Functional neuroimaging in child and adolescent psychiatry

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Introduction

During the past twenty years, there has been a dramatic increase in the amount of psychiatric research that has used functional neuroimaging to examine neural correlates of cognition, behavior, and emotion. The current widespread popularity of techniques like functional magnetic resonance imaging (fMRI) is driven by the ease of use, the superior spatial and temporal resolution of the data, the lower cost, and the greater availability of fMRI compared to other techniques like positron emission tomography (PET) or single photon emission computed tomography (SPECT). All these technologies can be used to identify which brain regions show neural activity during the performance of cognitive tasks or specific behaviors. This information is particularly useful for understanding psychiatric disorders. For decades, psychiatry has relied primarily on behavioral symptom assessment for accurate diagnosis and treatment planning. FMRI and other functional neuroimaging techniques provide an extraordinary research tool to help better understand the neurobiological underpinnings of common psychiatric disorders. More importantly, as our understanding of neural system function in specific disorders grows, these techniques have immense potential to be integrated into clinical practice by providing unique information to enhance clinical psychiatric care.

Currently, neuroimaging techniques are almost exclusively the domain of academic researchers. Relative to the volume of research done to identify and describe brain pathophysiology in psychiatric disorders, far less work has been done to demonstrate the possible clinical effectiveness of imaging methods. Therefore, there is little understanding in the general medical community of these techniques' strengths and limitations, how they are presently utilized to better understand psychiatric disorders, or how they may lend themselves to future clinical application. The purpose of this selective review is to provide an introduction to the

methods and capabilities of technologies currently used in psychiatric functional neuroimaging research. To better discuss these issues, this article also will review the current functional neuroimaging research literature for several child or adolescent psychiatric disorders, which exemplify the unique challenges in conducting clinical neuroscience research. The review will conclude by discussing how the current clinical neuroscience empirical knowledge base might be used to assist diagnosis, treatment planning, and treatment outcome evaluation, and how this type of research is underway at The Institute of Living at Hartford Hospital.

Functional Neuroimaging Techniques

Functional imaging techniques that localize neural activity within the brain vary between those that use ionized radiation (e.g., PET or SPECT) to obtain measures of metabolism or cerebral blood flow, and those that obtain images of neural activity by measuring biologically-induced changes to a strong magnetic field (e.g., fMRI and magnetoencephalography – MEG). For simplicity, this technical review will not further consider SPECT or MEG techniques, as the majority of clinical neuroscience research has been conducted using fMRI and PET methods. Reviews of these other techniques can be found elsewhere.[1, 2] PET measures brain activity by measuring the energy released from a positron-emitting radioisotope after it is injected into the body. The technique directly quantifies regional cerebral blood flow (rCBF) as a measure of neural activity by recording levels of released energy using a PET scanner. In contrast, fMRI typically measures brain function by rapidly acquiring images of brain cortex using magnetic resonance scanner settings that are sensitive to a naturally-occurring hemodynamic contrast. When regional brain activity increases, it exerts a metabolic demand that causes local changes in blood flow and blood volume. Oxygenated blood leaves the capillary bed to be replaced by an

inflow of more richly oxygenated blood. When this process occurs in the MR machine's magnetic field, it is possible to tune the MR image acquisition such that it is sensitive to changes in magnetic susceptibility created by vascular inflow and outflow.[3] Therefore, the signal measured during fMRI reflects a small relative change in signal intensity that serves as a proxy for neural activity. This type of fMRI data can be collected on most standard clinical imaging platforms that have undergone hardware upgrades to permit rapid and stable image acquisition. In recent years, the increasing use of fMRI has led to the marketing of several MR systems specifically designed with human brain imaging research in mind. These platforms are constructed with higher magnetic field strength to permit more detailed visualization of brain volumes. These systems also allow increased image acquisition speed. Both spatial resolution and acquisition speed are important factors in the quality and usefulness of fMRI data. Typical contemporary fMRI systems utilize a magnet with 1.5 or 3 Telsa field strength, have a practical lower limit of spatial resolution of brain function data at about 3 mm^3, and collect a whole brain volume every 1.5 to 3 seconds (though the exact characteristics vary from system to system depending on how the MR machine is utilized).

Each neuroimaging technique has it advantages and disadvantages. For example, the need to inject the body with ionizing radiation for PET limits the amount of total exposure for any given patient or research participant. This poses practical problems for studies that need repeated assessments, or ethical dilemmas as to whether to include healthy populations as control subjects in research.[4] Because the radioisotopes used for PET have short half-lives, they must be produced at high cost in a cyclotron relatively soon before use. Furthermore, PET also has less spatial resolution (usually 1 cm^3) relative to fMRI. On the other hand, these techniques directly assess changes in rCBF, whereas fMRI measures a signal that approximates hemodynamic

activity. PET also offers an advantage to some pharmacological studies. Specially manufactured radioisotopes can permit visualization of exact neurotransmitter binding sites in the brain using PET.[5] In contrast, because fMRI does not require radiation exposure, it can be used repeatedly. MR technology is more widely available; nearly every major hospital now has its own MR scanner for clinical imaging. The specially-trained experts needed to produce radioisotopes, the cyclotron, and other equipment needed for PET brain imaging typically are only available at major academic medical settings. As a result, the MR scanner is less expensive to run and will produce stable data as long as the scanner is well-maintained.

Making use of either PET or fMRI data follows a similar analytic framework. Consecutively-acquired images representing brain activity undergo statistical tests to determine whether local changes in signal correspond to events of interest that occur during data collection. Because neural activity signals measured by PET and fMRI change in a reliable manner over time, it is possible to predict in advance a model for how signal change will occur. For studies of 'resting' brain activity, the entire series of images can be averaged to assess which brain regions are active. However, in psychiatric research a frequent desire is to examine neural activity changes that occur in response to specific types of behavior, emotion, or cognitive function. Therefore, clinical neuroscience studies of psychiatric groups typically control what types of behavior occur in the scanner environment. Because PET and fMRI both limit naturalistic movement, these experiments typically use relatively simple cognitive tasks. Examples of these are focused attention tests, word reading, or coordinated manual behavior – anything that can be easily performed by watching a video screen and responding with a joystick or button response device. Advances in fMRI paradigm construction and data analysis techniques in the late 1990's have allowed great flexibility in designing experiments to measure particular behavior. In

contrast to PET, which requires contrasting blocks of time wherein participants might perform a series of 30 seconds blocks of a desired behavior, alternating between equal time of task and rest, event-related fMRI can quantify neural activity changes to brief events. Because it provides a means to examine complex cognitive function or behavior, event-related fMRI has proven to be more useful for many clinical neuroscience applications. In recent years, some investigators have pushed the capabilities of fMRI by using virtual reality environments to assess realistic situations like driving behavior[6, 7] or spatial memory[8, 9] – tasks that are analogues of animal research paradigms. More sophisticated methods of data analysis for fMRI and PET data have been devised, including techniques that identify and characterize systems of brain regions showing similar spatiotemporal patterns of neural activity.[10-12] These techniques allow researchers to identify groups of spatially distant brain regions that show similar patterns of activity, which suggests that they form neural networks. Currently, other novel analytic techniques are under development that will integrate different types of neurobiologically meaningful information (e.g., examining the association of localized neural activity impairment from fMRI with abnormalities of gross brain structure from a T_1 brain structure scan).[13, 14]

Current Uses of Functional Neuroimaging in Clinical Neuroscience Research

Most current neuropsychiatric research is oriented toward a careful, systematic exploration of the relationships among symptom aggregation, psychological dysfunction and possible pathophysiological processes.[15] Typically, such inquiry seeks to understand the neural basis of particular psychiatric symptom expression. A frequently used approach is to compare one group of psychiatric patients to a demographically similar group without that disorder, using a task to elicit neural activity that is theoretically related to the psychiatric diagnosis. The

overarching goal of such clinical neuroscience research is to better understand how overt emotional and behavioral disturbance relates to the operation of the complex, integrated neural systems of the brain, as mediated by genetic, neurochemical and morphological differences. In this way, researchers have made many important discoveries about many different psychiatric disorders; e.g., behavioral inhibition in childhood psychiatric disorders of impulse control such as Attention-Deficit/Hyperactivity Disorder, abnormalities of emotional response in mood disorder, or social function in pervasive developmental disorders. These particular disorders were chosen for review because the functional neuroimaging research base for them is more extensive compared to other common psychiatric disorders of childhood and adolescence.

Attention-Deficit/Hyperactivity Disorder

Attention-Deficit Hyperactivity Disorder (ADHD) occurs in at least 3 to 5% of school-aged children.[16] It is marked by symptoms of hyperactive-impulsive behavior and inattention that are developmentally inappropriate. Therefore, the core problems in ADHD appear as problems controlling behavior, elevated activity levels marked by motor restlessness, and attention dysfunction. Often, problems with motor restlessness, ongoing hyperactivity, sometimes physically dangerous behavior, and disciplinary problems resulting from children's inability to control activity levels in structured settings such as school are what bring ADHD youth to the attention of clinicians. The early emergence of these problems typically heralds the most severe, but most easily identifiable forms of ADHD. The Diagnostic and Statistical Manual for Mental Disorders (4^{th} edition; DSM-IV)[17] recognizes subtypes of ADHD: Predominantly Hyperactive-Impulsive, Predominantly Inattentive, and Combined Hyperactive-Impulsive/Inattentive. This subtyping distinction has gained empirical support in child

research[18], but has not yet been validated in adults except by reference to childhood history. Because of these differences in clinical presentation, there is continuing debate on whether ADHD is a unitary disorder or a collection of similarly-appearing disorders with different neurobiological substrates.[19] ADHD youth with hyperactivity/impulsivity is the best researched subtype; most experts agree that this group likely represents a coherent disorder.[20] Most experts also agree that Predominantly Inattentive ADHD likely represents a different subtype or different disorder altogether.[21-23]

Perhaps the most widely accepted neurobiological theory of ADHD was proposed by Barkley,[20] who argues that behavioral disinhibition is the central cognitive deficit in ADHD. He defined behavioral disinhibition as the failure to inhibit a prepotent response, stop an ongoing response, or to maintain a response in the presence of distraction/interference. There have been various alternative theories proposed to explain disinhibition, including disrupted conditioning and reward[24] or deviant motivational attitude.[25] However, most researchers define response inhibition impairment in ADHD as a deficiency in a higher-order executive inhibitory control process related to frontal lobe brain function. In neuroscience research, response inhibition is typically measured on tasks that assess the ability to inhibit or delay a behavioral response (i.e., "Go/No-Go tasks"). To date, five published fMRI studies have employed Go/No-Go tasks to compare children or adolescents with ADHD to age-matched non-ADHD controls. These studies typically find that ADHD youth commit greater numbers of errors on these tasks compared to non-ADHD subjects. Neuroimaging study results generally show ADHD hypoactivation in prefrontal cortex and basal ganglia. In the frontal lobe, less neural activity has been found in ventrolateral prefrontal cortex.[26, 27] However, these results conflict with other studies using slightly different tasks or analytic techniques that find ADHD hyperactivation in

these brain regions.[28, 29] Both Tamm and colleagues[30] and Durston and colleagues[27] have shown decreased activation of anterior cingulate cortex – a region closely linked to monitoring of errors[31] – in ADHD children or adolescents. In the basal ganglia, most fMRI studies show ADHD caudate hypofunction.[26-28] Moreover, in one of these studies, methyphenidate increased ADHD deficits in the striatum.[28] Some of these studies find additional diffuse activation in other brain regions in ADHD samples,[27, 29, 30] suggesting that ADHD youth may use compensatory neural networks to overcome cognitive deficits.

In addition to response inhibition tasks, other tasks have been used to study ADHD youth. Bush and colleagues used a version of the Stroop Task to examine the function of the anterior cingulate in ADHD.[32] This study of ADHD adolescents found decreased dorsal anterior cingulate activity, but activation of a possible compensatory frontostriatal and anterior insulae network. Several PET studies have examined ADHD teen brain function during performance of continuous performance tasks (CPTs), which require continually responding to rare stimuli over extended periods of time. In contrast to Go/No-Go tasks that assess response inhibition, these tasks measure sustained attention. Two such studies found reduced activity in left frontal lobe, thalamus and hippocampus in ADHD teens relative to non-ADHD control participants.[33, 34] Another fMRI study of simple and divided attention finds reduced neural activity in ADHD adolescents in left basal ganglia, which increased to non-ADHD levels following methyphenidate treatment.[35]

These studies support theories of frontostriatal dysfunction in ADHD, particularly with respect to ADHD youth's capacity for behavioral inhibition. However, there are several significant limitations to this emerging literature. First, other conceptualizations of 'disinhibition,' such as hypotheses regarding inability to delay gratification (i.e., reward and

reinforcement), have not been explored with neuroimaging tools. Task dependency is an important issue in interpreting these results. For example, Vaidya and colleagues[28] use two different Go/No-Go tasks in the same ADHD sample, and find two different patterns of brain function differences when compared to non-ADHD controls. This suggests that they way in which ADHD youth are asked to make use of information may be an important component in understanding their pathophysiology. Finally, sampling issues are paramount in psychiatric neuroimaging studies. As discussed by Schulz and colleagues[29], many children diagnosed with ADHD "outgrow" their symptoms such that they do not meet full criteria for the disorder in adolescence. This hinders comparability of Schulz and colleagues'[29] results to other ADHD neuroimaging studies, and emphasizes the need to fully understand developmental changes in disorders studied with neuroimaging tools. However, no published fMRI or PET study of ADHD children or adolescents has had a sufficiently large sample to permit a cross-sectional evaluation of age-related differences in brain activity. Furthermore, no ADHD neuroimaging study to date has employed a longitudinal design.

Major Depressive Disorder

Major Depressive Disorder (MDD) is a significant, often chronic and severe disturbance of mood associated with varying profiles of blunted emotional response, suicidal ideation, hopelessness, irritability/anger, lethargy and inattention.[17] MDD is estimated to affect approximately 1 in 30 adolescents[36] at any given time. Recent neuroimaging studies provide strong evidence that depression is a multidimensional disorder that affects separate, but functionally integrated cortical, subcortical, and limbic neural systems in the brain.[37, 38] MDD adults consistently have been shown to have reduced neural activity in rostral anterior cingulate

and dorsolateral prefrontal cortex, and hypermetabolism in amygdala, basal ganglia and ventromedial/orbitofrontal prefrontal cortex.[39-44] Less is known about brain function in MDD children and adolescents because only a handful of neuroimaging studies have been done. Moreover, existing studies have reported inconsistent results. MR spectroscopy studies of MDD children and adolescents find abnormalities in some of the same brain areas that show neurofunctional abnormalities in adults.[45-47] SPECT and PET evidence was found for reduced metabolic activity in unmedicated MDD teens in left frontal and temporal lobe.[48, 49] In contrast, another study found reduced left parietal lobe, thalamus and right caudate activity.[50] However, left temporal lobe structures (including amygdala) were hyperfunctional, consistent with most adult MDD work.[42] Therefore, extant research suggests both similarities and differences between MDD adults and MDD adolescents in patterns of neural dysfunction.

Perhaps the differences are not so surprising in light of recently obtained evidence for neural maturation across adolescence. These differences occur in many brain regions implicated in MDD. Gray matter density increases linearly until puberty and decreases during adolescence, peaking at age 12 in the frontal and parietal lobes, age 16 in temporal lobes, and age 20 in the occipital lobes.[51] On a complex attention task, Casey and colleagues show a relative reduction in the magnitude and extent of ventral prefrontal cortex activity with age.[52] There is evidence for gender differences in amydala activity across adolescence.[53] It also is possible that differences in MDD neural dysfunction between adults and adolescents might be related to differences in overt symptom expression. Several studies have found differences between adolescents and adults in MDD symptom presentation.[54-56] Compared to MDD adults, MDD adolescents have relatively less psychomotor retardation, and more problems with self-esteem, somatic complaints[57], irritability, anger[58, 59], and co-morbid anxiety.[55] Cross-sectional studies of symptomatology in

MDD teens from puberty to early adulthood show that MDD symptoms of anhedonia, hopelessness, hypersomnia, weight gain and social withdrawal are expressed more frequently with age.[56] It is not currently known whether these variations in symptom presentation reflect age-specific differences in the underlying pathophysiology of MDD. Because adolescent onset MDD is a high risk for recurrent adult depression[47], characterization of age-related changes in the (dys)function of neural circuits implicated in adolescent MDD may shed light onto biological contributions to severe and persistent MDD.

Autistic Disorder

Autistic disorder is a severe, pervasive developmental syndrome characterized by behaviorally-defined impairments in reciprocal social interaction, disordered communication ability, and restricted, odd or stereotyped behaviors. Increased awareness of autistic disorder in pediatric medicine, and the fact that symptoms are typically apparent by age 3, means that the disorder is usually diagnosed before school age. The disorder is thought to occur in as many as 1 instance per 1,000 people.[17, 60] Because of marked heterogeneity of symptom severity, cognitive ability, and developmental outcome, it is not yet clear whether autism is several similar-appearing, but distinctly different disorders, or several related disorders comprising an "autistic spectrum."[61] Although the past decade has seen numerous behavioral, cognitive, genetic, cytoarchitectonic, and gross brain structure studies of autistic persons, this data has not yet led to any single leading theory of autistic disorder pathophysiology. A general observation taken from existing evidence is that autism appears to be a genetically-related disorder of brain development, likely expressing itself at least in part during prenatal development.[62] The ultimate result of this disordered development may be the formation of disorganized neural networks

subserving cognitive and social function. However, there are very few functional neuroimaging studies in autistic children or adolescents relative to the number conducted in adults, likely due to the combined practical difficulties presented by working with younger ages and persons with mild to severely reduced intellectual ability. Existing functional neuroimaging evidence comes largely from a limited number of studies of higher-functioning, adult samples. Therefore, autistic disorder is an example of where our understanding of brain activity in a particular psychiatric disorder that arises in childhood is informed almost exclusively by work with adults. Much additional work is necessary to confirm that our emerging understanding of adult pathophysiology also applies to children and adolescents diagnosed with autistic disorder.

Some investigators suggest that clinical neuroscience research should focus on social deficits, as they alone are unique to autistic disorder.[63] Recent studies of social cognition have focused on the concept of "theory of mind." Theory of mind reflects a person's awareness of another's mental state and the ability to use that information to guide social behavior.[64] A neural network reflecting theory of mind function is believed to include orbitofrontal and ventromedial (i.e., medial frontal gyrus and anterior cingulate) cortex, amygdala, temporal pole, and right hemisphere temporal-parietal junction.[65-67] In one of the earliest studies of theory of mind brain function, Happe and colleagues used PET to examine brain activity in patients with Asperger's Syndrome, a disorder similar in many respects to autistic disorder.[68] They found no activation of medial prefrontal cortex during attribution of mental states to story passages. Baron-Cohen and colleagues showed that non-autistic adults activated a network of amygdala, superior temporal gyrus, and prefrontal cortex when inferring mental state from pictures of eyes.[69] In contrast, high-functioning autistic adults failed to engage the amygdala on this task.

Other investigators have focused on facial processing tasks that involve judgments of other persons' emotional or mental states. Schultz and colleagues found that autistic adults have less activation in fusiform gyrus during a facial discrimination task.[70] The fusiform gyrus is a brain area that reliably activates during processing of faces in non-autistic persons. The failure to activate fusiform in autistic disorder samples has been replicated several times.[71-73] Extending these results, Critchley and colleagues found that autistic adults also failed to activate the fusiform gyrus when appraising emotional facial expressions, suggesting they viewed faces as objects.[74] In another study, Ogai and colleagues find that during identification of disgusted faces, high-functioning autistic adults evince less activity in left insula and ventrolateral prefrontal cortex than matched non-autistic controls.[75] During processing of fearful faces, they had less activity in left middle frontal gyrus relative to non-autistic persons. Currently, there is no direct neuroimaging evidence that autistic children will have similar abnormalities of neural function. However, one recent study finds that non-autistic adolescent amygdala activity is modulated based on the demands of a face matching task. However, in autistic teenagers, no such modulation was found, suggesting a role for amygdala pathology in autistic youth. It remains to be determined whether such patterns of brain dysfunction in autistic adults reflect a cumulative developmental abnormality, or alternatively, whether these specific functional deficits are present in autistic disorder at an early age, possibly representing a pathonogmonic sign of the disorder.

Because of its use in facilitating social understanding, several recent neuroimaging studies have used fMRI to examine language function in autism. Haznedar and colleagues found reduced anterior and posterior cingulate activity during a verbal learning task in autistic and Asperger's Disorder adults.[76] Adults with autistic disorder fail to activate a voice-selective

region of bilateral temporal cortex (i.e., superior temporal sulcus) in response to voices, but did activate those regions in response to non-voice auditory stimuli.[77] This latter finding is supported by work with autistic children. There is PET and fMRI evidence for reduced metabolic activity in bilateral superior temporal gyri[78-80] when autistic children or adolescents were scanned during an alert resting state. Therefore, it is likely that bilateral temporal pathophysiology in autistic disorder is present across the lifespan.

Theory of mind is a complex psychological construct that subsumes numerous subordinate cognitive processes, including the need to integrate information to guide behavior. Based on the idea that social cognition requires higher-order integration, some investigators have examined autistic persons' neural activity during non-social tasks believed to be executive or supervisory in function. In one such study, Ring and colleagues used a visual search task to examine visual search executive ability in autistic adults.[81] This study found that autistic persons failed to activate regions of prefrontal cortex seen in non-autistic controls. Instead, they activated a network of occipito-temporal brain regions. In two separate studies of working memory (the ability to hold information in short-term "online" memory to guide future behavior), autistic adults showed deficits relative to non-autistic controls. In one study, Luna and colleagues found that autistic adults had hypofunctional dorsolateral prefrontal cortex and posterior cingulate during a spatial working memory task.[82] Using a difficult working memory task requiring manipulation of information in memory, Koshino and colleages showed an abnormal pattern of activation in autistic adults.[83] Whereas non-autistic adults showed more activation in left parietal regions relative to right, autistic participants showed the reverse. Moreover, functional connectivity analyses showed a hemispherically reversed association between prefrontal and posterior regions of activation. That is, prefrontal activation was

temporally correlated with left parietal activity in non-autistic controls, but was correlated with right parietal activity in autistic participants.

Summary of the Challenges Facing Child and Adolescent Functional Neuromaging Research

As touched upon by the above review of studies, neuroimaging research into child and adolescent psychiatric disorders poses unique challenges and problems. First, all such research must include a neurodevelopmental focus. As noted above, the brain continues to develop and specialize throughout adolescence and early adulthood. Second, classic and recently advanced frameworks[84, 85] propose that normal development is a trajectory influenced by both genetic and experiential influences. In this framework, environmental stressors act upon neurobiologically-determined vulnerability to result in psychiatric illness. This developmental perspective also suggests that early pathophysiological processes may cause a particularly detrimental effect on ongoing development, akin to the influence of early life brain injury on later functioning. This is exemplified in recent findings showing that the duration of untreated psychosis in first-episode schizophrenic patients is associated with worse long-term prognosis.[85] Another example is the proposal that early childhood trauma may alter neuromodulation of psychological reactivity, refocusing children to develop hypervigilant behavior.[86] Johnson[87] proposes that disruptions in normal development may result in a failure to properly localize brain activity to typically-used neural circuits or to exclusively mediate cognitive functions with appropriate neural circuits. Therefore, a differentiation must be made between factors that may increase the risk for a particular illness and those factors that may promote the disorder in conjunction with other stresses. A further complication is that many psychiatric disorders do not manifest until late adolescence or adulthood (e.g., schizophrenia), making it practically difficult to link

neurobiological risk factors with outcome decades later. Third, as reviewed above for depression, there is substantial research showing that common psychiatric disorders may manifest differently in children and adolescents compared to adults. Such differences make it necessary to ensure that adequate comparisons are being made among age groups. In addition to these age-specific problems, functional neuroimaging research of children and adolescence is hampered by the same factors that make adult psychiatric research practically difficult. For example, recent studies have shown that disorders that once were thought to be single behavioral phenotypes actually consist of subtypes (as exemplified by ADHD). Alternatively, some disorders known to emerge exclusively in childhood (e.g., ADHD and autistic disorder) have such different symptom profiles and associated findings in adulthood, it is necessary to focus on the challenging task of imaging younger, often severely impaired populations. Therefore, large samples of phenotypically distinct psychiatric patients stratified by age are needed to ensure the validity of the findings to any disorder under investigation.

Integration of Functional Neuroimaging and Clinical Psychiatry Practice

As reviewed above, the majority of existing functional neuroimaging studies has had the goal of describing brain activity related to psychiatric symptomatology. Despite impressive gains of our theoretical understanding of the biological basis for these disorders, this research as yet has had limited application to clinical psychiatric practice. Few researchers have attempted to perform the work necessary to validate the diagnostic specificity of neurofunctional abnormalities discovered in patient groups. In order to do this effectively, it is first necessary to characterize a pattern of neurofunctional impairment that appears uniquely characteristic of a particular illness, as has recently been begun with adult schizophrenia fMRI findings.[88]

However, it also is necessary to examine large numbers of patients in order to quantify the diagnostic sensitivity and specificity of fMRI or PET scan data. Perhaps more problematic is conducting tests of differential diagnosis. For example, many psychiatric symptoms are common between disorders (e.g., psychotic symptoms are often present in both schizophrenia and certain bipolar illness manifestations). Therefore, large samples are needed of both the psychiatric group in question as well as other similar-appearing or theoretically-related groups of patients in order to fully test and validate the use of brain function data for differential diagnosis. Current psychiatric neuroimaging work needs to shift some of its focus from merely characterizing the neural basis of symptom expression to a thorough examination of how brain function data in conjunction with other physiological or genetic information might be unique to a particular clinical presentation. Finally, in order for functional neuroimaging to be commonly used in psychiatric practice, it must be proven cost-effective. Any cost-effectiveness likely will be a product of a greatly enhanced ability for differential diagnosis in complex cases, or the accurate prediction of likely treatment response.

A systematic effort to describe biological changes that occur following treatments that successfully ameliorate symptoms has been all but missing from recent psychiatric neuroimaging research. This question is ideally-suited to fMRI which can observe patterns of neural activity associated with behavior or cognition. Although many neuroimaging studies detail changes in brain activity following psychotropic medication administration, a particularly neglected research area involves understanding the neural basis of psychotherapeutic change. Recent reviews[89-92] synthesize available research that suggests it would be useful to examine the neural correlates of psychotherapy change. There is ample evidence that experience alters neural structure and function.[84] One of the more influential recent findings is the observation that

neurogenesis does not halt during early development, but that certain brain regions important to cognition demonstrate ongoing new cell growth.[93] Moreover, this complex process can be disrupted by significant environmental events.[94] Such new cell growth in pathological neural systems may partially underlie successful treatment of psychiatric disorders.

Psychotherapy-induced changes in brain function can be measured using neuroimaging techniques like fMRI or PET. Several studies already have demonstrated that cognitive-behavioral therapies can alter brain activity in adults. Symptom remission in Major Depressive Disorder has been associated with reductions in frontal lobe structure over-activity.[95-97] Psychotherapy for phobic anxiety disorders alters limbic system function in social phobia[98] and lateral prefrontal cortex in specific phobia.[99] In some reports, response to psychotherapy produced similar changes in neural activity as that achieved with medication, as in the reduction of caudate hyperfunction in Obsessive-Compulsive Disorder[100] or reduction of prefrontal cortex over-activity in MDD.[95, 96] For treatment non-responders, there is evidence that these changes in neural activity do not occur, raising the possibility that these persons may have different pathophysiology.

Current Research and Future Directions

Future functional neuroimaging research of this type likely will show that fMRI and other neuroimaging techniques have great potential to identify risk factors for mental illness, predict treatment response by identifying necessary precursors to most likely treatment success or eventually to suggest new treatment strategies. Future applications of fMRI or other functional neuroimaging techniques may include the ability to custom-tailor psychiatric interventions, based on a patient's genetic and brain activity profiles. It is important to note that the methods

that must be employed to ensure quality functional neuroimaging research (e.g., large samples stratified by age, thorough psychiatric assessment, awareness of phenotypic differences within diagnostic categories, etc.) are the same steps that must be taken to make functional neuroimaging research applicable to the practicing psychiatrist. Only recently have the necessary components been available to make this possible. First, there is sufficient knowledge describing the major neural correlates of psychiatric illness to permit large-scale validation studies of the clinical utility of this knowledge, including new studies that seek to describe the impact of intervention on neurodysfunction. Second, neuroimaging resources are now prevalent enough to permit their widespread use in clinical care.

In 2001, the Olin Neuropsychiatry Research Center (NRC) was established at The Institute of Living to use the clinical neuroscience imaging tools described in this review to address these clinical issues. The Olin NRC's mission is to conduct neuroscience research of severe psychiatric illnesses and translate that research into new and effective treatments. One of the key tools is a state-of-the-art 3 Tesla Siemens Allegra MR scanner. This magnet is capable of echo-planar imaging for assessment of hemodynamic activity, diffusion tensor imaging (DTI) to measure white matter tract connectivity, MR spectroscopy to examine brain metabolism, and standard T_1 and T_2 imaging to quantify brain structure – all of which are valuable tools in clinical neuroscience research. The MR system also includes equipment for online recording of pulse, respiration, and galvanic skin response, and an MR-safe system to monitor eye movements and pupilometry. All of these measures enhance the ability to link brain activity profiles to physiological systems. The NRC is housed in the newly renovated Whitehall and Butler buildings. Whitehall includes 16,000 square feet of space for faculty offices, research assistant offices, clinical interview rooms, patient medical examination rooms, cognitive

assessment/rehabilitation rooms, electrophysiology laboratories, MR image reading room, MR control/projection rooms, and two computer lab spaces for research staff. Butler provides space for a virtual reality laboratory and nearly a dozen extra offices for patient clinical assessment.

The Center faculty are affiliated with Yale University and function on an academic model. As such, the faculty provide mentorship and training for undergraduate, graduate, and postdoctoral fellows. Olin NRC researchers have interests in many aspects of cognitive function, including working and long term memory, spatial navigation, salience detection, orienting processes, error monitoring, response inhibition, mental chronometry, language and attention. Various projects currently examine these cognitive processes in schizophrenia, Alzheimer's disease, mood disorders, Huntington's chorea, drug and alcohol abuse, autism, psychopathy, and others. The Center is supported by grants from the National Institute of Health, (NIMH, NINDS, NIA and NIDA) totaling several million dollars. There is a particular research focus on research of children and adolescents at the Olin NRC. Currently, the NIMH funds several neuroimaging projects that examine brain function in ADHD and Conduct Disorder. Studies of ADHD seek to better understand ADHD pathophysiology and to describe changes in brain function following successful psychostimulant medication treatment. One focus of the work with disruptive behavior disorders is to find unique patterns of neural dysfunction that may serve as diagnostic markers or predictors of treatment response. Collaborations with Yale University's Child Conduct Clinic have the goal of describing the changes in the brain function of Conduct Disorder diagnosed youth following successful treatment with cognitive behavioral techniques. In a similar vein, collaborations with the University of Connecticut are examining how psychotherapy treatment changes brain activity in teenage girls with histories of psychological and emotional trauma. Additional studies also are underway examining therapeutic changes in

adolescents with major depression at risk for suicide and changes over time in the brain function of teenagers identified through symptom profiles to be at-risk for psychosis (i.e., prodromal schizophrenia). Other studies seek to characterize the pathophysiology of autistic disorder. These studies are complemented by studies of normal developmental changes in brain structure and function throughout early development. All of these studies include large samples of participants who undergo detailed and thorough psychiatric assessment. In this way, the strengths of fMRI and complementary neuroscience tools can be fully brought to bear. These projects are helping to lay the groundwork for future exploration of how functional neuroimaging tools will ultimately prove useful for clinical psychiatry practice.

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