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Review

The Challenges and Promise of Neuroimaging in Psychiatry

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Neuroimaging is central to the quest for a biological foundation of psychiatric diagnosis but so far has not yielded clinically relevant biomarkers for mental disorders. This review addresses potential reasons for this limitation and discusses refinements of paradigms and analytic techniques that may yield improved diagnostic and prognostic accuracy. Neuroimaging can also be used to probe genetically defined biological pathways underlying mental disorders, for example through the genetic imaging of variants discovered in genome-wide association studies. These approaches may ultimately reveal mechanisms through which genes contribute to psychiatric symptoms and how pharmacological and psychological interventions exert their effects.

The demonstration, in 1976, that patients with schizophrenia had enlarged cerebral ventricles (Johnstone et al., 1976), seemed to usher psychiatry into a new era where neuroimaging would help identify mental disorders and ultimately clarify their mechanisms. In the cultural climate of the 1970s, such claims of tangible biological signs may have perturbed those who believed that mental disorders were the product of early life experience and other biographical influences. In the past 35 years, modern psychiatry has largely overcome such dualisms, and there is now general agreement that environmental influences can manifest themselves in observable brain changes as well as genetic factors. Perhaps the most remarkable result of this rapprochement between psychological and biological approaches to mental illness is the emergence of research programs mapping out neural correlates and predictors of psychotherapy successfully with functional neuroimaging (Beutel et al., 2003; DeRubeis et al., 2008; Kandel, 1999; Linden, 2006, 2008; Roffman et al., 2005).

Another important development has come out of the growing dissatisfaction with current diagnostic systems in psychiatry. Although the authors of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000) and the International Classification of Disease (World Health Organisation, 1992) were guided by the aim to make the diagnostic criteria more reliable, these criteria are still largely based on clinicians' assessments. Thus, patients whose symptoms are caused by very different biological processes may be subsumed under the same category, and some of them may receive inappropriate treatment as a consequence. In order to improve this situation, it has been suggested that the new DSM-5 incorporate etiological criteria. Yet reliable etiological models and biomarkers are currently not available for most psychiatric disorders, and even further clinical subtyping has not made the association with biological markers more stringent. Psychiatric diagnosis will thus continue to be based on descriptive criteria for the foreseeable future (First, 2010).

Neuroimaging in its various guises is likely to play a major role in the quest for a biological foundation of psychiatric diagnoses, if only because it is the only array of techniques that routinely provides direct access to the living human brain (Table 1). Imaging can complement clinical trials in phases 0/I/II to determine in vivo effects of drugs and appropriate dosages, and in phases III/IV for treatment monitoring and stratification of patient samples and flexible dose adjustment over time.

The State of Biomarker Development for Mental Disorders

A biomarker has been defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001). Biomarkers that indicate the presence of a disease can be used for diagnostic purposes, classification, or staging of disease or for the prediction of the course of the illness. Such prognostic biomarkers may be particularly useful if they predict the future occurrence of an illness in preclinical cases. In the context of clinical trials, biomarkers can be used for "proof of concept" where they indicate that an intervention affects disease-relevant pathological processes (Soares, 2010). Another use of biomarkers is for "proof of mechanism" where it is demonstrated that an intervention affects the desired biological process. A major application is to show that a drug engages with a target in vivo in the way expected from in vitro studies. Where the effects of a therapeutic intervention on the biomarker predict the desired clinical outcome, the biomarker could even be taken forward as a potential surrogate marker. A validated surrogate marker, which has to undergo approval according to strict criteria (Cummings, 2010), could permit a reduction of the participant numbers and duration needed to demonstrate clinically relevant effects (Hampel et al., 2011; Jagust et al., 2010).

Imaging biomarkers have been relatively successful in the field of neurodegenerative disorders. PET with ^{18}F-fluorodeoxyglucose (FDG) distinguishes Alzheimer's disease (AD) from other

Table 1. Comparison of Noninvasive Neuroimaging Modalities in Biomarker Research

Technique	Spatial Resolution	Temporal Resolution	Sensitivity to Specific Molecules	Retest-Reliability	Suitability for Multicenter Studies	References
Structural magnetic resonance imaging (MRI)	Millimeter, in some cases (ultra-high field) submillimeter	Can be used to track longitudinal changes	None, but can study effects of pharmacological intervention or genes	Good within scanners, moderate across scanners of the same type, poor across magnet field strengths	Yes if magnet of same field strength and rigorous protocol design / calibration / quality control	Reliability: Kruggel et al., 2010
Functional MRI (fMRI)	Millimeter	Seconds	See under structural MRI	Blood oxygen level-dependent signal (BOLD) activation studies: needs to be determined for each paradigm; published reports go up to 0.8; perfusion studies: high	Under development; requires scanners of same field strength and well standardized paradigms	Reliability: Blokland et al., 2011; Xu et al., 2010. Multicenter: Barch and Mathalon, 2011
Magnetic resonance spectroscopy (MRS)	Centimeter	Minutes	Millimolar	Reported as good for some brain regions and metabolites, optimized procedures for neurotransmitters (GABA, Glutamate/Glutamine) under development	Under development; for example, guidelines have been proposed for multiple sclerosis	Reliability: Geramita et al., 2011. Multicenter: De Stefano et al., 2007
Positron emission tomography (PET)/ single photon emission computed tomography (SPECT)	Centimeter (SPECT) to millimeter (PET)	Minutes	Picomolar	Needs to be determined for each ligand and region; for example reports for raclopride range from moderate to good	Standardization procedures have been developed, for example for FDG-PET in clinical trials of AD	Reliability: Alakurtti et al., 2011; Yoder et al., 2011. Multicenter: Jagust et al., 2010
Magnetoencephalography (MEG)	Centimeter	Milliseconds	See under structural MRI	Needs to be determined for each paradigm and parameter; for example, high for visual gamma activity	Under development	Reliability: Muthukumaraswamy et al., 2010. Multicenter: Gaetz et al., 2011
Electroencephalography (EEG) / event-related potentials (ERP)	Centimeter	Milliseconds	See under structural MRI	Depends on paradigm, high for P300 ERP in oddball studies	Quality assurance and standardization procedures under development	Reliability and multicenter: Luck et al., 2011

dementias (frontotemporal dementia and dementia with Lewy bodies) with high classification accuracy (Mosconi et al., 2010). FDG-PET has also shown promise in predicting future AD in people with mild cognitive impairment (MCI) and even in cognitively normal individuals (Mosconi et al., 2010). Imaging biomarkers have also been used for proof-of-concept in the evaluation of new interventions for dementia. For example, FDG-PET has been used to demonstrate partial reversal of deficits in glucose metabolism in AD in a phase I trial of deep-brain stimulation (Laxton et al., 2010). Amyloid imaging with PET can be used for the proof-of-concept and -mechanism of interventions that modify amyloid pathology through blockade of amyloidogenic enzymes or immunization (Scheinin et al., 2011). Although neither neuroimaging nor neurochemical biomarkers have thus far attained the status of approved surrogate end points for clinical trials in AD or MCI (Hampel et al., 2010), their predictive value may give them a place in clinical trials of MCI where they can enrich the trial population with individuals affected by the AD-related pathological process (Cummings, 2010).

Compared to the wide spectrum of neuroimaging biomarker applications in dementia research, biomarker use in psychotic or affective disorders has been largely confined to the proof of mechanism of new drugs. Radioligands for the targets of the drug (commonly neurotransmitter receptors or transporters) can be used to measure target occupancy and help determine what doses are needed for a desired level of occupancy. This approach has been particularly widely used in the investigation of dopamine receptor occupancy of antipsychotic drugs (Nord and Farde, 2011) and of serotonin transporter blockade of antidepressants (Meyer, 2007). Recent work has demonstrated a correlation between dopamine D2 receptor occupancy and clinical improvement after treatment with the antipsychotics aripiprazole (Kegeles et al., 2008) and quetiapine (Nikisch et al., 2010), but patient numbers, as in most PET studies, were small. Radioligands are also available for other potential targets of new antipsychotics, for example cannabinoid, tachykinin, glutamate, and nicotinic acetylcholine receptors (Takano, 2010) (Table 2). Such proof-of-mechanism studies can be useful both for the identification and rejection of new drugs (Wong et al., 2009). However, only a limited number of receptor subtypes or binding sites can be targeted, and often they do not include those that are of greatest current clinical interest (for example, the glycine and D-serine binding sites on the NMDA [N-methyl-D-aspartate]-type glutamate receptor; Takano, 2010). Moreover, almost all current targets are membrane proteins (see Table 2) and the postsynaptic signaling cascades, which are presumed to be of crucial relevance to the neural mechanisms of psychosis, depression, and addiction, for example (Kleppisch and Feil, 2009; Nestler et al., 2009; Wolf and Linden, 2011), are largely inaccessible to in vivo molecular imaging. Nevertheless, neuroimaging with radioligands and MRI techniques, particularly MRS, have a place in the evaluation of the pharmacokinetics and pharmacodynamics of new psychotropic drugs (Wong et al., 2009).

The progress with diagnostic or prognostic imaging biomarkers of mental disorders has been comparatively disappointing. For example, a recent study confirmed the specificity of ventricular enlargement for schizophrenia compared to affective psychosis. However, this study suggested that relatives of patients with familial schizophrenia (that is, with at least two known cases in the family) may also show this sign (McDonald et al., 2006). Thus, ventricle enlargement may be associated with the genetic risk of schizophrenia rather than the actual manifestation of the disease. Furthermore, the general problem with structural imaging findings in schizophrenia is that even where significant group differences have been reliably documented, the overlap with the healthy population is too large to allow for a diagnostic use. Structural imaging studies of white matter using diffusion tensor imaging (DTI) consistently report changes (smaller volume, lower fractional anisotropy) in the corpus callosum (Rotarska-Jagiela et al., 2008), even in untreated patients (Venkatasubramanian et al., 2010), but again the overlap with the healthy population is considerable. The same is true for the neurophysiological signatures of altered perceptual and cognitive processing in schizophrenia (Haenschel and Linden, 2011) or fMRI measures of connectivity of resting state networks (Greicius, 2008), none of which has attained biomarker status.

One reason for the failure, so far, of structural and neurophysiological measures to produce biomarkers of mental disorders might be that they lack the neurochemical specificity that is needed to detect a disease characterized by altered neurotransmitter or receptor function. Based on this rationale, SPECT or PET should be more successful, particularly in schizophrenia, where the treatment effects of antidopaminergic drugs point to an important role of the dopamine system. However, these techniques have so far not produced imaging biomarkers of schizophrenia either (Nikolaus et al., 2009). For example, the decrease of dopamine receptor occupancy after amphetamine challenge (interpreted as increased responsiveness of presynaptic dopamine release) (Abi-Dargham et al., 1998; Laruelle et al., 1996) shows too much overlap with the healthy population to allow for use as biomarker. Furthermore, patients with schizotypal personality disorder have similar changes (Abi-Dargham et al., 2004). Another key measure is the striatal uptake of ^{18}F-DOPA (dihydroxyphenylalanine), thought to reflect dopamine synthesis. The majority of studies in schizophrenia, particularly with patients in the acute phase of the illness, did indeed show increased uptake (Nikolaus et al., 2009; Urban and Abi-Dargham, 2010). However, a recent study did not find any differences between stable treated patients, unaffected twins, and controls (Shotbolt et al., 2011). The authors suggested that increased striatal ^{18}F-DOPA uptake may be a state marker of acute psychosis, which would vary over time and with treatment, rather than a vulnerability marker, which should be relatively stable over time.

The ideal biomarker has high diagnostic specificity and sensitivity and/or is a good predictor of outcome. It is therefore important to search for imaging parameters that show high variability between the clinical phenotypes of interest (e.g., diagnostic groups or treatment effects) but should not be influenced by random variability produced by differences in imaging hardware or software or by intraindividual variability that is not related to the clinical state. Although imaging methods are being developed to the standard required for biomarker research (Table 1), at the present time there does not appear to be a single neuroimaging parameter of biomarker quality to distinguish patients

Table 2. Important Molecular Targets of Noninvasive Imaging in the Human Brain

Biological System and Imaging Techniques	Specific Subsystem Targeted	Specific Target Molecules
NT Receptors (PET/ SPECT)	dopamine	D1,2,3 receptors
	serotonin	5-HT1A, 1B, 2A receptors
	glutamate	Metabotropic glutamate receptor 5; NMDA receptor
	histamine	H1, H3 receptors
	tachykinins	Neurokinin 1 receptor
	adenosine	A1, A2A receptors
	acetylcholine	Alpha4beta2 and Alpha7 subunits of nicotinic receptor; muscarinic receptor
	opioids	Mu, kappa, delta receptors
	cannabinoids	CB1 receptor
	GABA (gamma-aminobutyric acid)	GABA-A receptor (benzodiazepine binding site and Alpha5 subunit)
		Sigma receptor
NT Transporter (PET/ SPECT)	monoamines	Dopamine transporter; Vesicular monoamine transporter 2; serotonin transporter; norepinephrine transporter
NT Synthesis (PET/ SPECT, MRS)	monoamines	Aromatic amino acid decarboxylase
	GABA	
	glutamate / glutamine	
NT Metabolism (PET/ SPECT)	monoamines	Monoamine oxidase
	acetylcholine	Acetylcholine esterase Butyrylcholine esterase
General metabolism (PET)	glucose uptake	
	oxygen metabolism, blood flow	
Inflammation (PET)	microglia	Translocator protein (18kDa)
Neurodegeneration (PET)	extracellular changes	Amyloid plaques
	intracellular changes	Neurofibrillary tangles
Postsynaptic signaling and neuronal metabolism (MRS)		N-acetyl aspartate, myo-inositol
Drug metabolism (PET)	blood brain barrier / efflux transporters	P-glycoprotein

Sources: Molecular Imaging and Contrast Agent Database (MICAD), accessed on 27 November 2011 at http://www.ncbi.nlm.nih.gov/books/NBK5330/, and Nikolaus et al., 2009; Takano, 2010; Wong et al., 2009.

with a particular mental disorder from controls (let alone to distinguish between different mental disorders, which is arguably the clinically more relevant question). In the following sections I will discuss some fruitful avenues for identifying reliable biomarkers and the challenges inherent in these promising approaches.

Pattern Classification

Promise and Caveats

If single neuroimaging parameters have largely failed the biomarker test, perhaps combining different measures either from a single or several imaging modalities in a multivariate analysis will yield higher diagnostic accuracy. The basic idea behind the pattern classification approaches in neuroimaging is that the key differences between groups (e.g., patient versus control) or states (e.g., symptomatic versus remitted) may lie in the relationship between different parameters, for example the relative activation levels in different areas of the brain. Most neuroimaging pattern classification studies start from a very large number of features, up to the hundreds of thousands of voxels that can be captured in high resolution experiments (feature extraction, see Figure 1). These data are fed into a classifier algorithm, for example a support vector machine (SVM). This algorithm then finds the optimal separation between the two or more classes in question (task conditions or diagnostic groups).

Classifiers can be trained to any level of accuracy, but their predictive performance will vary based on the quality of the data and the number of parameters needed. The accuracy of the prediction needs to be tested on new cases that are different from the training set. The classifier assigns a label to each of the new cases, for example "group 1" versus "group 2" (Figure 1), and these labels are compared with the "real" diagnosis or a known outcome. With the small sample sizes used in MVPA classification studies thus far, this has commonly been achieved with cross-validation procedures such as the "leave one out procedure," where the classifier is trained on all cases but one and then tested for accurate classification of the remaining

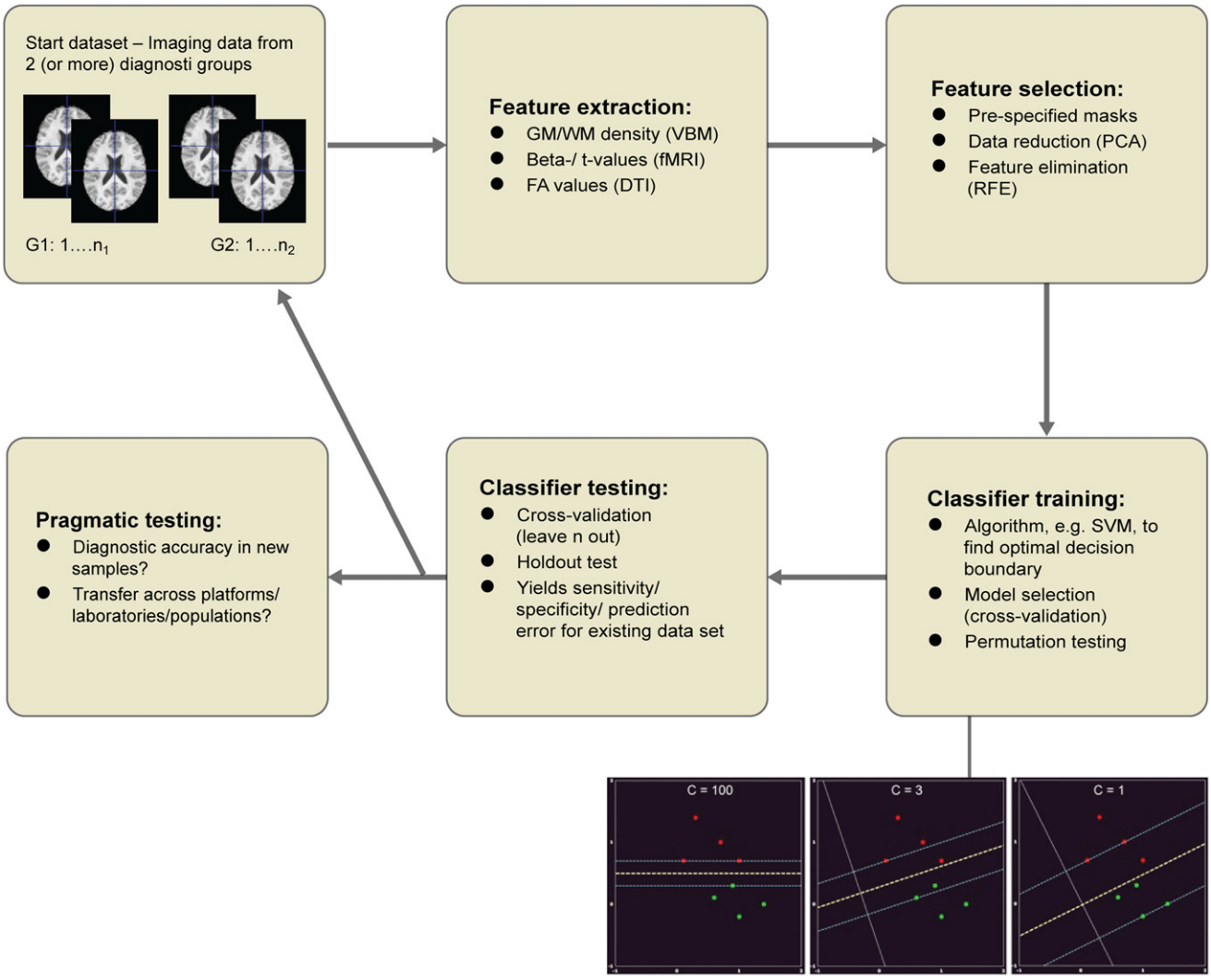

Figure 1. Flowchart of MVPA of Brain Imaging Data for Diagnostic Classification

Brain imaging data are obtained from two or more diagnostic groups and relevant features extracted, as in standard univariate analysis. Because data reduction is crucial to the success of this procedure, various strategies for feature selection can be performed, including principal components analysis (PCA) and iterative elimination of nondiscriminating features through recursive feature elimination (RFE) (De Martino et al., 2008). The preselected data are then fed into a classifier algorithm, which finds the optimal boundary between the two groups (e.g., the data points from the "red" and "green" groups in the right lower corner, figure panel courtesy of Professor Rainer Goebel, Maastricht University). The approach is similar with higher numbers of features, except that hyperplanes rather than lines will constitute the decision boundaries. The performance of the trained classifier then has to be tested in independent data. Even a good performance on cross-validation does not imply clinical relevance because the effects may be platform specific. An important pragmatic stage is therefore the testing of the classifier predictions in completely independent samples from other imaging centers, ideally even with slightly altered measurement parameters to test robustness.

case. However, testing the classifier on a completely independent ("hold out") data set is recommended in order to more robustly estimate the expected accuracy in real-life situations of clinical diagnosis or prognosis, where class membership is not a priori known.

Most diagnostic studies with multivoxel pattern analysis (MVPA) have been based on structural imaging and some have obtained classification accuracies around 90% (Table 3). Although at such levels of accuracy, MVPA analysis of structural scans may in principle aid clinical diagnosis, accurately classifying psychiatric disease in patients suffering manifest clinical symptoms is perhaps not the greatest challenge of psychiatry. A real clinical benefit might be derived from the early detection of cases at high risk and the prediction of natural history and treatment outcome. Koutsouleris et al. (2009) tested patients with prodromal symptoms of schizophrenia and obtained classification accuracies over 80% with whole-brain gray matter patterns between controls, early and late psychosis-risk states, as well as prediction of conversion to psychotic disorder. The effectiveness of medication in preventing psychiatric disease even in psychologically well-defined high-risk groups (such as prodromal patients for schizophrenia or MCI for AD) is still not

Table 3. Classification Accuracies of Selected Structural Brain Imaging Studies Employing Multivariate Analyses to Classify Patient Groups

Group Discrimination	Imaging Parameter	Sensitivity	Specificity	Accuracy	References
AD versus normal aging	Whole-brain gray matter morphometry	60.6–100	80–95	81.1–96.4*	Klöppel et al., 2008
AD versus FTD	Whole-brain gray matter morphometry	83.3	94.7	89.2	Klöppel et al., 2008
MCI versus normal aging	Shape of hippocampus	83%	84%	83%	Gerardin et al., 2009
SZ versus HC	Whole brain morphometry	73.9%	87.3%	81.1%	Davatzikos et al., 2005
Adults with ASD versus HC	Whole-brain gray matter morphometry	60% (RH) / 90% (LH)	70% (RH) / 80% (LH)	65% (RH) / 85% (LH)	Ecker et al., 2010
FXS versus controls	Whole-brain gray matter morphometry	96.1%	89.6%	92.9%	Hoeft et al., 2008

AD: Alzheimer's disease; ASD: autism spectrum disorder; FTD: frontotemporal dementia; FXS: fragile-X syndrome; HC: healthy controls: LH: left hemisphere; MCI: mild cognitive impairment; RH: right hemisphere; SZ: schizophrenia. *For analyses of different subgroups.

proven, and a better prediction of conversion risk through imaging would greatly aid clinical trials aimed at developing drugs that could be administered prophylactically in individuals with the highest risk. The prediction accuracies obtained by Koutsouleris et al. (2009) were in the upper range of those reported for purely clinical predictors (Klosterkötter et al., 2011), but a formal evaluation whether imaging biomarkers provide added value to clinical and psychometric predictors of psychosis is still lacking.

Gray matter volumetry is not the only parameter that has been utilized for such diagnostic and predictive purposes. Using DTI, Ingalhalikar et al. (2010) obtained high classification accuracy for schizophrenia in adults and for ASD in children. Similarly, Rathi et al. (2010) applied this method for early detection of first episode psychosis in schizophrenia. fMRI has also been used, particularly in depression, both during the resting state (Craddock et al., 2009) and during presentation of emotional facial expressions (Fu et al., 2008).

Although the classification accuracy of MVPA techniques has been high in several studies, they may not reveal much about the underlying neurobiology of the disorder. The mutual dependence of signal from different voxels often prevents simple neuroanatomical interpretations. However, the feature maps may provide some indication of which neuroanatomical correlates are particularly relevant for the diagnosis in question. For example, the patients with fragile X syndrome (FXS) showed a distinctive pattern of volume increases (basal ganglia) and decreases (frontal lobe) (Hoeft et al., 2008), and the late prodromal group showed relative gray matter decrease in many cortical areas but also increases in other areas including the thalamus (Koutsouleris et al., 2009). In the same study, those who would later develop schizophrenia ("converters") could be distinguished from the nonconverters on the basis of smaller gray matter volume mainly in limbic and temporal areas. These findings may support biological models positing progressive cortical volume loss as a risk factor for schizophrenia (Wood et al., 2008).

Biomarkers derived from pattern classification do not come with clear cut-off points and depend strongly on the experimental parameters (e.g., numbers of scanned voxels) and analytical approches (e.g., the algorithm used for feature selection), and their practical relevance therefore needs to be demonstrated in multicenter studies, where the prediction accuracy of a template derived from one scanner is tested in data sets from others (Klöppel et al., 2008). Such confirmation in independent test samples is also needed to overcome doubts about the prediction estimates obtained through cross-validation in small samples (Isaksson et al., 2008). However, based on the promising results obtained so far, it can reasonably be expected that pattern classification of brain imaging data, in combination with clinical and psychometric data, will improve our ability to predict the course of psychiatric diseases.

Reliability and Publication Bias

Although the reliability of structural imaging measures is high on the same scanner, it is insufficient when tested across scanners (Kruggel et al., 2010). However, improvements are to be expected from wider use of high-field scanners with better image quality and segmentation results. Replication is also likely to be better if at least the field strength is kept constant across sites. The successful discrimination of AD patients from controls in a multicenter study of structural imaging data is promising in this respect (Klöppel et al., 2008). Less information is available about the reliability of specific functional imaging measures, because these would in principle have to be computed for each individual cognitive paradigm. The literature on reproducibility of task-related activation converges to report consistency in the qualitative activation patterns, but considerable intraindividual variability, across scanning sessions (Gountouna et al., 2010) (Table 1). We are thus still far away from fMRI-based biomarkers at the individual level. The situation is similar for resting state measures, which have been too heterogeneous across individuals to allow for the development of stable biomarkers of disease (Greicius, 2008). However, recent work on graph theoretical metrics of functional connectivity has yielded promising results for the intraindividual reliability of some metrics (Braun et al., 2012). A first step toward the development of biomarkers from resting state activation metrics would thus be to achieve agreement on standardized analysis procedures based on the measures with the highest reproducibility.

Because most neuroimaging studies still have relatively low numbers (up to 20 for PET, up to 100 for MRI), multicenter studies or meta-analyses are considered to be important ways of increasing the confidence in imaging findings. One problem with meta-analyses, which may not be confined to the field of neuroimaging (Ioannidis, 2005), is the potential overrepresentation of positive findings in the published literature. A recent

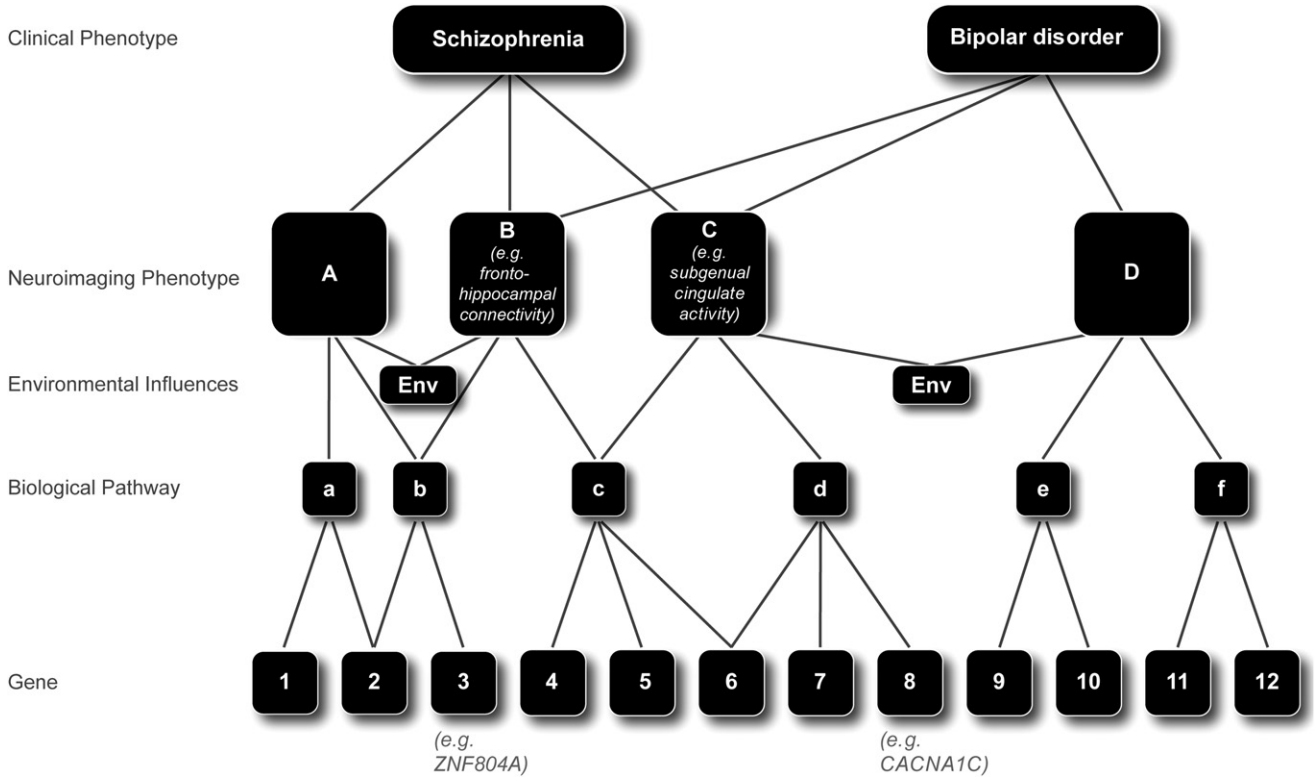

Figure 2. A Highly Simplified Model of the Genetic Pathways in Polygenic Psychiatric Diseases, Using the Examples of Schizophrenia and Bipolar Disorder

The multiple genetic variants that can contribute to the clinical phenotype (Genes 1 …) are likely to operate through a smaller number of intermediate biological pathways (a …), and not all of them may need to be altered to affect the respective pathway. One gene can contribute to multiple pathways (as in the case of hypothetical gene 2), and both genes and pathways can contribute to more than one disorder, resulting in the genetic overlap between schizophrenia, schizoaffective disorder and bipolar disorder. Genes can interact with each other and with environmental factors. The effects of the altered biological pathways on brain structure and function result in neuroimaging phenotypes, which can reflect the underlying genetic/biological processes more sensitively and specifically than the clinical phenotypes. Only a subset of genetic variants would be present in each case of psychosis, and their number and effect strengths would determine individual genetic risk. The examples of the *ZNF804A* (Esslinger et al., 2009a) and *CACNA1C* (Erk et al., 2010) variants are discussed in the text.

evaluation of meta-analyses of regional brain volume changes in psychiatric disorders reported evidence for a considerable over-reporting of significant group differences (except for the cerebral ventricles) (Ioannidis, 2011). Potential reasons include publication bias, selective reporting of brain regions showing group differences, and other arbitrary decisions that can be summarily termed "researcher degrees of freedom" (Simmons et al., 2011). However, the evaluation by Ioannidis (2011) did not include whole-brain volumetric studies that implement whole-brain correction for multiple comparisons, which should be less vulnerable to the selective reporting bias. Suggested improvements included the increase of power through multicenter studies, preregistration of clinical imaging studies, and definition of standardized analysis protocols (Ioannidis, 2011).

Genetic Imaging

Refining Molecular Methods

Clinical phenotypes in mental disorders may just be the endpoints of multiple converging pathophysiological pathways that are triggered by different combinations of genetic predisposition and environmental stress (Figure 2). As such, one way of improving the consistency of imaging findings in psychiatry may be to probe the biological pathways implicated in specific mental disorders. Current genetic models posit that multiple common variants with small effects or rare variants with larger effects confer the genetic vulnerability to psychotic disorders (Owen et al., 2010). Studies on patient samples that are not further differentiated by genotype may therefore obscure specific biological effects, whereas it may be possible to elucidate pathways to the disorder (Meyer-Lindenberg, 2010) through the effects of the risk variants on parameters of structural or functional neuroimaging, radioligand binding, or noninvasive neurophysiology. A particularly attractive aspect of this approach is that, in principle, it allows targeting any protein for which a functionally relevant genetic variant exists and would thus greatly expand the list of molecular mechanisms that can be investigated with neuroimaging (Table 2). It may also help overcome the lack of cellular resolution of current non-invasive neuroimaging techniques. Although high-resolution MRI at 7 Tesla can resolve the laminar structure of human cortex (Sánchez-Panchuelo et al., 2011), each layer contains a multitude of functionally and structurally diverse neurons that cannot be differentiated. Such differentiation of neurons within an area may be particularly relevant for psychiatric disorders, for

example the interplay between glutamatergic pyramidal neurons and GABAergic interneurons in prefrontal cortex (Lewis and Lieberman, 2000) or between medium spiny neurons expressing dopamine D1 or D2 receptors in the striatum (Lovinger, 2010; Moore et al., 1999). Although some information about specific molecular pathways may be obtained through combination of neuroimaging with pharmacological intervention, this is approach is limited by the availability of psychotropic agents that are approved for use in humans, and by the pleiotropic effects of most drugs. Genetic variants affecting specific components of a signaling pathway, for example transporters, receptors, metabolising enzymes, and postsynaptic proteins, may thus allow for a more fine grained dissection of its effects on brain and behavior (Bilder et al., 2004; Frank and Fossella, 2011).

Most work in noninvasive genetic neuroimaging has so far probed the effect of single genetic variants that appeared promising because of their neurochemical effects or their association with a clinical phenotype. Variants defined by a single-nucleotide change are referred to as ''single-nucleotide polymorphisms'' (SNPs), where commonly co-occurring SNPs form haplotypes. Large-scale mutations, such as losses of DNA (deletions) or duplications, can affect one ore multiple genes resulting in ''copy-number variations'' (CNVs), where there are fewer or more copies of one or several genes on a chromosome. Variants generally deemed suitable for the purposes of genetic imaging have been selected on the basis of one or more of the following criteria:

(1) Functional variants with a known neurochemical effect (e.g., Val158Met substitution [rs4680] in the gene for Catechol-O-Methyltransferase, *COMT* [Mier et al., 2010]; long/short repeat [5-HTTLPR] in the promoter of the *SLC6A4* gene, which codes for the serotonin [5-HT] transporter [Savitz and Drevets, 2009]).
(2) Common variants with small or medium contribution to disease risk, supported by GWAS (e.g., *ZNF804A* [Esslinger et al., 2009b] and *CACNA1C* [Erk et al., 2010] for psychosis).
(3) Rare variants with large contribution to disease risk: Williams syndrome (Meyer-Lindenberg et al., 2006); velocardiofacial syndrome (Karayiorgou et al., 2010); genes associated with familial AD, such as *presenilin* (Ringman et al., 2011).

Imaging Functional Polymorphisms

A polymorphism is called ''functional'' when it has a known effect on the function or abundance of the encoded protein, and any change in brain structure or function compared to the noncarriers is supposed to be effected by this neurochemical alteration (which presupposes that groups are as well matched as possible for other potential genetic or environmental differences). These genetic variants can thus serve as models for long-term pharmacological effects.

In the case of the *COMT* gene, the carriers of the variant that codes for methionine have lower enzyme activity and thus higher synaptic dopamine levels because COMT is one of the main catabolic enzymes for catecholamines. This genetic variant has therefore been proposed as an endogenous model of dopaminergic activation, especially for areas lacking the dopamine transporter. A recent meta-analysis of the imaging studies of the *COMT* Val158Met SNP has yielded evidence for higher prefrontal cortex (PFC) activation in carriers of the Met-allele during emotion tasks, but higher activation in Val-allele carriers during tasks probing executive control. This dissociation of higher PFC activation, interpreted as indicating less efficient or more noisy cortical activity, during cognitive and lower (more efficient) activation during emotional tasks may explain why the Val-allele seems to be associated with improved emotion regulation but impaired cognitive control (Mier et al., 2010). The interpretation of higher PFC activation as indicating impaired signal-to-noise, although compatible with the behavioral data and computational models of dopaminergic signaling in PFC (Winterer and Weinberger, 2004), is speculative and would have to be supported by recording from a behaving animal model, where noise components of neural activation can be identified more directly than in functional imaging (Gonzalez-Burgos et al., 2005).

The short variant of the s/l polymorphism in the *SLC6A4* gene leads to lower transcription of the gene and thus to lower levels of the serotonin transporter and higher levels of serotonin in the synaptic cleft. It was associated with increased relative activation of the amygdala to negative compared to neutral affective stimuli, an attentional bias toward negative material, and altered connectivity between the amygdala and prefrontal areas in several fMRI studies with healthy individuals and patients with depression (Savitz and Drevets, 2009). Variants on several other genes that are of interest to depression have also been associated with altered amygdala activation on functional imaging, although findings here have been less consistent (Savitz and Drevets, 2009). These included a functional variable number tandem repeat (VNTR) in the promoter of the monoamine-oxidase A gene that affects expression levels, a SNP (rs4570625) without known function in the gene for tryptophan hydroxylase-2, the rate-limiting enzyme for the synthesis of 5-HT in the raphe, and the *BDNF* Val66Met SNP (rs6265), which results in protein variants with different rates of secretion (Egan et al., 2003). The interest in BDNF (brain-derived neurotrophic factor) has been fuelled by the emergence of the neurotrophic theory of depression, which posits that reductions of hippocampal neurogenesis can lead to depressive phenotypes (at least in animal models) that can then be reversed by neurotrophins (Krishnan and Nestler, 2010) and possibly by antidepressants. An important aspect of genetic imaging, which is crucial for its validation, is the potential for the study of homologies of gene effects across species. For example the effects of the *BDNF* Val66Met variants on structure and function of the human hippocampus and on behavior can be compared with a Met/Met homozygous mouse model (Chen et al., 2006), where neural effects can be tested at much higher spatial and molecular resolution.

Imaging Disease-Associated Genetic Variants Identified by GWAS

Although imaging functional polymorphisms has yielded important insights in the downstream effects of the genetic variants, the clinical relevance of these loci is less clear. Although many of them had initially been implicated in mental disorders through candidate studies, genome-wide association studies (GWAS),

have largely failed to support them. Instead the GWAS, which operate without specific underlying biological models, which differentiates them from the candidate gene approach, have brought up risk loci for psychiatric diseases about whose function little, if anything, was known.

Although the effects of the newly identified genome-wide supported risk variants on protein structure and function will ultimately only be answered by molecular and cell biology, neuroimaging can provide global measures of the pathways involved (Inkster et al., 2010). For example, several SNPs on genes coding for subunits of the GABA-A receptor have been associated with bipolar disorder, but they do not alter protein sequence and their function is unknown (Craddock et al., 2010). One possibility is that they affect the expression levels of subunits and thus the functionality of the resulting GABA receptors, which could be tested with noninvasive markers of the GABA system derived from MEG and MRS (Muthukumaraswamy et al., 2009). This rationale is even more relevant for the rare CNVs that are enriched in autism, mental retardation, ADHD, schizophrenia, and possibly other mental disorders (Owen et al., 2010; Williams et al., 2010). These CNVs are only present in a small minority of cases and their immediate molecular effects therefore unlikely to explain the pathophysiological pathways underlying the disorder. However, many CNVs on different genes may affect the same functional system—for example NMDA receptor complexes in the case of schizophrenia (Kirov et al., 2011)—and thus converge on intermediate (neurobiological) phenotypes that can be mapped out with noninvasive techniques (Figure 2). One example is the mismatch negativity, a negative deflection of the event-related potential that is evoked by deviants in trains of auditory stimuli and can be modulated by antagonists of the NMDA receptor (Stephan et al., 2006). Such a noninvasive index of a putative pathological process might then become a proof-of-concept marker for intervention studies.

The choice of biological target for potential gene effects can be informed by endophenotypes, which are heritable traits that can be defined at any level from biochemistry to behavior. In order to meet the definition of an endophenotype for a particular disease (Gottesman and Gould, 2003), a trait needs to occur in both patients and unaffected relatives more frequently than in the general population. The crucial idea is that endophenotypes are more closely associated with specific genes than the clinical phenotype and can aid in the discovery of new disease genes or in the definition of genetic subtypes of the disease. Several such endophenotypes have been proposed on the basis of neuroimaging findings, for example, reduced GABA concentrations as measured by MRS in relation to major depression (Hasler and Northoff, 2011). Intermediate phenotypes derived from imaging can then be used both to refine the clinical phenotype (moving upward on Figure 2) and to identify the underlying biological and genetic pathways (moving downward on Figure 2), with the ultimate aim of producing psychiatric diagnoses with a firmer biological foundation and etiology. For example, the psychosis risk allele on the *ZNF804A* gene was associated with altered fronto-hippocampal connectivity (Esslinger et al., 2009a), and the risk allele on the *CACNA1C* gene with altered activation of the subgenual cingulate cortex (Erk et al., 2010), which had previously been proposed as neural correlates of schizophrenia and bipolar disorder, respectively (see Figure 2).

Genetic Imaging: Critiques and limitations

The field of genetic imaging has grown considerably over the last decade and has the attractive potential of bridging the gap between human cognitive neuroscience and research at the molecular level, but presently still faces important limitations. Most research so far has only looked at effects of single genes or even single loci, without applying the corrections for multiple comparisons across the genome that have become the standard for GWAS of clinical phenotypes. Although the choice of the particular genetic variant can often be supported by biological plausibility or association with a clinical phenotype, this approach makes the field vulnerable to false positive findings (Bigos and Weinberger, 2010). Genome-wide correction of associations with imaging phenotypes probably requires sample sizes at least in the hundreds, and several multicenter studies have now taken this approach, using single structural measures such as hippocampal (Potkin et al., 2009a) or caudate (Stein et al., 2011) volume or single functional measures such as frontal activation during working memory (Potkin et al., 2009c) as quantitative traits. This approach also opens up the possibility to discover new genetic variants that contribute to disease at least in subgroups of patients, thus fulfilling the promise of the endophenotype concept (Potkin et al., 2009b). However, success in implementing such an approach depends fundamentally on the quality of the selected imaging phenotype, and the replication of association data for the same phenotype has not thus far been successful (Potkin et al., 2009b, 2009c). The ideal scenario would combine genome-wide strategies with brain-wide imaging analyses. A recent study exemplifying this approach implemented a GWAS for imaging phenotypes across the whole brain in patients and controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Shen et al., 2010). However, this study employed parcellation of the brain into 142 subvolumes and then conducted 142 parallel GWAS on these measures and thus did not actually correct for the multiple phenotypes across the brain. A study that did apply such whole-brain correction (using the false discovery rate) did not find genome-wide significant association with brain structure in a sample of 731 participants from the ADNI cohort (Hibar et al., 2011b), although their pooling of patients with AD and MCI and healthy elderly controls may have decreased statistical power. Nevertheless it is likely that, in order to obtain the power to enable multiple comparison corrections with feasible sample sizes data reduction techniques will be mandatory. Various statistical techniques have been proposed for the joint multivariate analysis of genetic and imaging data (Hibar et al., 2011a; Vounou et al., 2010). Another strategy to increase the power of genetic imaging studies to detect clinical biomarkers would be to focus on variants of strong effect and high penetrance or to pool the effects of multiple variants with small effect (across the whole genome or across specific biological pathways) into polygenic risk scores (Holmans, 2010). The downside of this approach is loss of molecular resolution because polygenic scores integrate across different genes (and thus proteins) and CNVs with higher penetrance are normally so rare that individuals with different variants

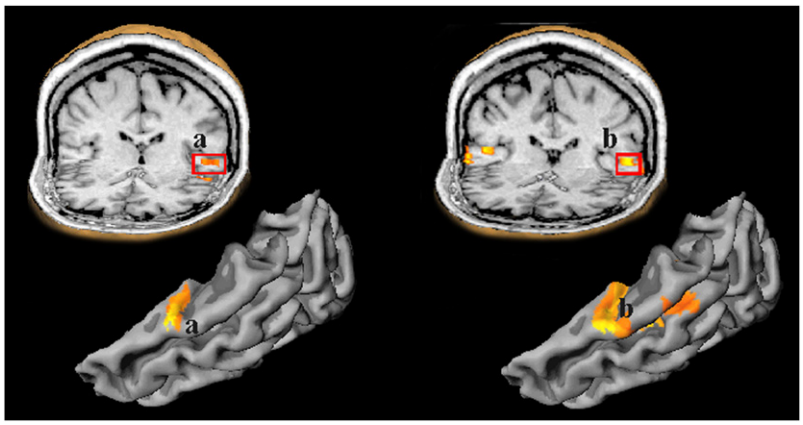

Figure 3. Activation of Left Primary Auditory Cortex during Auditory Verbal Hallucinations
Activation of left primary auditory cortex during auditory verbal hallucinations in a patient with schizophrenia (a), compared with bilateral activation during verbal stimulation (b). Reprinted from Dierks et al. (1999) with permission.

(ideally affecting the same pathway) would have to be pooled to achieve sufficient group sizes for statistical analysis.

The area of genetic imaging has been criticized for reporting unreasonably high effect sizes (or for claiming to find significant genotype effects in samples much smaller than those needed in clinical association studies). Estimates for the variance of functional imaging signal explained by single genetic variants have been up to 10% (for the 5-HTTLPR variant in relation to amygdala activation to emotional stimuli; Munafò et al., 2008). Although the heritability of amygdala activation in humans is unknown (a study in monkeys found heritability only for hippocampal but not amygdala glucose metabolism; Oler et al., 2010), moderate heritability has been reported for functional activation in other areas (Blokland et al., 2011). Moderate to high heritabilities have also been reported for brain volume measures from twin studies, although sample sizes were generally small (Peper et al., 2007), and a larger cohort study (Framingham Heart Study) found generally lower heritabilities (e.g., 0.26 for the frontal lobe and 0.46 for total brain volume) (DeStefano et al., 2009). Thus, the heritability of imaging phenotypes is generally lower than that of the clinical phenotype (up to 0.8 for schizophrenia, for example; Sullivan et al., 2003). Conversely, the effect sizes for associations between single risk loci and imaging phenotypes have generally been much higher than for those with the clinical phenotype. For example, the putative schizophrenia risk variant on the gene for nitric oxide synthase 1 (*NOS1*, rs6490121, reported in a GWAS by O'Donovan et al. [2008] but not replicated in further studies) explained 9% of the variance of the amplitude of the P1 component of the visual evoked potential (O'Donoghue et al., 2011), which is more than the 6% variance of the clinical phenotype explained by all significant variants collectively (Ripke et al., 2011). The underlying model assumes that many different combinations of genetic variants can contribute to the clinical phenotype, which is why the effect of any single variant on disease risk is very small, and that each gene can influence a different biological pathway (Figure 2). Conversely, the imaging endophenotype would be associated with fewer genetic loci. Thus, even if the heritability of the endophenotype is lower than that of the disease itself, its associations with specific genes may be more easily detectable. The ultimate test will be whether these genetic imaging associations replicate in independent samples. Thus the main methodological challenge for genetic imaging lies in protection against false-positive findings. In addition to rigorous corrections for multiple testing and replication experiments the solution might involve registration of studies, similar to the proposals for clinical imaging in general, and depositing sets of primary hypotheses.

Neural Correlates of States and Traits

Instead of trying to find biological correlates of complex clinical phenotypes, a more basic approach may be to focus on specific traits and states associated with particular mental disorders. Whereas traits are habitual patterns of behavior, thought, and emotion, states are temporary and are often elicited by identifiable stimuli or events. Thus, a mental disorder can be broken down into its main symptoms or states and its associated personality traits, and these can then be investigated separately by means of neuroimaging. Because single psychological states and traits may have clearer neural correlates than the complex clinical phenotype, this approach could be more sensitive than the comparison of diagnostic groups. However, this method has so far not led to the identification of more specific biomarkers or genetic loci of stronger effect than those associated with clinical diagnoses (Shifman et al., 2008). One possible solution is to obtain personality measures from questionnaires and correlate them with brain parameters that are supposed to be reasonably constant over time, for example regional volumetry, cortical thickness, or neurotransmitter concentrations measured with MRS (Boy et al., 2011). This approach faces the difficulty of finding reliable brain measures and correcting for the often large number of statistical tests at the whole brain level. The field is in many respects similar to that of genetic imaging because only weak associations have been established between single personality traits and mental disorder, and innovative ways of combining them to risk measures are needed to identify disease pathways with sufficient power.

More direct inroads into the neural basis of psychopathology can be made by scanning patients during spontaneously occurring or experimentally induced symptoms. For example, asking patients suffering from auditory verbal hallucinations to report the on- and offset of the voices during scanning allowed researchers to obtain the associated neural activation patterns from whole-brain correlation analysis (Dierks et al., 1999; Jardri et al., 2011; Silbersweig et al., 1995) (Figure 3). One important limitation of symptom mapping is that the symptoms and indeed their neural correlates may not discriminate well between

patients and healthy individuals. In the case of auditory hallucinations, activity in auditory cortex was observed both in patients with schizophrenia and in nonclinical hallucinators who report this isolated symptom, but without associated distress or functional impairment (Linden et al., 2011). The strength of symptom mapping thus seems to lie in its ability to detect neural correlates of specific psychopathological states, which can inform symptom-targeted treatments and aid in the monitoring of clinical effects (Linden, 2006), but not in the elucidation of antecedent causal mechanisms.

Nonpharmacological Treatment Strategies that Arise from Neuroimaging

There are various ways in which such symptom or trait mapping can be fruitful for translation. Multimodal imaging may reveal correlations between cognitive processes or motivational states and specific neurotransmitter systems, as shown for alcohol craving and dopamine receptor availability in the ventral striatum (Heinz et al., 2004). Functional imaging might also become a tool to infer mental states from brain activation for diagnostic purposes, although there are important ethical limitations to such intrusions into privacy. In a less contentious application, differences in imaging parameters might in the future help differentiate patients more likely to respond to a specific treatment. Functional neuroimaging of glucose and oxygen metabolism with PET and fMRI has already been used in the monitoring of pharmacotherapy, psychotherapy and cognitive interventions (DeRubeis et al., 2008; Linden, 2006; Vyas et al., 2011), but not yet yielded biomarkers that can assist in individual treatment decisions.

Finally, functional imaging might provide the basis for noninvasive or invasive therapies that specifically target the nodes and networks identified by neuroimaging. Examples include attempts at attenuating auditory hallucinations with TMS of the temporal lobe or improving treatment-resistant depression with deep-brain stimulation of the subgenual anterior cingulate cortex (George and Aston-Jones, 2010; Hoffman et al., 2003; Mayberg et al., 2005). One crucial methodological question for the development of new nonpharmacological treatments is whether to expect that treatment effects will only affect areas of primary dysfunction. Some of the imaging studies of therapy effects, for example in obsessive compulsive disorder, have indeed shown normalization of altered metabolic patterns after both psycho- and pharmacotherapy (Linden, 2006). Conversely, in other disorders, notably depression, the link between brain correlates of successful therapies and pre-existing brain dysfunction is less straightforward (Krishnan and Nestler, 2010; Linden, 2008). It is therefore conceivable that psychiatric treatments operate through mechanisms other than normalization of pathological brain networks, for example by activating compensatory pathways.

Functional neuroimaging has been singularly successful at identifying functional networks in humans. Most of clinical imaging has tried to identify dysfunctions in these networks in patient populations, and come up against the many difficulties discussed in this review. By comparison, much less effort has been spent trying to utilize the knowledge about these functional networks for the remediation of cognitive, emotional, or behavioral deficits. For example, a great deal is now known about the neural systems involved in emotion regulation (Ochsner and Gross, 2005; Phillips et al., 2008), and this information could be used to train patients with mood disorders (Clark and Beck, 2010). Potentially testing this theory is becoming more tractable with the advent of advanced neuroimaging techniques, particularly real-time fMRI. With real-time feedback about their regional brain activation, patients can be trained to regulate activity in specific areas or networks, a procedure termed "neurofeedback" (deCharms, 2008; Johnston et al., 2010; Weiskopf et al., 2003). In principle this provides the opportunity to influence localized brain activation non-invasively in a way that is controlled by the patients themselves and could allow them to regulate dysfunctional networks or activate compensatory pathways. fMRI-neurofeedback, targeting the anterior cingulate cortex, has shown preliminary success in chronic pain in patients with fibromyalgia (deCharms et al., 2005), and patients with Parkinson's disease may benefit from self-regulation of the supplementary motor area (Subramanian et al., 2011). Ultimately, though, any clinical application of neurofeedback and other brain-based therapies in psychiatric disorders will have to be integrated in a comprehensive biopsychosocial intervention program.

Conclusions

Neuroimaging plays a critical role in psychiatry as it can potentially be used to identify biomarkers of disease, prognosis, or treatment, elucidate biological pathways, and help redefine diagnostic boundaries and inform and monitor new therapies. Although several imaging and electrophysiological features have been consistently associated with mental disorders, none of them has the required sensitivity and specificity to qualify as a diagnostic marker. Promising results with low error rates for diagnostic or prognostic applications have been obtained through the use of multivariate classifier techniques, but these have rarely been tested across laboratories and not been validated in larger patient samples. Directions in neuropsychiatric imaging that appear promising transcend the constraints of the currently defined diagnostic boundaries. Functional imaging of genetic variants can be used to probe specific biological pathways associated with mental disorder and identify convergent mechanisms for clusters of risk genes to provide biological correlates of genetic load. A similar fractionation of mechanisms that contribute to psychiatric diseases might be achieved by state and trait mapping, based on psychopathological and personality models. The ultimate hope is that the better understanding of the biological pathways to psychiatric disease will result in the development of new treatments. The insight into the neural mechanisms of psychiatric symptoms achieved through neuroimaging has already informed new nonpharmacological interventions such as deep-brain stimulation, transcranial magnetic stimulation, and neurofeedback that are currently in clinical testing.

Early and prophylactic interventions present an emerging future direction in clinical psychiatry (McGorry et al., 2011), and neuroimaging has the potential to aid the identification of individuals at risk and monitor the effects of these interventions. Future aims in the development of surrogate treatment markers would

involve assessing whether psychological or pharmacological interventions normalize the patterns of brain structure or function that predicted disease risk. Another future direction with considerable clinical benefit would be the development of biomarkers that predict the response to a particular treatment and could then be used for therapeutic stratification. Despite available imaging techniques (Table 1) and molecular targets (Table 2), new ways of targeting intracellular processes are likely needed. A key persisting question for imaging research in psychiatry with respect to developing novel treatments is whether to focus on the detection of the primary pathology, or whether to probe the pathways that underlie resilience and recovery. There is thus ample scope for ongoing and new psychiatric imaging initiatives to establish biomarkers and targets for diagnostic and therapeutic applications.

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