Consensus Report of the APA Work Group on Neuroimaging Markers of Psychiatric Disorders
RESOURCE DOCUMENT

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Background

In May 2009, an Action paper was passed by the APA Assembly calling for the development of an APA Position Paper on the Clinical Application of Brain Imaging in Psychiatry. This action paper was developed in response to questions raised by claims being made that brain imaging technology had already reached the point that it was useful for making a clinical diagnosis and for helping in treatment selection. Given the APA's mission to educate both its members and the public-at-large about the science and clinical practice of psychiatry, the Workgroup was appointed under the auspices of the APA Council on Research in January 2010 to develop an evidenced-based review of the current state of the art of clinical utility of brain imaging for psychiatric diagnosis and for predicting treatment response in the following diagnostic areas: adult mood and anxiety disorders, psychotic disorders, cognitive disorders, substance use disorders, and childhood disorders including ADHD, Bipolar Disorder, Depression/Anxiety, and Autistic Disorder. This paper begins with a general introduction about the challenges in developing valid and reliable biomarkers for psychiatric disorders and then provides a comprehensive review of the current research on brain imaging biomarkers across the various diagnostic categories. Although there are a number of promising results presented, by the standards proposed in the introduction to this paper, there are currently no brain imaging biomarkers that are currently clinically useful for any diagnostic category in psychiatry.

Overview of Applications of Neuroimaging in Psychiatric Disorders

The application of neuroimaging technology in psychiatric research has revolutionized clinical neuroscience perspectives on the pathophysiology of the major psychiatric disorders. Research using a variety of types of neuroimaging techniques has shown that these conditions are associated with abnormalities of brain function, structure and receptor pharmacology. These data also corroborate the conclusions reached from genetic, endocrine, and clinical pharmacology research involving these disorders to suggest that under the current nosology the major psychiatric disorders likely reflect heterogenous groups of disorders with respect to pathophysiology and etiology.

Despite the invaluable leads that the neuroimaging studies have provided regarding the neurobiological bases for psychiatric disorders, they have yet to impact significantly the diagnosis or treatment of individual patients. In clinical medicine considerable interest has existed in developing objective, biologically-based tests for psychiatric illnesses. From the clinical perspective such advances could yield important benefits such as predicting treatment response, differentiating between related diagnostic categories, and potentially treating at-risk patients prophylactically to prevent neurotoxicity and clinical deterioration.

Nevertheless, the effect size of neuroimaging and other biological abnormalities identified to date in psychiatric disorders has been relatively small, such that imaging measures do not provide sufficient specificity and sensitivity to accurately classify individual cases with respect to the presence of a psychiatric illness. This review focuses specifically on the *potential* clinical utility of biomarkers assessed using modern neuroimaging technologies, and the *approach* required to validate imaging biomarkers for use as clinical diagnostics.

The Quest for Biomarkers in Psychiatry

Both the clinical practice of psychiatry and the development of novel therapeutics have been hindered by the lack of biomarkers that can serve as accessible, objective indices of the complex biological phenomena that underpin psychiatric illness. The inaccessibility of brain tissue, the lack of knowledge about pathophysiology, and the uncertain link between abnormal measurements on any

biological test and pathogenesis all have impeded the development of biomarkers for psychiatric disorders. As a result progress toward improving diagnostic capabilities and defining or predicting treatment outcome in psychiatry has lagged that achieved in other areas of medicine. Thus it frequently remains difficult to establish whether individual patients suffer from a particular disease, how individual patients can best be treated, and whether experimental treatments are effective in general.

The need for clinical biomarkers has become acute, as their absence particularly has hindered research aimed at developing novel therapeutics. Due at least partly to the lack of well-established pathophysiological targets for new drugs, relatively large numbers of experimental compounds are failing in increasingly expensive late-stage clinical trials. As a result, drug development pipelines are becoming dry, and several companies have discontinued their research and development of pharmaceuticals for psychiatric conditions. The ramifications of these limitations for clinical practice also are significant, as psychiatric nosology and diagnosis largely have remained at a standstill since the development of DSM-III, the clinical approach to treatment decisions for individual patients remains empirical ("trial and error"), and may patients are inadequately helped by extant treatments.

Current Application of Neuroimaging Biomarkers in Psychiatric Diagnosis

For over two decades imaging has maintained a well-established but narrow place in the diagnostic evaluation of patients with psychiatric disease, largely because of the usefulness of neuromorphological MRI in detecting and characterizing structural brain abnormalities such as lesions and atrophy. Thus the role of imaging in patients with psychopathology historically has been limited to one of exclusion of potentially etiological medical conditions: namely to rule out neoplasm, hematoma, hydrocephalus, or other potentially surgically treatable causes of psychiatric symptoms, or to detect the presence of cerebrovascular disease or gross atrophy.

Although clinically important, these conditions appear to play a role in the pathogenesis of psychiatric symptoms in only a small proportion of cases presenting for the evaluation of mood, anxiety or psychotic disorders.

Increasingly a major quest of researchers has been to identify neuroimaging results that offer diagnostic capabilities for particular psychiatric diseases as well as for their relevant differential diagnoses. Currently neuroimaging is not recommended within either the U.S. or the European practice guidelines for positively defining diagnosis of any primary psychiatric disorder. Nevertheless, advances in *research* applications of neuroimaging technology have provided leads that may foreshadow future *clinical* applications of imaging biomarkers for establishing diagnosis and predicting illness course or treatment outcome. The ensuing review discusses issues that have been addressed within other areas of clinical medicine to establish the validity and reliability of imaging diagnostics, with the aim of providing principles to guide the evaluation of neuroimaging applications in clinical psychiatry.

Biomarker Definition, Validation and Qualification

The NIH has defined a biomarker (i.e., biological marker) as: "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." (De Gruttola et al. 2001). A biomarker thus can define a physiological, pathological, or anatomical characteristic or measurement that putatively relates to some aspect of either normal or abnormal biological function. Biomarkers thus may assess many different types of biological characteristics or parameters, including receptor expression patterns, radiographic or other imaging-based measures, or electrophysiologic parameters.

The term "biomarker" connotes different meanings in different contexts, based upon the intended application of the information a biomarker provides. Within clinical medicine, biomarkers include measures that suggest the etiology of, susceptibility to, activity levels of, or progress of a disease. In addition, alterations in patient-associated biomarkers related to an intervention may be used to predict the likelihood of experiencing a robust clinical outcome or an adverse reaction to a treatment. Finally, in drug development a biomarker can be any measure of drug action that is proximal to its clinical effect, including biomarkers that correlate with drug response or quantify the extent to which a drug occupies specific receptors in a target tissue.

Notably, the U.S. Food and Drug Administration (FDA) recently has developed guidance that addresses multiple types of biomarkers that can be applied to drug development, including prognostic, predictive, pharmacodynamic, and surrogate biomarkers. A *prognostic* biomarker is a baseline patient or disease characteristic that categorizes patients by degree of risk for disease occurrence or progression. A *predictive* biomarker is a baseline characteristic that categorizes patients by their likelihood for response to a particular treatment. A *pharmacodynamic* biomarker is a dynamic assessment that shows that a biological response has occurred in a patient after having received a therapeutic intervention. A *surrogate* endpoint is defined as a biomarker intended to substitute for a clinical efficacy endpoint. Conceivably each of these biomarker types holds the potential to be

clinically useful in psychiatric research or practice. Nevertheless, in its guidance the FDA identified the most valuable role for biomarkers as their use in clinical *diagnostics*.

In considering the development of neuroimaging biomarkers as clinical diagnostics, the FDA guidance on biomarkers for drug development merits comment. Generally, the requirements of biomarkers for quantification of drug effects in research and development, which depend upon population means with variance estimates, converge with the requirements of diagnostics in clinical practice, which are assessed on a per patient basis. The common element in both is longitudinal quantification; both analyses require baseline and follow-up effects of treatments. For example, clinical evidence from the National Oncologic PET Registry motivated the expanded coverage by Medicare for FDGPET/CT in the detection and staging of cancer and in the monitoring of cancer treatment response. Thus as diagnostics, biomarkers are of interest to health care providers and consumers for parallel applications, since earlier detection of disease facilitates earlier intervention, which, when followed by effective, individualized treatment, can improve patient outcomes.

With respect to establishing the utility of a biomarker, it is useful to distinguish between the terms “validation” and “qualification”. *Validation* generally refers to the determination of the performance characteristics of a measurement —for example, the measurement’s reliability, sensitivity and specificity—in measuring a particular biological construct. The validation process is particularly relevant for securing regulatory approval to market techniques for commercial use as clinical diagnostics, as described in the subsequent section.

The term *qualification* refers to establishing the credibility of a biomarker in its application to questions specifically relevant to drug development. In drug development the ultimate use of a biomarker is as a *surrogate* end point, which requires that the biomarker has been *qualified* to substitute for a clinical standard of truth (i.e., the biomarker reasonably predicts the clinical outcome and therefore can serve as a surrogate). After a biomarker is "qualified" by the FDA, industry can use the markers in a similar context in multiple drug trials, drug classes, or clinical disorders, without having to repeatedly seek the agency's approval ["Qualification Process for Drug Development Tools," (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf)].

The FDA *qualification* process for biomarkers also encompasses guidance on drug-development tools, includeing radiographic or other imaging-based measurements. Qualification of a drug-development tool is based on a conclusion that within the stated context of use, the results of assessment with the tool can be relied upon to have a specific interpretation and application under regulatory review. The FDA guidance indicates, "While a biomarker cannot become qualified without a reliable means to measure the biomarker, FDA clearance of a measurement device does not imply that the biomarker has been demonstrated to have a qualified use in drug development and evaluation." Instead the qualification process is limited to specific patient populations and a specific therapeutic intervention. In addition to the biomarker assay *validation* data, clinical data are required to support the biomarker *qualification*. A corollary of this regulatory principle is that the FDA qualification of a drug-development tool for one application does not extend to its use in other applications.

Evaluating the Validity of Diagnostic Biomarkers in Clinical Medicine

The validity of a diagnostic biomarker for any medical disorder generally is established via evaluation of its sensitivity, specificity, prior probability, positive predictive value, and negative predictive value (Mayeux 1998). *Sensitivity* refers to the capacity of a biomarker to identify a substantial percentage of patients with the disease-of-interest (expressed as: true positive cases divided by [true positive cases plus false negative cases] x 100). Thus a sensitivity of 100% corresponds to a marker that identifies 100% of patients with the target condition. *Specificity* refers to the capacity of a test to distinguish the target condition from normative conditions (e.g., aging) and other pathological conditions (expressed as: true negatives divided by [true negative cases plus false positive cases] x 100). A test with 100% specificity would be capable of differentiating the target condition from other conditions in every case. *Prior probability* is defined as the frequency of occurrence of a disease in a particular population (true positives plus false negatives divided by the total population). A perfect biomarker would detect only true positives and no false negatives and thus would reflect accurately the prevalence of the disease in the population. Positive predictive value is the percentage of people who have a positive test who can be shown by a definitive examination (e.g., subsequent autopsy or biopsy) to have the disease (true positives divided by [true positives plus false positives]). A *positive predictive value* of 100% indicates that all patients with a positive test actually have the disease. For a biomarker to be considered useful clinically, it generally is expected to show a positive predictive value of approximately 80% or more (e.g., Consensus Report…1998). Negative predictive value represents the percentage of people with a negative test that subsequently proves not to have the disease on definitive examination (true negatives divided by [true negatives plus false negatives]). A *negative predictive value* of 100% indicates that the test completely rules out the possibility that the individual has the disease, at least at the

time the individual is tested. A reliable marker with a high negative predictive value is extremely useful in clinical medicine, although a test with low negative predictive value can in some cases still be useful if it also has high positive predictive value.

In the development of medical tests the threshold for distinguishing abnormal from normal alters the sensitivity and specificity in opposite ways. Thus if the threshold is set further from the distribution of normative values then the test becomes less sensitive for detecting true positives, but more specific for rejecting true negatives. The convention in establishing diagnostic tests for medical conditions has been to select an intermediate choice that minimizes the total error from both false positives and false negatives (Lilienfeld et al 1994).

In the case of AD the Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease, for example, recommended that in order to qualify as a biomarker the measurement in question should detect a fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases, and should have a sensitivity >80% for detecting AD and a specificity of >80% for distinguishing other dementias (Consensus Report….1998). The validation of diagnostic biomarkers for AD has been facilitated by the capability for confirming the diagnosis post mortem. Thus the current clinical criteria for returning a diagnosis of "probable AD" provide a sensitivity of about 85% when compared to autopsy-confirmed cases. In order for a diagnostic biomarker to be clinically useful, therefore, its sensitivity must exceed this value when correlated to neuropathology (otherwise there is no benefit to performing the test). For example, the validation of a diagnostic neuroimaging marker for β-amyloid pathology in AD, [F-18]florbetapir, is being evaluated partly on the basis of correlating florbetapir-PET data acquired antemortem with evidence of β-amyloid in the same subjects post mortem. The results rated as positive or negative for β-amyloid agreed in 96% of 29 individuals assessed in the primary analysis cohort. In a secondary analysis, non-autopsy cohort, florbetapir-PET images were rated as amyloid negative in 100% of 74 younger individuals who were cognitively normal (Clark et al 2011), suggesting that negative results on this test hold high negative predictive value.

Nevertheless, the outcome of the FDA evaluation of [F-18]florbetapir-PET for commercial use as a clinical diagnostic tool illustrates another central principle in the validation of an imaging diagnostic biomarker, namely that the reliability of ratings across radiologists must be relatively high. In January 2011, the Peripheral and Central Nervous System Drugs Advisory Committee of the FDA recommended against approval of the new drug application for [F-18]florbetapir injection, based largely on concerns about the variability of ratings across readers. The Advisory Committee chair said during an interview after the meeting, "We would like to see some structured training and evidence of consistency among readers" (http://www.medscape.com/viewarticle/739297). In the pivotal trial described in the previous paragraph, Clark et al. (2011) used the median of three readers' visual ratings on a five-point scale to assign the extent to which the PET scan was positive for amyloid protein binding. Since inspection of the data from individual readers ultimately raised questions about inter-rater reliability, the FDA response focused primarily on the need to establish a reader-training program for market implementation that would serve to ensure reader accuracy and consistency of interpretation of existing [F-18]florbetapir scans.

The need to ensure that readers consistently can detect clear positive or negative results extends to the clinical application of any imaging procedure for which the results depend on the subjective interpretation of a reader. For biological assays that can be objectively quantified, the accuracy often is characterized by comparing the assay results obtained for a known standard (e.g., a test sample with known concentration for the target compound) and the reliability or reproducibility is statistically expressed with respect to the variability in the quantitative results obtained after performing repeated testing on the same sample. In contrast, many types of clinical imaging assessments depend upon subjective interpretation, such as a radiologist's reading of a radiographic or nuclear medicine (e.g., PET, SPECT) image on the basis of gross visual inspection of the image. In this case, the variability of such interpretations is evaluated by characterizing the reliability and variability of the results obtained within and across raters.

Thus, intra-rater reliability can be established by assessing the extent to which readings performed *under blind conditions* by the same reader on the *same image* on different days are in agreement, and/or the extent to which the same radiologist renders the same results when comparing images obtained from the same patient on different days. Similarly, inter-rater reliability is assessed by having multiple radiologists read the same set of images while blind to the evaluations returned by the other readers. These intra-rater and inter-rater reliability assessments thus evaluate, respectively, the intra-individual variability (reflecting the failure of a reader to be consistent with himself or herself) and the inter-individual variability of interpretations (reflecting inconsistency of interpretation among different readers).

Challenges in Establishing the Validity of Diagnostic Biomarkers in Psychiatry

An important challenge in the application of neuroimaging to psychiatric diagnosis is that the clinical utility of such tests depends partly upon their ability to distinguish

multiple conditions from one other. In general both the intra-individual and inter-individual variability of interpretation increases in proportion to the number of diagnostic categories that are considered clinically relevant. In other words the fewer the categories into which readers are assigning results, the greater the degree of agreement between readers. This tendency was illustrated historically by the results of a landmark study that evaluated the variability in interpreting chest X-ray films during lung cancer screening (Lilienfeld and Kordan, 1966). The study radiologists showed 65.1% agreement when they were required to place the film results into one of five categories (suspected neoplasm, other significant pulmonary abnormality, cardiovascular abnormality, nonsignificant abnormality, and negative), compared to 89.4% agreement if they were instead required to place the results into only two categories (positive or negative for significant pulmonary abnormality). Presumably, a diagnostic biomarker assessment aimed at informing the differential diagnosis of psychiatric disorders would need to address more than two categories, however, increasing the variability of image interpretations across readers.

In psychiatry the need to differentiate various conditions from each other depends partly on the clinical imperative to return distinct treatment recommendations for different disorders. It might be argued, for example, that for a neuroimaging procedure to add clinical value in the evaluation of an adult patient with impaired attention, the differential diagnosis relevant to the treating physician includes major depressive disorder, bipolar disorder, attention deficit disorder, and anxiety disorders, at a minimum (American Psychiatric Association, 2000), since the standard of care differs between these categories. Thus, the variability across raters will be relatively higher (i.e., lower inter-rater reliability) for a diagnostic imaging study that must differentiate among several psychiatric disorders that share symptomatology but require distinct treatment approaches as compared to the case such as that described above for [F-18]florbetapir-PET, which hinges only on two categories (β-amyloid positive versus negative).

Furthermore, the determinations of positive and negative predictive value are limited by the absence of an established objective standard for establishing diagnosis in psychiatric disease (e.g., analogous to the neuropathologically verified diagnosis of AD). Thus the absence of certain knowledge about the pathophysiology of psychiatric disorders will hinder the development and validation of *diagnostic* biomarkers. Greater optimism has been associated with establishing *predictive* biomarkers of treatment response, *pharmacodynamic* biomarkers of the effect of pharmacological probes, and *surrogate* biomarkers of treatment outcome based on translational studies that ultimately can facilitate discovery of pathophysiology.

Nevertheless, it might be argued that the Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease (1998) reviewed above offers a template for developing diagnostic biomarkers of psychiatric disease. Of course, the fundamental recommendation that "in order to qualify as a biomarker the measurement in question should detect a fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases" cannot be applied directly to psychiatric disorders. Thus, the psychiatric imaging field is moving forward by establishing gold-standard diagnoses using criteria based conventions (APA, 2000). If this approach for establishing the "actual" diagnosis is accepted, then the remainder of this Consensus Report can be meaningfully adapted to biomarker validation in psychiatric disorders. This approach would argue that a diagnostic biomarker should have a sensitivity >80% for detecting a particular psychiatric disorder and a specificity of >80% for distinguishing this disorder from other psychiatric or medical disorders (Table 1). The biomarker ideally also should be reliable, reproducible, non-invasive, simple to perform, and inexpensive. Finally, the validating data used to establish a biomarker requires confirmation by at least two independent sets of qualified investigators with the results published in peer-reviewed journals.

Table 1. Recommended Steps in the Process of Establishing a Biomarker

1. There should be at least two independent studies that specify the biomarker's sensitivity, specificity, and positive and negative predictive values.
2. Sensitivity and specificity should be no less than 80%; positive predictive value should approach 90%.
3. The studies should be well powered, conducted by investigators with expertise to conduct such studies, and the results published in peer-reviewed journals.
4. The studies should specify type of control subjects, including normal subjects and those with a dementing illness but not AD.
5. Once a marker is accepted, follow-up data should be collected and disseminated to monitor its accuracy and diagnostic value.

Adapted from (Consensus Report…1998)

According to this standard, the psychiatric imaging literature currently does not support the application of a diagnostic biomarker to positively establish the presence of any primary psychiatric disorder. Although assessments of intra-rater and inter-rater reliabilities commonly are reported for quantitative neuroimaging measures, these have been limited to establishing *measurement* reliability (e.g., of cerebral volumes or neuroreceptor binding potential), but not to the reliability of diagnostic interpretation. **Thus the peer-reviewed scientific literature does not yet contain an example of a diagnostic imaging bio-**

marker with regard to a psychiatric disorder or treatment for which relatively high intra- and inter-rater reliabilities have been reported in two independent studies. Similarly, there is not yet a case in the literature where neuroimaging measures obtained from the same region(s)-of-interest has shown both a sensitivity of >80% for detecting a particular psychiatric disorder and a specificity of >80% for distinguishing this disorder from healthy controls or other relevant psychiatric disorders. Nevertheless, the ensuing sections review progress toward developing such biomarkers using state-of-the-art neuroimaging technologies. Notably this literature contains several examples of *individual* studies for which sensitivity and specificity approach or exceed 80%, and it is conceivable that some of these findings ultimately may be replicated in independent studies.

Progress Toward a Diagnostic Imaging Biomarkers of Depression

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While statistically significant group differences in various neuroimaging measures are commonly observed in patients with mood disorders, translating these findings into diagnostic tests for the *individual* patient has proven difficult. In general the conventional path to validating a diagnostic test is first to generate a potential discriminant function from a patient cohort, and then to test this discriminant function in an *independent* cohort. Currently, to our knowledge, no such tests have been validated through replication in independent cohorts subject to peer-review.

Difficulties are manifold. Mood and anxiety disorders are highly heterogeneous entities and there is considerable overlap in the statistical distributions between patients with mood disorders and healthy controls in regional brain volumes, receptor binding potential, BOLD hemodynamic response, blood flow, metabolism, and other neuroimaging measures. Secondly, neuroimaging techniques—especially fMRI—are highly sensitive to normal temporal fluctuations in patient physiology or to chemical substance intake that may have nothing to do with mood symptoms (e.g. caffeine consumption, nicotine) (1, 2), medical conditions that are commonly comorbid with mood disorders and may themselves affect imaging data (e.g. diabetes mellitus and hypertension) (3), medication, which may independently affect neurophysiology (e.g. lithium and antidepressants) (4), and scanner resolution and sensitivity (signal-to-noise), which will limit the type of morphometric and functional changes that can be measured accurately. The development of imaging-based diagnostic algorithms that are sufficiently robust to be applied across cohorts and sites will thus be a significant challenge. Thirdly, the statistical power of functional imaging scans, and the ability to discriminate white matter and gray matter boundaries using structural MRI, increases with time, potentially leading to a tradeoff between accuracy and time burden/cost. Fourthly, medication is a potent confound not only because it may affect brain structure and function, but also because it may bias classification algorithms. The algorithms may distinguish patients from controls based on the impact of different classes of medication rather than diagnosis-specific neurophysiology. Conversely, if an algorithm is developed on an unmedicated sample, it may be inaccurate when applied to a medicated subject.

Currently, researchers are still in the process of developing robust diagnostic classifiers within just one cohort of patients at a time. The challenge is to determine how best to identify the key prediction signals in the mass of data produced by neuroimaging. One approach is to use machine learning. Machine learning refers to a group of statistical methods that are used to develop algorithms to detect patterns or regularities within high-dimensional data. An empirical data training set—for example, the MRI data of DSM-IV-diagnosed patients versus healthy controls—is used to develop an algorithm that optimally distinguishes between these groups. Theoretically, the computer will then be able to make intelligent decisions about new cases based on the examples provided in the training set. That is, the program "learns" from experience.

Once an algorithm has been developed, the gold standard is to validate it on an independent cohort. However, as discussed below, the papers published to date have made use of a less stringent validation method—the "leave out one" approach. That is, all subjects except one patient-control pair are initially chosen to comprise the training set and an algorithm that best separates the diagnostic groups from each other is applied to the omitted pair to predict their diagnostic status or treatment response. The process is then iteratively applied to each subject pair to test the ability of the algorithm to distinguish between categories. That is, each omitted subject pair comprises one training example. The "leave out one" approach is less stringent because one would expect to find significant variation across subject samples. A proportion of this variation is likely to be noise—i.e., the confounding effects of temporal fluctuations, medications and other factors discussed above, and a proportion of this variation is likely to result from disease heterogeneity. Only by testing an algorithm on an independent cohort, can one demonstrate that the discriminator is robust to these confounds.

The accuracy of the algorithm is best characterized in terms of its sensitivity and specificity scores. Sensitivity refers to the test's ability to correctly detect a condition in those in whom it is present, while specificity refers to the ability of a test to limit false positives in those who do not have the condition.

Sun et al. (5) created cortical density maps for 36 healthy controls and 36 patients with recent onset schizophrenia-spectrum or affective psychosis. On a group level, the patients displayed reduced gray matter density in regions such as the anterior cingulate and lateral surfaces of the prefrontal and temporal cortices compared to the control group. Machine learning methods were then applied to the data to test whether these findings could be applied at the individual subject level. Using a sparse multinomial logistic regression classifier, 129 surface voxels were linearly combined for classification allowing for 86% accuracy in distinguishing between patients and controls. Clusters with the highest weightings included the frontal pole, superior and middle temporal regions of the left hemisphere, and the superior temporal, somatomotor, and subgenual anterior cingulate cortex (sgACC) regions of the right hemisphere.

Fu et al. (6) used the voxel-wise hemodynamic response to sad faces to distinguish acutely depressed patients with major depressive disorder (MDD, n=19) from healthy controls (n=19) with 82% sensitivity and 89% specificity. Regions with the highest vector weights included the dorsal ACC (dACC), middle and superior frontal gyri, hippocampus, caudate, thalamus, and amygdala. The same group achieved a less robust 65% sensitivity and a 70% specificity with the use of a working memory paradigm in 20 healthy subjects and 20 unmedicated patients with major depression (7). Interestingly, despite the difference in task paradigm there was some overlap in the regions that distinguished patients and controls in the sad face task – the caudate, and the superior and middle-frontal gyri.

In another study, the hemodynamic response of the default mode and temporal lobe networks during an auditory oddball paradigm was applied *a priori* to a sample of 14 medicated patients with bipolar disorder, type I (BD I), 21 medicated patients with schizophrenia, and 26 healthy controls (8). The authors were able to distinguish BD patients from patients with schizophrenia and healthy controls with 83% sensitivity and 100% specificity. The accuracy of the BD versus healthy control classification was not provided. Most recently, Hahn et al. (9) utilized three independent fMRI paradigms in an attempt to maximize classification accuracy: the passive viewing of emotionally-valenced faces, and two different versions of the monetary incentive delay task emphasizing potential winnings and potential losses, respectively. A decision tree algorithm derived from the combination of the imaging task classifiers produced a diagnostic sensitivity of 80% and a specificity of 87% in a sample of 30 patients with depression (both unipolar and bipolar) and 30 healthy controls.

Several studies have recently used machine learning methods to evaluate response to treatment with antidepressant medication. In one such study, a whole brain voxel-based morphometry (VBM) analysis predicted treatment response to fluoxetine with 89% sensitivity and 89% specificity. The same algorithm derived from the VBM analysis only differentiated MDD patients (n=37) from healthy controls (n=37) with 65% sensitivity and 70% specificity (10). Response to treatment was associated with increased gray matter density of the rostral ACC, left posterior cingulate cortex, left middle frontal gyrus, and right occipital cortex at baseline (10). Gong et al. (11) used structural MRI to predict antidepressant efficacy in 61 treatment naïve patients with depression. Patients who failed to respond to 2 adequate trials of an antidepressant were distinguished from treatment responders with 70% sensitivity and 70% specificity based on gray and white matter volumes: treatment responders had both greater and lower baseline volumes of different regions in the frontal, temporal, parietal and occipital cortices, as well lower baseline volume of the putamen (11). Costafreda and colleagues (12) reported that in 16 unmedicated patients who met criteria for a major depressive episode, pretreatment response to implicitly-presented sad faces in regions such as the dACC, midcingulate gyrus, superior frontal gyrus, and posterior cingulate cortex predicted subsequent response to cognitive behavioral therapy with a sensitivity of 71% and a specificity of 86%.

Other attempts at predicting response to treatment have been less successful. The functional imaging correlates of a verbal working memory task only predicted response to fluoxetine with 52% specificity, although sensitivity was 85% (7). Conversely, 62% of patients who achieved clinical remission and 75% of patients who did not remit following 8 weeks of antidepressant treatment, were correctly identified as responders and nonresponders, respectively, with a sad face processing task (6).

In sum, current diagnostic and treatment prediction methods have yielded sensitivities and specificities that range from 70-90%. That is, approximately 3 out of 10 patients with a mood disorder would be incorrectly diagnosed as healthy, and approximately 1 out of 10 healthy individuals would be incorrectly diagnosed with a mood disorder. Nevertheless, none of the above-mentioned studies have achieved this degree of diagnostic success in an independent cohort, and this will be a crucial test for the field. Ultimately, the patient burden and/or risk of the scan, together with its financial cost, will have to be balanced against the potential benefits of testing such as improved outcomes and more cost efficient treatment. The extent to which diagnostic and treatment misclassification will be tolerated by clinicians and the health care industry will ultimately be determined by this cost-benefit ratio.

Independent of the technical challenges involved in developing diagnostic algorithms, we raise the issue of whether the current approach to developing neuroimaging-based tests for the diagnosis of psychiatric disorders is philosophically flawed. The claim that the

machine learning approach will lead to objective biomarkers of psychiatric illness that will supplant the clinical interview is circular because the algorithms are trained to categorize patients based on clinical (i.e., DSM-IV) diagnoses. Yet the raison d'etre of the biomarker is the future supersession of the subjective diagnosis as the gold standard. Our current diagnostic categories may subsume multiple distinct disorders and thus attempting to forcibly align neurobiology with DSM diagnoses is arguably regressive. The identification of neurobiologically distinct subtypes of mood disorders may be a more fruitful approach to understanding the underlying biology of psychiatric illness (13). In contrast, research that aims to identify neuroimaging biomarkers of treatment response should be encouraged as this approach is not subject to the same tautological trap.

Progress Toward a Diagnostic Imaging Biomarkers of Psychotic Disorders

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Going back to the original observations of enlarged ventricles in schizophrenia (1, 2) as well as to observations of functional hypofrontality (3, 4) and increased striatal dopamine release [5] a broad range of reliable and well replicated changes in brain structure, function and chemistry have been revealed using modern neuroimaging techniques. As is the case for many other behavioral and neurobiological measures that have been shown to be altered in schizophrenia, these widely replicated group differences belie a substantial degree of overlap between individual subjects data from patients with schizophrenia compared to controls and other patient groups. This has placed a major limitation on the use of neuroimaging as a diagnostic biomarker of schizophrenia. As imaging methods have become more sophisticated, leading to the generation of massive multidimensional data sets, there has been a renewed interest in the diagnostic use of these methods by applying a new set of statistical and computation tools that have gained traction in areas of biomedicine. These new tools offer the hope of identifying subtle patterns in complex data sets that can be used to accurately identify group membership. This approach, known as Classification Analysis, applies statistical and/or computational methods to identify a "hyperplane" of features in high dimensional data that can be used to distinguish between groups. The goal of such an approach is to use individual subject MRI data (structural, functional or both) to differentiate between membership in diagnostic groups with high positive and negative predictive value.

This is a rapidly developing field and there are now a number of reports of what would be considered good classification rates for samples that include schizophrenia patients and either healthy controls or patients with bipolar disorder. This includes a small number of studies that report positive and negative predictive values that exceed 80% (6, 7) Demirci, see also Calhoun (8) who presented specificity and sensitivity data in this range). As discussed below, many of the studies published to date have significant methodological limitations and it is important to note that in no case has a method been independently replicated in an independent and comparable sample of patients and /or controls, one of the key requirements for diagnostic biomarker status as discussed above.

As this research approach has matured it has also become clear that there are a number of critical methodological issues that have limited progress toward that application of this approach to enhance clinical diagnosis. As discussed in Demirci et al (2008), a number of studies have only classification accuracy for the entire sample rather than separately for each group. High overall classification can be driven by very good classification performance for one group (either patients or controls) but poor performance for another, which would limit the clinical utility of such an approach. Many of the early classification studies were conducted in very small samples such that their generalizability would be questionable and as such must be considered proof of concept. There are a number of ways in which classification methodology can be biased, such as by selecting the features forming the basis of classification based upon the entire data set being classified or failing to keep test and training set separate during all steps of the analysis. These problems are present to some degree in a number of the published studies using classification methodology to distinguish schizophrenia patients from other groups.

In a recent critical review Demirci et al (2008) stress the importance of large, well characterized and described sample sizes, multi-site data sets, and unbiased use of classification methods along with detailed reporting of results in future classification studies using imaging data in schizophrenia patients.

In addition to differentiating patients from controls, efforts have been made to extend this approach to the important area of risk prediction. Risk syndromes for psychotic disorders, based upon clinical assessment techniques that detect the presence of sub-threshold symptoms[9] have been shown to be reliably applied in the research settings across the world and predictive of transition to psychosis in the 20-40% range. This relatively low positive and negative predictive value limits the utility of this approach for guiding treatment. A number of research groups have sought to identity structural and functional differences in the brain in the risk state and to evaluate the predictive value of these findings for clinical and functional outcomes. The results of these studies have been quite variable. For example, one of the leading groups in this area reported that the presence of reduced cortical

gray matter in prefrontal cortex and the temporal lobes are seen in at risk individuals who later made the transition to psychosis, while medial temporal lobe abnormalities accompanied the emergence of psychotic symptoms (10). A more recent paper from the same group, using different analytic methods, reported the opposite finding, with reduced prefrontal gray matter being related to the risk syndrome per se while reduced medial temporal lobe gray matter was related to transition. The latter study had one of the larger samples reported to date but clearly additional well powered studies and meta-analyses will be needed to clarify the relationship between changes in gray matter and psychosis risk in the clinical high risk syndrome. To date one study has reported the use of pattern classification analysis based upon structural MRI data to differentiate high-risk subjects from controls as well as those who later transition to psychosis versus those who do not. In this single study the classification success rate was over 80% for each group and also for a second independent healthy control group. Further replication in an independent at risk group will be needed to establish the reliability and generalizability of this potentially promising result (11).

Two final points related to the use of structural and functional MRI data for classification should be made. The first is that there is little standardization of either the acquisition or analysis methods and for this approach to have a clinical impact the field would need to develop consensus on this. More fundamentally, the validation of classification methods requires a diagnostic gold standard, and for mental disorders in general and schizophrenia in particular this is a tall order. DSM schizophrenia itself is clearly a heterogeneous disorder that has phenotypic overlap at the behavioral level as well as in brain structure and possible function and so it may be unrealistic to achieve a consistently high level of classification in clinical practice.

In summary considerable effort is currently being invested in using modern statistical and computational tools to utilize structural and functional MRI for diagnostic purposes in patients with schizophrenia and related disorders. This approach has yielded some promising results but also methodological caution that seems largely addressable as more rigorous studies are performed on a much larger scale than has been typical to date. While there is reason to be hopeful that these methods will eventually yield generalizable and replicable results that will permit their application in clinical practice, at this time classification analyses remain a research tool only.

Progress Toward a Diagnostic Imaging Biomarkers for Cognitive Decline

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In the past decade there has been a proliferation of studies examining cognitive decline in the elderly. Many of these studies have been small with small numbers of enrollees. It is becoming increasingly important to determine which studies and methods have achieved sufficient sensitivity and specificity that they can guide diagnostic or therapeutic decisions. The major focus of molecular and structural imaging for dementia has been on Alzheimer-type dementia (AD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB). These three types of dementia differ in terms of presentation, prognosis, etiology and response to therapeutics, although clinical overlap is not uncommon (1-5). We will highlight those studies with sufficient power to make meaningful conclusions concerning the role of imaging biomarkers in cognitive decline and dementia.

Traditionally, the clinical work up of dementia has focused on clinical assessment, neuropsychological testing, and exclusion of other etiologies. Recently, the National Institutes of Aging (NIA) and the Alzheimer's Association have issued new diagnostic criteria for AD and mild cognitive impairment (MCI) that build upon the 1984 NINDCS/ARDRA guidelines that suggest that the use of biomarkers and neuroimaging can enhance diagnostic confidence (3, 6). An important concept introduced in these guidelines is the AD pathophysiological process (e.g., β-amyloid deposition in the brain) which can be observed in some cognitively normal individuals and is thought to represent preclinical disease in this group of people. The AD pathophysiologic process is distinct from AD dementia which requires objective evidence of cognitive deficits established through clinical assessment. Autopsy studies have demonstrated that the accuracy of clinical diagnosis for AD is approximately 80% (7, 8). In addition to limitation in accurate diagnosis, reliance on clinical assessment alone may not be optimal for clinical trials for therapies that slow or prevent the progression of dementia because some of the preclinical AD pathophysiological processes appear to precede clinical manifestations of dementia by years. Biomarkers for the AD pathophysiological process could be used to select participants in clinical trials as well as to monitor response to therapies. It is important to note that new guidelines issued by the NIA and Alzheimer's Association restrict the application of imaging and CSF biomarkers to research applications and do not include these biomarkers in their clinical diagnostic criteria.

Structural Biomarkers

Very mild Alzheimer's disease (AD) or mild cognitive impairment (MCI) are characterized by magnetic resonance imaging (MRI) volumetric decreases in medial temporal lobe structures including the hippocampus (9) where hippocampal volume is correlated with beta-amyloid (Aβ□-associated memory decline (10, 11). Subjects with MCI who show abnormalities in MRI and/or CSF biomarkers are at greater risk for cognitive decline and progression to AD than subjects without these abnormalities (12). However, the cross-sectional sensitivity and specificity of volumetric differences compared with controls has not been demonstrated. At this time, therefore, structural MRI alone cannot be used to diagnose clinical dementia. In contrast, the sensitivity for detecting within-subject changes in structure is quite high. In one study, predictive prognosis of MR images obtained at one time point versus combining single-time-point measures with 1 year change measures were compared. To determine the value of including measures of longitudinal change in addition to the atrophy measures from a single-time-point MR imaging examination, individualized risk estimates were derived from the atrophy scores for thickness and volume measures calculated at the 1-year follow-up MR exam. Using the risk based on the atrophy progression scores, the discrimination improved significantly in the ability to predict conversion to AD, relative to predictive ability of using single-time-point measures (13). A study which examined subregional neuroanatomical volumetric change as a biomarker for AD to quantify the comparative sensitivity for detection of longitudinal atrophy changes, found that the regions with most sensitivity were entorhinal cortex and inferior temporal cortex (14). This could potentially provide a sensitive method to detect within subject change and potentially enough power to detect treatment induced change. For example, in prospective therapeutic trials, the number of intent-to-treat subjects necessary to detect differences in trajectory as a function of an intervention can be estimated (14). In addition to stand-alone prediction of AD, MRI has been used to augment CSF biomarkers. In MCI subjects who were abnormal on both CSF and MRI measures there was a 4 times higher risk to progress to AD within less than 2 years than those who were abnormal on only one of these measures (15, 16). On the other hand, another study found that the best predictors of progression to AD, such as entorhinal thickness or trail making test B was comparable to any combination of predictors (17).

PET and SPECT Biomarkers

Molecular imaging uses tracers whose in vivo uptake patterns and kinetics indicate and quantify the presence or activity of specific biochemical processes including receptors, transporters, enzymes and metabolic pathways. Currently, positron emission tomography (PET) and single photon emission computed tomography (SPECT) which use radiolabeled tracers are the primary molecular imaging techniques used for imaging in dementia in humans. PET has higher spatial and temporal resolution and is more easily quantified than SPECT. There has been a great deal of work of the past 3 decades using PET and SPECT for human neuroimaging clinically and in the research setting.

Molecular imaging has established utility for neuroimaging in dementia, particularly AD (18, 19). The glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), several ^{11}C- and ^{18}F-labeled tracers that bind Aβ plaques, the SPECT perfusion agents ^{99m}Tc-labeled ethyl L,L-cysteinate dimer (ECD) and hexamethylpropyleneamine oxime (HMPAO), and the dopamine transporter ligand FPCIT will be discussed in this section as biomarkers for specific dementias. [^{18}F]FDG and SPECT perfusion imaging have been evaluated in each of these types of dementia, while Aβ imaging has focused primarily on AD. FPCIT has been used primarily to differentiate dementia with Lewy bodies (DLB) from AD.

There are a number of other PET and SPECT tracers that have potential applications in dementia. Tracers targeting nicotinic and cholingergic acetylcholine receptors, acetylcholinesterase, dopamine D1 and D2 receptors, serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors, vesicular monoamine transporters (VMAT), and the peripheral benzodiazepine receptors in activated microglia have all shown differences between subjects with dementia compared to controls (19, 20). These tracers represent promising research tools, but there is not enough data to support their use as imaging biomarkers for dementia at this time.

Pathologic analysis of brain tissue obtained at autopsy is considered the best reference standard for establishing the sensitivity, specificity and accuracy of biomarkers in dementia. There are several considerations unique to PET and SPECT biomarkers for dementia. The methods used for image acquisition, reconstruction and analysis can affect the diagnostic performance of these imaging modalities, particularly when quantitative data analysis is performed. Because of spatial resolution limitations of PET and SPECT, brain atrophy can artifactually decrease measured tracer uptake and can be a potential confound to visual and quantitative analysis. Correction for atrophy can be performed based on anatomic imaging with CT or MRI.

Alzheimer's disease (AD)

1) [18F]FDG

[^{18}F]FDG-PET is the most widely used PET tracer in the United States for both oncologic and dementia imaging, and the regional uptake and retention of the PET tracer

FDG in the brain can provide a quantitative measure of brain glucose metabolism. Numerous studies have demonstrated progressively decreasing brain uptake of FDG in AD patients over time, predominantly in the parietotemporal, frontal and posterior cingulate cortices which is thought to reflect neuronal injury and loss. Currently, FDG-PET studies are reimbursed by the Centers for Medicare and Medicaid Services (CMS) for differentiating suspected AD from FTD. The clinical interpretation of FDG-PET studies for the diagnosis of dementia can be performed by qualitative visual analysis of the relative levels of FDG uptake in relevant regions of the brain. Quantitative analysis of regional FDG uptake can also be performed through comparison with normative databases, and there is data suggesting that this type of analysis can improve diagnostic accuracy, particularly for less experienced interpreters (21, 22).

The sensitivity of FDG-PET for the diagnosis of early AD is approximately 90% although the specificity for distinguishing AD from other types of dementia is lower (71-73%) in studies that used autopsy confirmation as the reference standard (22, 23). There is also data supporting the use of FDG-PET to predict which healthy individuals will develop mild cognitive impairment (MCI) and which individuals with MCI will progress to clinical AD (24, 25). Recent studies suggest that FDG may be a better marker for progressive cognitive decline compared to amyloid imaging and CSF measures of Aβ levels (26). However, there is also evidence that abnormal brain accumulation of tracers targeting Aβ occurs before changes in FDG uptake (27).

A relatively small number of studies have examined the ability of FDG to discriminate patients with AD from those with FTD or DLB. In FTD, the typical pattern of FDG hypometabolism predominantly involves the anterior aspects of the frontal and temporal lobes, often asymmetrically. In studies of subjects with AD and FTD, high specificities have been reported (93-98%) with more variable sensitivities (53-95%) (28-30). Some of this variation is likely due to differences in patient population, methods and reference standard (pathologic confirmation versus clinical diagnosis). In a study of 31 patients with autopsy-confirmed AD and 14 with FTD, FDG-PET was more accurate than clinical assessment and differentiated AD from FTD with a specificity of 98% and sensitivity of 86%.(29) The pattern of glucose hypometabolism is similar in AD and DLB, but occipital hypometabolism typically is present in DLB but not in AD which can be used to distinguish these dementias. In studies of subjects with AD and DLB, the reported sensitivities and specificities are variable with ranges of values of 75 -83% and 72-93%, respectively (31, 32).

2) Amyloid imaging

Abnormal homeostasis and aggregation of beta-amyloid (Aβ) is a hallmark of the pathologic diagnosis of AD and is thought to play a central role in the pathogenesis of AD (33, 34). The deposition of Aβ in the brain appears to precede the development of AD by up to 10-15 years (35, 36). A number of small molecule PET and SPECT tracers suitable for measuring Aβ in the living human brain have been developed over the past decade. One of the first amyloid imaging agent developed was the PET tracer [^{11}C]Pittsburgh compound B (PiB), and this tracer has been used extensively for research in subjects with AD and other dementias. More recently, several ^{18}F-labeled amyloid imaging agents have been developed and evaluated for Aβ imaging including florbetapir (AV-45), (37) flutemetamol, (38) florbetaben, (39) and FDDNP (40). These tracers are better suited to routine clinical use due to the longer half-life of F-18 compared to C-11 (110 min vs. 20 min). These tracers are similar in terms of mechanism of action by binding to the fibrillary form of the Aβ protein that occurs in amyloid plaques (41).

In April 2012, [18F]florbetapir was approved by the FDA for detecting abnormally increased β-amyloid deposition in the brain in patients with cognitive decline. Comparison with autopsy results demonstrated that positive florbetapir-PET studies corresponded to moderate or frequent Aβ plaques on neuropathology. Both flutemetamol and florbetaben are currently in late phase clinical trials and appear to have similar diagnostic properties based on the available published data.(42, 43) With this class of tracers moving from the research to the clinical setting, their proper use will require referring health care providers and imaging physicians to understand which patient populations will benefit from β-amyloid imaging as well as the implications of both positive and negative imaging studies. For florbetapir, a negative study (no abnormally increased cortical tracer uptake) is inconsistent with the diagnosis of dementia due to AD but does not exclude other dementias or neurological disorders that are not associated with β-amyloid pathology. In contrast, a positive study with florbetapir indicates the presence of abnormal levels of amyloid but does not by itself establish the diagnosis of AD dementia. As with PiB, positive florbetapir PET studies can occur in 20-30% of cognitively normal older people, (44) and the significance of this finding is an area of active research. Additionally, Aβ deposition has been reported in DLB, and AD pathology can potentially coexist with neurological conditions causing cognitive decline. Because abnormal Aβ PET and CSF studies are currently the earliest

known phenotypic marker of the AD pathophysiological process and appear to precede clinically detectable cognitive decline, these agents may be particularly useful if disease-modifying therapies become available.

The most rigorous published evaluations of the correlation between imaging findings and pathologic confirmation of AD at autopsy are currently available for PiB and florbetapir. Small studies comparing the brain uptake of PiB and Aβ plaques on histopathologic analysis have yielded mixed results, and sensitivity and specificity measurements cannot be provided based on this limited data.(45, 46) A recent study using florbetapir demonstrated 96% qualitative agreement of PET imaging with Aβ burden on histopathologic analysis in a group of 29 subjects (15 meeting pathologic criteria for AD, 14 free of Aβ pathology).(47) In the same study, 74 healthy controls less than 50 years of age all were negative for Aβ based on florbetapir-PET. One limitation of this study was the use of consensus reads between 3 nuclear medicine physicians with individual readers having more variable performance. The data reported by the FDA in the prescribing information document for florbetapir includes data from 59 subjects who had autopsies performed after florbetapir-PET, and the majority reader method provided sensitivity of 92% and specificity of 100%, although the sensitivity for individual readers ranged from 69-95%. (48)

3) Perfusion imaging

The use of lipophilic ^{99m}Tc-labeled complexes that readily cross the blood brain barrier (BBB) with subsequent trapping are well-established radiopharmaceuticals for measuring brain perfusion (49). Regional decreases in brain perfusion measured with the ECD and HMPAO are similar to the regional decreases in glucose metabolism in AD, and regional cerebral blood flow (rCBF) has been proposed as method for diagnosing AD (50). In general, direct comparisons between FDG-PET and rCBF measured with SPECT have shown higher sensitivity and specificity with FDG-PET (51). In the past, the large differential in cost and availability between PET and SPECT cameras and radiopharmaceuticals greatly favored the use of SPECT. However, the recent widespread adoption of FDG-PET for oncologic imaging has decreased this difference significantly.

Frontotemporal dementia (FTD)

1) [^{18}F]FDG-PET

[^{18}F]FDG has shown utility in distinguishing AD from FTD based on different patterns of decreased regional brain glucose metabolism. Unlike AD, the brain regions with the most marked relative decreased in [^{18}F]FDG uptake are in the frontal and/or anterior temporal cortices in FTD. Overall, studies of subjects with AD and FTD, high specificities have been reported (93-98%) with more variable sensitivities (53-95%) (28-30). The largest study assessing the ability of [18F]FDG to distinguish AD (n=31) from FTD (n=14) with pathologic confirmation found sensitivity of 86% and specificity of 97% (29).

2) SPECT perfusion

Measurement of rCBF with SPECT perfusion agents has been used to distinguish FTD from AD. In a study using 99mTc-labeled HMPAO in subjects with pathologically confirmed FTD (n=25) and AD (n=31), reduction of frontal rCBF permitted diagnosis of FTD with a sensitivity of 80% and specificity of 65% (52). When bilateral frontal reduced rCBF was present, the sensitivity was unchanged but the specificity increased to 81%. However, diagnosis based on SPECT alone was less accurate than clinical diagnosis.

3) Amyloid agents

There is currently insufficient data to define the role of amyloid imaging agents as a biomarker to distinguish FTD from AD, although the different pathophysiologies and several small studies suggest that Aβ imaging may be useful to distinguish FTD from AD. Together, these studies demonstrate that 11-25% of patients with clinically diagnosed FTD have abnormally increased cortical Aβ deposition as measured with [11C]PIB or [18F]fluorbetaben (53-55). None of these studies had autopsy confirmation, and the significance of the Aβ deposition in the FTD subjects is unclear. One hypothesis is the small percentage of patients with FTD and abnormal cortical Aβ deposition may be in part explained by co-morbid FTD and AD in the same patient.

Dementia with Lewy bodies (DLB)

1) [18F]FDG-PET

[18F]FDG has shown utility in distinguishing AD from DLB based on different patterns of decreased regional brain glucose metabolism.(56, 57) The pattern of decreased brain [18F]FDG uptake in DLB is similar to AD with the exception of involvement of occipital cortex, particularly the primary visual cortex, in DLB but not AD. In studies of subjects with AD and DLB, the reported sensitivities and specificities are variable with ranges of values of 75 -83% and 72-93%, respectively.(31) (32, 56) In a study combining both clinical and histopathologic confirmation of diagnosis, [18F]FDG-PET was found to have a 90% sensitivity and 80% specificity for distinguishing AD from DLB.(56)

2) SPECT perfusion

Studies examining the ability of ^{99m}Tc-labeled ECD and HMPAO to distinguish AD from DLB have shown similar sensitivity and specificity as [^{18}F]FDG-PET.(58) The regional pattern of decreased brain perfusion is similar to the pattern of glucose metabolism observed with [^{18}F]FDG. Some studies have reported 85% sensitivity and 85% specificity for this indication, (59) although other groups have found substantially lower values (sensitivity of 65%, specificity of 87%) (60). Additionally, these studies used clinical diagnosis as the reference standard and were not histopathologically confirmed.

3) Dopamine transporter (DAT) imaging

The SPECT agent [^{123}I]FPCIT (ioflupane) has been used to discriminated DLB from other dementias based on the loss of dopaminergic neurons which in turn leads to decreased DAT density in the striatum. This agent has also been used to study the loss of dopaminergic neurons that occurs in Parkinson's disease and related syndromes and is clinically approved for clinical use in Europe and the U.S. to distinguish Parkinsonian syndromes from essential tremor (61). A 2007 multicenter trial in Europe with 326 subjects demonstrated that FPCIT has a sensitivity of 78% and specificity of 90% for distinguishing DLB from other dementias, primarily AD, using clinical diagnosis as the reference standard (62). A smaller retrospective study (n=44) demonstrated lower sensitivity (63%) but higher specificity (100%) based on consensus diagnosis after 12 month follow up as the reference standard (63). A small prospective study that included 20 patients with dementia and pathologic analysis at autopsy, FPCIT was 88% specific and 100% specific for differentiating DLB from other dementias compared to lower values of 75% and 44%, respectively, based on initial clinical diagnosis (64).

4) Amyloid agents

There is insufficient data to use amyloid imaging agents to distinguish DLB from AD. The available data suggests that Aβ deposition occurs frequently in DLB and may correlate with cognitive deficits.(65, 66)

Progress Toward Diagnostic Imaging Biomarkers for Child Psychiatric Disorders

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Among the most important scientific trends in the past thirty years is the growing recognition that neuropsychiatric disorders are developmental disorders, with antecedents starting in childhood. Though in some respects, this "back-to-the-future" phenomenon takes us back to psychiatry's founding, it differs from prior incarnations in an important aspect: empirical data. Starting with the Decade of the Brain initiative in the 1990s and continuing with the present emphasis on translational research, studies have shown that psychiatric illness can start in childhood, and such patients have brain/behavior alterations from typically-developing controls (TDC) without psychopathology. This neuroimaging research is critically important to understanding the pathophysiology of child psychiatric disorders, holding the promise of future biomarkers that could augment clinical history for better, more specific, and earlier psychiatric diagnosis and treatment—akin to methods currently employed to fight cancer with greater and greater success.

To qualify as a potential biomarker, a finding must not only be a quantitative difference between participants with one or another specific condition, such as attention deficit hyperactivity disorder (ADHD), and typically-developing controls (TDC) without psychopathology, it must also be specific to ADHD relative to other psychiatric conditions. At least three possible study designs can examine specificity: (1) multi-group studies (e.g., ADHD vs. TDC vs. third group whose psychopathology is closely related to ADHD, such as oppositional defiant disorder or another form of cognitive impairment); (2) computer algorithms that predicts if a participant has ADHD or not based on neuroimaging parameters (also known as machine learning); or (3) studies employing pre- and post-treatment neuroimaging to identify neural predictors of treatment response. Finally, the finding would have to be independently replicated. Taken as a whole, at this point in time, although the majority of such findings in child psychiatric disorders demonstrate important, but relative, quantitative differences, the differences are not yet sufficiently large, specific, or replicated to serve as neuroimaging biomarkers that are useful in making a psychiatric diagnosis on a case-by-case basis. In fact, in terms of providing clinically useful information, few if any results suggest any diagnostic utility for imaging beyond ruling-out the presence of known neurological illnesses. Of course, the hope is that continued progress in current

methods will one day lead to improvements in this situation.

We focus our attention on three of the most important categories of child psychiatric disorders: (1) attention deficit/hyperactivity disorder [ADHD], (2) mood and anxiety disorders (including major depressive disorder [MDD], bipolar disorder [BD], and generalized anxiety disorder [GAD]), and (3) autism spectrum disorders (ASD; including autistic disorder and Asperger's disorder).

ADHD

Attention-deficit/hyperactivity disorder (ADHD)

ADHD is among the most common psychiatric disorders affecting children, with 6-9% of children and adolescents struggling with ADHD (1). ADHD involves developmentally-inappropriate symptoms of inattention, hyperactivity and impulsivity, with resultant functional impairment, including academic underachievement and school failure, problems in social relations with adults and peers, risk for antisocial behavior patterns including substance use, and increased levels of risky sexual behavior (2-4).

Research has suggested that fronto-striatal alterations lie at the core of ADHD. One of the most interesting lines of research supporting this position comes from longitudinal imaging studies of children with ADHD as they progress through adolescence and young adulthood. These structural MRI studies have demonstrated that ADHD is unlikely the result of a static, unchanging lesion, but rather represents a developmental lag in neural development (5-7). Moreover, this provides biological evidence for the persistence of ADHD into adulthood for some patients, in contrast to the belief that ADHD only affects children.

While these data are important advances that contribute to our understanding of the brain and behavior interactions underlying ADHD, there is no current neuroimaging biomarker for ADHD. The vast majority of neuroimaging studies to date demonstrate relative, quantitative differences between ADHD and TDC participants that are neither sufficiently large nor specific enough to be useful on a case-by-case basis as a diagnostic or treatment biomarker. Below, we discuss studies that have begun to address this scientifically and clinically important need.

Pediatric ADHD: Structural MRI Studies

As is true for many neuropsychiatric disorders, the vast majority of structural MRI studies in ADHD are cross-sectional studies that compare the volume of certain brain regions of interest (ROIs) in ADHD vs. TDC participants. However, a handful of studies have begun to test the specificity of such alterations.

Among the earliest examples was a 1996 study by Semrud-Clikeman et al. who used ROI measurements to predict group membership for children ages 6-16 years old who were diagnosed as either ADHD combined type (n =10), dyslexic (N=10), or TDC (n=10). Using predictive discriminant analysis based on six ROI measurements, including length of the left and right plana temporala, length of the left and right insula, and width of the left and right anterior frontal region, they achieved a 60% accuracy in predicting diagnosis. When the model expanded to include age and full-scale intelligence quotient (FSIQ), accuracy improved to 87%. Further testing showed that the left insula length, left planum length, and right frontal region width were particularly useful indices for discriminating between groups (8).

Additionally, Kates et al. 2002 examined the specificity of deficits in the frontal-striatal-thalamic circuitry in boys ages 7-12 years-old with ADHD (N=13), Tourette's syndrome (TS; N=13) and age- and gender-matched controls(N=13) using a frontal lobe subparcellation protocol that combined contiguous sulcal and gyral boundaries to derive frontal lobe modules based on prior functional studies. They found significantly reduced gray and white matter volumes in the PFC among ADHD boys vs. those with TS or TDC. However, these PFC differences were no longer significant when expressed as a ratio of total cerebral volume (9).

A third and more recent 2010 study by Soliva et al. used computer modeling to examine caudate body volume (CBV) as a potential neuroimaging biomarker for ADHD. Prior work had shown that ADHD vs. TDC participants had significantly decreased right CBV, but no significant changes in left CBV or bilateral caudate head volume (10). Soliva employed this finding to determine if the ratios of right CBV to total bilateral caudate volume(rCBV/tbCV) and right CBV to bilateral caudate body volume (rCBV/bCBV) could predict the diagnostic status of children with and without ADHD (ages 6-17; N=39 per group). Indeed, the rCBV/bCBV ratio was found to be statistically different between the groups (t=3.16, p=0.001) with a large effect size (Cohen's d=0.84). Using non-parametric receiving operator characteristic (ROC) analysis for the rCBV/bCBV ratio, they found an area under the curve (AUC) of 0.84, with a sensitivity of 60% and specificity of 95%. Assuming an ADHD prevalence rate of 10%, the rCBV/bCBV ratio method yielded a specificity of 94.74% and an estimated negative predictive value of 93.64%. Taken as a whole, this study suggests the critical importance of the caudate in ADHD, although the potential role of the CBV as a neuroimaging biomarker of ADHD requires independent replication and demonstration of specificity via a multi-group study involving a psychiatric control group of children whose psychopathology is closely related to ADHD, such as ODD or other cognitive issues (11). Moreover, the conclusions across

these first two studies are quite different, demonstrating the failure to provide independent documentation of comparable effects.

A fourth study by Lopez-Larson et al. (2009) provided an example of such a multi-group study. They conducted a four-group ROI analysis of children ages 6-19 years: (1) ADHD alone (N=23), (2) pediatric BD alone (N=30), (3) pediatric BD plus ADHD (N=23), and (4) TDC (N=29). They found that ADHD-only participants had significantly smaller amygdala, caudate, and putamen volumes compared to BD youths with and without ADHD and also to TDC with medium to large effect sizes. Although this study did not test the predictive value of the rCBV/bCBV ratio of Soliva et al. above, it did complement that study in supporting further study of caudate volume as a potential neuroimaging biomarker for ADHD (12).

Similarly, Liu et al. (2011) recently published very similar data examining a four-group ROI analysis of children ages 9 to 18 years-old with: (1) ADHD alone (N=11), (2) pediatric BD alone (N=12), (3) pediatric BD plus ADHD (N=17), and (4) TDC (N=24). Consistent with Lopez-Larson et al. 2009, Liu found that children and adolescents with ADHD had disorder-specific reductions in bilateral caudate and putamen volumes. Additionally, Liu identified BD-specific increases in caudate, putamen and globus pallidus volumes in youth with pediatric BD alone (13).

In a meta-analysis utilizing a combination of Activation Likelihood Estimation (ALE) and the rank approach used in Genome Scan Meta-Analysis (GSMA), Ellison-Wright et al 2008 examined structural MRI results from 7 studies comparing youth with ADHD (N=144) to TDCs (N=143). They found significant regional grey matter reduction in the right putamen/globus pallidus region for ADHD vs. TDC participants (14). Notably absent from structural neuroimaging literature examining biomarkers of ADHD are treatment studies which contrast morphometric differences before and after medication treatment. To our knowledge, no controlled trials have examined the effect of stimulant medication on structural brain abnormalities in youth with ADHD suggesting a critical area for future research. Additional limitations include small samples sizes, limited exploration of ADHD subtype effects, and examination of medicated youth with ADHD as opposed to youth with ADHD off medication. Furthermore, the aforementioned studies demonstrate few strongly replicated findings. For example, some have demonstrated basal ganglia volumetric alterations (12, 13), while others have not (6, 15, 16). These inconsistencies highlight the need for replication with larger sample sizes to resolve inconsistencies and examine potential effects of ADHD subtype and medication status.

Pediatric ADHD: Diffusion-tenor imaging (DTI)

DTI is another form of structural MRI whose goal is the evaluation of white-matter integrity and connectivity. Two studies have begun to advance the study of putative white matter biomarkers of ADHD by evaluating the specificity of such alterations vis-à-vis participants with other forms of psychopathology.

Pavuluri et al. (2009) conducted a three-group DTI study among children with ADHD (N=13), BD (N=13), or age- and IQ-matched TDC (N=15). They found that ADHD youths had significantly lower fractional anisotropy (FA) and regional fiber coherence index (r-FCI)—i.e., measure of the degree of coherence in a given fiber tract—in white matter fibers of the internal capsule coursing between the neocortex and the brainstem compared to BD and TDC youths. Moreover, ADHD youths had significantly greater apparent diffusion coefficient (ADC)—i.e., the average diffusion rate among different diffusion directions under a Gaussian distribution—than either BD or TDC participants in all eight white matter tracts. Both ADHD and BD youths had significantly lower FA in the anterior corona radiata (ACR) compared to TDC. From this, the authors concluded that ADHD is characterized by more diffuse white matter changes, whereas those in BD youths are more focal, residing in the prefrontal ACR and posterior cingulate (17).

Davenport et al. 2010 also conducted a three-group DTI study, comparing white matter integrity in adolescents ages 10-20 years old with ADHD (N=14), schizophrenia (N=15), or TDC (N=26). ADHD participants had signify-cantly higher FA in the left inferior and right superior prefrontal regions than either those with schizophrenia or TDC. In contrast, participants with schizophrenia had significantly lower FA in the bilateral cerebral peduncles, anterior and posterior corpus callosum, right anterior corona radiata, and right superior longitudinal fasciculus vs. those with ADHD or TDC. Both patient groups had lower FA in left posterior fornix than TDC participants. The authors conclude that although patients with ADHD or schizophrenia share some overlapping cognitive and behavioral deficits, such as deficits in working memory, sustained attention, and response inhibition (Barr, 2001; Oie & Rund, 1999), these deficits originate from different white matter alterations (18).

A recent review of the child/adolescent and adult ADHD DTI literature by Konrad and Eickhoff (2010) suggests the need for future studies to examine the trajectory of white matter development and anatomical connectivity as findings from structural studies emphasize reductions in overall white matter volume in youth with ADHD while studies in adulthood indicate an overall increase in white matter volume (19). Further, DTI studies suggest decreased coherence and integrity of white matter tracts connecting the right prefrontal cortex to the basal ganglia and in the tracts connecting the cingulate gyrus to

the entorhinal cortex in youth with ADHD compared to TDCs (20;21). Therefore, additional research is needed to elucidate how changes in anatomical structures over time in individuals with ADHD relate to connectivity both at rest and during task-engagement as well as relating DTI findings to functional brain networks.

Pediatric ADHD: Functional MRI (fMRI)

Event-related fMRI studies have evaluated the neural activation linked to several cognitive tasks associated with particular symptoms in ADHD. The following fMRI studies have begun to address questions of specificity inherent in delineating potential neuroimaging biomarkers.

Three studies by Rubia and colleagues have evaluated the specificity of brain/behavior alterations underling inhibitory control associated with ADHD. In the first, Rubia et al. 2008 conducted a multi-group event-related fMRI study of inhibitory control in boys ages 9-16 years with either ADHD (N=20), conduct disorder (CD, N=13), or TDC (N=20). They found that ADHD participants had specific decreases in neural activation during successful inhibition trials vs. CD and TDC participants in the left dorsolateral prefrontal cortex (DLPFC) and inferior PFC (22). In a related second study, Rubia et al. 2009 examined cognitive interference and attention using a Simon game task in boys ages 9-16 years with ADHD (N=20), CD (N=13), or TDC (N=20). No ADHD-specific brain activation changes were identified during interference inhibition. However, during the attention allocation aspect of the task, the ADHD group had a specific under-activation in the left ventrolateral prefrontal cortex (VLPFC), while both ADHD and CD participants had reduced activation in right dorsomedial prefrontal cortex (DMPFC) (23). A third study by Rubia et al. 2010, compared inhibitory control in boys ages 9-16 years with either ADHD (N=18), obsessive-compulsive disorder (OCD, N=10), or TDC (N=20). They found that ADHD participants had specific alterations in the right inferior PFC, but ADHD and CD participants had dysfunction in the right ventromedial orbitofrontal cortex (OFC) during successful inhibition and in left medial PFC during inhibition failures (24). Taken together, these studies suggest that PFC alterations during response inhibition may be specific to ADHD, though replication in larger, independent samples is needed.

Brotman et al. sought to determine the specificity of emotional face processing alterations previously identified in BD youths by conducting a four group study of children and adolescents ages 8-17 years with either: (1) ADHD (N=18), (2) BD (N=43), (3) severe mood dysregulation (SMD; N=29), or (4) TDC (N=37). ADHD participants had significantly increased neural activity in the left amygdala when rating their fear of emotionally neutral faces compared to BD, SMD, and TDC participants. Although ADHD is primarily considered to be a behavioral disorder, this finding aligns with others' suggestion of the need to study the neural underpinnings of affect in ADHD (25). Additional findings and implications with respect to pediatric BD are discussed below in the mood disorders section (26). Passorotti et al evaluated unmedicated ADHD patients (N=11), unmedicated BD youths (N=15), and TDC (N=15) on a motor response inhibition task. They found that ADHD participants had reduced activation in the ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC) vs. both BD and TDC participants (27).

Augmenting task-dependent event-related fMRI, the past several years have witnessed a groundswell of interest in task-independent fMRI—i.e., spontaneous fMRI neural activation data collected while the participant is at rest ("resting state" fMRI). Studies suggest that 95% of the brain's metabolism is devoted to such resting-state activity, in contrast to the estimated 5% devoted to task-dependent activities (28-30). Discovery science in resting-state fMRI is particularly robust in ADHD, due in part to the "1000 Functional Connectomes Project" whereby researchers have posted their resting state fMRI data on the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) website (www.nitrc.org/projects/fcon_1000), making it freely available to all those wanting to push the limits of what the data can tell us about the brain. This also includes the ADHD-200, a competition to encourage researchers to develop machine-learning methods to classify participants based on ADHD yes/no status (http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html).

This is likely to result in numerous future publications, though the first such study was conducted by Zhu et al. 2008. This study employed regional homogeneity (ReHo) methods to classify youth with ADHD (N=12) and TDC (N=12). They found a generalization rate of 85%, sensitivity of 78% and specificity of 91%. Several areas were identified as highly discriminative, including the anterior cingulate gyrus, PFC, putamen, occipital cortex, temporal cortex, cerebellum, and thalamus (31). To date, few functional neuroimaging studies of ADHD youth have employed meta-analytic approaches to examine consistencies within the literature. Of note, Dickstein et al. 2006 utilized ALE to evaluate 16 functional neuroimaging studies comparing patients with ADHD to TDCs. While studies included both adult and child/adolescent samples, results suggested a consistent pattern of widespread frontal hypoactivity involving the anterior cingulate, dorsolateral prefrontal, inferior prefrontal, and orbitofrontal cortices, portions of the basal ganglia and the parietal cortices in patients with ADHD compared to TDCs. Removal of adult studies did not result in the detection of additional regions of interest; however, effect sizes were reduced when examining child- or adolescent-only studies (32).

Moving forward, meta-analytic techniques, such as ALE, need to be employed focusing on functional

neuroimaging studies of only children and adolescents. Moreover, domain specific (e.g., motor inhibition, working memory, attentional control, etc.) meta-analyses of functional findings are needed given inconsistencies within the literature. Use of different behavioral tasks to assess functional differences also limits replication, and small sample sizes limit generalizability.

Mood and Anxiety Disorders

Beyond ADHD, neuroimaging research has also advanced our understanding of the brain and behavior interactions underlying pediatric mood (i.e., major depressive disorder [MDD] and bipolar disorder [BD]) and anxiety disorders. As in ADHD, the majority of studies to date have employed cross-sectional MRI methods to identify structural, DTI, and fMRI differences between participants affected by depression, anxiety, or BD compared to TDC. Given the considerable overlap between these disorders, although quantitative differences have been identified by such studies, there is considerable need to probe their specificity, to independently replicate their findings, and to delineate their longitudinal trajectory. Thus, there are no neuroimaging findings that would be considered biomarkers for pediatric mood and anxiety disorders on a case-by-case basis at present, though the discovery of such biomarkers is an important and needed goal.

Depression

Depression causes significant morbidity and mortality in children, adolescents, and young adults annually, including school and work absenteeism, substance abuse, and inter-personal conflict (33, 34). More disturbing is the fact that suicide perennially remains among the top four causes of death in those ages 10-24 years old in the U.S. (35).

Neuroimaging studies of pediatric depression have focused primarily on the amygdala as well as the PFC, including the OFC and anterior cingulate cortex. Yet, there is relatively little consistency in the direction (increased vs. decreased) of these findings, regardless of whether the neuroimaging method involves structural MRI, fMRI, or DTI. For example, of three structural MRI studies of amygdala volume in pediatric depression vs. TDC, one study reported bilateral decreases (36) while two failed to find such significant differences (37, 38).

Unfortunately, there are no studies employing machine learning or computer models of structural MRI, fMRI, or DTI data as potential diagnostic tools.

Depression: Structural MRI

Fallucca et al. 2011 conducted the only multi-group structural MRI study of pediatric depression, comparing those with MDD (N=24; mean age 13.96+2.41), obsessive-compulsive disorder (OCD; N=24, mean age 13.02+2.92), and TDC (N=30; mean age 14.11+2.57). Focusing on cortical thickness, they found that the right peri-calcarine gyrus, post-central gyrus, and superior parietal gyrus were thinner in depressed vs. OCD and TDC youths, whereas the left-sided temporal pole was thicker in depressed youths than in either group. Moreover, secondary analyses showed that these cortical thickness differences were primarily driven by children with MDD plus a family history of MDD (N=15) (39)—a finding directly in contrast with those of Nolan et al. 2002. Specifically, Noalan et al. did not find PFC volume differences when comparing depressed youth with depressed family members to TDC . Instead, they found that depressed youth with non-familial MDD had significantly larger left PFC than those with familial MDD or TDC (40). Such inconsistencies highlight the current state of the neural underpinnings of pediatric depression. To allow for comparison across studies, further efforts are needed utilizing standardized methods of assessment and longitudinal design that account for extraneous factors (e.g., family history, comorbid conditions, age, medication status).

Unfortunately, to the best of our knowledge, no structural MRI studies have employed machine learning or leveraged studies combining neuroimaging with psychopharmacological or psychotherapeutic treatment to advance our potential understanding of structural MRI biomarkers associated with pediatric depression.

Depression: Diffusion Tensor Imaging (DTI)

While a few DTI studies have examined potential white matter abnormalities associated with pediatric depression, none are known to gauge the specificity of findings through use of a multi-group design (41, 42).

Depression: Functional MRI (fMRI)

The state of fMRI research in pediatric depression mirrors that of structural MRI studies in that few have probed the specificity of difference between MDD vs. TDC youths.

In fact, only three known studies have begun to evaluate the specificity of emotional face processing in pediatric depression. In the first, Thomas et al. 2001 compared emotional face processing in girls with either MDD, anxiety (i.e., primary generalized anxiety disorder [GAD} or panic disorder), or TDC (N=5 in each of these three groups; mean age of each sample approximately 12 years). They found that depressed girls had significantly less left amygdala activity than anxious or TDC girls when viewing faces regardless of the stimuli's emotional content (43). One strength of this research is the use of a multi-group design—comparing youth with MDD to TDC and another clinical group. However, complicating these findings is the reliance on such small samples, as well the

comorbid conditions potentially unaccounted for. While none of the anxious youth were diagnosed with MDD, 2/5 youth with MDD had GAD.

In the second, Roberson-Nay et al. 2006 evaluated emotional face encoding using a subsequent memory paradigm. Specifically, participants first completed an event-related fMRI scan requiring them to attend to emotional face stimuli. Then they completed a post-scan memory task that required them to identify if they had, or had not, seen emotional face stimuli during their fMRI. Unlike Thomas and colleagues who found decreased amygdala activity among depressed youth, they found that MDD youths (N=10; age=13.8+2.7 years) had increased left amygdala activity when successfully encoding emotional faces compared to anxious (N=11; age=11.5+1.5 years) and TDC (N=23; age=14.8+2.2 years) participants (44). Again, a notable subset of depressed youth had comorbid anxiety (i.e., 4/10) while no anxious (i.e., 3 separation anxiety, 3 social anxiety, 9 GAD) were given a comorbid MDD diagnosis.

In the third study, Beesdo et al. compared face viewing in three groups of children ages 7-17 years: (1) MDD (N=26; 14 with comorbid anxiety and 12 without comorbid anxiety); (2) anxious youths without depression (N=16), and (3) TDC (N=45). Among their findings, they noted disorder-specific alterations when passively viewing faces, with MDD participants having decreased activation, and anxious participants having increased activation, when viewing fearful vs. happy faces. Addressing the potential of comorbidity lacking in other studies, Beesdo and colleagues found that excluding the subset of adolescents with comorbid MDD and anxiety did not alter results (45).

Forbes et al. 2010 then paired fMRI with a treatment study to evaluate neural predictors of treatment response. This study compared pre- and post-treatment neural activity on a reward anticipation task among depressed adolescents (N=13) receiving either cognitive behavioral therapy (CBT; N=7) or CBT plus a selective serotonin reuptake inhibitor (SSRI; N=6). Among their findings, they demonstrated that less medial PFC and greater striatal activity pre-treatment was associated with post-treatment clinical severity and reductions in comorbid anxiety symptomatology. Importantly 10 of 13 participants had co-morbid generalized anxiety disorder (GAD). This suggests that fronto-striatal activity may be important in pediatric depression, as well as highlighting the potential phe-nomenological and/or DSM-IV nosological conundrum of the overlap between MDD and GAD, especially in children where irritable mood can serve as a diagnostic symptom for either disorder (46).

Taken as a whole, although there clearly have been strides toward understanding the pathophysiology of pediatric depression, findings can best be described as preliminary as studies have used varying cross-sectional methodologies (e.g., different MRI tasks) with small samples of diagnostically complicated youth (e.g., presence of comorbid diagnoses). To better examine the diagnostic specificity of neural differences and gauge their worth as potential biomarkers, future studies should therefore aim to replicate previous findings with larger samples, using similar (if not the same) imaging paradigms—particularly to compare depressed youth to TDC, as well as other clinical groups.

Anxiety Disorders

There are more than ten separate anxiety disorders recognized by current psychiatric nosology as depicted in the *Diagnostic and Statistical Manual, 4th Edition-Text Revision* (*DSM-IV-TR*). While excessive fear, avoidance and/or worry are shared by all anxiety disorders, we will focus this review on the group of anxiety disorders often referred to as the "phobias"—i.e., generalized anxiety (GAD), social anxiety (SOC), panic (PD), separation anxiety (SAD), and specific phobias (SP) disorders as they are commonly collapsed under the umbrella term of 'anxiety disorders' in studies examining clinical features, functional impairment and neural underpinnings of the classification category. This grouping is largely consistent with the findings of several important studies describing the structure of psychopathology, as these disorders are described as the fear-based internalizing disorders (com-pared to dysphoric or distress disorders which include GAD, MDD, and dysthymia) (47-49). GAD was nevertheless included in this grouping given its relevance (and high co-occurrence) with other anxiety disorders, as well as the paucity of efforts existing to delineate the pathophysiology of GAD alone (50). With respect to other anxiety disorders, evidence suggests that OCD and post-traumatic stress disorder may have differing neurobiology from "phobic" anxiety disorders. That said, studies of anxiety implicate a "fear circuit" consisting of the amygdala, medial and lateral PFC, and hippocampus in the biology of anxiety disorders. More broadly, these studies include animal models, typically developing humans across the lifespan, and adult patients diagnosed with anxiety. Neuroimaging studies of pediatric anxiety have focused on these ROIs, though conclusions about potential biomarkers are again limited by relatively small sample sizes and the need for more studies that can test the specificity of such findings.

Pediatric Anxiety Disorders: Structural MRI

Structural MRI studies have implicated the amygdala in the pathophysiology of pediatric anxiety. However, the direction (increased or decreased) of these findings vs. TDC participants is often inconsistent. For example, De Bellis et al. found that GAD participants (N=12; age 12.7+2.4) had significantly larger right and total amygdala volumes vs. age-, sex-, height-, and handedness-matched

TDC (N=24; age=12.5+2.3years) (51). In contrast, Milham et al. found the opposite, with anxious youths (GAD, separation anxiety disorder, and/or social phobia; age 12.9+2.3) having decreased left amygdala volume and no difference in either right or total amygdala volume vs. age-, gender-, and intelligence-matched TDC (N=34; age 12.4+2.2 years) (52).

To the best of our knowledge, no study has tested the specificity of potential structural MRI alterations in pediatric anxiety disorders. This deficiency is related to the lack of large, well-powered multi-group studies, studies using machine learning or other computer algorithm, and studies linked to pharmacological or psychotherapy treatment.

Pediatric Anxiety Disorders: Diffusion Tensor Imaging (DTI)

Unfortunately, to the best of our knowledge, there are no DTI studies that evaluate the specificity of white matter abnormalities in pediatric anxiety disorders (i.e., GAD, SOC, SAD, PD, SP).

Pediatric Anxiety Disorders: Functional MRI

As in studies of pediatric depression, several studies have used event-related fMRI to examine the brain/behavior interactions underlying pediatric anxiety disorders. Also as in studies of depression, many of these have employed emotionally-valenced visual stimuli, including faces, and have focused on the amygdala given its role in both fear circuitry and face processing.

In fact, the multi-group studies by Beesdo et al. and Thomas et al. described above in the pediatric depression section are among the best examples. Specifically, Beesdo et al. found that anxious youths without depression (N=16) had significantly greater amygdala activation when passively viewing fearful vs. happy faces compared to those with MDD plus comorbid anxiety (N=26; age 14.08+2.23) and to TDC participants (N=45; age 13.93+2.18) (45).

Additionally, Thomas et al. found similar patterns of exaggerated amydala activity for a small sample of anxious youth (N=5; drawn from larger sample with mean age=12.8+2.1 years) vs. TDC participants (N=5; drawn from larger sample with mean age=12.1+2.6 years) and depressed peers (N=5; mean age=12.3+2.7 years). While both anxious and TDC youth showed overall increased amygdala activity when viewing faces regardless of emotional content, only the anxious youth had signify-cantly increased right amygdala activity when viewing fearful vs. neutral faces, and the magnitude of this neural activation correlated positively with child-reported anxiety on the Screen for Child Anxiety Related Disorders (SCARED). In contrast, the depressed group showed decreased left amygdala activity when viewing fearful faces (43).

Other fMRI studies, while not outright comparing two patient groups to TDC participants, have at least attempted to acknowledge the potential role of comorbid conditions.

In this vein, Monk et al. compared GAD participants (N=17; age=13.13+2.09 years) to TDC participants (N=12; age=14.33+1.67 years) while attending to emotional faces. Their main finding was that GAD participants had significantly increased amygdala activity vs. TDC when viewing angry faces, and that level of activation was significantly and positively correlated with anxiety disorder severity (based on participants' Pediatric Anxiety Rating Scale scores [PARS]). Post-hoc comparisons to test specificity showed that both GAD only (N=9) and those with both GAD and MDD (N=8) had greater amygdala activation than TDC, suggesting that comorbid depression was not driving their results (53).

Similarly, Lau et al. evaluated phenotype/genotype interactions among participants with GAD and/or MDD (N=31; age=13.52+2.32 years) to TDC participants (N=33; age=13.71+2.73 years) using neural activation from an emotional face attention task and genotypes of the serotonin transporter gene. Their main finding was a significant 3-way genotype X diagnosis X face emotion interaction, with GAD/MDD participants with two copies of the LA allele showed greater amygdala responses to fearful faces compared to GAD/MDD participants with S or LG alleles. This finding did not change when excluding patients with MDD only (54).

No studies have employed machine learning techniques to evaluate fMRI neuroimaging findings as potential biomarkers of pediatric anxiety disorders. However, McClure et al. have paired neuroimaging with treatment to explore potential neural markers of treatment response. Specifically, they demonstrated that greater pre-treatment amygdala activation during a face-attention task was significantly associated with better treatment response (based on Clinical Global Impressions Severity scores) for youth with primary GAD or SOC (N=12, age=11.8+1.8 years) receiving either 8-weeks of CBT (N=7) or fluoxetine (N=5). Of note, treatment type (psychotherapy vs. medication) was chosen by families, and all participants significantly improved during treatment, though neural predictors of treatment outcome were not compared across treatments (55).

To address this limitation, Maslowsky et al. 2010 extended McCLure's data by comparing ventrolateral PFC (VLPFC) and amygdala activity for GAD participants treated with CBT (N=7; age 13.4+1.7 years) and fluoxetine (N=7; age=13.3+2.5 years). While both groups significantly improved and had increased post- vs. pre-treatment VLPFC activity, only the CBT group had increased bilateral amygdala activity. Post-treatment VLPFC or amygdala

activation did not significantly relate to the decrease in anxiety symptoms from pre- to post-treatment (56).

In summary, the current state of neuroimaging as a potential biomarker of pediatric anxiety disorders resembles that of depression—i.e., these data are important clues about the pathophysiology of anxiety, but they are far from ready for clinical application to the diagnosis and treatment of anxiety disorders in children. For this to ever become a reality, we need more studies, involving large samples and longitudinal assessments. There is also a need to determine the specific brain/behavior interactions underlying particular types of anxiety, rather than clustering them.

Pediatric Bipolar Disorder (BD)

Pediatric bipolar disorder (BD) is among the most controversial of all psychiatric disorders affecting children and adolescents today. Although pediatric BD was once thought to be quite rare, recent studies demonstrate a marked increase in numbers of children and adolescents being diagnosed with BD. This rise from the mid-1990s through the present has been demonstrated in both inpatient psychiatric and outpatient medical settings in the U.S., as well as internationally, including Germany (57-59). Thus, there is a pressing need to understand the brain/behavior interactions underlying pediatric BD.

Research has focused on fronto-temporal neurocircuitry. In particular, researchers have explored the relationships between frontal regions of the DLPFC and VLPFC, temporal regions, including the amygdala, and striatal regions, including the caudate and accumbens area. As highlighted below, there are a number of multi-group studies and treatment/imaging studies that have begun to evaluate the specificity of these neuroimaging findings in BD youths, but there are few studies that employ machine learning or other computer algorithms to predict diagnostic status or treatment outcome. Such work is progressing, but is important to note that, as in the other disorders discussed, there is no current neuroimaging biomarker for pediatric BD that is useful on a clinical case-by-case basis.

Pediatric BD: Structural MRI

Structural MRI studies have implicated alterations in the fronto-temporal regions in the pathophysiology of pediatric BD. By far, the most consistent anatomical finding in pediatric BD is significantly reduced amygdala volume compared to TDC, now found in seven of nine cross-sectional structural MRI studies to date (60-66), but not in two others (12;67). In fact, this is more replicated than most neuroimaging findings across all forms of pediatric or adult psychiatric illness.

Although there are few multi-group structural MRI studies that compare BD youths to those with other forms of psychopathology, it is interesting to note that the two that failed to find significant decreases in amygdala volume were multi-group studies. Specifically, Lopez-Larson et al. studied four groups of children: (1) those with BD plus comorbid ADHD (N=23), (2) those with BD without ADHD (N=30), (3) those with ADHD without BD (N=23), and (4) TDC participants (N=29). They found that ADHD youths had significantly smaller total amygdala volume as well as total caudate and putamen volume vs. BD with ADHD, BD without ADHD, and TDC groups (12).

Frazier et al. also conducted a four-group cross-sectional MRI study, including the following: (1) BD plus psychosis (N=19), (2) BD without psychosis (N=35), (3) schizophrenia (N=20), and (4) TDC (N=29). There were no significant differences between BD and schizophrenia groups with respect to amygdala (or hippocampal) volume. However, they did identify a group X sex interaction, with schizophrenic males having the smallest left amygdala volume, while BD females having the smallest hippocampal volumes (67).

Other multi-group studies have evaluated volumetric alterations in other brain regions. For example, Liu et al. compared the following four groups of children and adolescents: (1) BD plus comorbid ADHD (N=17), (2) BD without ADHD (N=12), (3) ADHD without BD (N=11), and TDC (N=24). Although the ADHD-only findings have been discussed in the ADHD section, it is notable that Liu found that BD-only participants had larger caudate, putamen, and globus pallidus volumes than the other groups (13).

Chiu et al. evaluated anterior cingulate gyrus volume in children with (1) BD (N=16), (2) autism spectrum disorders (ASD, N=24), and (3) TDC (N=15). They found that BD participants had significantly smaller left ACG volumes compared to both the ASD and TDC participants. There was no such difference in right ACG volume (68).

Pediatric BD: Diffusion Tensor Imaging (DTI)

Few DTI studies have evaluated the specificity of white matter alterations to pediatric BD by conducting multi-group studies. In one, Frazier et al. compared children (1) with BD (N=10), (2) at-risk for BD by having a first-degree relative with BD (N=7), and (3) TDC (N=8). The BD group had decreased FA in the cingulate-paracingulate white matter vs. both at-risk and TDC participants, whereas both BD and at-risk participants had reduced FA in the bilateral superior longitudinal fasciculus (69). In another study, Pavuluri et al. compared FA in children with (1) BD (N=13), (2) ADHD (N=13) and (3) TDC (N=15). No findings distinguished the BD participants from either the ADHD or TDC groups (17).

Pediatric BD: Functional MRI (fMRI)

FMRI studies of pediatric BD participants have probed the brain and behavior interactions underlying a number of cognitive and emotional processes, including emotional face processing, attention, and cognitive flexibility. Most of these studies have identified relative differences between BD and TDC youths. However, some have begun to address issues of specificity by multi-group comparisons or by pairing imaging with treatment.

For example, Brotman et al. evaluated attention to emotional faces by comparing youths diagnosed with: (1) BD (N=43), (2) ADHD (N=18), (3) severe mood dysregulation (SMD (70); N=29), and (4) TDC participants (N=37). Whereas prior studies had demonstrated that pediatric BD participants had altered PFC–amygdala–striatal neural activation vs. TDC children when viewing faces, including pictures of faces with happy, angry, or neutral emotions (66;71;72), Brotman et al. did not find BD-specific findings. Instead, in addition to the ADHD-specific findings discussed in the ADHD-fMRI section, Brotman et al found that SMD participants had significantly decreased amygdala neural activation vs. those either meeting Leibenluft et al. 2003's criteria for narrow-phenotype BD (i.e., having clear-cut episodes of mania with elevated, expansive mood), or those with ADHD or TDC (26;70).

Thomas et al. used an implicit face-emotion processing task to demonstrate that BD participants (N=20) had significantly less amygdala activity in response to angry vs. neutral faces than either SMD (N=21) or TDC participants (N=16) (73).

Passarotti et al. employed an emotional valence Stroop task (i.e., requiring participants to match the color of a positive, negative or neutral word to a one of two presented colored circles) to study children and adolescents with either (1) BD (N=17), (2) ADHD (N=15), and (3) TDC (N=14). Both BD and ADHD participants had greater DLPFC and parietal cortex activation than TDC when viewing negative vs. neutral words. Despite these shared regions of hyperactivity, differences between the patient groups also emerged. Specifically, BD participants had greater activation in the VLPFC and ACC, whereas the ADHD group showed decreased VLPFC and ACC activity (74).

Passarotti et al. again compared youth with BD (N=23) or ADHD (N=14), and TDC (N=19) participants while watching faces. They found that BD participants had greater activity in regions implicated in emotional processing (e.g., left medial PFC, subgenual ACC), while the ADHD group showed greater activity in regions implicated in prefrontal working memory (e.g., left DLPFC, pre-motor regions) (75).

There are several treatment/imaging studies involving pediatric BD participants. For example, Chang et al. have examined the brain activity of BD adolescents (N=8) treated with lamotrigine. Specifically, they evaluated brain activity while viewing negative and neutral emotional pictures at baseline and following eight weeks of treatment (76). They found a significant decline in depressive symptoms that was also associated with decreased right amygdala activity when viewing negative pictures.

Pavuluri and colleagues have conducted a series of important studies comparing fMRI activity in BD youths before and after treatment with several anti-manic medications, including lamotrigine, risperidone, and divalproex. These studies employ block-design methodology, which is very good at detecting between-group differences in neural activation though its ability to detect group-by-cognitive task differences is limited compared to event-related fMRI experiments. Taken as a whole, these studies corroborate the fact that anti-manic medications differentially influence the neurocircuitry underlying pediatric BD (77-82).

Such studies, pairing neuroimaging and treatment, are very important to advancing our understanding of potential bio-behavioral markers that would guide treatment, akin to what is commonplace in cancer treatment. However, it is early in this process, with need for replication to ascertain what, if any, neural markers can ultimately guide treatment decisions or predict outcome.

Autism Spectrum Disorders

Autism spectrum disorders (ASD), including autistic disorder, Asperger's Disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS), are among the most common and impairing psychiatric conditions affecting children and adolescents today. In fact, the Centers for Disease Control has shown that the incidence of ASD had risen 10-fold from the year 1980 to the year 2000, now affecting as many as 1/88 children in the United States (83). As in other disorders, such as pediatric BD, it remains uncertain if this represents better awareness of ASD, over- or mis-diagnosis, or a combination.

Thus, there is a pressing need to understand the neural underpinnings of ASD. As in other disorders, studies have employed structural MRI, fMRI, and DTI to elucidate the underlying neurobiology associated with ASD. Most of these have examined brain changes in ASD children and adolescents from TDC, with few examining the specificity of these findings by comparing sub-types of ASD participants to one another (i.e., autistic disorder vs. Asperger's Disorder) or to those with other neuropsychiatric conditions (i.e., those with primary ADHD or other non-ASD developmental delay [DD]).

A plethora of brain regions from every lobe have been implicated in the neuropathology of ASD, from sub-regions of the PFC to temporal, parietal, and occipital cortex, as

well as the cerebellum (84;85). One important finding in ASD research has been early brain overgrowth in those affected by ASD. This has been demonstrated not only in neuroimaging studies, but also in studies examining head circumference and post-mortem neuropathology in those affected by ASD (86-92). However, for individual children, such findings are not yet useful as diagnostic biomarkers of ASD, whereby a measurement could rule in, or rule out, ASD.

It is beyond the scope of this piece to summarize the wealth of neuroimaging studies conducted with those affected by ASD across the lifespan. Thus, what follows represents only a sampling of this work. However, to date, no replicated MRI neuroimaging biomarker for ASD has been identified that can improve the specificity or quality of ASD diagnosis or its treatment.

ASD: Structural MRI

Multi-group studies have begun to probe the specificity of structural MRI alterations associated with ASD. For example, Kaufmann et al. evaluated cerebellar vermis volume in 3-9 year old boys with: (1) idiopathic autism (N=10), (2) Down syndrome plus autism (N=16), (3) fragile X syndrome plus autism (N=13), or (4) TDC participants (N=22). They found that the ratio of cerebellar vermis lobules VI-VII to total intracranial area was smaller only in those with idiopathic autism compared to the other groups, whereas increases in lobules VI-VII were seen in autism associated with fragile X syndrome (93). In another example, Petropoulos et al. failed to find specific alterations among 3-4 year olds with either (1) ASD (N=45), (2) TDC (N=26), and (3) DD (N=14), though they were examining a different brain region—the mid-sagittal corpus collosum—and also did not focus exclusively on boys (94)

Other studies have begun to compare structural MRI alterations between participants with ASD and those with other forms of developmental delay. For example, Petropoulos et al. compared 2-4 year olds with either (1) ASD (N=60), (2) TDC (N=10), and (3) developmental delay (DD; N=16). For this study, DD participants' delay was based upon impairments in standardized intellectual and adaptive tests, but not meeting ASD criteria by the Autism Diagnostic Observation Schedule–Generic (ADOS-G) or clinical evaluation. Covarying for age, they found that DD participants had prolonged cortical gray matter and white matter T2 vs. both ASD and TDC participants, whereas ASD participants had prolonged cortical gray matter, but not white matter, T2 only vs. TDC participants. They conclude that their data implicate a more general delay in neuronal maturation among DD participants, whereas ASD participants' delay may involve gray, but not white, matter (95).Herbert has compared ASD participants to those with developmental language delay (DLD). They found no significant differences in white matter volume between ASD and DLD participants, though both differed from TDC (96). A related study by Herbert et al. evaluated cortical asymmetry among boys ages 5.7-11.3 years with (1) ASD (N=16), (2) DLD (N=15), and (3) TDC (N=15). Compared to TDC participants, those with either ASD or DLD had a greater aggregate volume of significantly asymmetrical cortical parcellation units (leftward plus rightward; 41.7% ASD, 32.6%, 20.1%) and larger aggregate volume of right-asymmetrical cortex (28% ASD, 22% DLD, 7% TDC). This rightward bias was more pronounced in ASD participants than those with DLD. Moreover, DLD but not ASD participants had a small but significant loss of leftward asymmetry compared with TDC participants. From this, the authors conclude that the right-asymmetry increase may be a consequence of early abnormal brain growth trajectories in ASD and DLD, while higher-order association areas may be most vulnerable to connectivity abnormalities associated with white matter increases (97).

With respect to studies comparing ASD participants to those with other forms of psychopathology, Voelbel et al. 2006 compared 7-13 years old boys with (1) ASD (N=38), (2) BD (N=12), and (3) TDC (N=13). They found that ASD participants had greater left (LCV) and right (RCV) caudate volume when covarying for intracranial volume and stimulant use. Likewise, larger LCV and RCV in ASD predicted a riskier response strategy in an attention task, while the inverse was significant in TDC participants (98).

Similarly, Mostofsky et al. evaluated the relationship between motor cortex white matter volume and motor performance among 8-12 year old children with either (1) ASD (N=20), (2) TDC (N=36), and (3) primary ADHD (N=20). Motor impairments were evaluated using the Physical and Neurological Examination of Subtle Signs (PANESS). They found that the correlation between PANESS score and left motor cortex white matter volume significantly differentiated ASD children from those with either ADHD or TDC, with increased white matter volume predicting poorer motor skill. From this, the authors concluded that these alterations in cerebral volume in ASD participants may be more representative of global patterns of brain abnormalities likely mediating other aspects of ASD, including social and communication deficits (99).

Brieber et al. used voxel-based morphometry to evaluate whole-brain alterations between 10-16 year olds with (1) ASD (total N=15 including N=13 with Asperger's plus N=2 HFA) (2) ADHD (N=15), and (3) TDC (N=15). They found ASD-specific increases in gray matter volume of the right supramarginal gyrus, an area mediating mentalising and theory of mind abilities (100).

Several studies have begun testing the role of structural MRI parameters in confirming the clinical classification of ASD participants. For example, Akshoomoff et al. used discriminant function analysis of MRI brain measures, including cerebellar vermis volume, total brain volume,

and gray and white matter volumes, to classify ASD (N=52, ages 1.9-5.2 years) and TDC (N=15; ages 1.7-5.2 years) participants. They found that 95.8% of ASD and 92.3% of TDC participants were correctly classified. By adding functional measures, they correctly classified 85% of ASD cases as lower functioning and 68% of ASD cases as higher functioning (101). Relatedly, Jiao et al. 2010 used machine learning techniques to determine if thickness- and/or volume-based structural MRI parameters could accurately distinguish between children with ASD (N=22) and TDC (N=16). They found that thickness-based models were more effective than volume-based methods in differentiating ASD from TDC participants, with an 87% accuracy rate (102) In a separate, but related study, Jiao et al. 2011 used machine learning techniques to test if thickness- and volume-based measures could differentiate between 6-15 year olds with either Asperger's Disorder (N=5) or high-functioning autism (HFA; i.e., autistic disorder with normal IQ; N=13). However, they found that neither of these was able to effectively distinguish between these two groups (103).

Although such results are promising, they require further study, as there is no consistent, replicated structural difference, or pattern of differences, that yet would serve as a biomarker to of ASD. Additionally, these studies have not been able to consistently differentiate across the ASDs—i.e., to differentiate among participants with autistic disorder, Asperger's Disorder, or PDD-NOS. Moreover, these studies have not consistently differentiated participants with either HFA, low-functioning autism (LFA, autistic disorder with IQ<70), or Asperger's Disorder, including studies examining the amygdala or hippocampus ; cerebellum or cerebellar vermis; or total gray matter, white matter, or cerebral volume (104-107).

ASD: Functional MRI (fMRI)

Malisza et al. used fMRI to evaluate visual attention in children ages 9-14 years with (1) ASD (N=8), (2) ADHD (N=9), and (3) TDC (N=9). They found that the ASD group had greater activation in the occipital gyrus and less activation in the hippocampal gyrus than either ADHD or TDC participants, suggesting that attentional processing relies on different neural mechanisms in ASD and ADHD participants (108). Christakou et al. also used fMRI to examine sustained attention in boys ages 11-17 with ASD (N=20), ADHD (N=20), and TDC (N=20). ASD boys had increased cerebellar activation vs. ADHD and TDC participants, whereas ADHD boys had significantly reduced left DLPFC activation vs. ASD participants. They also found that ADHD and ASD boys had significantly reduced activation compared to TDC participants in bilateral striato-thalamic regions, left DLPFC, and superior parietal cortex as well as significantly increased precuneus (109).

Kaiser et al. evaluated the brain response to biological motion—meaning motion that looks like that of an animate object (e.g., an animal walking, running, or sitting in contrast to random motion, like swirling dots)—in participants ages 4-17 years old with either (1) ASD (N=25), (2) their unaffected siblings (N=20), or (3) TDC (N=17). ASD participants had specific decreases in neural activity in areas including the right amygdala, ventromedial PFC, and bilateral fusiform gyri. Interestingly, unaffected siblings had compensatory increases in brain activity vs. either those with ASD or TDC in the right ventromedial PFC—anterior and inferior to their other finding—as well as the posterior superior tempral sylcus. Thus, Kaiser's study suggests both state and trait neural alterations associated with ASD (110).

Greimel et al. examined empathy in (1) ASD adolescent boys (N=15 including N=12 with Asperger's syndrome plus N=3 HFA), (2) fathers of ASD participants (N=11), (3) TDC adolescent boys (N=15), and (4) fathers of TDC participants (N=9). Both ASD children and their fathers had significantly reduced activation of the right anterior fusiform gyrus compared to their age-equivalent TDC participants (111).

Among the studies using fMRI brain activation to evaluate diagnostic classification of participants, Lai et al. conducted a two-stage study of neural activation in ASD. First, they evaluated brain activation while listening to human speech in ASD (N=12) and TDC (N=15) participants. Then, they collected additional fMRI data in ASD participants while sedated for clinically-indicated MRI scans (N=27). They correctly classified 26 of 27 (96%) of the sedated ASD participants from the second experiment using the mean amplitude and spread of neural activity in the superior temporal gyrus from the first experiment (112). The future is likely to bring additional studies examining the potential of specific fMRI alterations in aiding diagnostic classification.

Functional MRI studies have found neural alterations in ASD. However, like structural MRI studies, these studies are limited by small sample sizes, lack of replication, and an inability to consistently discern between other disorders. Presently, there are no neuro-functional biomarkers that can diagnose ASD.

ASD: Diffusion Tensor Imaging (DTI)

Several recent DTI studies have begun to evaluate the specificity of white matter alterations among ASD participants. For example, Lange et al. examined white matter measurements from the superior temporal gyrus (STG) and temporal stem in males with either HFA or TDC (N=30 of each). With respect to the STG, they found reversed hemispheric asymmetry of two measures of white matter diffusion coherence: tensor skewness, and fractional anisotropy. Specifically, HFA participants had

greater STG tensor skewness on the right and decreased fractional anisotropy on the left compared to TDC participants. They also found increased omni-directional, parallel, and perpendicular diffusion in the right, but not left, temporal stem among HFA participants vs. TDC. Most interesting, these six measures had a very high rate of discriminating ASD from TDC participants, with 94% sensitivity, 90% specificity, and 92% accuracy in their original sample as well as a replication sample of males with idiopathic autism (N=12) and TDC (N=7) (113).

Barnea-Goraly et al. evaluated white matter integrity via DTI scans among children with ASD (N=13), their unaffected siblings (N=13), and a separate group of unrelated TDC (N=11). They found that children with ASD and, to a lesser extent, their unaffected siblings, had reduced white matter functional anisotropy (FA) in the right medial prefrontal white matter, right anterior forceps, corpus callosum, right superior longitudinal fasciculus, superior temporal gyrus, and temporoparietal junctions (114).

Ingalhalikar et al. 2011 devised and tested a DTI-based classifier system among ASD (N=45) and TDC (N=30) participants. Their model employed a high-dimensional non-linear support vector model to develop an abnormality score involving fractional anisotropy (FA) differences mainly in right occipital regions as well as in left superior longitudinal fasciculus, external and internal capsule while mean diffusivity (MD) discriminates were observed primarily in right occipital gyrus and right temporal white matter. Using this abnormality score, their ability to distinguish between ASD and TDC participants achieved 80% accuracy using leave one out (LOO) cross-validation, with high significance $p<0.001$, specificity ~84%, and sensitivity ~74% sensitivity (115).

In sum, DTI research is clearly an emerging and promising tool in understanding neurodevelopmental alterations associated with ASD. However, there is a need to both replicate the above findings, as well as to test their specificity by comparing ASD participants to those with other forms of developmental delay or other primary psychopathology.

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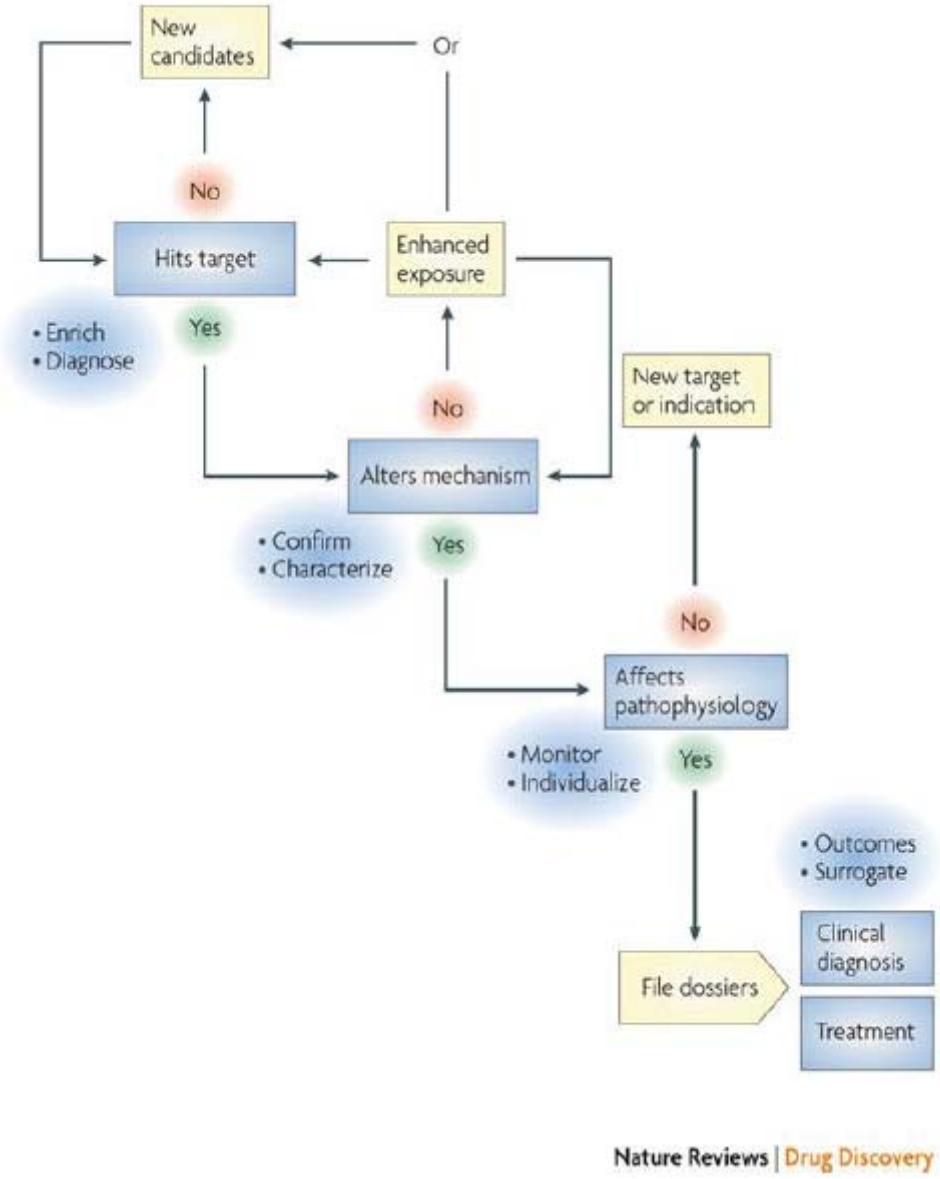

Figure Legend: Biomarkers can be categorized into four groups on the basis of their contribution to business, regulatory and clinical decision-making. Clinical decision-making can be further divided into clinical research and patient care diagnostic subcategories. The objective is to use biomarkers as early as possible in the drug development process. The initial step is to confirm that a test compound hits the target and to quantify the extent to which it does so. Next is to test three concepts in logical sequence. First, that hitting this target alters the pathophysiological mechanism. Second, that altering this mechanism affects the pathophysiology. Third, that affecting pathophysiology predictably improves the clinical status of the patients. Biomarkers qualified to confirm the presence of the target and or extent to which the drug candidate hits the target may be validated later as diagnostic tests for early detection or diagnosis (when that target is expressed differentially between healthy and diseased states). Biomarkers qualified for confirming and quantifying mechanistic effects may be validated later as diagnostic tests to inform choice of therapeutic regimen, either in choice of drug or initial dosing regimen. Biomarkers qualified for longitudinal quantification of patient response in terms of clinically relevant pathophysiology, may be validated later as diagnostic tests for monitoring and individualization of a therapeutic regimen. Biomarkers qualified for either monitoring or individualization of therapy on clinically relevant pathophysiology may also serve as surrogate end points to support regulatory decision-making. In addition, they can be used to ensure appropriateness of use, and as quantifiers of clinical outcomes to support reimbursement decisions. *From Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, Herholz K, Bokde AL, Jessen F, Hoessler YC, Sanhai WR, Zetterberg H, Woodcock J, Blennow K. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nat Rev Drug Discov. 2010 Jul;9(7):560-74.*

Resource Document on Brain Imaging and Child and Adolescent Psychiatry with Special Emphasis on Single Photon Emission Computed Tomography (SPECT)

Approved by the Joint Reference Committee, January 2005

The document was prepared by the Council on Children, Adolescents and Their Families.

Summary

Although knowledge is increasing regarding specific pathways and specific brain areas involved in mental disease states, at present the use of brain imaging to study psychiatric disorders is still considered a research tool. Continued study of child and adolescent psychiatric disorders using a variety of brain imaging methods, as well as refinements in imaging techniques, may result in evidence supporting the utility of these tools for clinical work in the future. Imaging research cannot yet be used to diagnose psychiatric illness and may not be useful in clinical practice for a number of years. In the future, imaging techniques may be useful to examine medication effects and predict medication response.

Specifically, no published investigation in the field has determined that any structural or functional brain abnormality is specific to a single psychiatric disorder. Additionally, imaging studies examine groups of patients and groups of healthy controls; therefore, findings may not apply to all individuals with a given disorder. Even when significant differences are identified between groups, there is a substantial overlap among individuals in both groups.

Particular caveats are indicated with regard to brain imaging involving radioactive nucleotides for children and adolescents because of children's known greater sensitivity to radiation and risk of radiation induced-cancer. The long term risks of initial and repeated exposure to intravenous radionucleotides are unknown.

We conclude that, at the present time, the available evidence does not support the use brain imaging for clinical diagnosis or treatment of psychiatric disorders in children and adolescents.

Overview

Brain imaging

Single photon emission computerized tomography (SPECT) is one type of functional neuroimaging, a category that also includes positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI). Functional neuroimaging yields metabolic or biochemical information, allowing localization of a neural function. As such it is distinct from anatomic imaging, such as radiography (X-Ray) or computerized tomography (CT), which illuminate structures in a static way. Functional neuroimaging of the brain is based on the experimental data that neuronal activation leads to increased metabolism. Using radionucleotides to ligands possessing high and selective affinity for neurotransmitter receptors or transporters allows for imaging of specific neuroreceptors (Shin, 2000).

Brain-imaging tools, such as (PET), (SPECT), MRS and (fMRI), can relate brain function to clinical features and medication responses (Brody et al., 2001; Ketter & Wang, 2002). MRS allows for identification of neurochemical abnormalities in specific brain regions and can identify neurochemical changes prior to and following medication administration. MRS is non-invasive and does not necessitate exposure to radioactive nucleotides. SPECT makes use of radioactive tracers tagged to a molecule, which can indicate glucose metabolism, oxygen consumption, or blood flow. Chemical imaging with a SPECT scan works with precursors such as tryptophan, dihydroxyphenalamine (Dopa) or enzymatic reactions that support neurotransmitters synthesis (Santosh, 2000).

History

SPECT was originally introduced in the 1980s (Goetz, 2003). Its usefulness was limited in the early years by poor image resolution. However, refinements in computer technology as well as in radionucleotides have resulted in much better image quality, although not as good as with PET. The equipment needed for SPECT is much less costly than that needed for PET scanners (which require a cyclotron) or MRI other forms of imaging. While PET, CT and MRI are limited to hospitals because of their cost, SPECT equipment is within range of outpatient office equipment. There are no regulations that prohibit

individual physicians from installing and using SPECT equipment in their offices, provided they have satisfied regulatory requirements. Because of its low cost, SPECT is being used in outpatient private practice, and some have advocated for its use in clinical diagnosis of psychiatric disorders (Amen, 2001).

Established Uses of Brain Imaging in Clinical Practice

Brain imaging does have important clinical uses. Structural and functional images of the brain play an important adjunct role in the diagnosis and treatment of many neurologic conditions. The usefulness of SPECT to study perfusion abnormalities in the brain as well as elsewhere (e.g., the myocardium, carotid arteries) is well established. SPECT has a role in the diagnosis of cerebral trauma, certain kinds of dementia, strokes, seizure disorders, and brain tumors, in which characteristic patterns of perfusion abnormalities are detectible (Engel, Jr., 2000; Goetz, 2003; Kuzniecky & Knowlton, 2002; Lee, Mintun, Buckner, & Morris, 2003; Slosman & Lazeyras, 1996). In addition, Brain SPECT with neuroreceptor imaging radiopharmaceuticals is used in cerebrovascular diseases, dementias, epilepsy, head injury, malignant brain tumors, movement disorders, and Gilles de la Tourette's syndrome (Camargo, 2001). This imaging modality has been used in diagnosis, prognosis assessment, evaluation of response to therapy, risk stratification, detection of benign or malignant viable tissue, and choice of medical or surgical therapy.

However, even in the diagnosis of neurological disorders, the use of brain imaging is not without controversy. Recent reviews have attempted to establish guidelines to avoid over use for such common conditions as headache (Lewis, 2002; Medina, Kuntz, & Pomeroy, 2001), and a cost-effectiveness study concluded that the addition of SPECT and fMRI did not offer advantages over the usual diagnostic work-up of Alzheimer's disease (McMahon, Araki, Neumann, Harris, & Gazelle, 2000). The primary clinical use of SPECT in psychiatry has been to rule out the neurological conditions listed above.

Brain Imaging in Research

Brain-imaging has been used extensively in research on psychiatric disorders, most notably, obsessive-compulsive disorder, schizophrenia, depression, panic disorder, and drug abuse. The findings, although not entirely robust, have generated many hypotheses about the patho-physiology of these disorders. The following is a brief summary of the research studies of psychiatric disorders in which brain imaging tools, including SPECT, have proven fruitful.

Attention Deficit/Hyperactivity Disorders

Findings in Attention Deficit/Hyperactivity Disorders are still provisional, but suggest minor structural changes in frontal and caudate areas, especially on the right side. Functional studies suggest reduced activation in these and other areas. A 2000 review of studies in children and adults concluded, "The techniques do not yet contribute to individual diagnosis" (Overmeyer & Taylor, 2000).

Autism

Autism has been studied in adults as well as children using MRI, fMRI, and SPECT. MRI studies have indicated a variety of diffuse anatomical differences, reflective of an early developmental change in the growth or pruning of neural tissue, rather than localized lesions; similarly, neurochemical studies suggest early, neuromodulatory discrepancies rather than gross or localized abnormalities. To date we do not have definitive answers to questions of how the brain functions differently in this disorder (Eigsti & Shapiro, 2003; Rumsey & Ernst, 2000).

Bipolar Disorder and Depression

Although over the past two decades, brain-imaging studies have examined the mechanisms possibly involved in the pathophysiology of bipolar and unipolar mood disorders, nearly all of these studies involve adults. Most studies have used PET scans (and none of the PET studies involve children). The available findings suggest subtle anatomical changes in sub-regions of the prefrontal cortex, medial temporal lobe and cerebellum, and functional abnormalities in brain circuits inter-connecting these same brain regions and the striatum in patients suffering from bipolar disorder. Neuroimaging studies have reported cerebral atrophy, ventricular enlargement, or cerebellar atrophy (Benabarre et al., 2002).

In terms of function, findings with PET have included decreased prefrontal cortical function concomitant with increased subcortical anterior paralimbic activity, (Drevets et al., 1997; Videbech, 2000). These findings are convergent, and support the hypothesis that depressive symptoms are caused by dysfunction of regions of the limbic system and the frontal lobes in close connection with the basal ganglia. A few studies point to the possibility that response to antidepressant treatment can be predicted from PET scans (Soares, 2003).

There are 2 published studies of SPECT and depression in adolescents (Tutus et al., 1998; Kowatch et al., 1999). The first, done in Turkey, involved 14 patients and 11 controls, found relatively reduced perfusion in the left anterofrontal and left temporal cortical areas in the depressed patients. When the patients were restudied after their depression

remitted, they did not differ significantly from the controls. The second study involved a comparison of 7 adolescent patients with MDD and 7 controls, and found relative rCBF increases in the depressed group as compared to normals in the right mesial temporal cortex, the right superior-anterior temporal lobe, and the left infero-lateral temporal lobe. The researchers found rCBF decreases in the depressed group as compared to normals in the left parietal lobe, the anterior thalamus and the right caudate. 4. They concluded that adolescents with MDD show rCBF abnormalities similar to those found in adult MDD rCBF studies, but cautioned, "Further controlled studies with larger numbers of MDD subjects and normal age- and gender-matched controls are necessary before any definetive conclusions can be made from these findings" (p. 643).

In a comprehensive review, Soares pointed out, "Even though preliminary findings from cross-sectional studies indicate anatomical, neurochemical, and functional brain abnormalities in bipolar patients in key regions involved in mood regulation, the relationship of such abnormalities with illness phase and their clinical relevance needs further investigation. The potential for utilization of brain-imaging tools to elucidate the pathophysiology of bipolar disorder is still largely unrealized, and it is anticipated that important new developments in this area will come about over the next years and beyond" (Soares, 2003). Another reviewer concluded, "Although it is not yet a clinical tool for bipolar disorders, (italics added) brain imaging provides useful research data to understand the fundamental neurobiology of mood disorders and to more effectively target therapeutics" (Ketter et al., 2002).

Obsessive-Compulsive Disorder

Obsessive compulsive disorder has been studied extensively with imaging and has shown the most consistent findings so far, with the orbitofrontal cortex and the caudate nucleus being implicated in PET studies (Santosh, 2000). PET indices of brain activity within the orbitofrontal cortex are inversely correlated with subsequent response to SRIs. (Rauch et al., 2002). Most studies have involved adults. There are reports of SPECT studies of this condition in the literature, some of which included adolescents, but these are mostly older studies. There is one case report of SPECT and an adolescent with OCD who showed changes after being treated with chlomipramine (Amen & Waugh, 1997).

Posttraumatic Stress Disorder (PTSD)

PET, SPECT and functional MRI have been used to study how individuals with PTSD respond when they are presented with trauma-related stimuli. A pattern of hyperresponsivity of the amygdala and anterior paralimbic structures (which are known to be involved in processing negative emotions such as fear), greater deactivation of Broca's region (motor speech) and other nonlimbic cortical regions, and failure of activation of the cingulate cortex (which possibly plays an inhibitory role) has been found (Pitman, Shin, & Rauch, 2001). There are no studies of children and adolescents with PTSD using SPECT.

Schizophrenia

The current understanding of schizophrenia as a neurodevelopment disorder is largely due to brain imaging studies (Batista et al., 1995; Eliez & Reiss, 2000; Hendren, De Backer, & Pandina, 2000).

SPECT has helped to elucidate the neurobiology of schizophrenia via the study of cerebral blood flow and neuroreceptors in this condition. There is converging evidence implicating three brain systems: frontal, temporolimbic, and basal ganglia. (Gur & Pearlson, 1993). PET and SPECT have revealed disturbances of cerebral blood flow and glucose metabolism in patients with schizophrenia. These tools have also proved useful in studying the relative receptor occupancy of typical and atypical antipsychotic medications. (McClure, Keshavan, & Pettegrew, 1998). There are several studies of first break schizophrenics using SPECT and these usually include older adolescents, but no such studies of children.

Provisional Nature of Findings

Despite the excitement neuroimaging has brought to the field of psychiatry, it remains an investigational tool. The hope is that the continued growth of knowledge will eventually have practical applications in guiding psychological and pharmacologic treatments, but the general consensus is that SPECT and other kinds of neuroimaging are not yet recommended for diagnostic evaluation and treatment monitoring in individual patients.

Additional concerns are relevant to the use of neuroimaging in children and adolescents with psychiatric disorders. To date, the overwhelming preponderance of studies have been in adults. PET and SPECT involve exposure to radioactive agents, and MRI and fMRI involve sedation. The long term effects of exposure of the immature brain to radiation are unknown. Concerns about the investigational uses of brain imaging for children revolve around the unclear risk-benefit ratio of such studies, as well as the difficulties involved in informed consent or assent with regard to a complex technology (Hinton, 2002). In a 10 year review published in the Journal of the American Academy of Child and Adolescent Psychiatry in 2000, Hendren and colleagues concluded, citing inconsistencies in data, "Although neuroimaging technology holds great promise for neurodevelopmental

research, it is not yet a diagnostic instrument."(Hendren et al., 2000). This opinion was echoed by Santosh, another review author, who states, "As yet, no specific and consistent abnormality has been detected in childhood psychiatric disorders." (Santosh, 2000). Even with the continued advances in the understanding of brain structure and function in psychiatric disorders since these reviews, brain imaging has still not progressed to the point of being useful for the clinical diagnosis of these disorders in individual patients. As of this writing, no studies have been published in journals indexed by the National Library of Medicine examining the predictive ability of neuroimaging for psychiatric disorders for either adults or children.

Some of the problems still to be resolved are the following:

- Findings have been inconsistent. Most studies have involved small numbers of patients, and children and adolescents have been even less well studied than adults. The studies have great discrepancies related to sample size, subject selection, imaging protocol and image analysis. Methodological differences among studies may further confound the results.
- There are few normative data sets on children (Hinton, 2002). Without normative data, interpretation of findings on individual patients is meaningless. In part this lack is due to ethical constraints on using brain imaging to study normal children.
- Some disorders may involve subtle changes in structure and/or function that are not apparent on brain imaging studies.
- The changes observed may not accurately reflect underlying neurobiological dysfunction in the brain structures being studied, but could be compensatory mechanisms reflecting adaptation to deficits in other aspects of brain function.
- Ethical dilemmas exist with regard to exposure of children to radiation when it is not useful to guide treatment.
- There are potential iatrogenic problems in labeling a child as psychiatrically disordered, or as free of psychiatric disorder, on the basis of data derived from neuroimaging studies, given the lack of data regarding the sensitivity and specificity of such information.

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