognitive function, capacity to respond to stress, and overall health (Lupien et al., 2009; Hackman & Farah, 2009; Hackman et al., 2010; Gianaros & Manuck, 2010). If not buffered by positive factors (e.g., protective genes, early intervention, warm caregiver relationships, and competent parenting), the interactive compounding of negative influences can result in a set of neurobehavioral characteristics that make substance misuse and antisocial behavior more likely (Dodge & Pettit, 2003; Andersen & Teicher, 2009; van Goozen & Fairchild, 2008; Eisenberg, Spinrad, & Eggum, 2010; Coccaro, Sripada, Yanowitch, & Phan, 2011; Iacono, Malone, & McGue, 2008; Rubia, 2011). The next sections describe what fMRI tells us about the major neurobehavioral characteristics associated with substance misuse and antisocial behavior, and how research in this area may inform prevention efforts.

Neurobehavioral Characteristics Associated With Later Substance Misuse and Antisocial Behavior

Experiencing multiple environmental risk factors during childhood has a cumulative neurobiological impact that increases the likelihood that an individual will experience delays in the development of executive functions, which are essential to success in life (Diamond, 2011). The neural building blocks of executive functioning begin developing early in life (Morasch & Bell, 2011) and can be detected reliably by standardized assessments as early as the preschool years (Davidson, Amso, Anderson, & Diamond, 2006; Wiebe et al., 2011). These abilities are strongly related to how well individuals perform in school, both academically and behaviorally (Lan, Legare, Ponitz, Li, & Morrison, 2011; Hughes & Ensor, 2011). Executive functions begin to emerge during adolescence but are not fully mature until at least the mid-20s (Luna, Padmanabhan, & O'Hearn, 2010).

For the purposes of this discussion, this paper will describe two closely related and often intermingled aspects of executive functions: (1) self-control, or self-regulation—the ability to delay gratification, control impulses, direct attention, and inhibit inappropriate behaviors; and (2) emotional regulation—the ability to recognize emotional arousal and the behaviors that stem from it and apply effort to express feelings appropriately or modify them to achieve a longer-term goal. Self-control is central to healthy and productive functioning throughout life (Mischel et al., 1989; Mischel et al., 2011). Self-control varies widely across individuals; such differences are evident during childhood and affect adult outcomes. A recent longitudinal study of more than 1,000 children in New Zealand found that in adults, poor physical health, substance dependence, insufficient personal finances, and criminal offenses all followed a gradient of self-control—with poor self-regulation during youth associated with worse adult prospects after other factors were taken into account (Moffitt et al., 2011). Although self-control has genetic and neural underpinnings, environmental factors can increase or diminish it—suggesting that interventions can improve this ability (Diamond, Barnett, Thomas, & Munro, 2007; Blair & Diamond, 2008).

Disruption of executive functions characterizes many mental health, social, and educational problems (Heatherton & Wagner, 2011; Blair & Diamond, 2008; Diamond, 2011). For example, impairment in developing executive functions during childhood is strongly associated with conduct disorder, which often precedes substance misuse and antisocial behavior among adults (Dodge & Pettit, 2003; Ellis, Weiss, & Lochman, 2009; Eisenberg et al., 2010; Iacono et al., 2008). During adolescence, the neurobehavioral characteristics of poor executive function, impulsivity, and problems with emotional control can manifest in extreme sensation-seeking (Castellanos-Ryan, Rubia, & Conrod, 2011) and an increased preference for immediate rewards rather than long-term benefits (Anokhin, Golosheykin, Grant, & Heath, 2011). This pattern increases the likelihood that individuals will make poor decisions—initiating smoking, drinking, experimenting with illicit drugs, early sexual behavior, and delinquent activity—that can derail healthy and productive developmental pathways (Schepis, Adinoff, & Rao, 2008; Eisenberg et al., 2010; Iacono et al., 2008; Moffitt et al., 2011; Perry et al., 2011).

Another neurobehavioral characteristic associated with risk for problem behavior is a hostile attributional style in which individuals misinterpret incidents as a threat to personal reputation and respond with aggression (Dodge, 2006). This disrupted social-information processing and the co-occurring development of a dysfunctional pattern of perceptions and interactions with others contribute to childhood conduct disorder and subsequent risk for aggressive and antisocial behavior (Dodge & Pettit, 2003; Dodge, 2006). Children at high risk for these problems are hypervigilant to threat, often misinterpret situations as hostile, respond with aggression, and show limited skills in generating competent solutions to social problems. The likelihood of having this trait is increased by life experiences—including physical abuse, harsh parenting, poverty and racism, and peer rejection—as well as biological predispositions such as impulsivity and poor executive functioning (Dodge & Pettit, 2003; Ellis et al., 2009).

Dysregulated socio-emotional processing sets up a situation in which children may be rebuked by teachers, rejected by peers, and disengaged from school. Differences among children are often exaggerated by school systems, and related problems worsened, by labeling, expectations, and self-fulfilling prophesies (Dodge & Pettit, 2003).

Interventions that address dysregulated socio-emotional processing and teach children alternative strategies have been shown to be effective at improving behavioral and academic outcomes (Powell, Lochman, & Boxmeyer, 2007). Without intervention, however, behavioral problems typically continue and worsen when individuals bond with others who are also aggressive and act out. Deviant peers and disengagement from school become particularly important during the transition from middle school to high school and may push the developmental pathway further toward adolescent delinquency and substance misuse (Dodge & Pettit, 2003; Gifford-Smith, Dodge, Dishion, & McCord, 2005; Dodge, 2006; Fishbein & Tarter, 2009).

fMRI Research on Substance Misuse and Antisocial Behavior, and Implications for Prevention

Increasingly, the neurobehavioral characteristics associated with substance misuse and antisocial disorders are viewed as rooted in dysfunctional cortico-limbic circuitry. fMRI research indicates that individuals with these problems demonstrate disrupted neural interactions between the prefrontal cortex and subcortical areas of the brain (Bechara, 2005; Sobhani & Bechara, 2011; Coccaro et al., 2011; Rubia, 2011). Executive functions depend on these circuits, that is, ones connecting the prefrontal cortex, the cingulate cortex (particularly the anterior portion), and the limbic system (Diamond, 2011). The inferior frontal gyrus area, in particular, has been linked to several types of self-control and the ability to inhibit impulses (Tabibnia et al., 2011).

The prefrontal cortex is a relatively large region of the brain, located behind the forehead, which is highly interconnected with many other parts of the brain—including various other cortical regions and areas below the cortex. Engaging the prefrontal cortex modulates the activity of limbic regions involved in emotion, motivation, and monitoring bodily states. Functioning of the prefrontal cortex underlies key

abilities related to behavioral health, including emotional regulation, delay of gratification in favor of long-term rewards, and the ability to inhibit and control behavior (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008; Benoit, Gilbert, & Burgess, 2011; Casey, Somerville et al., 2011).

The monoamine neurotransmitters—including dopamine, serotonin, and norepinephrine—are major players in the functioning of the prefrontal cortex. The prefrontal cortex and neural networks underlying executive functions are disrupted by dysfunction in these neurotransmitters (Posner & Rothbart, 2009; Robbins & Arnsten, 2009). Genes, particularly ones that encode proteins involved in monoamine transmission, and environmental factors (e.g., parenting quality) are known to shape these neural networks, providing a physical basis for the ability to regulate emotions and behavior (Posner & Rothbart, 2009; Robbins & Arnsten, 2009; Diamond, 2011).

Among substance abusers, overactive reward and impulsive subcortical systems override cognitive control input from the prefrontal cortex so that drugs have strong influence on decision making (Bechara, 2005; Diekhof, Falkai, & Gruber, 2008). The risk for substance misuse among adolescents is also thought to relate to weaker inhibitory circuits of the prefrontal cortex and overactive reward systems (Joseph, Liu, Jiang, Lynam, & Kelly, 2009; Castellanos-Ryan et al., 2011; Perry et al., 2011). Some have proposed that an imbalance of activity between the prefrontal cortex and limbic areas of the brain manifests itself in high levels of reward seeking and impulsivity, and low levels of inhibitory control (Schepis et al., 2008; Perry et al., 2011).

Although disorders characterized by aggression vary in their neurobiological profiles, fMRI research suggests that impairments in cortico-limbic circuitry play a role. Dysfunctional connections between the orbitofrontal and ventromedial areas of the prefrontal cortex and the amygdala have been observed in fMRI studies of adolescents with conduct disorder and aggression (Stadler, Poustka, & Sterzer, 2010; Crowe & Blair, 2008). The amygdala is critical for the formation of associations between stimuli and outcomes (both positive and negative) and emotional expression. The orbitofrontal cortex helps process reward and emotion, and plays an important role in decision making and inhibiting behavior. The ventromedial cortex, which is also important in decision making, is involved in encoding associations with rewards and punishments (Blair, 2008, 2010).

Disruptions in the integrated functioning of these neural circuits are thought to underlie problems involving processing of emotional stimuli and social information, and exerting cognitive control over affective responses that characterize aggression and antisocial behavior (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005; Sterzer & Stadler, 2009; Crowe & Blair, 2008; Blair, 2010). For example, individuals who display aggression that is reactive and impulsive show hyperactivity in the amygdala in response to emotionally evocative stimuli along with impaired functioning in prefrontal regions that would offset such heightened limbic activity (Blair, 2008, 2010; Rubia, 2011). In contrast, individuals who display aggression that is purposeful and goal-directed (called instrumental aggression) show decreased activity in the amygdala and orbitofrontal cortex in response to emotionally provocative stimuli or during emotional learning tasks. This latter pattern of brain activity suggests disruption in the neural circuits that guide emotional learning and decision making and may explain why these individuals respond with aggression rather than pro-social actions (Crowe & Blair, 2008; Blair, 2010).

The significant role neurobehavioral characteristics play in the risk for substance misuse and antisocial behaviors can inform preventive interventions. Neuroplasticity suggests that there are multiple opportunities to reduce these problems with available preventive interventions (Fishbein & Tarter, 2009; Dodge, 2006; Powell et al., 2007). Dodge and Pettit (2003) note that there are critical "switchpoints"—that is, developmental milestones at which intervention with individuals at risk are particularly helpful—that offer an "opportunity for re-alignment" (p. 363). If intervention does not occur during these critical times, neural connections may become so strong that associated behavioral problems may not be amenable to change (Dodge & Pettit, 2003; Dodge, 2006).

A great deal of neuroscience literature indicates that interventions to boost self-control and executive

functioning, particularly during early childhood, might reduce a wide range of educational and behavioral problems—including substance misuse and antisocial behaviors. The need for intervention is also suggested by the robust observation that early delays in executive functioning usually become larger as children grow older—that is, those who are behind early on usually do not catch up on their own (Diamond, 2011). During childhood, activities that exercise executive functions—including play, physical education, music, and art—improve these abilities and boost academic results (Diamond et al., 2007; Diamond, 2011; Diamond & Lee, 2011). Activities that strengthen the foundations of executive functions (e.g., inhibitory control, working memory, and cognitive flexibility) during early childhood help build the complex ones that emerge later in life (e.g., reasoning and problem solving).

Because external factors (e.g., poverty and stress) have a negative impact on prefrontal cortex development and executive functions, universal preventive interventions for families and children of low socioeconomic status are designed to enrich the home or school environment. Such interventions improve the early indicators of executive function and behavioral outcomes (Eckenrode et al., 2010; Kitzman et al., 2010; Olds et al., 2010; Olds et al., 2004; Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008). Researchers who advocate the promotion of self-control and other executive functions note that many children enter school without this key ability (Blair & Diamond, 2008; Diamond et al., 2007). They argue that teacher training in this important area and widespread implementation of educational programs that augment these skills would reduce behavioral problems and improve academic outcomes (Blair, 2002; Diamond, 2010). Programs designed to increase school readiness during early childhood—for example, Head Start, and an enriched version of that program that is especially designed to develop self-regulation and language skills called Head Start REDI—have demonstrated beneficial effects (Welsh, Nix, Blair, Bierman, & Nelson, 2010; Bierman, Domitrovich et al., 2008), including boosting executive function (Bierman, Nix, et al., 2008).

Efforts to improve these abilities are a major aspect of early childhood programs designed to avert or reduce the academic achievement gaps between low-income children and their better-off peers (Diamond et al., 2007). Because individuals who start out with poorer executive functions tend to show the greatest gains from early childhood programs, widespread implementation of interventions that improve self-control among low-income children could help prevent school failure (Blair & Diamond, 2008). One such intervention, called Tools of the Mind, strengthens self-regulation and other aspects of executive function and dramatically improves academic and behavioral outcomes (Diamond et al., 2007). A randomized trial of this teacher-implemented pre-school curriculum found that the intervention significantly reduced behavior problems among 3- and 4-year-olds compared with children in control classrooms (Barnett et al., 2008).

Preventive interventions implemented during the early school years increase children's awareness and control of their own behavior also improve their developmental trajectory. Programs in impoverished neighborhoods that include teacher training on managing classroom behavior increase children's social competence and emotional self-regulation and reduce conduct problems relative to those in comparison schools (Webster-Stratton, Reid, & Stoolmiller, 2008). One of the most rigorously studied interventions (the Good Behavior Game) reduced rates of drug and alcohol use disorders, regular smoking, and antisocial behaviors into young adulthood (Kellam et al., 2008). A wide variety of other interventions—particularly those that involve repeated practice and a progressively increasing challenge—also boost development of the neural networks underlying executive function and improve self-regulation during childhood (Posner & Rothbart, 2009; Diamond & Lee, 2011).

Although specific exercises do boost executive function, Diamond and Lee (2011) note that broader interventions—such as curricula designed to emphasize emotional, social, and physical development—may hold the most promise for improving all these abilities. Indeed, an evidence-based universal intervention, Promoting Alternative Thinking Strategies (PATHS) Curriculum, that promotes social and emotional skills—including inhibition of impulsive behavior, awareness and

regulation of feelings, accurate perception of the perspectives of others, correct identification of problems, and development of positive solutions and goals—improves verbal fluency and self-regulation (Riggs, Greenberg, Kusché, & Pentz, 2006). This teacher-led intervention helps children handle social tasks appropriate to their ages without aggression or other behavioral problems.

To counter adolescent risk for behavioral problems, some have suggested exercises that strengthen the inhibitory circuit between the prefrontal cortex, anterior cingulate cortex, and limbic regions (Perry et al., 2011). Studies with healthy young adults suggest that relatively short-term training in meditation improved attention, boosted mood, and decreased stress (Tang et al., 2007). Interventions that direct individuals to exert effortful control of negative emotions may also hold promise for bolstering the inhibitory circuit (Drabant, McRae, Manuck, Hariri, & Gross, 2009). Developing the ability to imagine distant outcomes and desires in detail seems to orient healthy adults toward future-minded choices (Peters & Büchel, 2010; Benoit et al., 2011), and prevention specialists might be able to apply this information to boost functioning among teens at risk for behavioral problems. Although much more research is needed in this area, a combination of behavioral research on exercises that improve inhibition and fMRI may lay the groundwork for the development and refinement of preventive interventions for adolescents.

Integrating fMRI into Prevention Research

As described previously, fMRI has great potential to improve the diagnosis and treatment of neurobehavioral disorders. Transdisciplinary teams including prevention researchers and neuroimaging specialists could engage in parallel efforts, with fMRI technology, to help prevent substance misuse and antisocial behavior. Although scientists are starting to use information on the neurobehavioral correlates of substance misuse and anti-social behavior to guide preventive interventions, such translational research is in its early stages. Perhaps infusing neuroscience will spur advancement and innovation (Fishbein, 2011).

For example, fMRI might provide valuable insights into why some individuals do not respond to some preventive interventions (such as those implemented in schools), laying the groundwork for programs that are tailored at the subgroup level (e.g., sensation seekers). Additionally, fMRI might point to the "active ingredient" in prevention programs and determine whether interventions designed to improve executive functions alter brain activity. Longitudinal studies might compare executive function and underlying neural activity in individuals who have participated in interventions that focus on developing self-control, attention, concentration, and problem solving (e.g., Tools of the Mind, and the PATHS Curriculum) with that of those in control groups.

The fMRI technique may also help improve prevention interventions and public health campaigns distributed via mass media. For example, fMRI can help elucidate the neural impact of public service announcements about substance misuse among smokers (Langleben et al., 2009). Findings from a recent neuroimaging study suggest that fMRI results may predict population responses to televised public service announcements. Among a group of heavy smokers with a strong intention to quit who viewed cessation ads, activity of the medial prefrontal cortex—but not self-reported perceptions—predicted pre-post campaign changes in the call volume activity of the advertised quit line. Although preliminary, the results raise the intriguing possibility that neural focus groups could test and improve public service announcements (Falk, Berkman, & Lieberman, 2012).

As noted previously, the rt-fMRI technique can serve as a therapeutic tool to strengthen brain activity in a particular region. Perry and colleagues (2011) suggest that this tool might be used to boost inhibitory control among youth at risk for substance misuse (those with a high degree of impulsive, sensation-seeking traits). A recent study found that people with schizophrenia can use rt-fMRI feedback training to regulate the activity of a specific brain region (the anterior insula cortex), which is associated with changes in emotion perception (Ruiz et al., 2011). This finding—the first with a patient population—supports the incorporation of rt-fMRI into therapeutic interventions.

RTI International's Transdisciplinary Science and Translational Prevention Program

In support of RTI International's mission to improve the human condition by turning knowledge into practice, the Transdisciplinary Science and Translational Prevention Program applies the latest research advances to the complex problem of drug abuse. The program integrates researchers and facilities across RTI International to conduct research in neurobiology, physiology, environmental science, and human mental and behavioral health. This transdisciplinary and translational approach allows the program to better define what factors and associated personality traits make people more susceptible to drug abuse, as well as the factors that protect against these problems (personal communication D. Fishbein, RTI International, October 26, 2010).

With this knowledge, program researchers strive to develop medical, psychosocial, and public health interventions and policies that are rooted in basic research, with the ultimate goal of promoting personalized and preventive medicine. They aim to determine the preventive interventions that work best for particular groups, why they work, and under what circumstances such measures are effective. This goal encompasses many research components—including the identification of the underlying pathophysiology of mental and behavioral disorders, mechanisms underlying intervention responsiveness, the extent to which factors associated with vulnerability are modifiable, and how interventions work. The program informs the development of novel, targeted, preventive interventions and policies regarding drug abuse and other risk behaviors.

At the Baltimore facility of RTI's Transdisciplinary Science and Translational Prevention Program, Diana Fishbein, PhD, and her colleagues are using neuroimaging techniques, neurocognitive tests, and other measures to advance these research goals. Of primary interest is the use of fMRI to measure the effect of prevention programs on the brain. In particular, the researchers are examining the effects of intervention on developmental pathways by comparing individuals who were exposed to intervention with those who were not exposed (personal communication with D. Eldreth, RTI International, July 7, 2011).

For example, they are using fMRI to determine how neural functioning, along with neurocognitive factors, moderate different behavioral responses among individuals who have participated in the PATHS Curriculum and those who have not. They hope to make a similar comparison between participants in the Good Behavior Game and those in control schools. By neuroimaging participants and controls who are now in their early 20s, the RTI team aims to document neural changes that may underlie the benefits of this intervention. The scientists also will compare individuals who are doing well behaviorally with those who are not (personal communication with D. Fishbein and D. Eldreth, RTI International, August 17, 2011). The team is also examining participants' level of neurocognitive functioning and whether those who show changes in these functions also show corresponding changes in academic and behavioral outcomes.

Based on what scientists know about the neurobiology of substance misuse and the intended impact of prevention programs to improve emotional regulation and self-control, the RTI researchers have hypothesized that areas of the brain that underlie executive functioning will show greater maturation among intervention participants. Fishbein and colleagues are focusing on the activity of neural areas known from prior research to underlie performance of the neurocognitive tasks being used by the RTI team. The long-term goal is to determine whether preventive intervention promotes cognitive and emotional regulation of neural processes and, if so, whether these developments occur in tandem with improved skills.

Although powerful fMRI techniques hold promise when applied to prevention science and practice, their expense (see the ubsequent section on fMRI limitations) and lack of portability constrain their use in prevention efforts. One way around this limitation is to use fMRI in foundational research to identify tasks, both emotion-regulatory and cognitive, that consistently recruit relevant brain areas. With that knowledge, scientists can then use those tasks to

measure specific functions as warranted, without imaging, as a low-cost, easy-to-administer test battery reflective of underlying mechanisms of interest.

A variety of assessments—including working memory tests, tests of the ability to pay attention and inhibit strong tendencies, and cognitive-affective shifting tasks—all engage the prefrontal cortex and may be useful measures of vulnerability (personal communication with D. Eldreth, RTI International, July 7, 2011). Once researchers identify particular neural signatures of non-invasive tests, these measures would provide more information about brain function than those currently in use. A wide range of professionals could administer these tasks in almost any setting (personal communication with D. Fishbein, RTI International, August 17, 2011).

Neuroimaging studies also indicate that the context in which individuals perform tasks influences the underlying brain activity. Tasks involving challenges, choices, and decisions seem to require a social context to fully engage the brain. This suggests that simulation tasks and those that integrate virtual reality would be more readily transferable to preventive applications than two-dimensional computer tasks (personal communication with D. Fishbein, RTI International, August 17, 2011).

The formative research to bridge brain scans, neurobehavioral tasks, and prevention could yield many advances, such as tasks that are useful in diagnosis, improved means to monitor changes during treatment to determine how well a therapy works, and an enhanced understanding of the etiology of disorders. Some of the tasks that increase progressively in complexity and difficulty could serve as part of preventive intervention by strengthening brain areas involved in important functions, such as the inhibition of impulses (personal communication with D. Fishbein, RTI International, August 17, 2011). Similarly, information on brain-task relationships from rt-fMRI studies could help scientists select activities to be included in interventions (personal communication with D. Eldreth, RTI International, July 7, 2011).

fMRI Limitations and Neuroethics

The power of fMRI technologies and their tremendous potential to inform translational neuroscience has engendered great enthusiasm. However, any review of such techniques must note their limitations. Moreover, the strong interest in neuroimaging among psychiatrists and other behavioral scientists whose work influences the treatment of people with mental disorders requires some discussion of ethical issues.

As with all scientific techniques, fMRI has limitations that researchers must be aware of as they interpret results. Although some argue that attempts to localize psychological function via functional neuroimaging are misguided (Miller, 2010), a more widely accepted caveat about fMRI is that correlations of brain activity patterns with behavior does not prove causality (Cacioppo et al., 2003; Beck, 2010). A structure's activity during a task does not necessarily mean it is generating the observed behavior or mental state. Similarly, the absence of activity in another brain region does not imply its lack of involvement in the function. Moreover, knowing whether the BOLD signal from a particular brain area is correlated with a task does not explain the mental state or behavior.

Links between behavior and a particular brain region revealed through fMRI, however, can guide researchers as they explore the function of the area using other methods that permit inferences about causality. Researchers must also correct for multiple comparisons in fMRI analyses, which yield a relatively high false positive rate and may lead to spurious associations (Beck, 2010). Well-designed studies in which researchers measure changes in behavior as participants control local neural activity via rt-fMRI may come closer to supporting causal inferences about brain function and behavior (Caria et al., 2012).

A key element of proper interpretation of fMRI is the presence of an appropriate and meaningful comparison; BOLD signals during a task must be contrasted with those from a baseline or control condition (Cacioppo et al., 2003). Moreover, as the rs-fMRI studies indicate, baseline conditions in imaging studies (such as looking at a hash mark in the middle

of a screen) do not translate into an absence of brain activity. Nevertheless, the interdisciplinary nature of neuroscience bolsters confidence in fMRI results and working hypotheses. Neuroimaging researchers who work with colleagues from complementary fields are better able to get a bearing on meaningful brain-behavior relationships and avoid oversimplification of complex functions (Decety & Cacioppo, 2010).

Interdisciplinary teams have brought a new approach to fMRI that may help home in on causal brain-behavior relationships. Some fMRI researchers are using mediational analyses, an approach from epidemiological research, to examine multiple correlations (Eisenberger, Taylor, et al., 2007; Kober et al., 2010; Ide & Li, 2011). Such analyses help identify causal relationships between particular brain areas and behavioral results, but full explanations still require the convergent findings from multiple methods.

Additionally, different types of experimental designs are expanding the inferences that can be derived from fMRI data. Traditionally, activity of a particular brain region is the dependent variable in fMRI studies. In a new approach, researchers measure task-related neural activity as a dependent variable during the laboratory phase of a study and then use it as an independent variable to predict behavior during a follow-up period. For example, neural responses to two types of smoking-cessation communications—messages tailored to the individual (Chua et al., 2011) and television advertisements from public health organizations (Falk, Berkman, Whalen, & Lieberman, 2011), respectively—predicted observers' success in quitting in the short term. Similarly, Berkman and colleagues (2011) combined fMRI and measurement of cigarette craving via text messaging to demonstrate that enhanced activity on a task that requires inhibitory control predicted better control over the desire to smoke during a quit attempt. The stronger research design of such studies improves confidence in the use of fMRI as a tool for practical applications (e.g., testing and improving health messages) and for suggesting neural mechanisms that underlie changing a health-related behavior.

The relatively small number of subjects in functional neuroimaging studies and the use of various protocols among investigations of the same behavior limit the generalization of fMRI results. Wager and colleagues (2009), however, argue that meta-analysis—examining the findings of many studies in a particular area of inquiry—can help evaluate the consistency and specificity of neural correlates linked with various behaviors and cognitive processes. Moreover, advanced analytical techniques can contribute to functional mapping by identifying distributed networks of brain structures that work together from patterns of co-activation. For example, investigators have used meta-analysis to clarify the neural underpinnings of cognitive functions (Arsalidou & Taylor, 2011; Kim, 2011).

Rapid advancements in neuroscience, the persuasive power of neuroimaging technology among the public, and the inherent limitations of the technique naturally present ethical issues. Neuroethics encompasses a range of ethical considerations and concerns about all types of brain research (Cheung, 2009; Illes & Bird, 2006). The use of neurotechnologies, including fMRI, in psychiatry presents particularly complex ethical issues relevant to discussion of functional neuroimaging for translational purposes (Walter, Berger, & Schnell, 2009). Psychiatry, in particular, has always involved ethical issues because of uncertain diagnoses, the stigma surrounding behavioral problems, skepticism about treatments, and concerns about therapy as an attempt to change the way people feel, think, and behave. Cheung's (2009) review points out a core issue: How should psychiatrists use the vastly expanded knowledge about the brain? Although many psychiatric researchers have embraced neuroimaging, they view the use of fMRI to make clinical decisions in this field as "a distant proposition" (Cheung, 2009 p. 395).

At this time, fMRI advocates mainly see the technique's potential to contribute much needed objective, biological information to the diagnostic process in psychiatry. However, fMRI does not pinpoint the source of pathology but rather provides neural correlates. Because atypical activity patterns in a brain scan do not imply illness in the absence of symptoms, brain scans would not be the sole diagnostic in psychiatry (Cheung, 2009). Furthermore, group differences between reference and patient populations may not apply to individuals

(Walter et al., 2009). Any biological assay to predict disease and clinical outcomes must be used and interpreted cautiously, and the results communicated carefully with appropriate caveats and attention to confidentiality (Illes & Bird, 2006).

However, fMRI may eventually support the validity of subjective diagnostic assessments and focused clinical descriptions of disorder subtypes. A biological explanation of symptoms does not necessarily ease the negative perceptions conveyed by psychiatric diagnoses and the associated stigma, self-stigma, and self-fulfilling prophesies (Cheung, 2009). Although the use neuroimaging genetics may improve diagnostic capabilities in psychiatry, the ethical issues—including stigma, potential for discrimination, privacy, and commercialization—are magnified with this combination of powerful technologies (Tairyan & Illes, 2009). As just one part of diagnosis, the expense of brain scans and access to the technology for disadvantaged people raise concerns (Cheung, 2009; Illes & Raffin, 2005). In cases where people with psychiatric illnesses have committed crimes, brain imaging raises a challenging set of questions about the nature of self-determination, free will, and legal responsibility for actions (Cheung, 2009; Illes & Bird, 2006).

The ethical issues of fMRI as a diagnostic tool for neurobehavioral problems are amplified in the context of child psychiatry (Illes & Raffin, 2005), where informed consent and the ability of the patient to make treatment decisions are of particular concern. Some express apprehension that scans might result in labeling, mislabeling, and self-fulfilling prophesies that change an individual's life course. Neuroethicists also note that fMRI diagnostics may be eventually used to judge children's propensity for behaviors rather than assess problems that have already emerged (Illes & Raffin, 2005), which may put them at risk for inappropriate interventions (Fenton, Meynell, & Baylis, 2009).

A major concern is that brain scans in child psychiatry (e.g., as an aid in diagnosis) may lead to their use to make decisions regarding children in other arenas—for example, educational systems and courts (Fenton et al., 2009). Some have expressed apprehension that schools might one day coerce students to get fMRI scans for placement in ability-related streams, for example (Illes & Raffin, 2005). Courts might use brain scans to decide whether youth are competent to stand trial as adults or receive adult punishments (Fenton et al., 2009). Neuroethicists point out that the state already has tremendous power over the lives of children in the education and court systems, and they call for extreme caution regarding fMRI's potential influence on the complicated decisions regarding the welfare of children.

If fMRI plays a role in the treatment of neurobehavioral problems, Walter and colleagues (2009) have concerns that brain scans may result in a focus on pathological mechanisms rather than rather than understanding the person. Another worrisome possibility is "treating the scan" (Cheung, 2009 p. 395)—intervening in a way that changes fMRI-measured brain activity rather than addressing the environmental or behavioral factors related to patients' problems. Mismatches between brain scans, symptoms, and clinical improvement would present a host of vexing questions for psychiatrists (Cheung, 2009).

Neuroethicists also point out that any therapeutic advances from fMRI and other technologies might lead to attempts to enhance normal function among those who can afford it, further exacerbating social inequalities (Racine & Illes, 2006; Cheung, 2009). They note that pharmaceuticals prescribed for those with neurobehavioral disorders (e.g., attention deficit, Alzheimer's, and depression) have been obtained by healthy people for the purposes of life enhancement (e.g., exam preparation, improving memory, and mood elevation), akin to plastic surgery. As Illes and Raffin (2005) suggest, direct-to-consumer advertising and the current absence of regulation for neuroimaging may facilitate use of brain scans and therapeutic interventions among already advantaged people seeking a neurological competitive edge.

Future Applications and Conclusions

Functional magnetic resonance imaging (fMRI) is a powerful, non-invasive tool that visualizes brain activity. The related techniques of event-related (task-based) fMRI, resting-state fMRI (rs-fMRI), and real-time fMRI (rt-fMRI) are widely used in research. This

important subfield of translational neuroscience—particularly when combined with other approaches—is contributing to the diagnosis and treatment of neurobehavioral problems and psychiatric disorders.

In one important area of translational research, the development of biomarkers for diagnosis and prognosis, scientists are integrating fMRI findings with new technological approaches. The most promising new approaches, driven by advances in molecular biology and bioinformatics, come from fields where scientists are mapping the entire complement of an important biological entity—including genes (genomics), proteins (proteomics), or metabolites (metabalomics). These studies attempt to integrate all that is known about the biology of an entire system, including how all the components interact with each other and the environment to determine health and disease (Petrella et al., 2008). Although identifying the totality of these biological entities requires substantial groundwork, the payoff in terms of understanding individual vulnerability to diseases is expected to be enormous.

The "-omics" findings can greatly expand the amount of information obtained from simple, noninvasive laboratory tests. Blood, urine, and saliva samples collected today are only analyzed for a small fraction of the biochemicals present (Quinones & Kaddurah-Daouk, 2009). Once scientists identify and validate the patterns of genes, proteins, and metabolites associated with particular diseases, then samples can be tested for unique profiles to aid early diagnosis. These -omics-based diagnostic markers may prove to be more efficient and cost-effective than current techniques, and researchers plan to incorporate them into the development of medications and behavioral interventions (Filiou & Turck, 2011: Linden, 2012).

Current "-omics" research is laying the foundation for future biomarkers. Researchers are mapping these potential biomarkers among various patient populations, including those with psychiatric and neurological diseases (Quinones & Kaddurah-Daouk, 2009). For example, researchers are developing both proteomic (Lista, Faltraco, & Hampel, 2012) and metabalomic (Kaddurah-Daouk et al., 2011) profiles of Alzheimer's disease.

Characterization of the entire human DNA sequence has major implications for scientific understanding of the brain and neurobehavioral disorders. Almost two-thirds of the approximately 30,000 genes in the human genome are associated with brain function (Petrella, Mattay, & Doraiswamy, 2008). These genes encode for neurotransmitters, enzymes, neural growth factors, and other nervous system components.

Given the complexity of neurobehavioral disorders, a large panel of biomarkers will undoubtedly be necessary for accurate diagnostic and prognostic use in psychiatry. Filiou and Turck (2011) point out the importance of integrating "-omics" and neuroimaging data in efforts to characterize psychiatric diseases and develop differential diagnosis in psychiatry (Linden & Thome, 2011; Thompson, Martin, & Wright, 2010; Wiedemann, 2011). By combining biomarkers—such as altered protein levels, brain activity patterns, and genetic information—scientists expect to connect molecular profiles with neural functioning and performance on particular behavioral and cognitive tasks. For example, "-omics" may reveal molecular and biochemical patterns underlying problems with stress regulation; the understanding of anxiety disorders may require that researchers connect this information with fMRI data showing responses to threatening stimuli. With a combination of these powerful approaches, scientists expect to map the biological pathways from genes to brain circuits and networks and then to cognitive and behavioral characteristics related to specific disorders.

Historically, the prevention field has incorporated neither the principles of neuroscience nor its methods, including fMRI. Gradually, this is changing; some innovative prevention researchers are starting to translate knowledge about the neurobiology underlying behavior problems, discovered through the use of fMRI techniques, with the hope of improving interventions. Substance misuse and antisocial behavior, for example, are associated with particular neurobehavioral characteristics, which suggest specific areas for intervention. Researchers at RTI's Transdisciplinary Science and Translational Prevention Program are ahead of the curve, having already begun to integrate fMRI technology into several of their studies.

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