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Review

Clinical applications of the functional connectome

F. Xavier Castellanos [a,b,*], Adriana Di Martino [a], R. Cameron Craddock [b,c], Ashesh D. Mehta [d], Michael P. Milham [b,c,**]

[a] Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, New York University Child Study Center, New York, NY 10016, USA
[b] Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA
[c] Center for the Developing Brain, Child Mind Institute, New York, NY 10022, USA
[d] Department of Neurosurgery, Hofstra North Shore LIJ School of Medicine and Feinstein Institute for Medical Research, Manhasset, NY 11030, USA

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ABSTRACT

Central to the development of clinical applications of functional connectomics for neurology and psychiatry is the discovery and validation of biomarkers. Resting state fMRI (R-fMRI) is emerging as a mainstream approach for imaging-based biomarker identification, detecting variations in the functional connectome that can be attributed to clinical variables (e.g., diagnostic status). Despite growing enthusiasm, many challenges remain. Here, we assess evidence of the readiness of R-fMRI based functional connectomics to lead to clinically meaningful biomarker identification through the lens of the criteria used to evaluate clinical tests (i.e., validity, reliability, sensitivity, specificity, and applicability). We focus on current R-fMRI-based prediction efforts, and survey R-fMRI used for neurosurgical planning. We identify gaps and needs for R-fMRI-based biomarker identification, highlighting the potential of emerging conceptual, analytical and cultural innovations (e.g., the Research Domain Criteria Project (RDoC), open science initiatives, and Big Data) to address them. Additionally, we note the need to expand future efforts beyond identification of biomarkers for disease status alone to include clinical variables related to risk, expected treatment response and prognosis.

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* Correspondence to: F.X. Castellanos, Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, One Park Avenue, 7th Floor, New York, NY 10016, USA. Fax: +1 646 754 5211.
** Correspondence to: M.P. Milham, Center for the Developing Brain, Child Mind Institute, 445 Park Avenue, New York, NY 10022, USA. Fax: +1 646 625 4371.
E-mail addresses: Francisco.Castellanos@nyumc.org (F.X. Castellanos), Michael.Milham@childmind.org (M.P. Milham).

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Introduction

As well documented in this issue, mapping the functional connectome is now in the foreground of neuroscience research, with a frequently enunciated goal of attaining clinical utility. Indeed, the rate of growth for studies incorporating resting state fMRI (R-fMRI) approaches has overtaken that of traditional task-based fMRI (Snyder and Raichle, 2012), with an increasing focus on clinical questions (Kelly et al., 2012). Despite the multiple advantages that attach to R-fMRI approaches vis-à-vis clinical samples (Fox and Greicius, 2010), progress towards advancing the clinical enterprise has been disappointingly slow. This situation was recently analyzed in the wider context of clinical neuroscience (Kapur et al., 2012) and the lessons drawn are particularly germane to R-fMRI and efforts to map the functional connectome.

In this selective overview, we focus on R-fMRI because its relatively widespread availability and amenability to large-scale aggregation across imaging centers and populations (Milham, 2012) make possible attaining data sets on scales comparable to genetic investigations (e.g., Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). We examine common elements that need to be considered to make the efforts of mapping the functional connectome relevant to clinicians. These include validity, reliability, sensitivity, specificity, positive and negative predictive values of potential biomarkers. Beyond these, our rudimentary knowledge of brain disorders also requires that we adopt intermediate strategies, as recommended by Kapur et al. (2012).

We will assess the evidence and gaps in relation to validity, reliability, sensitivity and specificity of efforts to map the functional connectome using R-fMRI, primarily in the context of diagnostic prediction studies. We also examine the nascent literature applying R-fMRI methods for neurosurgical planning, as this best exemplifies person-centered clinical applications.

Biomarkers

Central to the development of clinical applications with R-fMRI is the discovery and validation of biomarkers. The NIH Biomarkers Definitions Working Group defined a biomarker 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" (Atkinson et al., 2001). The Working Group noted that potential clinical applications of biomarkers include: 1) determination of the presence or absence of a disease (i.e., diagnosis), 2) staging of a disease, 3) determination of risk prognosis, or 4) prediction and monitoring of clinical response to an intervention.

However, enthusiasm regarding biomarker discovery has led to some misconceptions. First, biomarkers are associative by definition, but not necessarily causal. They can directly or indirectly index disease processes anywhere along the disease pathway. Second, they do not necessarily convey neuroscientific meaning; brain-related biomarkers can index any single feature or combination of features relating to brain physiology or anatomy. Thus, they may not be interpretable based on our current understanding. As discussed in the section on Sensitivity and specificity of R-fMRI measures in the context of predictive modeling, the potential high-dimensionality of feature sets used for prediction, and non-linearity commonly introduced into predictive modeling techniques mean that the biological meaning of a biomarker may not be straightforwardly discoverable. Finally, identifying a significant association between some feature (or combination of features) and a clinical variable does not equal discovery of a clinically useful biomarker. As is apparent from Fig. 1, even relationships with large effect sizes have modest predictive value when the ultimate intent is disease prediction or clinical monitoring. Thus, the elusive goal continues to be to "carve nature at the joints," as famously enunciated by Thomas Huxley, so as to obtain sufficiently large effect sizes.

Elements of clinically useful tests

Determination of clinical utility depends at a minimum on the following properties:

- Validity (accuracy): the extent to which a measure captures the "true" value; generally computed by measuring agreement between two measures obtained by *maximally different* methods
- Reliability (precision): the consistency with which repeated measures assess a given trait; computed by measuring agreement between two measures obtained by the same or *maximally similar* methods
- Sensitivity: ability to correctly identify affected individuals
- Specificity: ability to correctly exclude unaffected individuals

While validity and reliability can be considered independently of the disease to which the clinical tool will be applied, sensitivity and specificity are directly determined by the intended application. There is no established cutoff for determining utility based on sensitivity or specificity; rather, utility derives from a combination of the intent and the implications of positive findings. For example, screening tools aim to rule in all affected individuals (high sensitivity), at the cost of being overly inclusive (low specificity). This bias must be considered in light

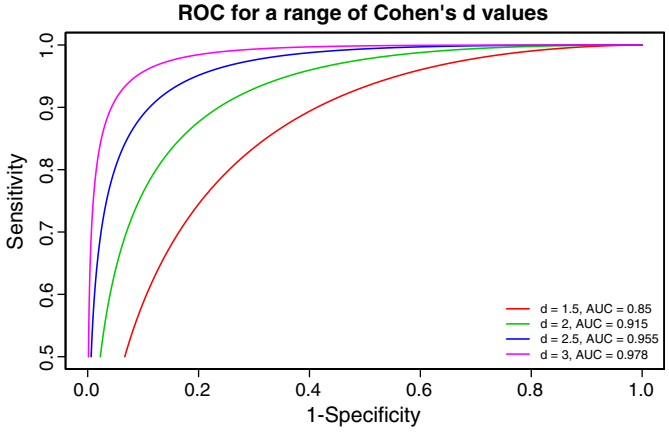

Fig. 1. Receiver operating characteristic (ROC) curves for between-group differences with a range of large effect sizes.

of the potential harm that can result from follow-up procedures after a positive screening result. In contrast, for diagnostic tests, greater value is put on arriving at a correct diagnosis (high specificity) at the cost of being less inclusive (lower sensitivity). Similar tradeoffs are encountered when clinical tools are used to assess and monitor disease severity, as sufficient sensitivity must be achieved to detect changes in disease severity, while maintaining adequate specificity to avoid confounding by artifactual factors or physiologic processes.

Additional features for successfully developing a clinical tool include widespread availability, repeatability with low risk of harm and being easily administered to both non-clinical and clinical populations. MRI based methods are widely available and can be repeated without known evidence of harm. In terms of ease of administration, MRI is intermediate between electroencephalography and radioligand-based methods, which are much less spatially localizing, on one hand, and invasive, on the other.

Validity of R-fMRI measures

A key challenge for neuroimaging methods is establishing validity or accuracy of our measures, i.e., are we measuring what we think we are (e.g., Sechrest, 2005)? Validity can be differentiated based on the strength of the evidence. At one end, *criterion validity* compares the measure of interest to an independent measure designated as the criterion or "gold standard" measurement. While structural imaging can reference dissection- and histology-based findings as gold-standards, R-fMRI lacks a gold standard. In theory, intracranial recordings should provide such an anchor, but their utility is limited by their invasive nature. Encouragingly, initial efforts to validate R-fMRI using intracranial approaches such as electrocorticography and cortico-cortical evoked potentials have demonstrated good correspondence with R-fMRI results (He et al., 2008; Keller et al., 2011). At the other extreme is *face validity*, in which findings are simply consistent with "common sense" expectations. Initial R-fMRI studies only aspired to face validity, as they were limited in focus (e.g., to the motor system). As the field has matured, more R-fMRI measures are attaining *construct validity*, defined as ability to accurately measure the construct of interest (Cronbach and Meehl, 1955). For example, the biological relevance of functional connectivity has been buttressed by demonstrations that it responds to surgical intervention (Johnston et al., 2008; Pawela et al., 2010) and varies with levels of consciousness (Noirhomme et al., 2010). The consistency of R-fMRI findings across neural systems with our knowledge of human brain architecture and with findings from other imaging modalities confirms that construct validity is often being attained, as briefly reviewed below.

Evidence supporting validity of R-fMRI measures

The popularity of R-fMRI functional connectivity has been spurred by the close correspondence between the statistical maps resulting from R-fMRI analyses and task-based fMRI coactivations (Biswal et al., 1995; Damoiseaux et al., 2006; Mennes et al., 2010, 2013; Smith et al., 2009). Particularly convincing are data-driven (e.g., independent component analysis-based) demonstrations of spatially independent intrinsic connectivity networks corresponding to those previously established by neuropsychological and task-based imaging studies (Beckmann et al., 2005; Damoiseaux et al., 2006; Filippini et al., 2009; Fox et al., 2006). The conclusion that patterns of synchrony in spontaneous fluctuations of blood oxygen level dependent (BOLD) signals delineate functional brain circuits that are at least partially underpinned by anatomically definable tracts has been most convincingly supported by comparisons with definitive tract-tracing methods in the non-human primate (Kelly et al., 2010; Margulies et al., 2009). The link between BOLD spontaneous fluctuations and the functional circuitry of the brain was further supported by prediction of intrinsic functional connectivity from responses evoked in cortex in epilepsy patients with intracranial electrodes (Keller et al., 2011). Additional evidence of the validity of indexing the functional connectome on the basis of low frequency fluctuations in BOLD signal was provided by examining the correspondence between BOLD fluctuations and electrophysiological high gamma power signals recorded directly from the cortical surface in presurgical epilepsy patients (Keller et al., 2013). Also suggestive of validity have been reports of changes in the functional connectome following learning in healthy volunteers (Albert et al., 2009; Lewis et al., 2009; Ma et al., 2011; Taubert et al., 2011).

Indirect and incomplete evidence of validity is provided by the burgeoning literature reporting between-group differences in various aspects of the functional connectome, which tend to focus on univariate differences (e.g., Filippi et al., 2012; Kelly et al., 2012; Sheline and Raichle, 2013; Vissers et al., 2012; Wang et al., 2012; Xia and He, 2011; Zhang and Raichle, 2010).

Gaps and needs in evaluating the validity of R-fMRI measures

The validity of R-fMRI was threatened by findings that artifactual signals can produce apparent connectivity patterns that are strikingly similar to networks of interest (Birn et al., 2006, 2008b; Lund, 2001). For example, patterns of functional connectivity derived from respiratory signals have been shown to resemble those typically observed in the default network (Birn et al., 2006, 2008a). Fortunately, later studies have shown that careful correction for physiological artifacts do not markedly diminish R-fMRI findings — in fact, they can improve them (Chang and Glover, 2009; Marx et al., 2013). Nevertheless, greater effort needs to be given to both the development of data-driven approaches to the identification and removal of physiological signals and usage of external information (e.g., physiological recordings) (Chang and Glover, 2009; Fox et al., 2009; Marx et al., 2013).

Another area that needs further exploration involves the spectral properties of the spontaneous BOLD signal fluctuations that contribute to functional connectivity measures (Biswal et al., 1995; Zuo et al., 2010a). A recent analysis suggests that the apparent low frequency structure of BOLD fluctuations reflects temporal blurring of the hemodynamic response function rather than the frequency properties of the underlying neuronal signals (Niazy et al., 2011). These findings echo prior demonstrations of potentially useful information residing above 0.1 Hz (Fornito et al., 2011; Salvador et al., 2008) and if replicated and characterized more thoroughly, suggest that R-fMRI studies, which typically low-pass filter at 0.1 Hz, are discarding valuable information.

Additional challenges relate to selecting nodes for analyses and defining their connectivity. Although brain areas for functional connectivity analysis have been defined using various parcellation schemes based on anatomical features, evidence is accumulating that these are inadequate for defining functionally meaningful areas (Craddock et al., 2012; Smith et al., 2011). Alternatively, methods exist for defining brain areas based on homogeneity of function (Bellec et al., 2006; Blumensath et al., 2013; Craddock et al., 2012). Issues remain on how to optimally define borders for regions and how to best determine optimal resolution (number of nodes and their size). Once nodes are specified, further challenges remain in defining their connectivity. A straightforward approach is to use bivariate measures of statistical dependency such as Pearson's correlation. However, full correlation can include artifactual connections, such as those dependent on a third source, which can be addressed with partial correlation (Marrelec et al., 2006; Smith et al., 2011). Adequately estimating statistical dependencies is error-prone because of the limited number of observations commonly available in R-fMRI data. This can be addressed in part using regularization methods (Ryali et al., 2012; Smith et al., 2011; Varoquaux et al., 2010). Finally, choosing the optimal way to threshold correlations or connections is also problematic. Ideally, one would estimate the significance of a correlation based on the number

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of degrees of freedom, but since fMRI signals are temporally autocorrelated, the precise number of degrees of freedom is unknown. Alternatively, non-parametric methods, such as wavestrapping (Breakspear et al., 2004) or circular block bootstrap (Bellec et al., 2010), can be employed.

Finally, we note the challenges of how to conceptualize the accuracy of indirect connections in the functional connectome, which have no underlying structural connectivity (e.g., Margulies et al., 2009). When benchmarked against the structural connectome, these connections can be viewed as compromising the accuracy of R-fMRI approaches. However, if the functional and structural connectomes are viewed as distinct entities, such connections may be viewed as an inherent characteristic of the functional connectome (likely produced by polysynaptic connections or subcortical contributions) and not necessarily a feature to be removed.

Reliability of R-fMRI measures

Reliability is defined as the consistency between measurements, and is commonly conceptualized as an index of the degree to which observed measures can be attributed to true scores vs. measurement error. Measurement error can be systematic or random. Based on the frame of reference for comparison between measurements, several classes of reliability estimates are defined: inter-rater (i.e., between experimenters/evaluators), test–retest reliability (between test administrations), inter-method reliability (i.e., between methods/instruments) or internal consistency reliability (i.e., between components/portions of a test session). For any measure, the square root of reliability sets an upper limit on the maximum obtainable validity (Nunnally, 1978). Sensitivity and specificity are similarly limited by reliability.

The unconstrained nature of R-fMRI raised initial concerns regarding its reliability, whether consistency of findings over time (test–retest) or consistency across scanners (inter-method) or sites (inter-rater). While R-fMRI studies have generally assumed signals of interest to be stationary, recent work has identified potential changes over component time-units of a given scan (internal consistency). As described below, efforts to date have primarily focused on test–retest reliability across scans (short and long-term), although recent studies are examining the consistency of findings within a given scan (Chang and Glover, 2010), as well as across magnets and sites (Biswal et al., 2010; Fair et al., 2012; Tomasi and Volkow, 2010).

Evidence supporting reliability of R-fMRI measures

Test–retest reliability represents the most commonly assessed form of reliability in the imaging literature. Moderate-to-high test–retest reliability (intraclass correlation coefficients >0.5 and occasionally reaching ~0.9) of R-fMRI metrics has been confirmed in healthy adults by multiple groups (Braun et al., 2012; Chou et al., 2012; Faria et al., 2012; Fiecas et al., 2013; Kristo et al., 2012; Liang et al., 2012; Mannfolk et al., 2011; Meindl et al., 2010; Shehzad et al., 2009; Van Dijk et al., 2010; Wang et al., 2011, 2013; Zuo et al., 2010a, 2010b, 2013). Fewer studies have been conducted with older participants (Blautzik et al., 2013; Guo et al., 2012; Song et al., 2012) and only one in children (Thomason et al., 2011), patients with schizophrenia (Turner et al., 2012), and patients with mild cognitive impairment (Blautzik et al., 2013). Still, the news is generally good, with acceptable to good test–retest reliability for a wide range of measure describing the functional connectome across intervals as long as one year (Blautzik et al., 2013; Chou et al., 2012; Shehzad et al., 2009; Zuo et al., 2010a, 2010b, 2013). For comparison, these generally surpass the test–retest reliabilities of diagnostic assessments of the major psychiatric disorders recently documented in the DSM-5 Field Trials (Regier et al., 2013).

Gaps and needs in assessing the reliability of R-fMRI measures

A key limitation of the existent R-fMRI literature is the lack of rigorous examination of key features capable of compromising reliability (e.g., eyes open or closed, time of the day). Knowledge of such factors is crucial — both for careful design and analysis of multi-site studies, as well for efforts to obtain diagnostic or treatment response information. Although not commonly examined in a reliability framework, several studies have demonstrated factors capable of introducing systematic measurement error into R-fMRI studies if not properly controlled. In particular, scanning with eyes open vs. closed during R-fMRI scans yields systematically different results (Ben-Simon et al., 2008; Brandt, 2006; Chen et al., 2008; Marx et al., 2004; McAvoy et al., 2008; Uludag et al., 2004; Yan et al., 2009; Yang et al., 2007; Zou et al., 2009). For example, spontaneous occipital fluctuations are substantially larger during eyes closed than during fixation with eyes open (Bianciardi et al., 2009). Factors related to scan order and session duration are also starting to receive attention. For example, Yan et al. (2009) observed significant differences between the first and second scans in a session. Other pragmatic factors, such as satiety status (Lohmann et al., 2010) or morning–evening variations (Shannon et al., 2013) have received scant attention. The limitation of these studies from the point of view of reliability is that they were conducted as within subject-analyses (e.g., hunger vs. satiety) rather than quantifying the impact of satiety or circadian factors on test–retest reliability. Fortunately, re-analysis of such datasets could easily yield estimates of test–retest reliability.

In considering reliability, we note that artifactual signals can contribute to reliability just as much as signals of interest. For example, Yan et al. found that in-scanner motion can artifactually enhance test–retest reliability (Yan et al., 2013). Generally unexplored is the potential impact of factors such as age or disease status on reliability — both of which can impact between- and/or within-subject variations which directly determine reliability estimates. Of relevance to clinical applications, low test–retest reliability is a limiting factor for longitudinal studies of development, aging and response to intervention.

Sensitivity and specificity of R-fMRI measures in the context of predictive modeling

Sensitivity and specificity are a central focus of multivariate predictive modeling (MPM) analyses which aim to identify biomarkers of neuropsychiatric diseases. Most of these studies are based on diagnostic prediction of psychiatric disorders previously examined in group comparisons using R-fMRI (e.g., Craddock et al., 2009).

Predictive modeling is typically performed in a supervised learning setting, in which each feature (e.g., correlations between regions) has a label which can correspond to disease status, severity, treatment outcome, or other phenotypic variables (Hansen, 2007). Various modeling approaches can be applied to "learn" or "train" a mathematical relationship between the features and labels. The accuracy of the model is estimated using a procedure called cross-validation, in which the data are iteratively split into a subset used to train the model, and a subset used for testing. The trained model is applied to the testing data to decode the variable of interest from the data; these predictions are compared to the true labels for the testing data to estimate prediction accuracy (Bishop, 2006; Pereira et al., 2009). This procedure provides a framework for estimating sensitivity and specificity, which are key for evaluating biomarker performance (Craddock et al., 2009). Other concepts that are important for predictive modeling are feature extraction and feature selection. Feature extraction involves transforming the data so that they are better conditioned for modeling (e.g., principal component analysis (PCA) dimensionality reduction) (Bishop, 2006) and feature selection, which involves identifying the subset of features that are most important to the model (Guyon and Elisseeff, 2003). As the advantages and disadvantages of each analytical approach are

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beyond the scope of this paper, we refer elsewhere for an instructive overview (Pereira et al., 2009).

Evidence regarding sensitivity and specificity in R-fMRI predictive modeling studies

As summarized in Table 1, the literature on predictive modeling on functional connectivity (as of 2/1/2013) addresses schizophrenia (n = 9 studies, Bassett et al., 2012; Du et al., 2012; Fan et al., 2011; Liu et al., 2012; Shen et al., 2010; Tang et al., 2012; Venkataraman et al., 2010, 2012; Yu et al., 2013), attention-deficit/hyperactivity disorder (ADHD; n = 10, Bohland et al., 2012; Cheng et al., 2012; Colby et al., 2012; Dai et al., 2012; Dey et al., 2012; Eloyan et al., 2012; Fair et al., 2012; Sato et al., 2012; Sidhu et al., 2012; Zhu et al., 2008), major depression (n = 3, Craddock et al., 2009; Lord et al., 2012; Zeng et al., 2012), autism (n = 2, Anderson et al., 2011; Murdaugh et al., 2012), epilepsy (n = 1, Zhang et al., 2012) prenatal cocaine exposure (n = 1, Deshpande et al., 2010) and multiple sclerosis (n = 1, Richiardi et al., 2012). Beyond differences in the disorders examined, studies vary in modeling approach, feature selection or extraction algorithms as well as cross validation employed.

The indices (i.e., features) of intrinsic functional architecture utilized also vary. Most authors have opted for exploratory whole brain approaches using graph theory measures or whole-brain intrinsic functional connectivity based on the application of structural or functional parcellation atlases. Others have focused on regional measures of variance (Cheng et al., 2012; Sato et al., 2012), and regional or global graph statistics (Bassett et al., 2012; Cheng et al., 2012; Dai et al., 2012; Dey et al., 2012; Lord et al., 2012; Sato et al., 2012; Zhang et al., 2012; Zhu et al., 2008). Fewer studies have focused on indices of functional architecture emerging from models of the pathophysiology of the disorder. In one example (Craddock et al., 2009), functional connectivity of 15 regions-of-interest emerging from the depression literature were entered into the prediction analyses. Interestingly, selecting brain regions on the basis of expert opinion improved overall prediction accuracy from 53% for whole-brain unbiased exploration to 75% in a study of schizophrenia (Venkataraman et al., 2012). Yet, none of these studies alone or in combination point toward a common feature or feature set for each of the disorders examined. Instead, they should be considered proofs-of-concept on which the next wave of examinations will be built.

Gaps and needs in predictive modeling with R-fMRI measures

Better datasets

Most studies (but see exceptions, e.g., Colby et al., 2012; Fair et al., 2012; Yu et al., 2013) have focused on two-class prediction — probands with a diagnosis are contrasted to healthy controls. These first generation studies have been conducted with generally small samples (mean group size is 27.6 ± 17.5) with the exception of the efforts based on the ADHD-200 Competition (ADHD Consortium, 2012). In 2012 the ADHD-200 Consortium made available a dataset of individuals with ADHD and controls (ages 7–21 years; 285 individuals with ADHD and 491 controls in the training set; 78 individuals with ADHD and 93 controls reserved for the holdout set) and announced a global competition to develop novel diagnostic predictive algorithms and to identify potentially useful ADHD biomarkers (ADHD Consortium, 2012). As a result, nine papers were published on ADHD classification using intrinsic functional connectivity indices alone or in combination with other modalities (Bohland et al., 2012; Chang et al., 2012; Colby et al., 2012; Dai et al., 2012; Dey et al., 2012; Eloyan et al., 2012; Fair et al., 2012; Sato et al., 2012; Sidhu et al., 2012). This represented a marked increase from the one prior study on ADHD diagnostic prediction (Zhu et al., 2008). While the ADHD-200 Global Competition demonstrated the utility of data sharing to promote discovery science, similar gaps and needs can be identified across the entire field. The ADHD-200 Global Competition also underscored that there is still much work to be done to achieve biomarkers based on R-fMRI metrics. For example, the best classifier performance in the competition was achieved not by using R-fMRI features, but by taking advantage of the male predominance and the tendency to manifest lower IQ which characterizes ADHD (ADHD Consortium, 2012; Brown et al., 2012).

Biomarker identification and evaluation will require massive datasets that provide sufficient variance for the disease under inquiry, while also including other disorders so that specificity can be ascertained (Dudley and Butte, 2009). Acquiring such large samples, in a reasonable amount of time, requires collaborative data collection efforts that span many imaging sites. Ideally such collaboration would be coordinated, such as the Alzheimer's Disease Neuroimaging Initiative (Mueller et al., 2005), in which variance in experimental procedures, such as scanning protocols, has been minimized. But such initiatives are costly. Alternatively, efforts such as the International Neuroimaging Data-sharing Initiative (INDI) (Mennes et al., 2012), 1000 Functional Connectomes Project (Biswal et al., 2010), and consortia like the ADHD-200 (ADHD Consortium, 2012) and the Autism Brain Imaging Data Exchange (ABIDE) (Di Martino et al., in press) are amassing such datasets post-hoc. Although each of these are confounded by between site variation in experiment protocols, they provide the best current hope for identifying biomarkers, until large coordinated initiatives are established.

Real world assessment of biomarker properties

Overall, as shown in Table 1, the reviewed studies yielded moderate-to-excellent accuracy, sensitivity, and specificity — providing an optimistic outlook for functional connectivity based clinical diagnostics. But these estimates of external validity (generalization ability) do not provide a realistic picture of the positive (probability of having the disease given a positive test) and negative (probability of not having the disorder given a negative test) predictive value of the biomarker. This requires incorporating information about disorder prevalence (Grimes and Schulz, 2002). We calculated these measures for the reviewed literature using recent estimates of disorder prevalence from Centers for Disease Control and Prevention Mortality and Morbidity Weekly Reports. Positive and negative prediction values (PPV and NPV, respectively) are calculated from sensitivity (SS), specificity (SP) and prevalence (Prev) using the following equations (Altman and Bland, 1994):

$$\mathrm{PPV} = \frac{\mathrm{SS} * \mathrm{Prev}}{\mathrm{SS} * \mathrm{Prev} + (1-\mathrm{SP}) * (1-\mathrm{Prev})}. \quad (1)$$

$$\mathrm{NPV} = \frac{\mathrm{SP} * (1-\mathrm{Prev})}{\mathrm{SP} * (1-\mathrm{Prev}) + (1-\mathrm{SS}) * \mathrm{Prev}}. \quad (2)$$

There is a remarkable disparity between the performance estimates reported in the literature and clinical utility, some of which lead to strikingly different conclusions about the relative quality of modeling approaches. For example, the performance (prediction accuracy, sensitivity, specificity) of the modeling approach employed by Tang et al. (2012) (93%, 86%, 100%, respectively), and Du et al. (2012) (93%, 93%, 93%) are very similar. The two methods would be tied if the J-statistic (J = SS + SP − 1) (Youden, 1950) were used to compare them, but PPV gives a drastically different picture (100% vs. 27.4% for Tang et al. and Du et al., respectively). This disparity is due to the low population prevalence of schizophrenia (0.6%), which results in Eq. (1) being dominated by specificity, resulting in a 72.6% change in PPV from a 7% change in specificity. A consequence of this phenomenon is that the best performing classifiers for diagnosis are those that model healthy individuals well, and are hence of limited utility for understanding disease processes. We note that specificity is calculated based on the ability to differentiate the

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Table 1
Predictive modeling based on intrinsic brain functional architecture.

Author, year	Disorder	N			Age group[a]	Features	Prediction method	Feature selection approach	Cross validation	Accuracy	Sensitivity	Specificity	Disorder prevalence[b]	Real world predictive values		Notes
		Pt	NC	Other										Pos	Neg	
Craddock et al. (2009)	MDD	20	20	–	Adults (unmatched)	iFC among 15 ROI relevant for depression	Linear SVC	RF, RRFE, RFE, TF	LOO	95%			4.1%	–	–	Holdout sample included 6 patients with MDD. SVM performance varied as a function of the feature selection approach; several circuits previously implicated in MDD were relevant for discrimination. Classification accuracy = 63% w/o feature selection.
									Holdout[d]	83%	–	–				
Lord et al. (2012)	MDD	22	22	–	Adults	Graph theory: participation index, betweeness centrality, efficiency	Linear SVC	Minimum redundancy maximum relevance;RFE	Split–half (two–fold)	90% to 99% (2 to 6 features)	99%	99%		80.9%	100.0%	Some regions involved in Craddock et al. (2009), were also reported as discriminating features here (rACC, thalamus).
Zeng et al. (2012)	MDD	24	29	–	Adults	Whole brain iFC	Linear SVC	Kendall tau rank correlation coefficient	LOO	94%	100%	90%		29.9%	100.0%	The most discriminating functional connections mainly located in DN, affective network, visual cortical areas and cerebellum.
Shen et al. (2010)	SCZ	32	18	–	Young adults	Whole brain iFC	Quasi–nearest neighbour classifier	Kendall tau rank correlation coefficient	LOO	92%	94%	75%		2.2%	100.0%	Feature extraction with locally linear embedding & C–Means clustering. 3D PCA and SVC also utilized; SCZ–related decreases in frontal–parietal and temporal iFC with cerebellum.
Fan et al. (2011)	SCZ	31	31	–	Young adults	ICA–based networks	Linear SVC	Forward component selection	LOO	87%	90%	84%		3.3%	99.9%	Feature extraction with Grassman manifold. Accuracy based on feature combination of DN and temporal lobe ICA–based networks.
Bassett et al. (2012)	SCZ	29	29	–	Adults	Graph theory: largest connected component in the graph	Linear SVC	Group comparisons	Split–Half (Two–fold)	75%	85%	64%		1.4%	99.9%	Weaker iFC in SCZ for circuits based on olfactory cortex, temporal pole, AG, parahippocampus, amygdala, caudate, pallidum, posterior parietal cortex.
Tang et al. (2012)	SCZ	22	22	–	Young adults	Whole brain iFC	Linear SVC	Kendall tau rank correlation coefficient	LOO	93%	86%	100%		100.0%	99.9%	68% of discriminating features represented iFC decreases in SCZ, primarily in visual cortical network, DN, self referential network and sensory–motor networks.
Venkataraman et al. (2010, 2012)	SCZ	18	18	–	Young adults	SCZ expert selected regions	Random forest analysis	Gini importance	NR	75%	–	–	0.6%	–	–	Both papers used same sample and methods; 2012 paper reported correlations with symptoms. SCZ exhibited increased iFC between parietal and frontal regions, and decreased iFC between parietal and temporal regions, and between the temporal cortex bilaterally. Decreased parieto–temporal iFC related to severity of positive symptoms, increased fronto–parietal iFC related to negative & general symptoms.
						Whole brain iFC				53%	–	–		–	–	
Du et al. (2012)	SCZ	28	28	–	Adults (unmatched)	ICA–based networks	PCA–FDA	TF	LOO	93%	93%	93%		7.4%	100.0%	Prediction using network derived from task based fMRI (auditory oddball task) yielded better performance (Accuracy = 98%). Algorithm tested both with individual ICA and different combinations of the ICA networks separately for R–fMRI and fMRI; combinations always performed better.
Liu et al. (2012)	SCZ	24	22	25[d]	Young adults	Whole brain iFC	NonLinear SVC Multiclass:one against one	–	LOO	79%	72%	86%		3.0%	99.8%	NC siblings of patients with SCZ. Feature extraction with PCA. Separate classifiers were used for SCZ vs. HC and SCZ vs. NC. We report performance of SCZ vs. HC[d].
Yu et al. (2013)	SCZ	24	22	25[d]	Young adults	Whole brain iFC	Linear SVC Multiclass:one against rest	–	LOO	62%	67%	87%		3.0%	99.8%	NC siblings of patients with SCZ. Feature extraction with PCA. Most discriminative features DN and cerebellum iFC[d].
Zhu et al. (2008)	ADHD	12	12		Adolesc.	Reho	PCA-FDA	-	LOO	85%	78%	91%		40.2%	98.2%	Reho-based classification better than gray matter-based classification; ACC, putamen, temporal cortex, cerebellum thalamus best discriminators.
Dey et al. (2012)	ADHD	285	491	-	Child, adolesc., young adults	Graph theory: degree, 3-cycle	PCA-LDA	Randomized optimization	ADHD200 Holdout[c]	70%	49%	87%		22.6%	95.6%	Each index was measured on whole brain and on an ADHD-relevant mask. We report the best overall accuracy (3-cycle on ADHD relevant mask).

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Colby et al. (2012)	ADHD	163 (C)	491	111 (I)	Child, adolesc., young adults	Combination of functional and structural features	RBF kernel SVC	RFE, multiple SVM–RFE	ADHD200 Holdout	55%	33%	79%	7.20%	10.9%	93.8%	Functional features for cortical and subcortical areas included: iFC, graph theory metrics, nodal power spectra, global iFC and Reho. Structural features included cortical thickness, gray matter volume, surface area and surface vertices, cortical mean curvature, gaussian curvature, cortical folding, cortical curvature index, and regional volume, voxel intensity mean, and SD for subcortex.
Dai et al. (2012)	ADHD	285	491	–	Child, adolesc., young adults	Cortical thickness, gray matter probability, ReHo, iFC	RBF kernel SVC & MKL	Filter–based, RFE	ADHD200 Holdout	68%	38%	84%		15.6%	94.6%	MKL used to classify on the basis of multimodal features; it yielded best perfomances which are reported here. Accuracy 58% when 3 classes tested (ADHD–C, ADHD–I, NC).
Bohland et al. (2012)	ADHD	285	491	–	Child, adolesc., young adults	Structural functional and phenotypical	Linear SVC	2 sample t–test; nested CV, RFE	ADHD200 Holdout/ site	44–74%	–	–		–	–	Phenotypic variables alone provided good prediction accuracy, which was enhanced by incorporating features from functional and structural neuroimaging.
Eloyan et al. (2012)	ADHD	285	491	–	Child, adolesc., young adults	Motor network parcellations iFC, whole brain iFC, motion parameters	Aggregate of four classifiers	Multiple	ADHD200 Holdout	61%	21%	94%		21.4%	93.9%	A correlation graph for a motor network parcellation was highlighted as a promising biomarker.
Sato et al. (2012)	ADHD	285	491	–	Child, adolesc., young adults	Reho, ALFF, ICA network	Multiple classifiers	Multiple	ADHD200 Holdout	67%	65%	70%		14.4%	96.3%	Combining ALFF and Reho discriminated ADHD from NC but w/limited accuracy. Combining the three features discriminated ADHD–C vs ADHD–I (67% accuracy). Relevant features were broadly distributed in the brain. Highly similar results across methods tested.
Sidhu et al. (2012)	ADHD	141	429	–	Child, adolesc., young adults	Combination of phenotypic and functional data	Linear SVC	None	ADHD200 Holdout	63%	–	–		–	–	Feature extraction with FFT, PCA and FFT+PCA. ADHD subtypes also classified against NC. 69% accuracy for 3 group classification.
									10–fold	76%	–	–		–	–	
Cheng et al. (2012)	ADHD	101	143	–	Child	ReHo, ALFF, Pearson correlation, spatial correlation	RBF kernel SVC	BWAS	LOO	76%	63%	85%		24.6%	96.7%	ADHD–C (n=38) and ADHD–I (n=63) included. The most discriminative features were associated to frontal and cerebellar regions.
Fair et al. (2012)	ADHD	112 (C)	455	80 (I)	Child, adolesc.	iFC of selected seeds based on meta–analysis of cognitive tasks	Linear SVC	TF	LOO	77%	75%	77%		20.2%	97.5%	Each ADHD subtype (C=combined, I=inattentive) was tested against the NC group. Top row refers to ADHD–C and lower row to ADHD–I. Also tested 3–group classification yieding 63% accuracy. Data preprocessed using different motion corrections; results reported here obtained with the group level motion correction.
										81%	80%	83%		26.7%	98.2%	
Zhang et al. (2012)	Epilepsy	100	80	–	Young adults	Community matrix K; interhemispheric asymmetry in IFC	Linear SVC	Sparse regression	LOO	84%	83%	85%	1.00%	5.3%	98.5%	Mostly partial epilepsy; medicated. Multiple features and approaches used; results reported here based on combining community matrix K and iFC asymmetry.
Anderson et al. (2011)	ASD	40	40	–	Young adults adolesc.	Whole brain iFC relationship with age	Quasi–nearest neighbor classifier	2 tailed t test	LOO	79%	83%	79%	1.0%	3.8%	99.8%	Holdout sample included 8 patients with autism & 13 NC.
									Holdout	71%	75%	69%		2.4%	99.6%	
Murdaugh et al. (2012)	ASD	13	14	–	Young adults	Seed based iFC:AG, MPFC PCC	Logistic regression	None	LOO	96% (AG), 70% (MPFC, PCC)	–	–		–	–	Pseudorest (i.e., task regressed). ASD have reduced iFC between AG and occipital region and increased iFC between AG and supplementary motor cortex.
						Whole brain iFC				78%	77%	79%		3.6%	99.7%	
Deshpande et al. (2010)	Prenatal cocaine exposure	30	26	–	Adolesc.	iFC & EC	Linear SVC	RFE	10–fold	90%	–	–	7.20%	–	–	Functional connectivity measured without GSR was also tested; here we report results obtained with GSR. Task based effective connectivity also tested as well as phenotypic information.
Richiardi et al. (2012)	MS	22	14	–	Adult	Whole brain iFC	Functional trees	Permutation test	LOO	88%	82%	86%	0.10%	0.6%	100.0%	Feature extraction with direct graph embedding method.

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disease state from healthy controls, and not for differentiating among diseases. Future studies will need to incorporate larger datasets that span multiple disorders to adequately evaluate the clinical utility of prospective biomarkers (Dudley and Butte, 2009).

The manner in which training levels are generated also impacts the clinical utility of a learned model. A common presumption of predictive modeling for disease state classification is that current standards of most clinical diagnoses (e.g., clinical interview and self report assessments) are limited because they are subjective and that we need better objective diagnostic markers (Linden, 2012). But the labels used to train classifiers are determined using the same clinical diagnostic criteria that are acknowledged as imprecise. As a result, the model can only be optimized to attain the same level of diagnostic confidence as was obtained by the initial methods. Although the resulting model may incorporate measures of physiology, it is not necessarily any more sensitive to biological factors than other methods. One way to address this issue is to employ modeling methods that treat the labels as noisy, or otherwise incorporate some measure of label confidence (Lawrence and Schoelkopf, 2001).

Needs and gaps in applying predictive modeling to brain mapping

Although prediction ability is an end in itself, we often desire to be able to map the brain regions and interactions that are most relevant to the prediction. Machine learning algorithms are highly optimized for obtaining accurate prediction but tend to be black boxes, from which the information that led to the prediction is not easily extracted. Feature weights, which determine the prediction equation, can be extracted from linear models and visualized, but this is rarely possible for non-linear (kernel) methods (Bishop, 2006). Once extracted, there is no clear statistical theory for thresholding the weights to determine which have statistically significant involvement, although non-parametric methods such as bootstrapping can be used (McIntosh and Lobaugh, 2004). Instead practitioners turn to *feature selection* methods to identify the most relevant subset of features for the predictive model.

Feature selection methods can be categorized as filter methods, wrapper methods and embedded methods, all of which impact the interpretation of the results in different ways (Guyon and Elisseeff, 2003). Filter methods apply a (typically univariate) statistical test to exclude features that are not statistically dependent on the training labels. When univariate methods are used as a filter, features may be excluded that would otherwise improve prediction if multivariate interactions were considered. Wrapper methods address this issue by optimizing the feature set based on prediction ability. Model training is performed several times with a different subset of features, and the subset with the best prediction accuracy is chosen. Embedded methods directly incorporate constraints into the modeling algorithm to reduce the feature set. All of these methods must be run inside cross-validation (CV) to avoid overfitting and optimistic estimates of the ability of the model to generalize (Pereira et al., 2009). This often leads to different features being selected for each iteration of CV, which complicates the issue of feature interpretation, e.g. the same model learned from a different subset of observations identifies a different set of features (Craddock et al., 2009). Additionally, the constraints used in model learning impart different properties to the selected features. For example, LASSO (least absolute shrinkage and selection operator), a popular embedded method, limits the number of non-zero feature weights in the model to the number of observations. Additionally, when highly correlated features exist, LASSO will tend to exclude a subset of them even though they may possess predictive power (Wang et al., 2007). Thus, features identified using this method do not represent all of the features that are involved in a disease process of interest and the exclusion of a feature does not mean that it is not involved in the disease process.

If features are appropriately scaled prior to model training then the model weights can be interpreted as a measure of a feature's relative importance to the model (Guyon and Elisseeff, 2003). Additionally, it is tempting to interpret the sign of the model weight as an indication of the relationship between the feature and the predicted label (Mourao-Miranda et al., 2005). For example, a positive weight might indicate that the feature is greater for the class corresponding to positive labels, or is positively correlated with a continuous label. However, when using multivariate methods, these relationships are much more complicated. The sign of a feature's weight does not necessarily match group differences identified through univariate methods, and it may change based on the inclusion of another feature (Craddock et al., 2009). Details of the modeling algorithm must also be considered when interpreting model weights. In support vector classification, model weights reflect the border between groups, whereas in Fisher's linear discriminant analysis, the weights reflect differences between group means (Bishop, 2006).

Multivariate regression algorithms are an alternative to classification that has been used to predict brain maturity from resting state functional connectivity (Dosenbach et al., 2010). Only one study to date has leveraged continuous measures of disease severity with pattern recognition (Lynch et al., 2013). Such regression-based methods are obviously of interest for the dimensional perspectives being increasingly embraced, as discussed below in the section on Nosological limitations and extreme comparisons. The only impediment to the wider application of multivariate regression approaches is the requirement for sufficiently large data sets.

Finally, we note that although leave one out cross validation methods are typically used to train and test predictive models, they are prone to overfitting, particularly when large numbers of models are tested with small samples (Rao et al., 2008). To generate estimates of prediction accuracy that can be considered for real world applications, completely independent datasets should be used to train and test a given model, which also requires large, well-characterized datasets.

Neurosurgical planning — an opportunity for clinical application of R-fMRI methods

Functional brain mapping may be used both to predict the efficacy of neurosurgical treatment and to avoid neurological deficit. Brain surgery typically involves the lesioning, inactivation by brain stimulation or removal of a pathological region (e.g., for tumor, tremor, psychiatric disorders or epilepsy). Precisely identifying both the pathological regions to treat as well as the functional regions to spare is the key to an optimal outcome (Haberg et al., 2004). Challenges arise due to the fact that

Notes to Table 1

ADHD: attention-deficit/hyperactivity disorder; ADHD-C: combined type ADHD; ADHD-I: inattentive type ADHD; adolesc: adolescents; AG: angular gyrus; ALFF: amplitude of low frequency fluctuations; BWAS: brain-wide association study; DN; default network; dACC: dorsal anterior cingulate cortex; EC: effective connectivity; FFT: fast Fourier transform; iFC: intrinsic functional connectivity; iFN: intrinsic functional networks; GSR: global signal regression; LOO: leave-one-out cross validation algorithm; MDD: major depressive disorder; MKL: multikernel learning; MPFC: medial prefrontal cortex; NC: neurotypical controls; PCA: principal component analysis; FDA: PCA–Fisher discriminant analysis; PCA-LDA: PCA-linear discriminant analysis; PCC: posterior cingulate cortex; pt: patient; RBF: radial basis function; ReHo: regional homogeneity; RF: reliability filter; RFE: recursive feature elimination; ROI: region of interest; RRFE: reliability reverse feature elimination; SCZ: schizophrenia; SVC: support vector classification; TF: *T* test filter.[a]Groups matched for age unless specified. School-age = 6–12, adolescents:13–19, young adults 20–30; adults 30–60; elderly >60.[b]Disorder prevalence was based on the most recent Centers for Disease Control and Prevention Morbidity Mortality Weekly Reports for all targeted disorders except multiple sclerosis (MS); MS prevalence based on a CDC study published in Prev Chronic Dis 2010.[c]Hold out sample included 93 NC and 78 ADHD.[d]NC siblings of patients with SCZ.

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sensorimotor and language regions cannot be identified by anatomy alone (Ojemann, 1979; Steinmetz et al., 1990) and when pathological regions are not readily detectable with structural imaging. This is further complicated when we consider that many neurosurgical treatments are directed towards disorders of brain networks, as is likely the case for epilepsy (Spencer, 2002), movement disorders (Niethammer and Eidelberg, 2012), and psychiatric disorders (Llinas et al., 1999).

Electrical stimulation mapping — a questionable gold standard

Investigators are currently focusing on improving existing methods to define "eloquent" (sensorimotor and language) areas that must be preserved during surgical procedures using R-fMRI methods (Martino et al., 2011; Zhang et al., 2009). The gold standard for localization of function remains direct cortical electrical stimulation mapping (ESM) with over 100 years of neurosurgical experience (Horsley, 1909; Pendleton et al., 2012). For this, a patient must remain awake while having a craniotomy and direct cortical stimulation is applied to small (1 cm) patches. This temporarily mimics the effect of ablation while cognitive function is tested (Ojemann, 1979). Awake craniotomy can result in patient anxiety, increased operating time and difficulty with anesthesia. Intraoperative ESM can produce seizures and the absence of ventilator control in an awake patient can produce hypercarbia and consequent brain swelling (Silvergeld, 2001). An alternative approach frequently used in epilepsy surgery involves implanting invasive electrode arrays to precisely identify the seizure onset zone as well as to perform ESM extraoperatively (Bancaud et al., 1970; Wyler et al., 1984). However, this too carries risks, including requiring two procedures to implant and explant electrodes, patient discomfort, brain swelling and infection (Hamer et al., 2002). A sampling problem is inherent to ESM in that intraoperative time limits testing to a few sites, and extraoperative mapping is limited by the extent of the electrode array. Also, ESM cannot be used to test function of tissue within the depths of sulci unless a time-consuming intrasulcal dissection is performed or penetrating depth electrodes are implanted. Finally, ESM may falsely localize function by activating distant areas through corticocortical connections, questioning its status as the gold standard (Sinai et al., 2005).

Gaps and needs in the use of task-based fMRI for neurosurgical planning

Clearly, a noninvasive methodology to image cortical function without sampling bias that is sensitive to activity in deeper regions and that does not disrupt function would be desirable. While task-based fMRI has been used extensively to study normal brain function, the clinical utility of this method has yet to be firmly established (Hill et al., 2000; Mehta and Klein, 2010; Roux et al., 2003). A major factor that limits clinical utility involves poor task performance in patients with cognitive impairment and neurological deficits — the very patients who need neurosurgical intervention (Pujol et al., 1998). The low amplitude of task-related changes in the BOLD signal requires repetition, resulting in fatigue that is further complicated when multiple functions must be tested. Unlike most clinical studies where inferences are made by comparing results across groups, neurosurgical planning requires a precise within-subject spatial correspondence of intraoperative navigation with preoperative results (Kekhia et al., 2011). Due to these issues, the correspondence of ESM results with preoperative task-based fMRI is inconsistent (Kunii et al., 2011; Mehta and Klein, 2010; Roux et al., 2003; Ruge et al., 1999; Rutten et al., 2002).

Readiness of R-fMRI-based neurosurgical planning

Due to minimal requirements for subject performance and the large amplitude spontaneous fluctuations of the BOLD signal, R-fMRI may be quite useful when neurosurgical planning requires localization of brain function (Bottger et al., 2011; Matthews et al., 2006; Shimony et al., 2009; Tie et al., 2013; Zhang et al., 2009). A brief (6–10 min) scan can produce consistent maps of functional zones within single individuals reliably (Kokkonen et al., 2009; Tie et al., 2013) and with an even higher correspondence with results of ESM than task-based methods (Zhang et al., 2009). Resting functional connectivity may also be used to define pathology that is elusive using standard structural imaging. Brain tumor infiltration alters intrinsic functional connectivity — this provides information regarding the residual presence of function and also defines the extent of brain tumor invasion that may not be evident on structural MRI (Martino et al., 2011). In patients undergoing epilepsy surgery, areas within the ictal onset zone show increased R-fMRI intrinsic functional connectivity compared to data from a large (N = 300) normative sample (Stufflebeam et al., 2011). However, others have shown seizure-generating areas that are functionally disconnected from non-irritative brain areas both with R-fMRI (Bettus et al., 2010, 2011; Pittau et al., 2012) and using electrocorticography (Warren et al., 2010). These findings pave the way to use functional connectivity measures to guide the placement of invasive electrodes for confirming the localization of epileptic foci as well as to guide the extent of resection for both brain tumors and epileptogenic zones.

Intrinsic functional connectivity measures may also predict surgical outcome, and this may be particularly useful in determining whether a particular individual or a disease syndrome in general is appropriate for neurosurgical intervention. Increased contralateral connectivity with temporal lobe epilepsy has been shown to predict failure of unilateral temporal lobectomy (Negishi et al., 2011). Increased connectivity within the posterior cingulate has been shown to correlate with postoperative memory decline after ipsilateral temporal lobe resection (McCormick et al., 2013). Network measures using metabolic imaging to aid in the medical and surgical evaluation of movement disorders is well-established (Eidelberg, 2009). Both noninvasive magnetoencephalography (Martino et al., 2011) and invasive electrocorticography (Schevon et al., 2007; Warren et al., 2010) have demonstrated that synchrony measures predict the extent of brain tumors and the epileptogenic zone. It remains to be determined whether R-fMRI connectivity measures will detect intrinsic network abnormalities better than metabolic or electrophysiological methods. However, within-individual correspondence of electrophysiological and fMRI-based resting connectivity measures (He et al., 2008; Keller et al., 2011, 2013) suggests that R-fMRI should provide substantial supplemental information with superior spatial resolution and sampling in a less invasive fashion.

In summary, R-fMRI functional connectivity holds great promise for advancing neurosurgical treatment. Efforts are well under way to improve surgical treatment for epilepsy, movement disorders and brain tumors. The ability to resolve intrinsic functional connectivity networks opens a window of possibility to predict results using invasive brain stimulation for the treatment of other neurological disorders, such as dementia and coma, as well as a variety of psychiatric disorders.

Prerequisites for attaining clinical utility with R-fMRI measures: rethinking practices

Significance chasing and approximate replications

A recent commentary noted that clinical neuroscience, including neuroimaging, is characterized by "significance chasing with underpowered studies," and "approximate replications" (Kapur et al., 2012). Clinical neuroimaging studies routinely report statistically significant results with 15–30 subjects per group. Though this is understandable given the challenge and expense of recruiting clinical samples to meet typically restrictive criteria, such sample sizes are vastly underpowered given the high dimensionality of imaging data. Statistical correction for multiple comparisons often proves to be insurmountable for investigators, necessitating limiting the scope of explorations of the connectome (e.g., to specific circuits or networks) or loosening statistical thresholds

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and expanding the type 1 error rate. Not surprisingly, failure to replicate is the rule (Ioannidis, 2005). As a result, roughly similar findings (e.g., same general brain structure/region, different subdivision) are interpreted as *approximate replications*, and methodological differences and sample size limitations are cited as likely explanations for failure to truly replicate (Kapur et al., 2012).

This situation is not limited to neuroimaging — large-scale datasets are required for attaining scientifically valid biomarkers. The molecular genetics community first confronted this challenge at the 1996 Bermuda Summit. The resulting Bermuda Principles were adopted to effect radical culture change through open data sharing http://www.genome.gov/10506376. They specifically mandated: 1) release of sequence assemblies larger than 1 kb within 24 h, 2) immediate publication of finished annotated sequences, and 3) making the entire sequence freely available in the public domain. With a few notable exceptions (Milham, 2012; Weiner et al., 2012), the neuroimaging community has been slow in embracing open data sharing. Change in the cultural ethos supported by financial investment from funding agencies is needed to implement an open science culture needed to generate the prerequisite large-scale neuroimaging datasets.

Nosological limitations and extreme comparisons

As recently highlighted by the U.S. National Institute of Mental Health (NIMH) Research Domain Criteria Project (RDoC) http://www.nimh.nih.gov/research-funding/rdoc/index.shtml, the lack of specificity between findings of abnormal brain function and categorical diagnostic classifications of psychiatric illness precludes the identification of meaningful biomarkers to inform clinical diagnosis or prognosis, or to provide novel targets for therapeutic interventions. The default network (DN) is a case in point, given the ever-increasing number of diagnostic categories in which DN abnormalities are being reported (Fox and Greicius, 2010). The DN is a distributed set of brain regions associated with spontaneous cognition, internalized thought and emotion regulation that are consistently deactivated during the performance of goal-driven cognitive tasks (Andrews-Hanna, 2012; Andrews-Hanna et al., 2010; Raichle and Snyder, 2007). Dysregulation of the DN commonly manifests as failure to deactivate during goal-directed cognitive task performance or abnormal activation during tasks probing emotion and internal mentation, and is associated with a broad array of psychiatric disorders (e.g., ADHD, autism, depression, social phobia, PTSD) and their related symptoms (e.g., rumination in depression, attention lapses in ADHD) (Zhang and Raichle, 2010). The lack of a specific association of DN dysregulation with any one disorder prevents disorder-centric perspectives from achieving a more comprehensive understanding of DN dysregulation as a pathophysiologic process. Beyond implicating DN dysregulation in these disorders, current imaging methods and diagnostic category-based frameworks are unable to provide an understanding of the underlying mechanisms at the systems level and their behavioral associations (Castellanos and Proal, 2012).

The NIMH has recently called for an alternative approach to understanding mental illness in terms of its underlying pathophysiology rather than symptomatology. Specifically, NIMH has cited the need for a neuroscience-based classification approach for parsing psychiatric illness ("neurophenotyping"), and is encouraging the RDoC framework as a first step in its evolution. The guiding principles of RDoC entail adopting a dimensional perspective that is agnostic about current diagnostic categories while intentionally crossing multiple levels of analysis (i.e., genes, molecules, cells, circuits, physiology, behavior, self-reports, experimental paradigms).

Importantly, the RDoC framework addresses another key limitation of the current clinical neuroimaging literature — namely, reliance on extreme comparisons (i.e., prototypical patients against super healthy controls) (Kapur et al., 2012). Although this strategy is powerful for implicating abnormal brain function (e.g., DN dysregulation) or structure in any given disorder, it does not provide a means for assessing the specificity of findings to the disorder under inquiry (Kapur et al., 2012). Accordingly, such studies are not informative regarding challenging differential diagnoses or for parsing the many comorbidities often present in affected individuals (Kelly et al., 2012). Given the high heterogeneity within categorical diagnostic groups and blurry boundaries between disorders which are the general rule, efforts that directly address heterogeneity are expected to lead to better identification of biomarkers. Two recent examples include Chabernaud et al. (2012), which demonstrated the presence of dimensional brain-behavior relationships for internalizing and externalizing symptoms extending across categorical diagnostic boundaries (i.e., ADHD vs. typically developing children), as well as relationships that differed between categories, and the ADHD-200 Consortium, which demonstrated distinct neural signatures underlying ADHD subtypes (combined type, predominantly inattentive)(Fair et al., 2012).

Hypothesis-driven versus exploratory/discovery science

Hypothesis-testing has represented the predominant model in the functional neuroimaging community since its inception — largely due to reliance on relatively small sample sizes and focus on task-based imaging approaches. However, 21st century science is increasingly being defined by large-scale discovery science-based efforts to understand complex systems using massive datasets. Referred to as "Big Data" research, these efforts are yielding unprecedented results in domains ranging from genetics (ENCODE Project Consortium, 2013) to physics (The ATLAS Collaboration, 2012), astronomy (Raddick and Szalay, 2010), and medicine (Conger, 2012). The seeds of discovery science have particularly taken root in the R-fMRI imaging community. Grassroots initiatives, such as the 1000 Functional Connectomes Project (FCP) (Biswal et al., 2010), and International Neuroimaging Data-sharing Initiative (INDI) (Mennes et al., 2012) have yielded datasets sufficient in size to demonstrate the feasibility and utility of generating novel hypotheses via discovery science. Efforts such as the Brain Genomics Superstruct Project http://clinicaltrials.gov/ct2/show/NCT01552460, the Nathan Kline Institute-Rockland Sample (Nooner et al., 2012) and Openfmri.org https://openfmri.org/ are tantalizing the community with the prospect of more carefully coordinated, large-scale datasets, such as the Human Connectome Project (Van Essen et al., 2012), upon which discovery can truly be carried out.

The Big Data research model represents the best hope for the R-fMRI community to deliver on the promise of clinical applications within a reasonable time. But as noted, biomarkers are not necessarily neuroscientifically meaningful or interpretable; rather they are indicators of some link to a disease process. There is also tremendous value in using a priori knowledge and targeted hypotheses to narrow the range of exploration, thereby moderating computational complexity. In the final analysis, neither hypothesis-driven nor exploratory research will be sufficient on its own. Exploratory results emerging from Big Data are no less likely to be false (Ioannidis, 2005). Large datasets can yield statistically significant yet trivial results and no result is believable until it has been replicated in independent adequately powered samples and preferably by independent investigators.

Breaking through the age barrier

While the challenges of discovering biomarkers in adults are substantial, they pale by comparison to the difficulty and importance of carrying out this work in a developmental framework. About 2/3 of psychiatric disorders originate in the first two decades of life (Kessler et al., 2005), with several manifesting symptoms within the first two to three years of life (e.g., autism, selective mutism, pediatric anxiety disorders, intellectual disability). Accordingly, the psychiatric community is increasingly turning to brain imaging with hopes of developing objective tools akin to pediatric physical growth charts, which would allow for monitoring brain development from early infancy. Such normative

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assessments would introduce the concepts of early detection, intervention and prevention to psychiatry. Sleep-based imaging studies of intrinsic brain function are diminishing many of the challenges associated with task-based studies of the developing brain (Dinstein et al., 2011), with data successfully collected even in the neonatal (Gao et al., 2009) or fetal stages of life (Thomason et al., 2013).

Importantly, the potential of sleep-based imaging studies of early developing populations needs to be tempered with methodological and interpretational considerations. Most notably, an emerging literature has suggested that while the wakeful and sleeping intrinsic functional architectures are grossly similar (Fransson et al., 2009; Liu et al., 2008; Redcay et al., 2007), dynamic modulation between states exists (e.g., the anterior–posterior connectivity of the DN decreases markedly during deep sleep) (Boly et al., 2012; Brodbeck et al., 2012; Horovitz et al., 2009; Samann et al., 2010; Spoormaker et al., 2012). The implications are two-fold. First, findings (e.g., population differences and dimensional brain-behavior relationships) obtained during sleep may not necessarily generalize to wakeful states, and vice versa. Second, efforts focused on mapping lifespan trajectories from birth to adulthood (i.e., longitudinal and cross-sectional studies) cannot assume that sleep-based imaging during early development and wakeful imaging starting in childhood can be treated as equivalent. Rigorous examination, and possibly multimodal imaging (e.g., simultaneous R-fMRI/EEG), will be required to link trajectories obtained during sleep with those in wakeful states. Additional tasks include the need for continued refinement of protocols to accomplish sleep-imaging studies in toddlers (e.g., habituation to scanner sounds) (Redcay et al., 2007) and exploration of the changing impact of physiologic parameters (see section on Gaps and needs in evaluating the validity of R-fMRI measures) on imaging over the course of development (e.g., pulse rates vary by age: newborn — 70 to 190 beats/min, preschool-age — 80 to 120, 16 year-old — 60 to 100; respiration: newborn 30–60 breaths per minute, preschooler — 20 to 30, 16 year-old: 12–20).

Finally, it is worth noting that while sleep-based R-fMRI imaging studies will undoubtedly play a crucial role in mapping human brain function during early brain development, they are unlikely to be ideal for clinical applications in the long run. The challenges of obtaining scans without sedation, the risk of which is generally not justifiable for research in children, and the stubbornly high costs of fMRI, limit the ability to obtain serial scans in at-risk or affected individuals. Thus the greatest value of MRI data may be in leveraging the value of ancillary methods that are less cumbersome or expensive, e.g., EEG, optical imaging (Cooper et al., 2012; Mesquita et al., 2010; Niu et al., 2012; White and Culver, 2010) and future techniques yet to come.

Conclusions

Fueled by the success of R-fMRI, functional connectomics is emerging as a mainstream tool for brain-based biomarker identification for neurological and psychiatric illness. The present work reviewed the extant evidence fueling the growing enthusiasm in the field, while highlighting major gaps and needs at every stage of the scientific process (e.g., study design, sampling, data acquisition, data analysis, interpretation) that can hamper progress and potentially lead the field astray. Fortuitously, the recent success of R-fMRI is coinciding with conceptual and cultural breakthroughs (e.g., the RDoC-based dimensional reconceptualization of psychiatric illness, open science initiatives, the emergence of the Big Data research model, and increased application of multivariate pattern analysis), that are providing a compass for the field. Importantly, while the bulk of the research reviewed in the present work focused on the diagnosis of psychiatric illness, this is only a piece of the puzzle. As recently noted by Kapur et al., the real impact of imaging-based biomarkers will be through the identification of biological mechanisms that can lead to effective stratification based on disease risk, expected treatment response and prognosis. These are the ambitious goals and hopes of functional connectomics in the era of Big Data.

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Conflicts of interest

The authors declare no conflicts of interest.

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