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Using Neuroimaging to Predict Behavioral Outcomes

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By

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Abstract
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The emerging field of "neuroprediction" or "predictive analytics" in mental health has promise for revolutionizing clinical practice by moving towards personalized or precision medicine. The core idea is that brain measures at a given time may predict individual future behavioral outcomes, presumably because specific structural or functional brain characteristics constrain the trajectories of evolving behavior over time. For basic science, discovery of such brain measures identifies particular neural circuits that constrain specific future behaviors. For clinical science, such brain measures may support identification of vulnerabilities that could be treated preventively to minimize poor mental health outcomes.

In this thesis, I first provide an overview of the key questions and challenges in the field of predictive analytics, aiming to (1) propose general guidelines for predictive analytics projects in psychiatry, (2) provide a conceptual introduction to core aspects of predictive modeling technology, and (3) foster a broad and informed discussion involving all stakeholders including researchers, clinicians, patients, funding bodies and policymakers. Next, I discuss two strategies for identifying, in a developmental context with children, brain vulnerabilities for future mental health difficulties. First, I used resting state functional connectivity, measured via functional magnetic resonance imaging (fMRI), to discover whether children without depression but with heightened familial risk for major depression disorder (MDD) had brain differences indicative of risk for depression. At-risk children, compared to children not at familial risk, exhibited significant differences in functional brain connectivity in three brain networks. Classification between at-risk versus control children based on resting-state connectivity yielded high accuracy with high sensitivity and specificity that was superior to traditional clinical rating scales. Second, I examined whether variation in functional connectivity could predict the trajectory of clinical symptomology over the ensuing four years in a longitudinal study with a normative child sample. Variation at age 7 in specific networks predicted individual children's developmental trajectories at age 11 towards attentional problems characteristic of Attention Deficit Hyperactivity Disorder (ADHD) or internalizing problems characteristic of MDD. The predictive network for internalizing problems was one of the networks that had been atypical in children at familial risk for MDD. These studies identify variation in brain networks indicative of risk for two of the most common disorders of adolescent mental health, and suggest that such measures may support targeted early and preventive interventions. The conclusion of the thesis provides a discussion of these findings, future directions, theoretical implications, clinical applications and ethical considerations.

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INTRODUCTION

The value of brain-based prediction for mental health derives from the great need to better help people with mental health challenges. Despite much progress in basic neuroscience, from optogenetics to gene editing, and despite over 20,000 MRI publications on neuropsychiatric disorders (and many more publications using other brain measures), there has been little progress in diagnosing or treating mental health disorders. Indeed, there is evidence for worsening mental health in the population. For example, suicide is perhaps the most tragic outcome of failed treatment, and suicide rates in the United States have steadily climbed over this century, tripling in girls ages 10-14.

Unfortunately, there is to date no biologically informed basis by which to select an effective treatment program for an individual and it can take years to get a successful intervention, if ever. Moreover, diagnosis is typically done by crisis, often too late to substantially alter the trajectory of the course of the disorder. Two potential relatively near-term benefits of human neuroscience are 1) neuroprediction (predictive analytics) aimed at personalized or precision medicine for selection of an optimal treatment, and 2) improved identification of individuals at risk for mental health difficulties, so that preventive treatment can reduce or even avert future difficulties.

In this thesis, I first provide an overview of the key questions and challenges in the field of predictive analytics in mental health. Next, I describe strategies for identifying brain vulnerabilities for future mental health difficulties in children at familial risk for MDD as well as in a normative child sample, specifically in the context of resting state networks (RSNs). Regions of the brain that are highly temporally correlated during rest form resting state profiles which are intrinsic, spontaneous, low-frequency fluctuations in the fMRI blood-oxygen-level dependent (BOLD) signal that define specific networks of the brain in the absence of any task (Biswal et al., 1995). I first examined RSNs in non-depressed children with a family history of MDD who are at 3-5 fold increased risk for developing MDD. I then examined RSNs in longititudinal study of a normative sample of children. Expansion of findings to such a sample would allow for early identification and preventive treatment regardless of family history.

There is great heterogeneity in the functional organization of the brain that is captured by RSNs. In fact, they may be considered "fingerprints" of the human brain, as they can accurately identify an individual from among large group (N=126) of individuals (Finn et al., 2015). Furthermore, RSN profiles are known to be robust and reliable (Damoiseaux et al., 2006; Chen et al., 2008; Shehzad et al., 2009; Van Dijk et al., 2009; Zuo et al., 2010a ,b, Finn et al., 2015).

RSNs are particularly relevant to studying psychiatric and pediatric populations because 1) they are task-independent, so individual differences in task performance cannot explain differences observed in the BOLD data, 2) they are easy and fast to acquire which make them more accessible to a wide variety of people including young children and a wide range of clinical populations, and 3) they are plastic and have been shown to change during typical development (e.g., Chai et al., 2014) can be modulated by behavioral (e.g., Yuan et al., 2016; McFadden et al., 2013) or pharmacological interventions (e.g., Salinas et al., 2017; Whitfield-Gabrieli et al., In Press).

Chapter 1

Predictive Analytics in Mental Health: Applications, Guidelines, Challenges and Perspectives

(Reference: Hahn T., Nierenberg A., Whitfield-Gabrieli S., *Molecular Psychiatry*, 2017)

With the bold promise to revolutionize clinical practice in psychiatry, the emerging field of Predictive Analytics in Mental Health has recently generated tremendous interest, paralleling similar developments in personalized and precision medicine. Here, we provide an overview of the key-questions and challenges in the field, aiming to 1) propose general guidelines for Predictive Analytics projects in psychiatry, 2) provide a conceptual introduction to core-aspects of predictive modelling technology, and 3) foster a broad and informed discussion involving all stakeholders including researchers, clinicians, patients, funding bodies, and policymakers.

Mental disorders are among the most debilitating diseases in industrialized nations today.[1, 2] The immense economic loss[3-5] mirrors the enormous suffering of patients and their friends and relatives.[6-12] In addition, health care costs as well as the number of individuals diagnosed with psychiatric disorders are projected to disproportionately rise within the next twenty years.[13] With an ever-growing number of patients, the future quality of health-care in psychiatry will crucially depend on the timely translation of research findings into more effective and efficient patient care. Despite the certainly impressive contributions of psychiatric research to our understanding of the aetiology and pathogenesis of mental disorders, the ways in which we diagnose and treat psychiatric patients have largely remained unchanged for decades.[14]

Recognizing this translational roadblock, we currently witness an explosion of interest in the emerging field of *Predictive Analytics in Mental Health*, paralleling similar developments in personalized or precision medicine.[15-19] In contrast to the vast majority of investigations employing group-level statistics, *Predictive Analytics* aims to build models which allow for individual (i.e. single-subject) predictions, thereby moving from the description of patients ("hindsight") and the investigation of statistical group differences or associations ("insight") toward models capable of predicting current or future characteristics for individual patients ("foresight"), thus allowing for a direct assessment of a model's clinical utility (Figure 1).

Within this framework, we can differentiate three main areas of clinical application of *Predictive Analytics* models in mental health:

1. The **prediction of therapeutic response** can support the selection of optimized interventions, through comparative effectiveness research, thereby improving the trial-and-error-based approach common in psychiatry. For example, genetic variants have been linked to the outcome of psychotherapy as well as to therapeutic response to pharmacological interventions[20,21]. This individualized treatment optimization might maximizes adherence and minimizes undesired side-effects. Importantly, it also allows clinicians to focus resources on patients who will most likely benefit from the first-line treatment and allocate other resources to those who will require second line or other treatments. Finally, identifying treatment-resistant individuals with high accuracy would also simplify the development and evaluation of novel drugs and interventions

as research efforts could be more focused.

2. **Supporting differential diagnoses** is crucial, whenever the clinical picture alone is ambiguous. Providing additional model-based information to clinicians thus enables a timely administration of disease-specific interventions. Similar to the prediction of therapeutic response, this increases adherence and minimizes undesired side-effects. The differentiation of patients suffering major depression from patients with bipolar disorder before the first manic episode is but one example illustrating clinical utility in this area.
3. Models **predicting individual risks** are important in two respects: On the one hand, short-term predictions of risk can greatly improve outpatient management – for example with regard to prodrome detection in schizophrenia. On the other hand, long-term risk prediction would allow for a targeted application of preventive measures in early stages of a disorder or even before disease onset. Equally important, individual risk prediction could greatly increase the efficiency of the development and evaluation of preventive interventions as research efforts could be focused specifically on at-risk individuals.

In summary, valid models in this area would be instrumental, both, for minimizing patient suffering and for maximizing the efficient allocation of resources for research. For example, children and adults are diagnosed with Attention-Deficit-Hyperactivity-Disorder (ADHD) every day and prescribed medications with little or no scientific evidence as to which patient will be likely to benefit from one or the other of the two major classes of medications (methylphenidate or amphetamine) or unlikely to benefit from either medication. In the same vein, the STAR*D study – a large evaluation of depression treatment including 4,041 outpatients – showed that approximately 50% of patients respond[22]. In both cases, patients would greatly benefit from Predictive Analytics models predicting which treatment would be most effective (for a wide range of predictions possible based on neuroimaging data today, see 17).

Against this background, Predictive Analytics in general and its potential applications in (mental) health have simultaneously been met with exuberant enthusiasm as well as with substantial skepticism: On the one hand, some see "previously unimaginable opportunities to apply machine learning to the care of individual patients"[15], prompting others to even propose "a shift from a search for elusive mechanisms to implementing studies that focus on predictions to help patients now".[23] On the other hand, critics have pointed out problems of an all too care-free view of Predictive Analytics in general and Big Data in particular.[24] Considering the tremendous investment into Big Data infrastructure and Predictive Analytics capabilities in all areas of science and in the private sector[16], most will agree, however, that this technology – to quote a recent New York Times article[24] – "is here to stay", but that we ought to see it as "an important resource for anyone analyzing data, not a silver bullet". From this, the question arises: How can we best steer the development and implementation of Predictive Analytics technology to effect the clinical innovations demanded by researchers and practitioners alike?

Now that evidence from initial proof-of-concept studies is accumulating in all areas – from genetics to neuroimaging, from blood-based markers to ambulatory assessments – and the approach is gaining momentum (for reviews, see [17, 19, 25-31]), this question is particularly pressing. As the field of *Predictive Analytics in Mental Health* is faced with strategic choices which will have formative influence on research and clinical practice for the decades to come, we seek to move beyond the numerous descriptions and reviews of this beginning transformation of psychiatry by 1) proposing general guidelines for Predictive Analytics projects in psychiatry, 2) providing a conceptual introduction to the core-aspects of predictive modelling technology which distinguish *Predictive Analytics in Mental Health* from other areas of medicine or predictive analytics applications, and

3) fostering a broad and informed discussion involving all stakeholders including researchers, clinicians, patients, funding bodies, and policymakers. To this end, we will, first, provide an overview of the steps of a Predictive Analytics project. Secondly, we will consider the challenges that arise from the unique, multivariate and multimodal nature of mental disorders and argue that the combination of expert domain-knowledge and data integration technology is the key for overcoming, both, the conceptual and practical obstacles ahead. Finally, we will briefly discuss perspectives for the field.

Predictive Analytics projects in mental health

Every Predictive Analytics project can be described as a series of steps aimed at ensuring the utility (i.e. the validity and applicability) of the resulting model. While this process is similar for all Predictive Analytics projects, numerous questions, problems and opportunities are unique to the area of mental health. The guiding-questions in Box 1 are intended primarily as a means to support explicit reflection of the essential steps of a project – from defining objectives to deploying the model. Thereby, we hope to foster a broad discussion leading to common standards and procedures in the field.

Predictive Analytics efforts in psychiatry parallel developments in other fields of medicine. Generally, we have witnessed a trend towards ever more precise specification of the genetic, molecular and cellular aspects of disease. This so-called Precision Medicine approach (for an overview, see e.g. the US National Academy of Sciences report on the topic32), in many cases, led to the realization that disease entities which appear to be a single disorder actually have distinct genetic precursors and pathophysiology. For example, cancer diagnosis is – for many forms of cancer – defined by analysis of genetic variants based on which the optimal treatment can be predicted.33 While communalities are particularly obvious with regard to technology, researchers in psychiatry are also faced with rather unique challenges.

Apart from the massively multivariate and multimodal nature of mental disorders which we will discuss in detail below, a traditionally much discussed issue arises from the often-times fuzzy and relatively unreliable labels of disease entities in psychiatry. As predictive models learn from examples, training a model aiming to support the differentiation between patients suffering from Major Depressive Disorder (MDD) and individuals with Bipolar Disorder prior to conversion (i.e. before any (hypo)manic symptoms have become apparent), for instance, might proof difficult simply because it may be very hard to reliably categorize patients with certainty. In practice, most studies either mitigate this problem by employing resource-intensive, state-of-the-art diagnostic procedures in combination with multiple clinical expert ratings or circumvent it by acquiring data first and then waiting for the quantity of interest to become more easily accessible (e.g. until the end of a therapeutic intervention or until a disorder actually manifests in at-risk individuals screened years ago). Complementing these efforts to render labels more accurate, fuzzy and unreliable labels can also be handled directly using machine learning algorithms specifically designed for this purpose (for a straightforward introduction, see 34, 35). While currently, it seems as if researchers in psychiatry almost exclusively rely on the optimization of data acquisition rather than trying to inherently model label uncertainty, combining the two approaches might be highly beneficial.

In addition, current disease entities as defined by DSM-5 or ICD-10 are very heterogeneous regarding, both, (neuro)physiology as well as clinical endophenotypes.36 On the one hand, this will make the classification of disease entities difficult as each entity is in fact a conglomerate of different (neuro)physiological and behavioral deviations. On the other hand, the underlying causes or correlates of therapeutic response or disease trajectory may qualitatively as well as quantitatively

vary for different, more homogeneous sub-samples of the data. While this makes training predictive models more difficult (i.e. either more training data or more prior information will be needed), machine learning algorithms are generally well equipped to handle such cases. In fact, learning multiple rules mapping features to labels are quite common (model averaging, stacking and voting are but three ways outlined in the next section to handle this). That said, homogeneous disease entities would not only make discovering rules easier (especially on small datasets), but definitely lead to more interpretable models which – though not technically the goal of predictive analytics – is still desirable from a scientific point of view. Most importantly, however, discovering homogeneous disease entities would enable us to move beyond merely reproducing the presently established diagnostic classification using considerably more expensive and complicated procedures. While this has thus far been a seemingly unattainable goal not only for DSM-5, the recent success of so-called unsupervised machine learning approaches might reinvigorate this line of research (for an introduction to unsupervised machine learning, see 37).

Challenges arising from the unique multivariate and multimodal nature of mental disorders

While the guidelines outlined above provide a straightforward framework for Predictive Analytics projects in psychiatry, the main challenge for the field arises from the unique, multivariate and multimodal nature of mental disorders. In the following, we will outline the conceptual and practical problems in more detail and argue that the combination of expert domain-knowledge and data integration technology is the key when aiming to construct valid predictive model for clinical use.

Modeling massively multivariate data

Overwhelming evidence shows that no single measurement – be it a gene, a psychometric test or a protein – explains substantial variance with regard to any practically relevant aspect of a psychiatric disorder (compare e.g. [38]). To the contrary, it has been recognized that multiple measures are necessary to gain meaningful information even within a single modality. It is this profoundly multivariate nature of mental disorders that has driven researchers to, for example, conduct genome-wide association studies and acquire whole-brain neuroimaging data.

When aiming to build predictive models, this complexity necessitates the use of methods suitable for high-dimensional datasets in which the number of variables (i.e. measurements) may far exceed the number of samples (i.e. patients). Generally, the so-called Curse of Dimensionality is addressed in three ways (for an excellent review detailing this issue, see [39]). First, unsupervised methods for dimensionality reduction – such as Principal Component Analysis (PCA) – may be used. These algorithms apply more or less straightforward transformations to the input data to yield a lower-dimensional representation. Also, they can extract a wide range of predefined features from raw-data. For example, distance measures can be extracted from raw protein sequences for classification in a fully automated fashion.[40] Second, techniques integrating dimensionality reduction and predictive model estimation (e.g. regularization, Bayesian model-selection and cross-validation) may be applied. In essence, they use penalties for model complexity, thereby enforcing simpler, often lower-dimensional models. Simply speaking, models containing more parameters must enable proportionally better predictions to be preferred over simpler models. These algorithms are at the heart of predictive analytics projects and include well-known techniques such as Support Vector Machines and Gaussian Process Classifiers as well as the numerous tree algorithms (for details, see 37, 41). Third, feature-engineering – i.e. all methods aiming to create useful predictors from the input data – can be used. In short, feature-engineering aims to transform the input data (i.e. all measures acquired) in a way that optimally represents the underlying problem to the predictive model. An illustrative example comes from a recent study

which constructed a model predicting psychosis onset in high-risk youths based on free speech samples. Whereas it would have been near impossible to build a model based on the actual recordings of participants' speech, the team achieved high accuracy in a cross-validation framework using speech features extracted with a Latent Semantic Analysis (LSA) measure of semantic coherence and two syntactic markers of speech complexity[42]. While these results still await fully independent replication, the approach shows that transforming the input data (speech samples) using domain-knowledge (in this case the knowledge that syntax differs in certain patients) can greatly foster the construction of a predictive model. Demonstrating the problem-dependent nature of feature-engineering, it might have been much easier to decode, for example, participants' gender from the actual recordings than from LSA measures given the difference in pitch between males and females. In that it links data acquisition and model algorithms, feature-engineering is not primarily a preprocessing or dimensionality-reduction technique, but a conceptually decisive step of building a predictive model.

While important for all modalities, feature-engineering often plays a particularly crucial role when constructing predictive models based on physiological or biophysical data. On the one hand, these data are often especially high-dimensional (e.g. genome, proteome or neuroimaging data with regularly tens of thousands of variables), thus often requiring dimensionality-reduction. On the other hand, alternative transformations of the raw-data can contain fundamentally different, non-redundant information. For example, the same fMRI raw-data – i.e. measures of changes in regional blood-oxygen levels – can be processed to yield numerous, non-redundant representations (e.g. activation maps or functional connectivity matrices). In addition, domain-knowledge regarding the choice of relevant regions-of-interest or atlas parcellations also fundamentally affects the representation of information in neuroimaging data.[43] As different parameters can be meaningful in the context of different disorders, these examples powerfully illustrate the fundamental importance of domain-knowledge in feature-engineering. The sources of domain-knowledge needed to decide which data representations might be optimal with regard to the problem at hand may range from large-scale meta-analyses, reviews and other empirical evidence to clinical experience.

Taking the traditionally somewhat subjective "art of feature-engineering" a step further, are automated feature-engineering algorithms. The former are akin to other unsupervised methods for dimensionality reduction, but can *learn* meaningful transformations from large, unlabeled datasets (e.g. using Deep Learning algorithms [44]). In short, these algorithms form high-level representations of more basic regularities in the data (for a large-scale example, see [45]). It is these high-level representations which can then be used to train the model. For example, we might use large datasets of resting-state fMRI to automatically uncover regularities (such as network-structure) using unsupervised learning. These newly constructed features might then provide a lower-dimensional, more informative basis for model-building in future fMRI projects. Note that domain-knowledge is not provided directly, but learned from independent data sources in this framework. While these techniques appear highly efficient as no expert involvement is required, discovering high-level features for the massively multivariate measures commonly needed in psychiatry will require extraordinarily large – though possibly unlabeled – datasets as well as computational power beyond the capabilities of most institutions today. Considering the developments in other areas such as speech recognition, we believe, however, that the significance of automated feature-engineering techniques can only grow in the years to come.

In many ways, the theory-driven approach to Computational Psychiatry is following an at least equally promising – albeit extreme opposite –strategy: This approach builds mechanistic

models based on theory and available evidence. After a model is validated, model parameters encapsulate a theoretical, often mechanistic, understanding of the phenomena (for an excellent introduction, see [39]). In many ways, the resulting models thus constitute highly-formalized (one might say "condensed") representations of domain-knowledge, custom-tailored to the problem at hand. Unlike virtually all other approaches to feature-engineering, computational models allow researchers to test the validity of data-representations while simultaneously fully explicating domain-knowledge. While certainly more scientifically satisfying and theoretically superior to feature-engineering, constructing valid models is far from simple. Thus, we believe that this technology will gain in importance to the degree that building valid models proofs feasible, further intertwining theoretical progress and Predictive Analytics.

Having discussed feature-engineering in greater detail, it is important to point out that model construction algorithms are not limited to the use of one single data-representation. To the contrary, it is a particular strength of this approach – with algorithms usually allowing for massively multivariate data and model integration –that multiple, meaningful data representations can be combined to enable valid predictions (for a more detailed discussion of model integration, see below).

Summarizing, the acquisition of high-dimensional data is regularly required to capture the massively multivariate nature of the processes underlying psychiatric disorders. Even on a single level of observation, we thus need to deal with the Curse of Dimensionality. To this end, model building commonly includes steps such as simple dimensionality-reduction techniques (e.g. PCA) and penalizing model-complexity as part of machine learning algorithms. Most importantly, however, feature-engineering is used to create data-representations from the input data which enable machine learning algorithms to build a valid model. Feature-engineering may draw on partially (meta-analyses or clinical experience) or fully formalized domain-knowledge (e.g. parameters from previously validated computational models) or a combination thereof. This prominent role of domain-knowledge underlines the interdependence of classic scientific approaches seeking mechanistic insight fostering theoretical development and Predictive Analytics approaches in mental health. While theoretical progress and meta-analytic evidence aid the construction of optimal features, a predictive analytics approach, in turn, allows for a direct assessment of the clinical utility of group-level evidence and theoretical advances. Thus, it is evident that these two branches of research are not mutually exclusive, but complementary approaches when aiming to benefit patients.

Incorporating (interactions across) multiple levels of observation

Substantially aggravating the problem of dimensionality discussed above, mental disorders are characterized by numerous, possibly interacting biological, intrapsychic, interpersonal and socio-cultural factors.[46, 47] Thus, a clinically useful patient representation must probably, in many cases, be massively multimodal, i.e. include data from multiple levels of observation – possibly spanning the range from molecules to social interaction. All these modalities might contain non-redundant, possibly interacting sources of information with regard to the clinical question. In fact, it is this peculiarity – distinguishing psychiatry from most other areas of medicine – which has hampered research in general and translational efforts in particular for decades now. As applying a simple predictive modelling pipeline on a multi-level patient representation would increase the already large number of dimensions for a unimodal dataset by several orders of magnitude, it might seem that Predictive Analytics endeavors are likely to suffer from similar if not larger problems. Indeed, neither of the dimensionality-reduction, regularization or even feature-engineering approaches outlined above is capable of seamlessly integrating such ultra-high-dimensional data

from so profoundly different modalities. Considering the tremendous theoretical problems of understanding phenomena on one level of observation, we also cannot rely on progress regarding the development of a valid theory spanning multiple levels of observation in the near future. Likewise, detailed domain-knowledge across levels of observation is extremely difficult to obtain as empirical evidence as well as expert opinions are usually specific to one modality. Given the extreme amounts of data and the combinatorial explosion due to their potential interactions, fully automated feature-engineering approaches across levels of observation (as opposed to such techniques for single levels of observation) also appear unlikely in the near future. Finally, the often qualitatively different data sources alone – including genetics, proteomics, psychometry, and neuroimaging data as well as ambulatory assessments and information from various, increasingly popular wearable sensors – would make this a herculean task.

A somewhat trivial solution would be to limit the predictive model to a single level of observation. If high-accuracy predictions can be obtained in this way – which might be considered unlikely at least for the most difficult clinical questions – such unimodal models are always preferable due to their comparatively high efficiency. Apart from the inherent multimodal nature of mental disorders which might render unimodal models less accurate, it is, however, exactly these efficiency considerations which obviate the need for Predictive Analytics research to consider multiple levels of observation. In order to identify the most efficient combination of data sources in a principled way in the absence of detailed cross-modal expert knowledge and evidence, we have to *learn it from the data*. To this end, a plethora of machine learning approaches which can be broadly described as *model integration techniques* – have been developed.

Probably, the most intuitive way to combine information from different high-dimensional sources is by voting. In this framework, a predictive model is trained for each modality and the majority vote is used as the overall model prediction. In a binary classification – if we wish to predict therapeutic response (yes, patient will benefit vs. no, patient will not benefit from the intervention) from five multivariate data sources – we first train a model for each modality. Then, we count the number of models predicting a response (#yes) and the number of models predicting no response (#no). The final prediction of therapeutic response is given by the option receiving more votes across modalities. A slightly more sophisticated approach is stacking or stacked generalization. Here, again, a model is trained for each modality. The predictions are, however, not combined by voting, but used as input to another machine learning algorithm which constructs a final model with the unimodal predictions as features (note that both examples might technically be considered automatic feature-engineering techniques). In addition to these simple approaches, numerous other techniques (e.g. (Bayesian) Model Averaging, Bagging, Boosting or more sophisticated ensemble algorithms) exist – each with different strengths and weaknesses which affect the computational infrastructure needed and interact with data structure within and across modalities. That said, most Predictive Analytics practitioners would agree that models – in the field – are most often constructed by evaluating a large number of approaches, i.e. by trial-and-error relying on computational power. However, it cannot be emphasized enough that this strategy must rely on the training data only. At no time and in no form, may the test set – i.e. the samples later used to evaluate (out-of-bag) model performance – be used in this process. Only in this way, we guarantee a valid estimation of predictive power in practice. Note that the techniques for model combination can generally be used also to construct predictive models from unimodal multivariate datasets as well (see for example [43, 48]; for an in-depth introduction, see [49]). Given the multimodal nature of psychiatric disorders, however, they hold particular value for cross-modal model integration.

Importantly, the construction of models from multimodal data does not mean that the final predictive model used in the clinic must also be multimodal. To the contrary, by training models with multimodal data, we not only guarantee maximum predictive power, but also gain empirical evidence regarding the utility of each modality. Analyzing the final model, we can investigate which modalities (and which variables within each modality) contribute substantial, non-redundant information. In an independent sample, we could then train a model based only on those modalities (or variables) most important in the first model. With this iterative process, we can obtain not only the most accurate, but also the most efficient combination of modalities and variables in a principled manner. Thus, final models might only consist of very few modalities and variables fostering their widespread use also from a health economics point of view.

Perspectives

Effective translation of research findings into clinical practice using Predictive Analytics will not only require the combination of expert domain-knowledge and data integration technology as outlined above. Effective translation will also need to address more general issues regarding the organization and structure of the emerging field. This will require joint efforts from all stakeholders including researchers, clinicians, patients, funding bodies, and policymakers. One such example is the Patient Centered Outcomes Research Network (PCORnet.org) and its associated psychiatric networks, the MoodNetwork, the Interactive Autism Network, and the Community and Patient-Partnered Centers of Excellence which focuses on behavior disorders in underserved communities.[50]

Given the often sensitive nature of the data needed to build predictive models – which might for example include electronic health records – an adequate level of security must be maintained at all times. Whether this speaks for decentralized infrastructure or outsourcing to specialized institutions is likely to remain a matter of intensive debate. As an example, PCORnet uses a federated datamart with a common data model infrastructure for multiple health care systems across the US that includes over 90 million people. Similar discussions will probably arise with regard to the predictive models themselves. Whereas only easy access to validated, pre-trained models will make them widespread, useful tools in the clinic, predictive models might also enable the prediction of sensitive personal data from the combination of seemingly harmless information an individual might readily provide. Thus, it is in the interest of all stakeholders to reach a public consensus regarding the regulation of access to pre-trained models before practically applicable models become available. While some level of regulation is likely beneficial with regard to industry use, it will be essential for efficient model construction to encourage model sharing (similar to data sharing) for research purposes. Especially for multimodal models, sharing modality-specific, pre-trained models (e.g. in dedicate model databases) will save substantial amounts of time and money. Finally, we need experts to consider the legal implications of deploying models (publicly or within the field) which predict health-related information which potentially guides medical decisions.

From a more applied perspective, we believe that technology will continue to simplify data acquisition and improve data quality in the years to come, thus bringing predictive Mobile Health (mHealth) applications within reach. While holding great promise, especially mHealth applications raise the question of whether it is generally better to rely on mechanistic predictors or instead on a pragmatic approach.[23, 51] While we firmly believe that the identification of causal relationships provides the most robust and scientifically satisfying features for prediction, we expect a pragmatic approach to prevail in the years ahead for two reasons. First, while causal predictors might be most effective, they will often be inefficient. For example, measuring variables of brain metabolism causally linked to a disorder might enable the construction of highly accurate predictive models. If

however, we can use cheaper and more readily obtainable (e.g. smartphone-based) measures not causal to the disorder with comparable or even slightly lower predictive power, those would probably be more efficient and thus more useful to clinicians in practice. Secondly, as decades of research have only begun to uncover causal links on single levels of observation, we think it highly unlikely that unified theoretical models across levels of observation will be established even in the mid-term.

To promote the endeavor of creating individualized predictive models to improve patient care and maximize cost efficiency in psychiatry, concrete steps can to be taken by institutions, researchers and practitioners. For example, we have recently seen numerous educational efforts such as organizing workshops and seminars on the various technical topics. Conferences such as the European College of Neuropsychopharmacology (ECNP) Congress or the Resting-State Conference and many others will continue to host sessions and satellite symposia dedicated to predictive analytics. Common in the field of machine learning, but currently scarce in psychiatry, predictive analytics competitions in which teams compete for the best predictive model performance (e.g. ADHD-200 global competition) bring together clinicians, researchers, and machine learners and may accelerate the availability of pre-trained, validated models in the mid-term as well as make this research more visible to the public.

Although patients, clinicians, and researchers share a common interest in improving mental health outcomes, there will need to be a thoughtful balancing of issues related to privacy, data security, and ethics in relation to the contrasting priorities and roles of various stakeholders. Currently, research and curation of shared data bases arise primarily from publicly funded, academic research groups, where data sharing is viewed as a common good to support greater utilization of large datasets to enhance predictive accuracy. A private business, on the other hand, could have the different role of using predictions to make decisions about reimbursing health care options or to advise on hiring practices or to identify potential customers for advertisements. Although these contrasting goals could lead to some tensions about the use of predictive analyses, there are examples where a public-private hybrid could be advantageous. For example, because intervention research is costly and complex, it tends to have limited numbers of subjects and relatively short durations (such as evaluation immediately after an intervention). Public-private partnerships could take advantage of the ongoing administration of treatments to very large numbers of subjects over extended time periods.

In summary, we believe that unimodal feature-engineering and model integration across levels of observation will be the key to highly accurate and efficient Predictive Analytics Models in mental health. Successful Predictive Analytics projects will thus require 1) substantial domain-knowledge to enable optimal feature-engineering for the often massively multivariate datasets obtained on each level of observation and 2) profound machine learning expertise with a focus on model integration techniques. With technology rapidly simplifying data acquisition and model construction, we urge all stakeholders including researchers, clinicians, patients, funding bodies, and policymakers to initiate an open discussion regarding key-issues such as data-sharing and model access-regulations to enable Predictive Analytics technology to close the gap between bench and bedside.

Box 1. Predictive Analytics project in Mental Health research

Every Predictive Analytics project can be described as a series of steps aimed at ensuring the utility of the resulting model. Here, we provide guiding-questions covering issues essential to ensure the validity and applicability of such a model.

Defining objectives.

- Is the prediction of an unknown (e.g. future) quantity required (for machine learning approaches to data analysis, see [52, 53]; for the interdependent relationship between group-level analyses and predictive analytics, see [54])?
- What is the desired scope of the model? While models based on a heterogeneous population (e.g. diverse comorbidities, age-range etc.) have a much broader field of application and thus higher utility, they might require much more training data.
- Will the link between predictors and the to-be-predicted quantity remain stable in the future (cf. [55])?

Acquiring data.

- How to choose potentially informative predictors? While drawing upon available group-level evidence (e.g. meta-analyses) is reasonable, even predictors displaying substantial association with the target on the group-level are not guaranteed to allow for single-subject prediction. Thus, expert knowledge and evidence from prior predictive analytics models will be essential.
- How to build efficient models? Predictors might contain redundant information with respect to the target, thus rendering the assessment of more than one inefficient. If prior information is lacking, it might be better to base the model solely on easily obtainable data; even if the model's predictive power is slightly decreased. For example, a model using Smartphone-based ambulatory assessments and actimetry data only might be more efficient – and thus more useful in practice – than a more accurate model based on a combination of whole-genome data and neuroimaging measures. As a rule of thumb, measures routinely obtained in the clinic should be used wherever possible.
- Is it necessary to obtain new data? Generally, any dataset acquired for group-level investigations may be suitable also for predictive model building, stressing the relevance of data sharing for the field. Importantly, constructing clinically applicable models will require fully independent data for model construction and validation (for details, see [17]).

Building the model.

- Which machine learning approach should I use? In theory, no learning algorithm can be superior on all possible problems.[56] Thus, the goal must be to identify the best approach given the concrete problem and data at hand. Generally, every approach will require finding the right combination of learning algorithm(s) and data representation (commonly referred to as *feature-engineering;* for a general introduction, see [37, 39]). In practice, this is empirically determined based on the training data.
- How is the predictive model generated? Generally, machine learning algorithms as used in this context are presented with example inputs (features) and the corresponding desired outputs (targets). The goal of this "training" is for the algorithm to learn a general rule that maps features to targets. This rule constitutes a valid predictive model if it correctly maps features to targets not only in the training sample, but also in an independent, previously unseen test sample.

Using the model in clinical practice.

- How can a validated model be deployed? For patients to benefit from Predictive Analytics models, they need to be available to as many clinicians as possible. One option might be to provide online applications to which service users can upload patient data and receive the desired prediction(s).
- How can the future validity of the model be ensured? To this end, continuously monitoring real-life performance is crucial. This can be achieved if users provide feedback regarding the accuracy of the prediction at a later point in time. In addition, the data provided by service users might be used to increase the amount of training data for the model, thus adding to its reliability, accuracy and scope.

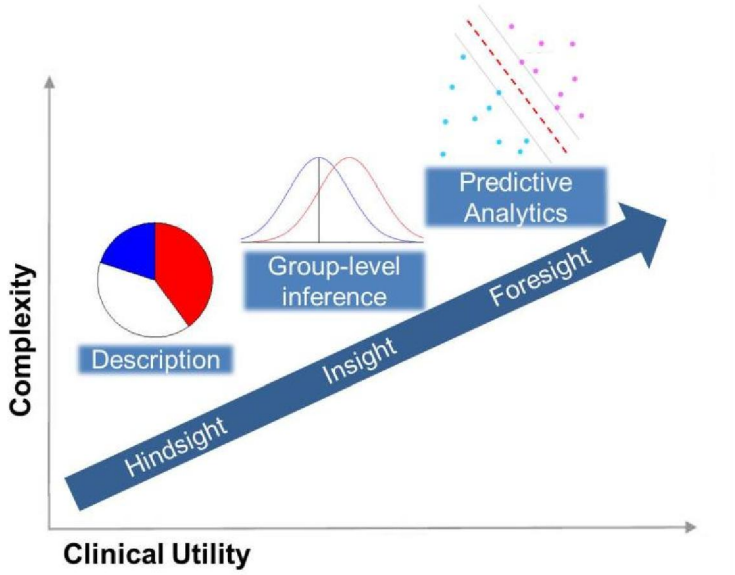

Figure 1. *Predictive Analytics in Mental Health* is moving from the description of patients ("hindsight") and the investigation of statistical group differences or associations ("insight") toward models capable of predicting current or future characteristics for individual patients ("foresight"), thereby allowing for a direct assessment of a model's clinical utility.

In Chapter 1, I described ways in which neuroimaging could be used in the context of predictive analytics. Although predictive analytics of response to treatment for mental health disorders could improve the individual efficacy of treatments, treatments to functional disorders are inherently reactive to suffering and incapacity. More desirable would be a proactive approach in which RSN pathologies would be identified in children who are known to be at familial high risk for a disorder, but who are not yet ill. Once these RSN pathologies are identified, proactive treatment could be implemented. In Chapter 2, I describe ways in which neuroimaging could be used to identify resting state network pathologies in children who are at familial risk for MDD but who are not currently diagnosed with any disorder.

Chapter 2
Altered Intrinsic Functional Brain Architecture in Children at Familial Risk of Major Depression

(Reference: Chai J., Hirshfeld-Becker D., Doehrmann O., Leonard J., Biederman J., Gabrieli J, Whitfield-Gabrieli S., *Biological Psychiatry*, 2016)

Abstract

Background: Neuroimaging studies of patients with major depression have revealed abnormal intrinsic functional connectivity measured during the resting state in multiple, distributed networks. However, it is unclear whether these findings reflect the state of major depression or reflect trait neurobiological underpinnings of risk for major depression.

Methods: We compared resting-state functional connectivity, measured with functional magnetic resonance imaging (fMRI), between unaffected children of parents who had documented histories of major depression (at-risk, n = 27; 8-14 years of age) and age-matched children of parents with no lifetime history of depression (controls, n = 16).

Results: At-risk children exhibited hyperconnectivity between the default mode network (DMN) and subgenual anterior cingulate cortex (sgACC) / orbital frontal cortex (OFC), and the magnitude of connectivity positively correlated with individual symptom scores. At-risk children also exhibited (1) hypoconnectivity within the cognitive control network, which also lacked the typical anticorrelation with the DMN; (2) hypoconnectivity between left dorsolateral prefrontal cortex (DLPFC) and sgACC; and (3) hyperconnectivity between the right amygdala and right inferior frontal gyrus, a key region for top-down modulation of emotion. Classification between at-risk children and controls based on resting-state connectivity yielded high accuracy with high sensitivity and specificity that was superior to clinical rating scales.

Conclusions: Children at familial risk for depression exhibited atypical functional connectivity in the default-mode, cognitive-control, and affective networks. Such task-independent functional brain measures of risk for depression in children could be used to promote early intervention to reduce the likelihood of developing depression.

Introduction

Neuroimaging in patients with major depression (MDD) has revealed abnormal activation patterns in multiple brain networks, including the default mode (DMN), cognitive control, and affective networks. The DMN, anchored in the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC), is suppressed in healthy adults during tasks that demand external attention, but does not show the typical pattern of task-induced deactivation in adults and adolescents with MDD (1–3). The cognitive control network, including dorsal lateral prefrontal cortex (DLPFC), which is typically activated during cognitively demanding tasks, has shown decreased activations in adults with MDD (4, 5). The affective network includes the amygdala and other limbic-region structures (6, 7), and most saliently for MDD, the subgenual anterior cingulate cortex (sgACC), which is considered a core region in the functional and structural pathophysiology of MDD (8–10). The affective network exhibits abnormal activation patterns during emotion processing in adults with MDD (11–13). These abnormal activations in distributed networks may account for cortico-limbic dysregulation in MDD (8,14).

Mirroring these brain activation abnormalities, patients of different ages with MDD have shown abnormal intrinsic functional connectivity of the brain measured via resting-state fMRI (rs-fMRI) (15). First, increased resting-state connectivity within the DMN and between the DMN and sgACC has been reported in adults (16,17) and adolescents (18) with MDD. Hyperconnectivity of sgACC correlated with duration of current depressive episodes in adults (16) and with emotional dysregulation in pediatric depression (19). These results support the possibility that DMN-sgACC hyperconnectivity might underlie depressive rumination (20). Second, several studies reported decreased resting-state connectivity within the cognitive control network in adult patients with MDD (21–23). In line with this evidence, MDD has been conceptualized as an imbalance between the DMN and the cognitive control network (24–26). Third, atypical connectivity between the amygdala and cortical structures has been found in adults (27,28) and children (29) with MDD and is thought to reflect deficits in emotion regulation.

Despite evidence of abnormal functional connectivity across distributed brain networks in patients with MDD, it is unclear whether these differences reflect the state of current depression versus neurobiological traits that predispose individuals to be at risk for MDD. One approach to distinguishing between current state and predisposing traits is the study of unaffected individuals at heightened risk for MDD, such as unaffected children at familial risk for MDD by virtue of having a parent with MDD. Such familial history increases the risk of MDD in offspring by three- to five fold (30), and increases the risk of a broader spectrum of mood and anxiety disorders (31). Understanding whether rs-fMRI findings represent trait or state markers of MDD in the young can lead to the identification of informative neural biomarkers of risk for mood and anxiety disorders and help develop early intervention strategies to mitigate this risk. Rs-fMRI also possesses significant translational strengths in its short duration of scanning, and the lack of task performance demands that can complicate interpretation of activations.

In the present study, we examined rs fMRI in unaffected children at familial risk for MDD and other mood and anxiety disorders by virtue of being offspring of parents with MDD (at-risk group) and compared them with age matched children who were offspring of parents with no lifetime history of any mood disorder (control group). Two previous studies examining at-risk children and adolescents found decreased connectivity between amygdala and frontal-parietal network in unaffected children of depressed mother and in children with early onset depression (29), and decreased connectivity within the frontal-parietal cognitive control network in unaffected adolescent girls with parental depression (32).

Based on previous functional connectivity results in patients with MDD, we focused on functional connectivity differences between at-risk and control children in the DMN, the cognitive control network, and the affective network, using a seed-based functional connectivity approach. We examined connectivity differences from the two midline anchor regions of the DMN (MPFC and PCC), which are associated with self-referential processing (33) and self-focused rumination in MDD (20,34), and from seed regions in left and right DLPFC and amygdala. We tested: 1) whether unaffected at-risk children exhibit patterns of abnormal functional connectivity similar to those reported in patients with MDD, and 2) whether connectivity of DMN-sgACC is related to symptom scores in at-risk children. To further test whether resting-state connectivity can be a useful neural biomarker for risk for MDD, we built classification models based on resting-state d ata to discriminate at-risk versus control children.

Methods and Materials

Participants

We initially recruited 38 offspring ages 8-14 years of parents with lifetime history of MDD (at-risk group) and 30 age-matched offspring of parents with no lifetime mood disorder (control group). The study was approved by the Institutional Review Boards at the Massachusetts General Hospital and at the Massachusetts Institute of Technology. Parents provided written informed consent for their and their child's participation, and youths provided written assent. Exclusion criteria included the presence of acute psychosis or suicidality in a parent or a child; the presence at any point in the lifespan of bipolar disorder in the parent, autism in the child, or a lifetime history of a traumatic brain injury or neurological disorder in the child.

The final sample included in the analyses consisted of twenty-seven at-risk and sixteen control participants with no prior history of depression or current clinical-range symptom scores. Those participants who did not complete the scan, had excessive head movement during the scan, or had a history of depression or clinical range symptom scores were excluded. See Supplementary Information for details.

Diagnostic Assessment

At enrollment for the present study, each child and both parents in each family were assessed for current and lifetime mood disorders (MDD, bipolar disorder, and dysthymia), using structured clinical interviews in which the mother was the informant. Interviews about parents used the depression, mania, dysthymia modules, and psychosis modules from the Structured Interview for DSM-IV (35) and those about the child used the depression, mania, dysthymia, and psychosis modules from the Schedule of Affective Disorders and Schizophrenia for School-Aged Children–Epidemiological Version (KSADS-E) for DSM-IV (36).

Other Assessments

Cognitive Function: To compare cognitive function between groups, we used the Kaufman Brief Intelligence Test-2 (KBIT-2), a 20-minute screen for verbal and nonverbal cognitive functioning (37).

Current Symptoms, Parent Report: To assess current behavioral and emotional symptoms in the children, we asked mothers to complete the Child Behavior Checklist (CBCL) (38) (see Supplementary Information for details) about all children. The CBCL includes a total problems score, as well as scores reflecting internalizing (affective and anxiety) and externalizing symptoms (attentional problems and disruptive behavior). T-scores of 70 and above have been shown to discriminate clinical-range from non-clinical range children (38).

Current Symptoms, Self-Report: To assess current depressive symptoms by self-report, we administered the Child Depression Inventory (CDI) (39) to all children. See Supplementary Information for details of the CDI.

Participant Demographics (Table 1)

Children in the at-risk and control groups did not differ significantly in age, gender distribution, or IQ (ps > .3). The at-risk group had marginally higher CBCL total ($p = .05$), internalizing ($p = .096$), and anxiety scores ($p= .08$), but did not differ significantly in CBCL exte rnal problem scores ($p= .34$). None of the children had clinical-range CBCL scores (> 70). CDI total scores did not differ significantly between the two groups ($p = .26$). Additionally, by parent report, the children were largely pre-pubertal (with the exceptions of 4 at-risk and 3 control children).

Imaging Procedure

Data were acquired on a 3T TrioTim Siemens scanner using a 32-channel head coil. T1-weighted whole brain anatomical images (MPRAGE sequence, 256x256 voxels, 1x1.3-mm in-

plane resolution, 1.3-mm slice thickness) were acquired. After the anatomical scan, participants underwent a resting fMRI scan in which participants were instructed to keep their eyes open and the screen was blanked. Resting scan images were obtained in 67 2-mm thick transverse slices, covering the entire brain (interleaved EPI sequence, T2*-weighted images; repetition time = 6 s, echo time = 30 ms, flip angle = 90, 2x2x2 mm voxels). The resting scan lasted 6.2 min (62 volumes). Online prospective acquisition correction (PACE) was applied to the EPI sequence (40) (see Supplementary Information). Two dummy scans were included at the start of the sequence.

Functional connectivity analysis

Rs-fMRI data were first preprocessed in SPM8, using standard spatial preprocessing steps. Images were slice-time corrected, realigned to the first image of the resting scan, resampled such that they matched the first image of the resting scan voxel-for-voxel, normalized in MNI space, and smoothed with a 6-mm kernel (full width at half maximum). Functional connectivity analysis was performed using a seed-driven approach with in-house, custom software "*CONN*" (41,42) . We performed seed-voxel correlations by estimating maps showing temporal correlations between the BOLD signal from our *a priori* regions of interest and that at every brain voxel. We performed resting-state connectivity analysis from the DMN seeds (MPFC, PCC), cognitive control network seeds (bilateral DLPFC), and bilateral amygdala seeds (Figure 1). The DMN and DLPFC seeds were defined as 6-mm spheres around peak coordinates from (43). The amygdala seeds were defined from the WFU Pick Atlas (44).

Physiological and other spurious sources of noise were estimated and regressed out using the anatomical CompCor method (aCompCor) (45). Global signal regression (GSR), a widely used preprocessing method was not used because it artificially creates negative correlations which prevents the interpretation of anticorrelation (46) and can contribute to spurious group differences in positive correlations (47). Instead, aCompCor allows for interpretation of anticorrelations and yields higher specificity and sensitivity compared to GSR (41). See Supplementary Information for details on the aCompCor. A temporal band-pass filter of0.008 Hz to 0.083 Hz was applied simultaneously to all regressors in the model. Residual head motion parameters (3 rotation and 3 translation parameters, plus another 6 parameters representing their first-order temporal derivatives) were regressed out. Artifact/outlier scans (average intensity deviated more than 3 SD from the mean intensity in the session or composite head movement exceeded 1mm from the previous image) were also regressed out. Head displacement across the resting scan did not differ significantly between the two groups for either frame-to-frame translations in x, y, z directions (at-risk: mean = .19 mm l .11; control: mean = .16mm ± .11; p = .33) or frame-to-frame rotations (at-risk: mean = .0044 m .002; control: mean = .004 ± .003; p = .66). The number of outliers also did not differ significantly between the groups (range: 0 to 9; at-risk: mean = 2.7 ± 2.2; control: mean = 2.1 ± 3.1; p = .47). Outlier images were modeled as nuisance covariates. Each outlier image was represented by a single regressor in the GLM, with a 1 for the outlier time point and 0s elsewhere.

Time series of all the voxels within each seed were averaged, and first-level correlation maps were produced by extracting the residual BOLD time course from each seed and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed z-scores using the Fisher transformation to allow for second-level General Linear Model analyses. DMN connectivity was calculated from the averages of the time series from MPFC and PCC seeds (48,49), given their similar connectivity patterns. Functional connectivity of left and right DLPFC were analyzed separately, as were left and right amygdala due to evidence of differential roles in emotion processing (50). First-level connectivity maps for each participant were entered into a between-

group t-test to determine connectivity differences for each seed between groups. Clusters-level threshold was set at $p < .05$ using false discovery rate (FDR) correction for multiple comparisons (51), with voxel-wise t-value threshold of 2.42 ($df = 41$; $p < .01$). Bonferroni correction was applied to the FDR-corrected cluster-level p-values to correct for multiple comparisons of the five a priori seeds tested (DMN, left and right DLPFC, and left and right amygdala). Regions that showed significant connectivity differences between groups were further examined for their connectivity values (significantly above or below zero) using one sample t-tests in each group. Based on prior evidence of DMN-sgACC hyperconnectivity in MDD and its implication in depressive rumination (20), we examined the within group correlations between DMN-sgACC connectivity values and CBCL scores. Given the higher CBCL total score in the at-risk group, we re-tested group differences by including CBCL total scores as a covariate.

Classification models of at-risk children and controls discrimination

We trained two linear classification models using logistic regression, implemented in machine learning software Weka (52), in order to categorize individual participants to the at-risk or control groups based on their rs-fMRI or behavioral data. To create robust prediction models that can be generalized to new cases, we performed leave-one-out cross-validation so that each individual was classified on the basis of data from the other individuals. Specifically, data from all participants except one were used as the training set to build a classification model, and the remaining participant was classified with the model and used as the validation case. This procedure was iterated for each participant and used to estimate specificity/sensitivity from the out-of-sample predictions. In the first model, we used anatomically defined regions-of-interest (ROIs) that were independent from the regions that showed between-group connectivity differences. Connectivity values between the five *a priori* seeds and 116 clusters defined by the AAL atlas (53) were estimated and used in the prediction model. We constructed a second model based on CBCL scores (total, internalizing, externalizing, anxiety), to compare with classification accuracies from the model based on rs-fMRI data in anatomically defined ROIs.

Results

Increased connectivity between DMN and sgACC/OFC in at-risk children

Compared to the control group, the at-risk group exhibited increased positive DMN connectivity with a cluster in the sgACC extending into medial orbital frontal cortex (OFC) bilaterally (Figure 2A-B; Table 2A). Among the at-risk children, connectivity between the DMN and sgACC /OFC correlated significantly and positively with CBCL internalizing scores (at-risk: $r = .53$, $p = .003$, Figure 2C) and CBCL total scores (at-risk: $r = .39$, $p = .04$); there was no such correlation among the control children. Connectivity strengths within the DMN did not differ significantly between groups.

Decreased anticorrelation between DMN and inferior parietal lobule in at-risk children

Compared to the control group, the at-risk group exhibited higher positive connectivity between the DMN and the right inferior parietal lobule (IPL) (Figure 3; Table 2A). Instead of the anticorrelation exhibited in the control group ($t(15) = -5.99$, $p = .004$), the at-risk group exhibited a positive correlation between the DMN and the right IPL ($t(29) = 2.25$, $p = .03$).

Decreased connectivity within cognitive control network in at-risk children

Compared to the control group, the at-risk group exhibited decreased positive connectivity between the right DLPFC seed and the right frontal-parietal control network regions including the right IPL and the right DLPFC (BA46) (Figure 4; Table 2B), and decreased connectivity between left DLPFC seed and the left IPL (Table 2C).

Decreased connectivity between L DLPFC and sgACC in at-risk children

Compared to the control group, the at-risk group exhibited decreased connectivity between the left DLPFC seed and sgACC *(bilateral)*, right lingual gyrus, right superior frontal gyrus, and bilateral inferior temple gyri, and increased connectivity between left DLPFC and supplementary motor cortex (Table 2C). Left DLPFC and sgACC were anticorrelated in at-risk children only ($t(29) = -3.36$, $p=.002$; Figure 5).

Increased connectivity between amygdala and inferior frontal gyrus (IFG) ***in at-risk children***

Compared to the control group, the at-risk group exhibited increased connectivity between the right amygdala and both the right IFG and the right supramarginal gyrus (SMG) (Figure 6; Table 2D). Instead of the of the negative correlations exhibited in the control group, the at-risk group exhibited positive correlations between right amygdala and right IFG (controls: $t(15) = -3.54$, $p = .003$; at-risk: $t(29) = 4.67$, $p < .001$), and between right amygdala and right SMG (controls: $t(15) = -2.53$, $p = .02$ at-risk: $t(29) = 4.53$, $p < .001$). Connectivity from the left amygdala did not differ between the two groups.

Group differences after controlling for symptom scores

After controlling for CBCL total scores, differences between the at-risk and control groups remained largely similar to the above reported results (Table S1).

Classification of at-risk children and controls

The classification model based on connectivity data in ROIs defined from the AAL atlas yielded 79% accuracy, 81% sensitivity, and 78% specificity. Connectivity between left DLPFC and right supramarginal gyrus, between left DLPFC and left inferior temporal cortex, between DMN and left rectus (medial OFC and sgACC), between DMN and left IFG, between DMN and left/right inferior temporal cortex contributed most to the classification. The model based on CBCL scores yielded only 64% accuracy with 80% sensitivity, and 27% specificity.

Discussion

We found differential intrinsic functional connectivity patterns in unaffected children with familial risk for MDD compared to children without such familial risk in the DMN, the cognitive control network, and the amygdala. At-risk children showed hyperconnectivity between the DMN and the sgACC/OF. Furthermore, although none of the at-risk children was clinically depressed, DMN-sgACC/OFC connectivity was positively correlated with individual CBCL scores among those children. At-risk children also showed hypoconnectivity within the cognitive control networ k, lacked the typical anticorrelation between the DMN and the right parietal region, and exhibited lower connectivity between left DLPFC and sgACC. In addition, at-risk children showed hyperconnectivity between amygdala and the right IFG. Finally, classification between at-risk children and controls based on resting-state connectivity yielded high sensitivity and specificity. These findings appear to identify trait neurobiological underpinnings of risk for major depression in the absence of the state of depression.

Increased connectivity between DMN and sgACC in at-risk children, and the positive correlation between DMN-sgACC connectivity and current symptom scores, are consistent with findings reported in adult (16, 17) and pediatric (19) patients with MDD. The fact that these findings were observed in unaffected children at familial risk for MDD suggests that hyperconnectivity with sgACC is not a consequence or manifestation of MDD, but instead may be a biomarker of predisposed risk for MDD. The at-risk children also exhibited an atypical anticorrelation between sgACC and left DLPFC. In line with our finding, stimulation of the sgACC resulted in attenuation of hyperactivation in sgACC and increased activation in previously

underactive DLPFC in adults with MDD (54). The left DLPFC region that showed maximum anticorrelation with the sgACC has been identified as a target for TMS treatment of MDD (55). A prospective study would be needed to determine if atypical sgACC connectivity at this age predicts later development of MDD.

The lack of typical anticorrelation between the DMN and supramarginal gyrus / inferior parietal lobule, an important attention control region (56,57), in at-risk children is consistent with cognitive control deficits in depressed adult patients (58,59) and reduced DMN deactivation during an emotional identification task in depressed adolescents (3). Greater anticorrelation between DMN and cognitive control networks in healthy adults has been linked to better performance in cognitive control and working memory tasks (60,61) and may reflect an individual's capacity to switch between internally and externally focused attention (62). This dynamic interplay between DMN and cognitive control networks in MDD was examined in a task-based connectivity study. During an external attention condition, adults with MDD exhibited increased DMN connectivity and decreased cognitive control network connectivity (25). The present study suggests that an imbalance between DMN and cognitive-control networks is a developmental risk factor for MDD.

With regards to decreased connectivity within the cognitive control regions in at-risk children, a previous study of adolescents with familial risk for depression also reported reduced connectivity between cognitive control regions (32). In that study, lower connectivity in the control network was associated with more severe parental depression symptoms. These results in at-risk children and adolescents are consistent with findings from depressed adults of reduced connectivity in attention control regions including the DLPFC (23). Studies consistently show that the DLPFC is under-activated in depressed adults (63), which might contribute to their difficulty in cognitive control and emotion regulation (64). It is possible that children at-risk for depression have an under-connected control network that is also a developmental risk factor for MDD.

There was increased connectivity between the right amygdala and the right IFG and supramarginal gyrus in at-risk children. The right IFG is a key region in emotion regulation (65). The top-down IFG-amygdala circuitry is disrupted during emotion regulation in adults with mood disorders (66,67). A study of children with MDD and children of mothers with MDD also reported reduced negative correlation between the amygdala and lateral parietal regions including the supramarginal gyrus (29). The atypically high level of connectivity between amygdala and emotion regulation and cognitive-control regions might reflect emotion dysregulation in MDD.

To test whether intrinsic functional organization of the brain, as measured by rs-fMRI, can be a potential biomarker for risk for depression in children, we performed a classification analysis to discriminate children in the at-risk group and control group based their resting-state functional connectivity data. This classification based on functional connectivity yielded high accuracy, sensitivity, and specificity in discriminating between children at risk for MDD and controls compared to classification based on CBCL scores. Importantly, the rs-fMRI classification was based on analyses that, at the level of each individual child, were independent of the group differences in functional connectivity. Such generalizable and individually robust classification is important if brain measures are to be used for early identification (68). Future prospective and longitudinal studies can determine whether such biomarkers predict which high-risk children progress to MDD and whether early intervention reduces the likelihood of developing MDD. Also, perhaps such biomarkers may be helpful in identifying children at risk for developing depression independent of parental histories of depression.

Our findings need to be viewed in light of some methodological limitations. First, we did not exclude children born prematurely, and premature births can lead to neurological complications.

However, we did exclude children with known developmental delays such as autism and intellectual disability. Second, because parental MDD confers a spectrum of risk to offspring (31,69), the at-risk children were also at risk for anxiety and other disorders. Parents with MDD also have higher rates of comorbid anxiety than the general population. Thus we cannot rule out that the brain differences we found were due to the children being at risk for anxiety and other disorders. Third, although our sample size of at-risk children (N=27) was moderate, the control group was small (N=16). Lastly, our resting-state scans were acquired with a repetition time (TR) of 6 seconds, which is longer than most resting state fMRI studies so that we could acquire high-resolution whole-brain data (2mm isotropic voxels) without the use of parallel imaging. A previous study found there was no significant difference in correlation strengths within and between resting-state functional networks when comparing TR = 2.5 and 5 seconds resting scans, and that correlation strengths stabilized with acquisition time of 5 min (TR = 5) (70). In the current and previous studies using the same acquisition parameters (TR = 6 s) (71), we observed the typical resting-state network patterns observed in other studies. Nonetheless, an additional issue of the long TR is that cognitive and emotional processes internally initiated at the beginning and the end of each scan can be different. We cannot rule out the possibility that the group difference observed here might be in part due to systematic differences in chronometry between the two groups.

The present study consisted of a sample of pre-adolescent children who were at familial risk for depression but not currently affected with depression and therefore functional connectivity differences cannot reflect an expression of depression as could be the case in patients with ongoing MDD. Rather, the differences in intrinsic functional brain architecture likely reflect neural traits that predispose children towards MDD or related disorders. Importantly, we demonstrated that discrimination between at-risk and control children occurred with high sensitivity and specificity based on resting-state functional connectivity. Future studies that track the development of children at familial risk for MDD and determines which children develop MDD or other mood and anxiety disorders are needed to build predictive models based on findings from the present study so as to identify high-risk individuals for early intervention.

Tables:

Table 1. Participant demographic and clinical information. Mean ± SD where appropriate. F, female; M, male; CBCL, Child Behavior Checklist; CDI, total score on the Child Depression Inventory; *t*(df), between-group *t-statistic* and degrees of freedom; *p*, between-group test p value.

	Control (*N = 16*)	At-risk (*N = 27*)	*Statistical Evaluation*
Age	11.3 ± 2.14	11.2±1.67	*t*(41)= .17, p=.86
Gender	8 F, 8 M	13 F, 14 M	$\chi 2$ =. 14, p = .9
IQ (KBIT)	117 ± 10.5	120.6 ± 12.0	*t*(41)=.99, p =.33
Mother affected	0	18	
Father affected	0	14	
Both parents affected	0	5	
CBCL total	41.0 ± 11.8	48.8 ± 10.0	*t*(35) = 2.07, p = .046
CBCL internalizing	44.3 ± 8.50	50.1 ± 9.83	*t*(35) = 1.71, p = .096
CBCL externalizing	45.1 ± 10.5	47.8 ± 9.30	*t*(35) = 0.96, p = .34
CBCL anxiety	51.5 ± 2.78	55.2 ± 6.56	*t*(35) = 1.79, p = .08
CDI	4.33 ± 5.54	6.57 ± 4.64	*t*(35) = 1.16, p= .26

Table 2. Between-group connectivity differences from A) default mode network (DMN), B) right dorsolateral prefrontal cortex (DLPFC), C) left DLPFC, and D) right amygdala. BA, Brodmann area; *k*, cluster size in mm^3. Peak coordinates (x y z) based on MNI (Montreal Neurologic Institute) brain. *t*, peak t value from the cluster (degrees of freedom = 41); *p*-value, FDR-corrected cluster-level *p* value; sgACC, subgenual anterior cingulate cortex; OFC, orbital prefrontal cortex; SMG, supramarginal gyrus; STG, superior temporal gyrus; All reported clusters survived Bonferroni correction of $p < .05$ for the number of seeds tested (five).

A) DMN connectivity					
	BA	*k* (mm^3)	x, y, z	*t*	*p*-value
At-risk > Control					
L sgACC/ OFC	25/11	2544	-8, 22, -20	4.44	< .001
R supramarginal gyrus	40	2152	64, -40, 26	4.47	< .001
R mid cingulum	24/31	2808	18, -34, 38	4.50	< .001
Control > At-risk					
None					
B) R DLPFC connectivity					
	BA	*k* (mm^3)	x, y, z	*t*	*p*-value
At-risk > Control					
None					
Control > At-risk					
R DLPFC	46/9	2920	42, 28, 22	4.57	< .001
R inferior parietal lobule	40	1424	46, -50, 58	3.89	.01
C) L DLPFC connectivity					
	BA	*k* (mm^3)	x, y, z	*t*	*p*-value
At-risk > Control					
Medial frontal gyrus	6/24	2072	0, -2, 48	3.66	.005
Control > At-risk					
R sgACC	25/11	2480	10, 18, -18	4.62	< .001
L inferior parietal lobule	40	2248	-50, -56, 54	4.93	.003
L lingual gyrus	18	2760	-14, -82, -14	5.77	< .001
R lingual gyrus	18	1976	32, -70, -14	4.24	< .001
R superior frontal gyrus	8/6	8616	14, 34, 60	5.25	< .001
R inferior temporal gyrus	21	8392	60, -14, -20	6.88	< .001
L inferior temporal gyrus	21	3120	-60, -14, -20	5.00	< .001
D) R Amygdala connectivity					
	BA	*k* (mm^3)	x, y, z	*t*	*p*-value
At-risk > Control					
R Inferior frontal gyrus	47	2608	44, 40, 4	4.41	< .001
R SMG/STG	40/22	1456	42, -40, 16	3.94	< .001
Control > At-risk					
None					

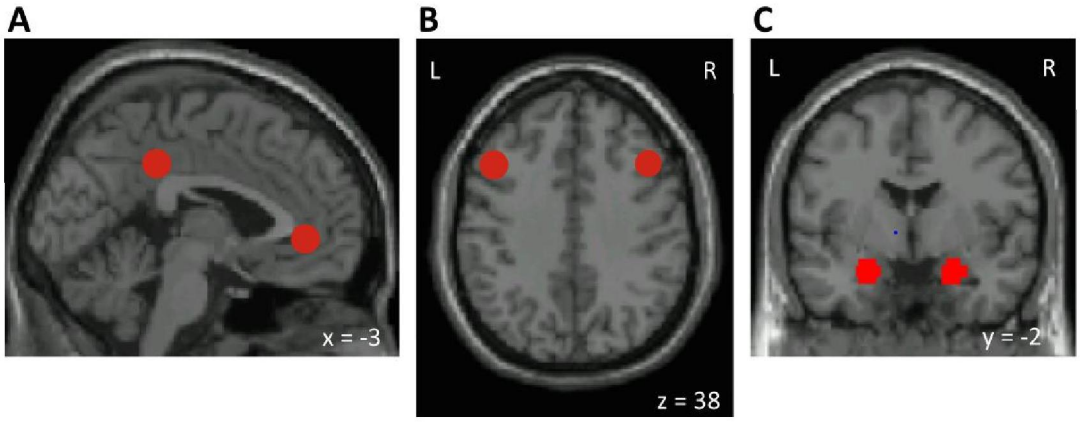

Figure 1. Seeds (regions of interest) used in the study. A) Default network (DMN) seeds (posterior cingulate cortex and medial prefrontal cortex), B) left and right dorsolateral prefrontal cortex (DLPFC) seeds, C) left and right amygdala seeds. L, left hemisphere. R, right hemisphere. Images are presented in neurological convention in all figures (left side of the brain is on the left side of the image).

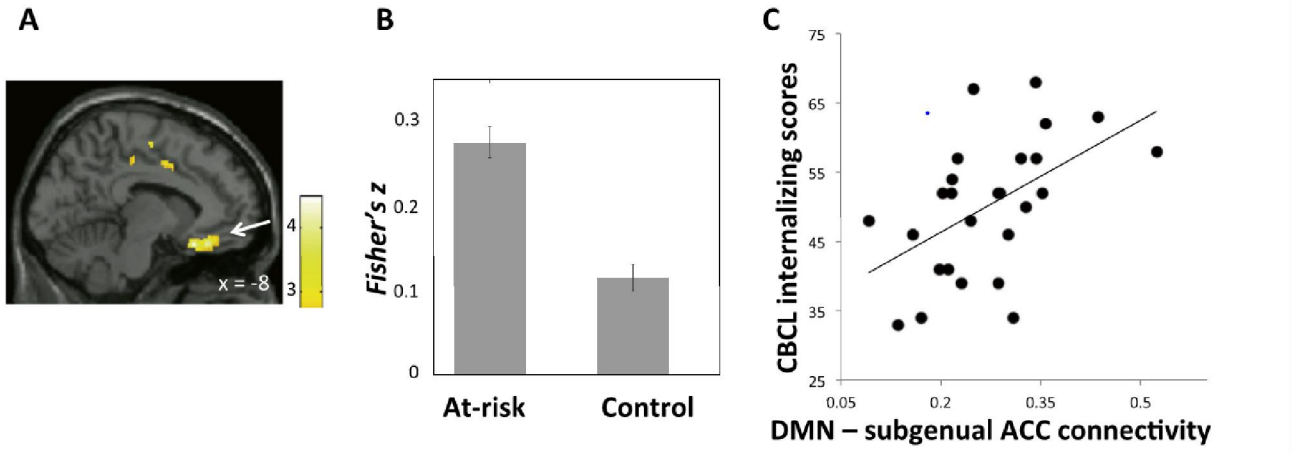

Figure 2. A) Region in subgenual anterior cingulate cortex (ACC) / orbital frontal cortex (OFC) (white arrow) that exhibited higher connectivity with the default mode network (DMN) in the at-risk than the control group. Color bar represents t-values from between-group t-test (at-risk > control). B) Mean DMN-sgACC/OFC connectivity (Fisher's z) in each group. Error bars represent standard errors of the means. C) DMN-sgACC/OFC connectivity plotted against CBCL internalizing scores within the at-risk group.

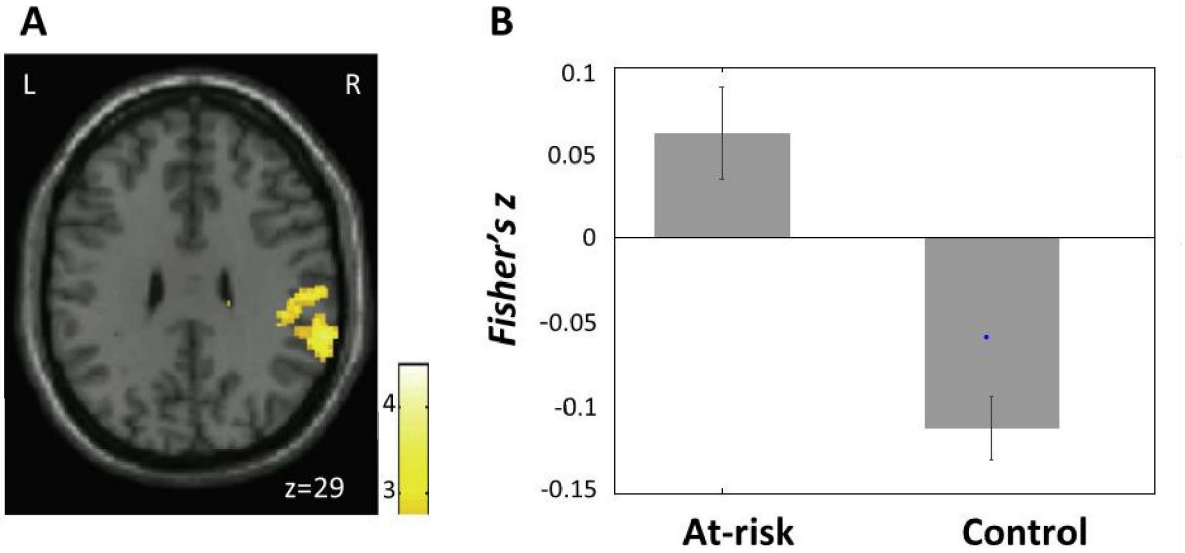

Figure 3. A) Region in the right inferior parietal lobule that exhibited higher connectivity with the default mode network (DMN) in the at-risk than the control group. Color bar represents t-values from between-group t-test (at-risk > control). B) Mean connectivity between DMN and the inferior parietal lobule cluster shown in A) in each group. Error bars represent standard errors of the means.

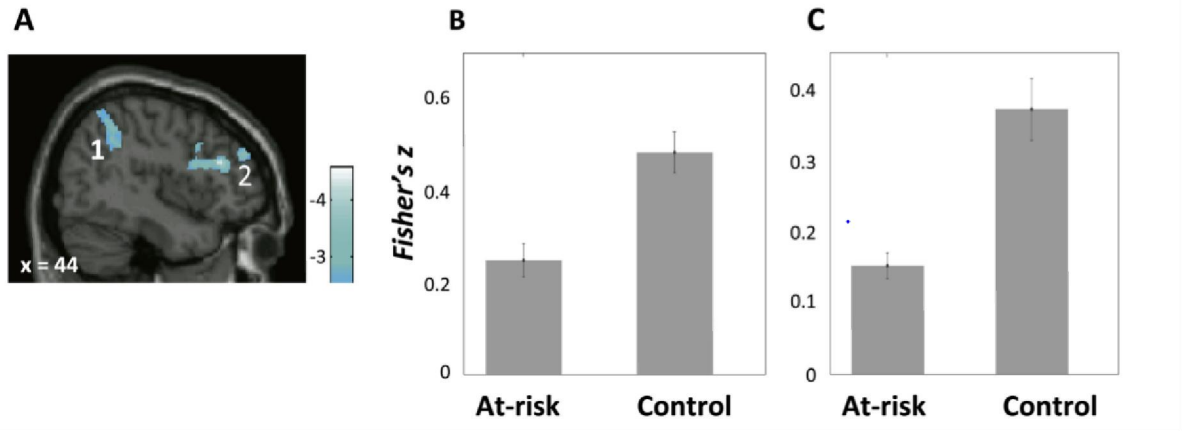

Figure 4. A) Regions that exhibited lower connectivity with right dorsolateral prefrontal cortex (DLPFC) seed in the at-risk than the control group; (1) right inferior parietal lobule; (2) right DLPFC. Color bar represents t-values from between-group t-test (control > at-risk). B) Mean connectivity (Fisher's z) between the right DLPFC seed and the right inferior parietal lobule cluster (1) in each group. C) Mean connectivity (Fisher's z) between the right DLPFC seed and a cluster in the right DLPFC (2) in each group. Error bars represent standard errors of the means.

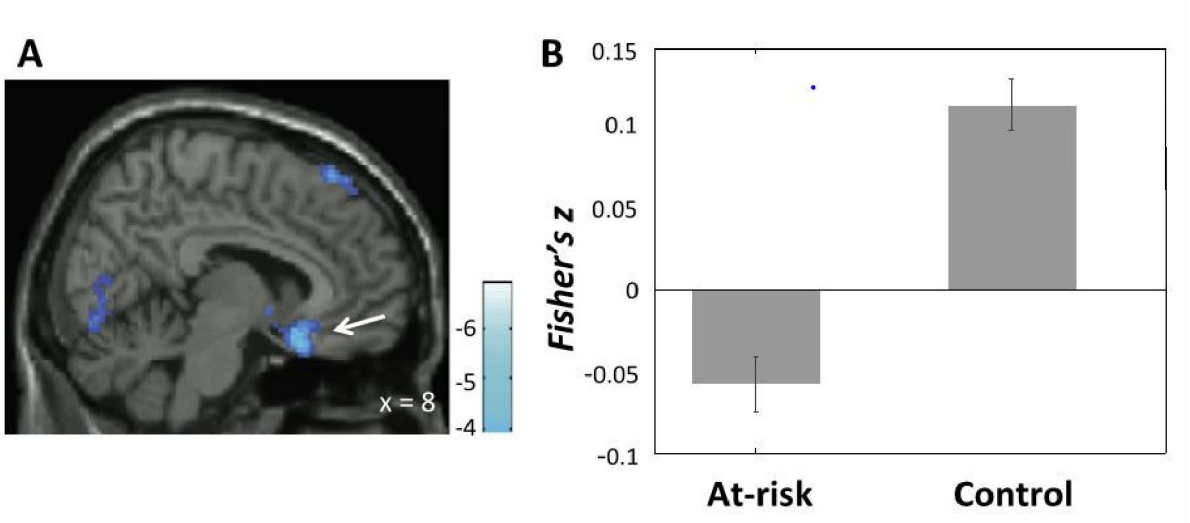

Figure 5. A) Region in the subgenual anterior cingulate cortex (sgACC) (white arrow) that exhibited lower connectivity with left dorsolateral prefrontal cortex (DLPFC) seed in the at-risk than the control group. Color bar represents t-values from between-group t-test (control > at-risk). B) Mean connectivity (Fisher's z) between the left DLPFC seed and the sgACC cluster shown in A) in each group. Error bars represent standard errors of the means.

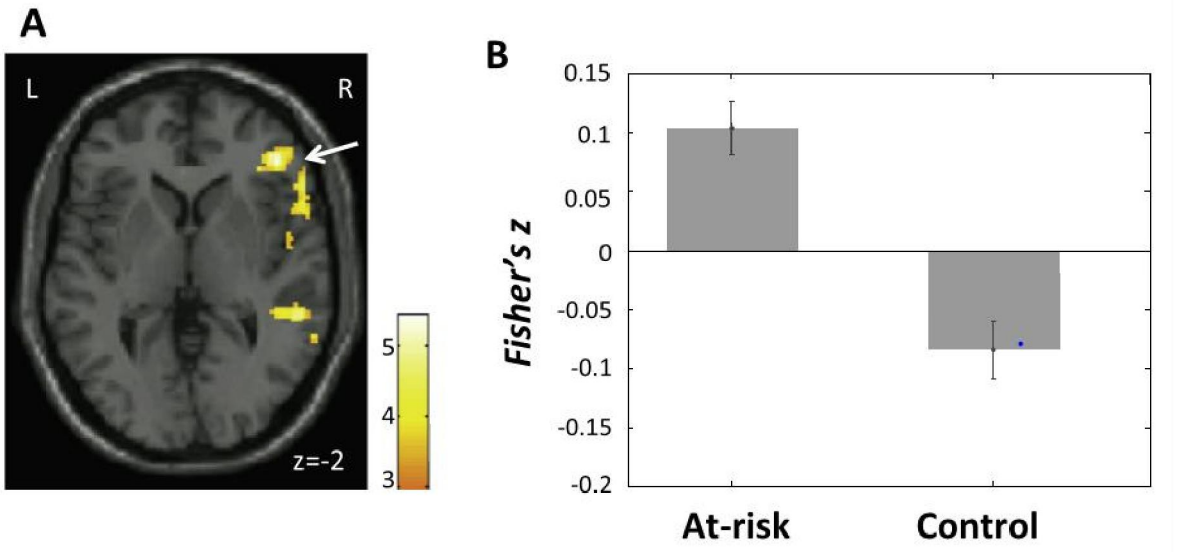

Figure 6. A) Region in the right inferior frontal gyrus (IFG) (white arrow) that exhibited higher connectivity with right amygdala seed in the at-risk than the control group. Color bar represents t-values from between-group t-test (at-risk > control). B) Mean connectivity (Fisher's z) between the right amgydala seed and the right IFG cluster shown in A) in each group. Error bars represent standard errors of the means.

In Chapter 2, I described ways in which neuroimaging could be used to identify resting state network pathologies in children who are at familial risk for MDD but who are not currently diagnosed with any disorder. Such early biomarkers could provide a *proactive* approach in which individuals at high risk for a disorder are identified and early interventions could be instantiated. However, such cross-sectional analyses do not provide information on how individuals will behaviorally progress over time. Only longitudinal analyses would validate whether variation of RSNs would predict progression of psychiatric symptoms at a later age. Secondly, should such RSN characterization become clinically useful, we would not want to limit it to children with family histories of psychiatric disorders. In Chapter 3, I expand on the previous findings by investigating longitudinally a non-selected or normative sample of children. Discovering RSN predictors on this sample could allow for early identification of RSN pathologies and support preventive treatment regardless of family history.

Chapter 3

Intrinsic Brain Architecture Predicts Future Attentional and Mood Problems in a Normative Pediatric Sample
(Reference: Whitfield-Gabrieli S., Wendelken C., Bailey S., Cutting L., Bunge S.A. In Prep)

Abstract

We tested whether the intrinsic functional architecture of the human brain, as measured by resting state fMRI, can predict individual children's developmental trajectories towards attentional problems characteristic of Attention Deficit Hyperactivity Disorder (ADHD), or internalizing problems characteristic of major depression (MDD). To this end, we analyzed neuroimaging and behavioral data from an existing longitudinal study of children assessed at age 7 (N=94), and again at age 11 (N=54). We preregistered a set of analyses aimed at testing whether specific connectivity patterns would predict scores on the Child Behavior Checklist (CBCL)[1], a parental report assessment used to screen for emotional, behavioral, and social problems and to predict psychiatric illnesses. As hypothesized, greater connectivity at age 7 between medial prefrontal cortex (MPFC), a core node in the default mode network (DMN), and dorsolateral prefrontal cortex (DLPFC) predicted the development of attentional problems characteristic of ADHD by age 11. Exploratory analyses also revealed that weaker connectivity between a region implicated in mood, the subgenual anterior cingulate cortex (sgACC), and DLPFC at age 7 predicted the development of internalizing behaviors by age 11. Logistic Regression Analyses of resting state metrics revealed that sgACC-DLPFC connectivity was a more accurate predictor than initial CBCL measures of whether a child would progress to a subclinical score on internalization, which is itself highly predictive of a future psychiatric diagnosis[2,3]. Thus, stronger MPFC-DLPFC connectivity, known to be related to lower cognitive functioning, was a predictor of the development of attentional problems, and weaker sgACC-DLPFC connectivity was a better predictor of the development of mood problems than a standard screening tool. Such neuroimaging biomarkers provide early identification of vulnerabilities in neural systems and may support preventive treatment of at-risk children prior to the emergence of full-blown psychiatric disorders.

Introduction

The regulation of both cognition and emotion is thought to depend upon top-down modulation of multiple neural circuits by prefrontal cortex, and in particular the dorsolateral prefrontal cortex (DLPFC)[4-8]. Because prefrontal-dependent cognitive control mechanisms regulate the focus of attention and regulate mood, it stands to reason that they play a key role in mental health[8,9]. There is indeed ample evidence that adult psychiatric patients exhibit an attenuation or failure of top-down control mechanisms in depression[10-12], anxiety[13], and Attention Deficit Hyperactivity Disorder (ADHD)[14]. Given that these prevalent mental health problems tend to emerge during childhood and adolescence[15-17], it is important to know whether dysregulated top-down control can be detected even before behavioral symptoms are evident.

The strength of coupling between regions involved in top-down control and their targets can be measured with resting state fMRI (rs-fMRI). Regions of the brain that are highly temporally correlated during rest form resting state profiles which are intrinsic, spontaneous, low-frequency fluctuations in the fMRI blood-oxygen-level dependent (BOLD) signal that define specific networks of the brain in the absence of any task[18]. There is great heterogeneity in the functional organization of the brain that is captured by RSNs. In fact, they may be considered "fingerprints" of the human brain, as they can accurately identify individual subjects from a large group (N=126) of individuals[19]. Furthermore, RSN profiles are known to be robust and reliable[19-25].
RSNs are particularly relevant to studying psychiatric and pediatric populations because 1) they are task-independent, so individual differences in task performance cannot explain differences observed in the BOLD data, 2) they are easy and fast to acquire which make them more accessible to a wide variety of subjects including young children and a wide range of clinical populations, and 3) they are plastic and have been shown to change during typical development[26] and can be modulated by behavioral[27,28] or pharmacological interventions[29,30].

An RSN that is particularly relevant for mental health is the Central Executive Network (CEN), of which the DLPFC is a key node. The CEN has been associated with externally focused attention[31] and goal-directed behavior[32-34]. In neurotypical adults, the CEN is negatively correlated – i.e., anticorrelated – with the default mode network (DMN), an RSN associated with internal mentation and self-referential processing, whose key nodes include the medial prefrontal cortex (MPFC)[35-39]. The decoupling of these RSNs has been found to be adaptive: Greater MPFC-DLPFC anticorrelations are associated with superior cognitive control and cognitive performance, such as greater working memory capacity[40-43]. In addition, there is a selective growth of anticorrelations between the MPFC and DLPFC in typically developing children[26], which is consistent with the findings that top-down control mechanisms improve markedly over childhood and adolescence[44]. Rs-fMRI studies have shown an association between diminished MPFC-DLPFC anticorrelations and cognitive impairment in Attention Deficit Hyperactivity Disorder (ADHD)[45].

The CEN also plays a role in regulating mood through its interactions with the subgenual anterior cingulate cortex (sgACC). The sgACC is part of the affective network, which is involved in emotion processing[46-53], and has anatomical connections to hypothalamus, amygdala, entorhinal cortex, nucleus accumbens and other limbic structures[50]. There are several lines of evidence showing that top-down modulation of the sgACC is dysregulated in adults with major depressive disorder (MDD). Neuroimaging studies have reported decreased metabolism and decreased gray matter volume in patients with MDD[54], and a decreased number of glia in sgACC[55]. Furthermore, deep brain stimulation of the sgACC results in attenuation of hyperactivation in sgACC and increased activation in previously underactive DLPFC in adults with MDD[56]. In addition, the left DLPFC region that shows maximal anticorrelation with the sgACC in rs-fMRI has been identified as an optimal target for TMS of MDD[57]. The sgACC has also been shown to exhibit decreased connectivity with cognitive control regions in children with a history of preschool-depression[58]. Finally, left DLPFC and sgACC exhibit hypoconnectivity (anticorrelated activation) in children at familial risk for MDD[59].

In sum, prior research on adult patient populations reveals that atypically strong functional connectivity between DLPFC and MPFC is characteristic of ADHD, whereas atypically weak connectivity between DLPFC and the sgACC is characteristic of MDD. Here, we build on this prior work by asking whether the strength of connectivity between these regions can predict a progression towards attentional or mood disorders in childhood. Rather than comparing children diagnosed with psychiatric disorders and typically developing children, we examined longitudinal

data from a community sample of children.

Specifically, we tested whether DLPFC-MPFC and DLPFC-sgACC connectivity at age 7 predict scores at age 11 on a questionnaire used to screen children for behavioral problems, the Child Behavior Checklist (CBCL). The goals of this research are twofold: first, to better understand how changes in brain connectivity over childhood relates to cognitive and affective development, and second, to evaluate the predictive validity of DLPFC-MPFC and DLPFC-sgACC connectivity for future mental health problems in children who have not been identified previously as being at elevated risk for the development of a psychiatric disorder.

Numerous studies have demonstrated a high rate of reliability between the CBCL scales and actual psychiatric diagnosis[60,61]. For example, CBCL Attention Problem scores are highly correlated for the screening of and prediction of ADHD[62,63]. A subthreshold elevation on the anxiety/depression subscale of the CBCL in preadolescence is a predictor for future development of the diagnosis of MDD[3]. However, neuroimaging measures may, in conjunction with clinical measures, allow us to identify with greater confidence and at an earlier age children at the greatest risk for development of psychiatric disorders.

In the present study, then, we investigated whether rs-fMRI data can be used to predict future CBCL scores in a community sample of 54 children. Specifically, we tested whether the individual differences in MPFC-DLPFC connectivity at age 7 predict subsequent change in attention four years later, as measured by the CBCL "Attentional Problems" measure at age 11. Additionally, we tested whether individual differences in sgACC-DLPFC connectivity at age 7 predicts subsequent change in Anxiety/Depression four years later, as measured by the CBCL "Internalization" and Anxiety/Depressed subscale at age 11. We have pre-registered our hypotheses at the opensciencefframework (OSF); https://osf.io/7cfvq/.

Methods

Participants: Ninety-four participants were included in this study which were part of a developmental longitudinal study, "Predicting Late-Emerging Reading Disability" (LERD; Vanderbilt University; PI: L. Cutting). LERD had a longitudinal design in which all baseline or Time 1 (T1) data were collected from participants at age 7 (N=94; 53 M, 41 F) and subsequently at 1-year intervals for four years. Data at Time 4 are available for 54 of the original participants.

Exclusion Criteria: Children were eligible for the LERD study if they met the following general exclusion criteria: No uncorrected vision or hearing problems, no mental retardation (IQ<70), no limited proficiency in English, no brain injury (e.g., history of head trauma, meningitis, epilepsy, etc.), no severe psychiatric disorders (major depression, Tourette's syndrome, obsessive-compulsive disorder), and no ferromagnetic material in their body (e.g., braces). However, because the LERD study related to reading disability (RD) and there is a comorbidity of RD with ADHD, children with ADHD (as well as other mild psychiatric conditions, e.g., oppositional-defiant disorder, adjustment disorder, mild depression) were not excluded from participation.

For the purposes of this paper, we excluded those children who were on medication and performed predictive analyses with and without the children who were diagnosed with ADHD.

ADHD Diagnosis: ADHD status was determined by DSM-IV criteria, which requires that symptoms be present in at least two settings. Therefore, two questionnaires were administered to each child's parent and teacher. For an ADHD diagnosis, participants had to meet the criterion of scoring above the 93rd percentile on at least one of two parent questionnaires/rating scales, and on at least one of the two teacher questionnaires/rating scales (ADHD Rating Scale-IV[64,65]). Participants classified as having ADHD also had to meet DSM-IV diagnostic criteria for ADHD

based on Diagnostic Interview for Children and Adolescents-IV (DICA-IV[66]) interview (past or present) conducted with the parent and signs/symptoms must have been present before age 7 and have persisted for longer than 6 months. Children were only considered free of ADHD if they did not meet criteria on the parent and teacher questionnaires/rating scales used to diagnose ADHD and on the DICA-IV. Seven patients who completed the study were diagnosed with ADHD and four of them were on medication. We statistically controlled for all of the ADHD subjects as well as for those four participants who were diagnosed with ADHD and were on medication.

CBCL Scoring: The CBCL records behavioral problems and competencies of children ages 6 to 18 years based on parental reports. Normed on a nationally representative sample of 1,753 youths, it includes the following eight empirically based syndrome scales: 1) Aggressive Behavior, 2) Anxious/Depressed, 3) Attention Problems, 4) Rule-Breaking Behavior, 5) Somatic Complaints, 6) Social Problems, 7) Thought Problems, and 8) Withdrawn/Depressed, as well as summary scores reflecting "Internalization" and "Externalization." Internalizing Problems sums the Anxious/Depressed, Withdrawn, and Somatic complaints scores, while Externalizing Problems combines Rule-breaking and Aggressive behavior. The standard scores are scaled so that 50 is average for the youth's age and gender, with a standard deviation of 10 points. Higher scores indicate greater problems. For each syndrome, scores can be interpreted as falling in normal, borderline, or clinical ranges of behavior. Researchers typically use T scores of 60-70 (>1SD <2SD) as medium level of symptoms (or "subthreshold" elevations), and T scores above 70 (>2SD) as syndromatic.

Data Acquisition: Data were acquired at Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva MRS scanner with a 32-channel head coil. One 5.9-minute resting state EPI scan was collected with the following parameters: TR=2200ms, TE=30ms, 35 slices, 3 mm isotropic voxels.

Resting state fMRI Analyses: Resting state fMRI data were analyzed in *Conn* (http://www.nitrc.org/projects/conn)[67], which incorporates methods to both minimize the influence of head motion artifacts and allow for valid identification of correlated and anti-correlated networks[68].

Preprocessing: Spatial preprocessing of functional volumes included slice timing correction, realignment, normalization, and smoothing (8mm FWHM Gaussian filter), using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

Denoising (e.g., Motion and Physiological Aliasing): To address potential spurious correlations in resting state networks caused by head motion, we used a procedure to identify problematic time points during the scan, using the Artifact Detection Tools (ART, http://www.nitrc.org/projects/artifact_detect) which is implemented in *Conn*. Specifically, an image was defined as an outlier image if the head displacement in x, y, or z direction was greater than 1.0 mm from the previous frame, or if the global mean intensity in the image was greater than 3 standard deviations from the mean image intensity for the entire resting scan. The temporal timeseries characterizing the estimated subject motion (3 rotation and 3 translation parameters, plus another 6 parameters representing their first-order temporal derivatives) and artifactual covariates (one covariate per artifactual time point consisting of 0's everywhere and a "1" for the artifactual time point), were used as nuisance regressors in the first level General Linear Model (GLM).

The anatomical image for each participant was segmented into white matter, grey matter, and cerebrospinal fluid (CSF) masks using SPM12. To minimize partial voluming, the white matter and CSF masks were eroded by one voxel, which resulted in substantially smaller masks than the original segmentations[69]. The eroded white matter and CSF masks were then used as noise regions

of interest (ROI). Signals from the white matter and CSF noise ROIs were extracted from the unsmoothed functional volumes to avoid additional risk of contaminating white matter and CSF signals with grey matter signals. The BOLD timeseries within the subject-specific white matter mask (5 PCA parameters) and CSF mask (5 PCA parameters), were then used as temporal covariates and removed from the BOLD functional data using linear regression, and the resulting residual BOLD timeseries were band-pass filtered ($0.01Hz < f < 0.10Hz$).

Global signal regression, a widely used preprocessing method, was not used because it mathematically mandates negative correlations that prevent the interpretation of anticorrelations[70] and can contribute to spurious group differences in positive correlations[71]. Instead, the anatomical CompCor (aCompCor) method of noise reduction[72] as implemented in Conn and described above, allows for interpretation of anticorrelations and yields higher specificity and sensitivity compared with global signal regression[69].

Seed Definitions: The default mode network seed was defined as a 10mm sphere around the peak coordinates from literature (MPFC: (-1, 47, -4)[31]). The selection of these coordinates was based on a number of papers illustrating that a) this MPFC seed region has significant anticorrelations with DLPFC, which correlates with executive function[43], b) there is a selective growth of anticorrelations between this MPFC seed and DLPFC in typically developing children[26], and c) there is a significant reduction of MPFC-DLPFC anticorrelations in adult psychiatric populations with cognitive impairment, such as in ADHD[45], Bipolar Disorder[73], and Schizophrenia[74]. In order to define the sgACC seed to investigate the relationship between sgACC-DLPFC connectivity and the CBCL Internalization, we used Independent Component Analyses to define this component (see below).

Seed-to-voxel Bivariate Correlation: First-level correlation maps were produced by extracting the residual blood oxygen level–dependent (BOLD) time course from each seed and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed z-scores using the Fisher transformation to improve the validity of second-level General Linear Model analyses. Fisher-transformed r-maps from each seed were submitted to a second-level analysis of covariance (ANCOVA) regressing the changes in the CBCL measures (T4-T1) onto brain responses, controlling for the effect of initial severity (initial CBCL). To create a robust prediction model that could be generalized to new cases, we performed leave-one-out cross-validation, which minimizes potential biases due to voxel-selection in our predictive models. Crossvalidated scatter plots were computed as follow: 1) for each subject, a second-level analysis looking for voxel-level associations between connectivity with MPFC and change in attentional problems was run entering only the remaining N-1 subjects; 2) the suprathreshold cluster from this analysis was used a subject-specific mask of DLPFC in the left-out subject, and functional connectivity between MPFC and DLPFC for this individual subject was computed as the average of the Fisher-transformed correlation coefficients between MPFC and each voxel in this mask; and 3) the previous two steps were repeated for each subject to obtain a list of MPFC-DLPFC connectivity values, which were then plotted against the corresponding subjects' change in attentional scores.

In addition, we implemented a replication analysis wherein we correlated the connectivity between the MPFC seed and an independent DLPFC mask defined from the literature[26].

ICA analyses: Independent Component Analyses (group-ICA[75]) were used to identify the emotional regulation network (ERN), including the sgACC. Group-level components were estimated using a 64-dimensions subject-level dimensionality reduction step, followed by 40-component group-level dimensionality reduction and fast-ICA with a hyperbolic tangent contrast

function. The ERN was identified as the component with highest loading at the sgACC coordinates (5, 25, -10) (I9 seed[76]). ERN subject-level component-score maps were averaged across participants and thresholded using a combination of T>6 voxel-level "height" threshold and a FWE-corrected p<.001 cluster-level threshold. This analysis resulted in a positive cluster including sgACC as well as bilateral amygdala and hippocampus, and two negative clusters in bilateral DLPFC areas. Average ICA subject-level component scores over the resulting DLPFC cluster was used in subsequent analyses as a measure of the negative association (anticorrelations) between the ERN and DLPFC for each subject, specifically between the sgACC and left DLPFC.

Longitudinal Analyses: In order to explore whether individual differences in DLPFC connectivity predicted future negative behavioral outcomes, we performed cross-validated prediction analysis to investigate whether T1 resting state correlations predict progression of subsequent change of CBCL (T4-T1) behavioral measures after factoring out T1 CBCL behavior. First, we tested whether stronger MPFC-DLPFC resting state correlations at T1 predict future change in CBCL attentional problems, after controlling for the initial attentional score at T1. Second, we used a data-driven Independent Component Analyses (ICA) approach as described above to define a component which consisted of the left DLPFC-sgACC. We then tested whether the connectivity of this component predicted worsening of internalization across three subscales, and subsequently examined the internalization subscales separately: a) anxiety/depression, b) withdrawn behavior, and c) somatic complaints.

Logistic regression for CBCL Internalization (and anxiety/depression subscale). As per CBCL diagnostic category definitions, we subdivided participants into a "subclinical" category for individuals with a CBCL Internalization (and anxiety/depression) score >= 55, and a "typical" category for those whose scores on this subscale fell below this cut-off based on the literature[3]. We used logistic regression of initial severity (initial CBCL scores) and T1 resting state measures combined with leave-one-out cross-validation – that is, all participants except one were fit and predicted the out-of-sample participants' outcome category; this procedure was iterated for each participant and used to build cross-validated predictions and estimate specificity/sensitivity from the out-of-sample predictions. We did not have a sufficient number of subjects with subclinical scores for the CBCL Attentional Problems at T4 to perform this Logistic Regression for that CBCL scale.

Results

Behavioral results*:*

A summary of the CBCL data is provided in Table 1. Many children did not exhibit changes in CBCL scores, but others exhibited worsening (higher CBLC scores at T4) or improvement (lower CBCL scores at T4) over the course of 4 years (Figures 2, 3; Table 1). Twice as many children developed worse internalizing problems over the four years (39% of children) compared to those with worsening attentional problems (17% of children). A crosstabulation Chi-square test revealed that the prevalences differed between the two measures ($\chi 2(2) = 7.1$; $p = 0.029$). Although there were children who were already subclinical for both attentional problems and internalization at Time 1, there was not selective attrition – that is, the CBCL scores did not differ between those who did and did not complete the study.

Head Motion*:*

The average number of outliers across all timepoints, based on thresholds described in the methods, was 17.03 out of 160 timepoints. Excluding these timepoints preserved enough data to achieve a stable estimate of resting state networks[77]. Three subjects were dropped due to excessive head

motion. Although rs-fMRI/behavior correlations have been called into question due to the fact that motion often correlates with the behavioral measure of interest[78], in this sample, Time 1 motion parameters did not correlate significantly with CBCL behavioral measures (or progression of CBCL measures (t4-t1), p's > .15).

Neuroimaging results:

First, we tested for a replication (and extension) or our previous results indicating that children (ages 8-12) had positive MPFC-DLPFC resting state connectivity (as opposed to the MPFC-DLPFC anticorrelations evident in teenagers and young adulthood). We performed a one-sample t-test of the MPFC seed resting state functional connectivity at T1 (n=94, age 7). We then calculated the mean resting state correlations between the MPFC seed region and an *a priori* seed region of interest in DLPFC[26]. Cross-sectional analyses at T1 revealed that, on average, children 7 years of age did not exhibit significant MPFC-DLPFC anticorrelations that are evident in adults, but rather exhibited positive MPFC-DLPFC correlations (Figure 1). These results replicate those observed previously in children ages 8-12[26]. We had hypothesized that stronger MPFC-DLPFC correlations would correlate with worse attention at T1, but anticipated that there would be insufficient variance in the CBCL attentional scores to establish a significant brain-CBCL relation in this sample, as specified in the pre-registration. Indeed, we did not observe any significant correlations between the MPFC-DLPFC connectivity and CBCL attentional scores at a height threshold of $p<.001$ uncorrected (or even at a liberal threshold $p<.01$ uncorrected).

Because there was not much change in CBCL overall but great inter-subject variability in amount of change, we sought to use T1 neuroimaging data to predict CBCL change from T1 to T4. We found that relatively higher MPFC-DLPFC resting state correlations at T1 predicted the subsequent worsening of attention, such that greater positive MPFC-DLFPC correlations at T1 were associated with worsening of attentional problems four years later: (($T(49) = 2.38$, $p = 0.01$, controlling for medication, Figure 2) and ($T(49) = 1.02$, $p = 0.030$, controlling for those children who were diagnosed with ADHD), and $T(50) = 2.36$, $p = .01$ without controlling for ADHD subjects); reported p-values are one-sided due to our *a priori* and preregisterd hypotheses).

Because we implemented this analysis using leave-one-out cross-validation, this is a true prediction as opposed to a simple correlation, a distinction that is frequently lost in the neuroimaging literature[79]. Moreover, we replicated this finding by implementing an independently defined *a priori* DLPFC mask[26], showing a significant correlation between the MPFC-DLPFC connectivity at T1 and the worsening of attentional problems from T1 to T4 ($r = .40$; $p = .04$).

Next, we tested whether the independent ICA derived left DLPFC-sgACC anticorrelations would predict worsening of internalization (and anxiety/depression, withdrawn, somatic subscales). We found that left DLPFC-sgACC connectivity predicted internalizing changes ($T(49) = -2.4$, $p = 0.010$; controlling for medication (figure 3) and ($T(49) = -2.15$, $p = .018$, controlling for ADHD) and ($T(50) = -2.61$, $p = .008$, not controlling for ADHD or medication), such that stronger anticorrelations at baseline were associated with worsening CBCL scores (Figure 3). In addition, left DLPFC and sgACC connectivity predicted progression of internalization subscales: a) *anxiety/depression* ($T(49) = -2.64$, $p = 0.005$, controlling for medication), such that stronger anticorrelations were predictive of worse outcomes, and b) *withdrawn* ($T(49) = -2.38$, $p = 0.01$, controlling for medication), such that stronger anticorrelations were predictive of worse outcomes. By contrast, left DLPFC-sgACC connectivity was not associated with *somatic-complaints* ($T(49) = -0.88$, $p = 0.192$, controlling for medication).

Logistic regression: Logistic Regression Analysis, using left DLPFC - sgACC resting state connectivity measures, predicted whether an individual child would fall into the Subclinical

Internalization category above and beyond the initial CBCL measures (Figure 4). This analysis yielded 77% accuracy, 87% sensitivity, and 74% specificity.

Discussion

Here, we used resting state networks to identify the neural mechanisms underlying the emergence of adaptive behavior during middle childhood, and identified neural signatures of maladaptive behavior that could lead to future mental health problems and potentially to psychiatric diagnoses. First, we found that MPFC-DLPFC anticorrelations, known to be related to cognitive functioning, are a positive predictor of attentional development. Diminished DMN-CEN anticorrelations may reflect an attenuation of top-down control mechanisms and an inability to allocate resources away from internal thoughts and feelings and towards external stimuli in order to adaptively perform difficult tasks[74,80]. Thus, 7-year-olds who exhibit MPFC-DLPFC anticorrelations may have the capacity to toggle between internal and external foci of attention, while those children who have diminished MPFC-DLPFC anticorrelations may not have this ability. The failure to decouple these networks may be an early indicator of attentional problems, or may in fact preclude the development of age-appropriate attentional skills. Second, we found that sgACC - left DLPFC anticorrelations predict the progression of Internalization symptoms related to MDD. Stronger sgACC-left DLPFC anticorrelations at this young age may already reflect an attenuation or failure of top-down control mechanisms that are evident in adult MDD. Thus, the functional connectivity of specific neural systems in middle childhood forecasts individuals' resilience or vulnerability in cognition and emotion over the ensuing four years of development.

Plasticity in Resting State Networks

Although variation in resting state networks forecasts the progression of attentional and emotional problems, there is strong evidence that such networks are plastic, and thus may be altered by supportive interventions. Resting state functional connectivity is thought to reflect habitual network activations[81] that can be remodeled by long-term[82] and even brief[83] interventions. Resting state functional connectivity can be altered by behavioral interventions such as Cognitive Behavioral Therapy (CBT)[27], exercise[28], and mindfulness meditation[84,85]. Mindfulness meditation training has been previously shown to enhance cognitive functioning, and a recent study reports that mindfulness intervention modulates the CEN (e.g., DLPFC), as well as the affective network (AN) (e.g., sg-ACC)[84,85]. In a large sample of children ranging from grades 1-12, mindfulness meditation improved cognitive performance and resilience to stress[86]. In a randomized controlled trial, children, 11 years old, who received mindfulness training showed a selective increase in MPFC-DLPFC Anticorrelations (as compared to the CN group), and the degree of change positively correlated with an increase in attention[87]. In addition, neurotechnological approaches have been shown to alter RSNs, such as real-time fMRI neurofeedback training in controls subjects as well as patients with MDD and Schizophrenia[87-89]. Finally, pharmacological interventions have also been shown to normalize or ameliorate pathological RSNs[30,90]. It is likely that supportive behavioral interventions are especially salient in attempts at preventive treatments in children who can be identified as being on a trajectory towards ADHD or MDD but who do not currently meet critera for these diagnoses.

Limitations

One limitation relates to the fact that we used only one brain imaging modality as a predictor in this study. In future work, multi-modal imaging could further enhance predictive accuracy[91-93].
A second limitation is that it would be nice to have more rigorous clinical outcome measures for

the kids beyond the parental subjective questionnaire. Finally, little is known about the underlying neural mechanisms of these anticorrelations. Future research could combine resting state functional MRI with MR spectroscopy to gain insights regarding neurochemical modulation of functional connectivity. In addition, the electrophysiological correlates of the anticorrelations remain unknown. Future research could involve collecting simultaneous EEG and resting state fMRI with a view to identifying an electrophysiological signature of these anticorrelations and, in future, developing an EEG biofeedback intervention.

Conclusion

A fundamental goal of neuroscience research on mental health disorders is to understand the neurobiological roots of those disorders so as to better target treatment and perhaps even prevent the development of those disorders. Given the relative infrequency of even such common disorders as ADHD or MDD, a fruitful strategy has been to examine brain differences in children at heightened familial risk for a disorder. Indeed, such studies have revealed structural and functional brain differences in children who are not diagnosed with MDD but have familial risk[59,94-96]. Perhaps because ADHD is often diagnosed at a young age, there are few if any such studies of brain differences predating clinical manifestations of ADHD.

Many children, however, develop ADHD or MDD without a documented family history of either disorder. It is important, therefore, to understand the neurobiological roots of ADHD and MDD in unselected groups of children, as was done in the present study. These findings reveal that variation in brain function, as elucidated by specific resting state networks, forecast the development of particular forms of psychopathology (e.g., attentional problems or internalization) that are highly predictive of psychiatric diagnosis in children who were not pre-selected to be at familial risk. These findings not only further our understanding of the neurobiological vulnerabilities that foster the deterioration of mental health, but also could inform early identification and preventative treatment for children who, regardless of a documented family history of mental disorders, have a neurobiological vulnerability for ADHD or MDD.

Table 1.

T1	Attention	Internalization	Anxiety/Depression	Withdrawn	Somatic
Mean	56.29	160.02	53.27	53.39	53.37
STD	8.13	13.02	5.3	5.48	5.48
# Subclinical (>60)	24	10	13	14	9
% Subclinical	25%	11%	14%	15%	10%
T4					
Mean	54	160.13	53.11	53.15	53.87
STD	7.46	14.02	5.54	6.32	4.86
# Subclinical (>60)	10	6	9	8	9
% Subclincial	20%	11%	17%	15%	17%
p(T1/T4)	0.09	0.9	0.87	0.88	0.89
Mean Change	-1.4	1.27	0.5	-0.17	1.17
Range Change	[-16 12] = 28	[-41 32] = 73	[-17 12] = 29	[-12 15] = 27	[-17 12]=29

Table 1. CBCL Measures for Time 1 (7 years of age) and Time 4 (11 years of age). Higher scores indicate worse problems. A CBCL score of 60-70 (>1SD <2SD) is generally considered to represent a medium level of symptoms “subclinical” or “subthreshold”.

Figures:

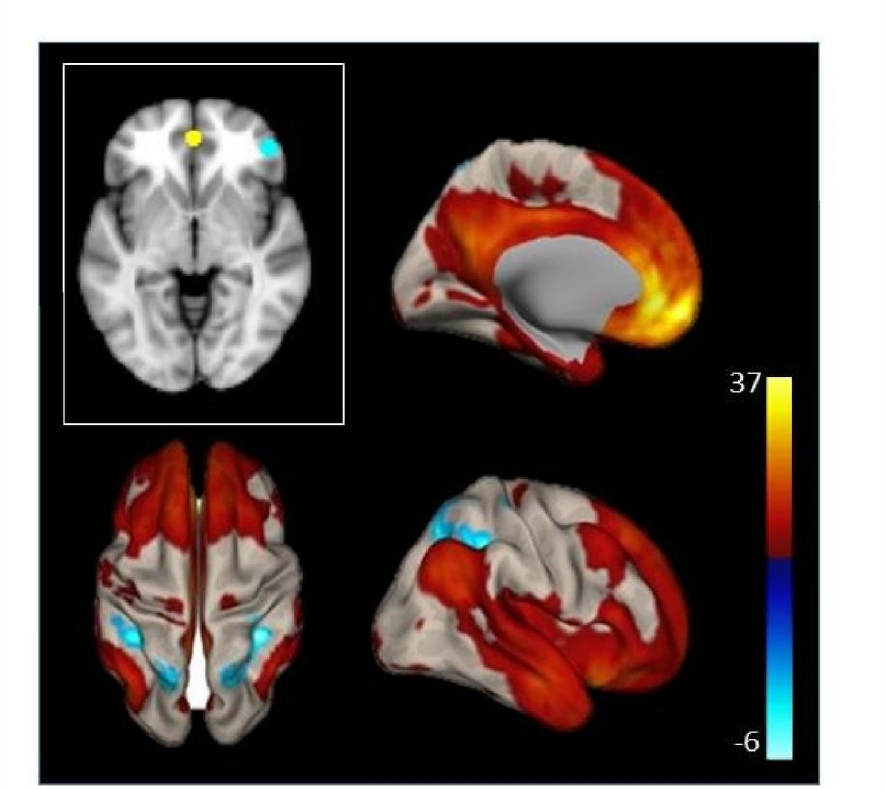

Figure 1. On average, children 7 years of age exhibit positive MPFC-DLPFC resting state connectivity (n=94, age 7): a) MPFC seed (yellow) and DLPFC mask (blue) b) Whole brain MPFC seed driven resting state functional connectivity map.

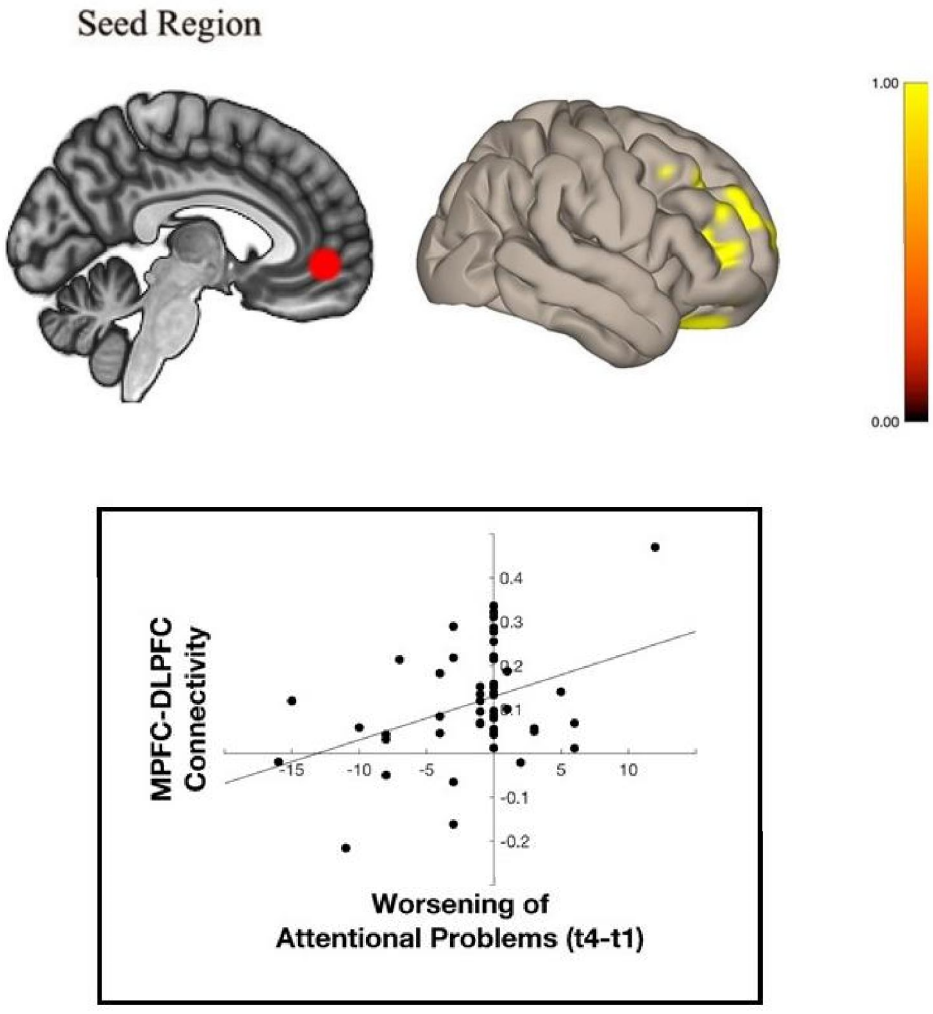

Figure 2. Longitudinal prediction of progression of attentional problems over four years (ages 7-11). Weaker T1 MPFC-DLPFC anticorrelations are associated with worsening of attentional problems 4 years later. Note: negative change scores indicate improvement, and positive change scores indicate decline over four years. The colorbar reflects the posterior probability values of voxels showing association between MPFC connectivity and changes in Attentional Problems with LOOCV.

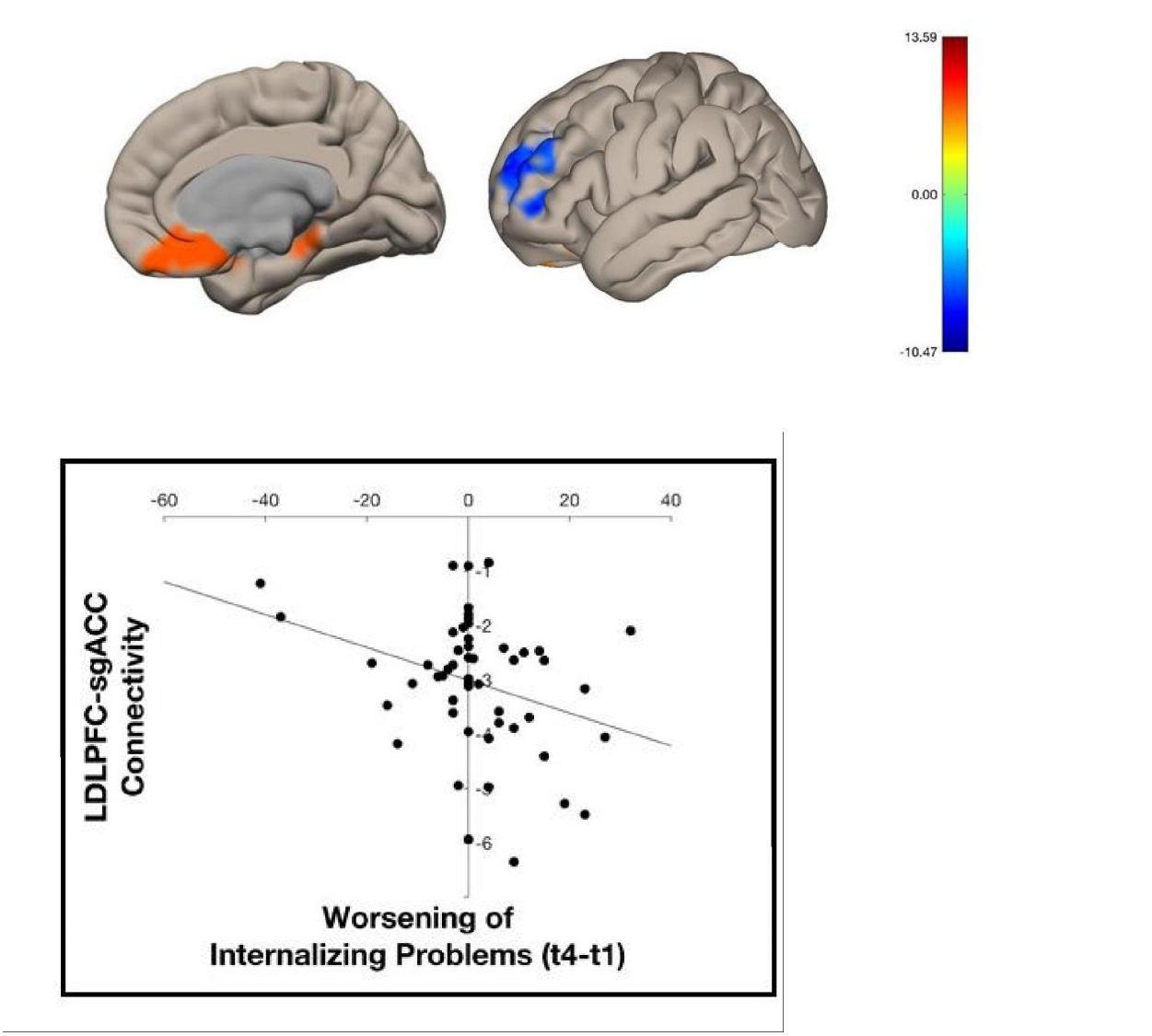

Figure 3. Longitudinal prediction of progression of Internalization problems over four years (ages 7-11). Left DLPFC and sgACC predicted progression of Internalization (and anxiety/depression and withdrawn subscales) such that greater anticorrelation at Time 1 (7 years old) predicted worsening of internalization four years later (11 years old). Note: negative change scores indicate improvement, and positive change scores indicate decline over four years.

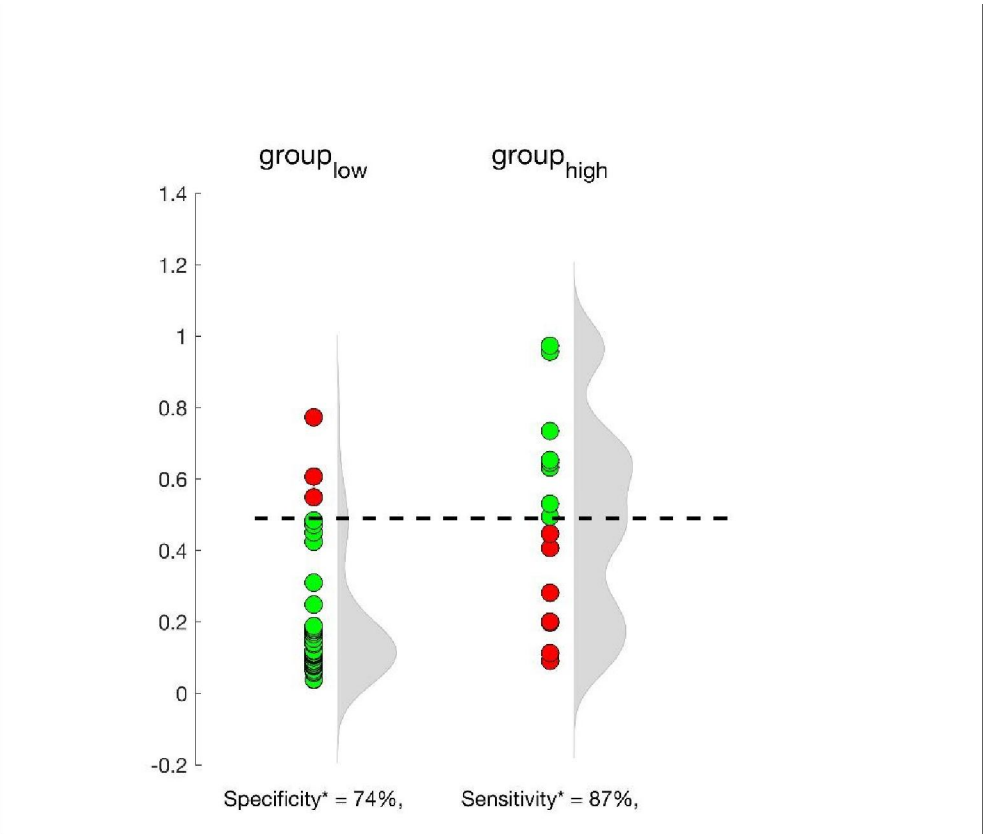

Figure 4: Logistic regression using left DLPFC-sgACC to predict Internalization problems at T4 (>=55), controlling for Internalization scores at T1. Green left: true negatives; Green right: true positives; Red left: false positives; Red right: false negatives. The histograms represent the distribution of the risk of internalization problems at T4 (as predicted by subgenual-DLPFC connectivity at T1) displayed separately for those subjects with low- (left) vs. high- (right) internalization problem scores at T4.

CONCLUSION

Mental disorders are among the most debilitating diseases in industrialized nations today (Kessler et al., 2009). Further, health-care costs as well as the number of individuals diagnosed with psychiatric disorders are projected to disproportionately rise within the next 20 years (Bloom et al., 2011). The future quality of health care in psychiatry will benefit from a timely translation of basic research findings into more effective and efficient patient care. In this thesis, I have discussed ways in which human brain imaging may have translational potential in terms of 1) neuroprediction, aimed at personalized or precision medicine for selection of an optimal treatment, and 2) improved identification of individuals at risk for mental health difficulties, so that preventive treatment can reduce or even avert future difficulties.

In Chapter 1, I provided an overview of the key questions and challenges in the field of predictive analytics in mental health aiming to (1) propose general guidelines for predictive analytics projects in psychiatry, (2) provide a conceptual introduction to core aspects of predictive modeling technology, and (3) foster an informed discussion amongst researchers, clinicians, patients, foundations and policymakers. Importantly, I described ways in which predictive analyses (e.g., prediction of therapeutic response) can support the selection of optimized interventions, thereby improving the trial-and-error based approach common in psychiatry.

Although predictive analytics of response to treatment for mental health disorders could improve the individual efficacy of treatments, treatments to functional disorders are inherently *reactive* to suffering and incapacity. More desirable would be a *proactive* approach in which individuals at high risk for a disorder are identified and treatment is preventive. Brain measures characteristic of risk in children could support such a proactive approach.

In Chapters 2 and 3, I presented findings which provide evidence that resting state fMRI measures of functional connectivity help identify brain differences in children selected to be at heightened familial risk for MDD and in a normative sample of children followed longitudinally who developed symptoms related to MDD or ADHD. For example, children at familial risk for MDD exhibited significantly greater sgACC-DLPFC anticorrelations than children not at familial risk, and in a normative sample not selected to be at risk, greater sgACC-DLPFC anticorrelations predicted a worsening of the CBCL internalization, as well as the anxiety/depression subscale. Thus, variation in the resting-state properties of a single neural network was associated with both heightened familial risk and heightened longitudinal progress towards MDD.

Future progress in this direction can be considered in terms of basic neuroscience (a better neurobiological understanding of these functional connectivities) and clinical neuroscience (application of this knowledge toward treatments).

Future Directions (Neurobiology of Resting State Functional Connectivity)

FMRI measures of BOLD signals are indirect and heterogeneous measures of brain function in general, and the neurophysiological basis of resting state fluctuations are especially unclear. Several of the variations in functional connectivity that were most diagnostic of vulnerability in the present studies occurred in brain regions that are anticorrelated in adults, and that appear to progress

during child development from being correlated to anticorrelated (Chai et al., 2014). Variation of DLPFC anticorrelations are indicative of risk for two of the most common disorders of adolescent mental health (ADHD and MDD). Despite the apparent significance of resting state connectivity, t he neural and molecular mechanisms underlying such correlations and anticorrelations are still no t well understood.

Resting state functional connectivity has been associated with neurotransmitter concentrations (e. g., Fox & Raichle, 2007; Nasrallah et al., 2014), white matter fiber density (e.g., Hu et al., 2016) a nd regional cerebral blood flow (e.g., Liang et al., 2013). For example, one study used fMRI of bl ood-oxygenation-level–dependent and arterial-spin–labeling perfusion contrasts to investigate the relationship between functional connectivity and regional cerebral blood flow (rCBF) during rest. The resting state functional connectivity had a striking spatial correlation with rCBF, and the correlation was stronger in the DMN (including MPFC) and the ECN (including DLPFC) compared with visual and sensorimotor networks (Liang et al., 2013).
In addition, spontaneous BOLD follows a 1/f distribution and this 1/f distribution has also been observed in studies of spontaneous electroencephalography (EEG) (Linkenkaer-Hansen et al., 2001; Stam et al., 2004), magnetoencephalography (MEG) (Linkenkaer-Hansen et al., 2001), local field potential recordings (Leopold et al., 2003), and cerebral blood flow (Lowen et al., 1997). Importantly, one study showed that only frequencies below 0.1 Hz contribute to regionally specific BOLD correlations, while faster frequencies relate to cardiac or respiratory factors (Cordes et al., 2001).

Because rapid excitatory glutamate (Glu) and inhibitory γ-aminobutyric acid (GABA) signals mo dulate local and long-range cortical neural circuits, studies relating Glu and GABA to cortical net work function may be particularly relevant to elucidating the underlying mechanism of anticorrela tions. In humans, this could be examined by combining magnetic resonance spectroscopy (MRS) measures of these neurotransmitters with resting state fMRI measures of salient anticorrelations. F or example, an as yet unpublished study used functional MRI to measure whole-brain BOLD sign al during resting state and task evoked conditions, and MRS to quantify GABA and glutamate con centrations, in nodes within the DMN and CEN (MPFC and DLPFC, respectively) in 19 healthy i ndividuals. GABA concentrations in the MPFC were consistently and significantly associated wit h DMN deactivation during a working memory task and with anticorrelation between DMN and C EN at rest and during task performance (Fei et al., In Prep).

In addition, the electrophysiological correlates of anticorrelations are unknown. Future research could involve collecting simultaneous EEG, with a Direct Current (DC) amplifier, and resting state fMRI with a view to identifying an electrophysiological signature of these anticorrelations in the low frequency range (<.1) that is typically done in rs-fMRI. Most studies combining EEG and fMRI focus on higher EEG frequency bands because low frequencies are typically filtered out of the signal. It may be better to identify electrophysiological correlates in the same ultra-slow frequency bands (e.g., Buzsáki & Draguhn, 2004; Martino et al., 2016) that characterize typical resting state fMRI measures.

Future Directions (Applications)
Promising Interventions and Surrogate Endpoints to Monitor Treatment Efficacy
Because resting state networks are plastic, they can be modulated by behavioral or pharmacological

interventions. One such class of treatments is cognitive behavioral therapy (CBT), which is usually performed as a combined parent-child treatment in preadolescent children. Another intriguing preventive treatment is mindfulness-based intervention in children, particularly in relation to improving cognitive performance and resilience to stress. A review of school-based mindfulness interventions in 1348 students instructed in mindfulness (876 controls) in children ranging from grades 1-12 noted significant improvements for cognitive performance and decreased self-perception of stress (Zenner et al., 2014). An as yet unpublished study found that mindfulness-based intervention may act upon the specific MPFC-DLPFC anticorrelation that predicted the growth of symptoms of inattention in Chapter 3. One hundred sixth-graders (11 years of age) participated in a randomized controlled trial (RCT) at a charter school in Dorchester, MA, USA. The *Intervention Group (Mindfulness Training or MT)* received a mindfulness curriculum (wws.calmerchoice.org) during their last 45 minutes of their school day, 4 times a week for 8 weeks whereas an *Active Control Group (CON)* received SCRATCH computer programming. Forty of the children (20 MT) additionally underwent MRI scans at MIT. From before to after training, the MT group had a selective increase in MPFC-DLPFC anticorrelations (as compared to the CON group), and the increase in MPFC-DLPFC anticorrelations positively correlated with an increase performance on an attention task (Bauer et al., In Prep). In addition, neurotechnological approaches have been shown to alter RSNs, such as real-time fMRI neurofeedback training in controls subjects as well as patients with MDD and schizophrenia (Garrison et al, 2013; Sacchet & Gotlib 2016; Bauer et al., In Prep). Finally, pharmacological interventions have also been shown to normalize or ameliorate pathological RSNs (Whitfield-Gabrieli et al., In Press; Fisher et al., 2014).

Measurements of resting state networks may serve as surrogate endpoints to monitor the efficacy of a treatment. Initial randomized clinical trials (RCTs) of CBT or mindfulness will have to follow children over multiple years to provide evidence that preventive treatment is actually effective because MDD or ADHD could be expressed over multiple years (a true endpoint). After that, however, patients, families, and clinicians will want more rapid evidence (surrogate endpoint) that a treatment is effective for an individual so that an effective treatment is maintained or an ineffective treatment is terminated. Plasticity in predictive networks could provide information about whether a preventive treatment is altering specific functional connectivity in desired directions (increase or decrease).

Clinical Applications and Ethical Considerations of Predictive Brain Vulnerabilities

Currently, mental health disorders are treated on a wait-to-fail basis, with treatment typically offer ed after a person is severely debilitated. By then, a person's life has had an accumulated downwa rd spiral in terms of worsened relations with family and friends, deteriorating school performance for children and adolescents, and lost wages and productivity at work for adults.

Predictive brain measures, in combination with behavioral and perhaps genetic measures, might b e able to identify individuals at risk and justify preventive treatment that is offered before the dow nward spiral of severe dysfunction. Although the present research used MRI, an important directi on for future research is to learn whether recordings from scalp electrodes using electroencephalo graphy (EEG) could serve a similar function. There has been steady technical progress in EEG re cordings, including wireless devices that employ dry electrodes. Such an EEG device could be de ployed widely in physician offices and hospitals. If this were to be achieved, widescale predictive brain screening could occur.

If the sensitivity and specificity of neuroimaging screening were to meet useful criteria, a number of important ethical and policy questions would arise. A risk would be that such screening would be used to select people for jobs and school admissions rather than providing at-risk individuals with early treatment. Further, one would have to consider how to communicate such risk to an adult or child so that knowledge of the risk is helpful rather than discouraging or destructive. Most importantly, it would be essential that helpful treatments be coupled to the risk assessments so that knowledge of the risk can be a beneficial trigger for benign intervention.

Preventive treatment is paradoxical in that a treatment would be initiated for a mental health *risk* rather than a mental health *problem*. For this reason, benign behavioral treatments with few or no side effects would be preferred over pharmaceutical treatments that often have associated side effects.

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