Will neuroimaging produce a clinical tool for psychiatry?

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Abstract

The increasing incidence, awareness, and social and economic impact of mental health disorders, the current *status quo* of treatment options and their limited success, and the extensive investment into brain imaging research raises an important question for the future behavioral medicine: will neuroimaging produce a clinical tool for psychiatry? Significant advances in neuroimaging over the past two decades allow psychiatric clinicians to peer into the living, functioning brain. Neuroimaging has been used to diagnose mental illnesses, to predict treatment outcomes, to find new stratifications of psychiatric disorders, and to provide therapy. The development of computational techniques, alongside several population neuroimaging efforts worldwide, increase the prospect for a first neuroimaging-based clinical tool. In this article, we describe the formidable challenges to creating such a tool and forecast how current institutions can solve them through social, technical, educational, and policy changes, improving data sharing practices, advances in technology, and integration between neuroimaging and other emerging information streams.

Introduction

The explosion of brain imaging studies over the last two decades has raised the prospect that the next stage of psychiatric practice should, or will, include biologically-informed approaches to disease prognosis and diagnosis. Indeed, the ability to measure mental state from the body rather than infer through signs and symptoms, would likely transform the practice to align it with known, underlying biology¹. The public availability of data and the growth of machine learning tools and computational infrastructures have also opened many avenues for humanitarian uses of neuroimaging². This unprecedented focus on using neuroimaging to understand human cognition in health and in disease has led naturally to the question of whether imaging will produce a tool for clinical use to diagnose or treat psychiatric conditions.

Brain imaging in psychiatry

It is no longer controversial to assert that psychiatric illnesses are manifestations of brain dysfunction. As neuroimaging technologies that can measure brain structure and function have matured, a significant focus has been on uncovering biomarkers of psychiatric illnesses towards guiding treatment selection and predicting treatment outcome. After all, such tools, if they are accurate and based on sound clinical-neuropathological associations, would help clinicians resolve substantial uncertainty with regard to heterogeneity in psychiatric symptomatology and help further define the exact nature of illness etiology and optimal choice of therapies.

Tools that capture the brain's structure or function non-invasively broadly include a wide range of technologies such as Electroencephalography (EEG), Magnetoencephalography (MEG), Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), functional Near Infrared Spectroscopy (fNIRS), and others. In general these technologies allow many different facets of exploration, with different technologies measuring different aspects of cognition at different spatial and temporal resolutions, as well as with different proxies for neural function. EEG and MEG measure currents and magnetic fields generated by neural circuits in the brain, PET measures cerebral

blood flow, or responses to binding sites of specific radioactive markers, and MRI can measure blood oxygenation levels, blood flow, proton density, water diffusion, and chemical spectral signatures amongst others. In many ways, these measurements are proxies for neural function and dynamics. Yet, these measurements have proven helpful in unravelling many aspects of cognition and many aspects of neurological and psychiatric disorders. The next two sections focus on a subset of neuroimaging discoveries related to magnetic resonance imaging and targeting diagnoses, prognoses, and biotyping (see Box 1), as well as the advent of neuroimaging-based therapeutics that have shown promise in the treatment of psychiatric disorders.

Box 1. Terminology

Machine/Statistical learning: A field of study that focuses on development of statistical models to uncover and learn patterns in data. In general models are learned on one dataset and tested or validated on a different dataset. This allows such models to predict or associate information in a more generalizable manner. Practically speaking, applying machine learning to a particular problem may require new algorithms to extract novel features from data, in addition to selecting features and models in an unbiased manner, training these models on datasets capable of representing as much of the diversity of clinical population(s) under study, and then validating these models using previously unseen data.

Diagnosis: The identification of a psychiatric illness with the intent to determine if any, and what type of, intervention is needed to reduce, and more preferably, eliminate the illness. In current psychiatric practice, the diagnosis is carried out via an evaluation of symptoms alongside patient history and familial context. The intent of this article is to introduce the possibility of using neuroimaging as an alternative or an adjunct to the current approaches, to improve treatment of such illnesses.

Prognosis: The ability to determine the likely course of a psychiatric illness, including, but not limited to, duration, effect on daily life, and response to or remission from treatment.

Biotyping: The ability to use genomic, endophenotypic, and other clinical measurements (e.g., neuroimaging, wearables, voice and language, neuropsychological, cognitive tests, blood-based) as a means to better relate individuals to each other, in order to create groups that will respond favorably to treatments or interventions tailored for that group. The extension of this idea is precision psychiatry, where every individual can be treated optimally based on their own genotype and phenotype, potentially taking into account relatedness to other individuals.

Diagnosis, prognosis, and biotyping using neuroimaging

The majority of neuroimaging studies in psychiatry have focused on distinguishing brain measurements between groups, where one group has a psychiatric illness, and the other does not. Greater accessibility to mental health datasets, the pooling across studies, and the increase in study sizes have contributed to more studies incorporating machine learning into such analyses. The use of machine learning to create predictive models for diagnoses, treatment outcome, or biotyping has increased stemming from the cross-disciplinary engagement of researchers across machine learning, brain imaging, and psychiatry, coupled with the availability of open resources, both data

and computational platforms.

Diagnoses. Neuroimaging studies have uncovered many relations between measures of brain structure (e.g., regional volume, thickness, diffusion-based measures) and brain function (e.g., task responses and resting state measures) and related psychiatric diagnoses. Using machine learning on brain imaging data, several studies have developed mathematical algorithms that can discriminate healthy individuals from individuals with mental illnesses. Such methods have been applied to major depression³, schizophrenia⁴, autism and attention-deficit hyperactivity disorder (ADHD)⁵, bipolar disorder⁶, amongst others. Such methods have also been applied across disorders to diagnose chronic psychiatric illnesses⁷.

Prognoses. Neuroimaging based diagnosis alone, especially at a potentially higher cost relative to a clinical visit can only be justified if such diagnosis is more consistent, or can lead to better prognosis, for instance by guiding treatment selection for optimal clinical outcome. A review by Janssen et al.⁸ noted a few efforts across different psychiatric disorders, such as major depressive disorder⁹, social anxiety disorder¹⁰, amongst others.

Biotyping. Some studies have used neuroimaging to define new phenotypic profiles or biotypes that may be more aligned with treatment, but may also provide a different perspective on how psychiatric illnesses are characterized. Some examples include work on schizophrenia¹¹ and depression⁹, with this latter work also demonstrating that these biotypes of depression also respond differentially to treatment.

Translational Challenges of Psychiatric Neuroimaging

The promise of these technologies has been evident from the earliest days, and yet the realization of this promise – i.e., translation to clinical practice – has lagged behind, met with a host of valid concerns still being addressed: (1) What is the specificity and sensitivity of any brain-based measure of a psychiatric state or trait feature? (2) What are the relative costs of employing neuroimaging to inform diagnostic or prognostic evaluation, and what is the evidence for a favorable cost-benefit ratio, relative to treatment as usual? and (3) How well does a brain-based measure generalize across disease diagnoses?

Most studies have focused on a particular disorder rather than choosing amongst many for diagnosis, or choosing amongst many treatment options for prognosis, or considering shared biotypes relative to classic categories of mental illnesses. These studies have largely been unimodal, focusing on a specific imaging modality rather than trying to combine information from different types of imaging, although multi-modal approaches are emerging¹². Even promising biotype reports, such as one which recently reported subtypes of major depression based on neuroimaging findings,⁹ have had difficulties with replication¹³. In many cases, the focus has been on just imaging rather than a complementary scheme that combines imaging with other sources of information, such as genetics, medical information, family history, or more objective ways of quantifying behavior. The number of individuals used in these studies has also been limited relative to the variation of symptomatology present in many of these disorders.

Advances in quantitative imaging have not yet been applied systematically to the study of mental illnesses. The spotlight has been on the clinical diagnosis or prognosis, and not on potentially confounding factors, such as the diversity of software and hardware options that impact processing of brain imaging data across scanners and sequences, participants at different age, and clinical variations in assigning diagnosis labels or severity levels to conditions. These issues are addressable, and given the stakes remain high to push the technology to its limits, the field will likely address many of them. How quickly it happens will depend on the level of attention paid to relevant clinical, technical, and operational details.

Neuroimaging therapeutics

Neuroimaging in psychiatry is not just about diagnosis and prognosis. Another avenue is the ability to use neuroimaging based biofeedback¹⁴ – i.e., real-time functional MRI (RT-fMRI) where signals from an individual's brain can be processed on the fly and delivered back to them – as a way of actually *treating* individuals with a mental illness. In general, this method of so-called “neuro-feedback” therapy involves training an individual to learn to regulate brain activity, typically in a brain region or a network of regions, based on visual or auditory feedback of the current brain state of the individual. Alongside a clinician or researcher coaching the individual to adopt certain mental strategies (e.g., theory of mind, mental imagery, meditation), clinical trials are using neurofeedback to address aggression, auditory hallucination in psychosis, Tourette syndrome, anxiety, addiction, stress, and several on major depressive disorder. In a completed trial, feedback from the amygdala has been used successfully to reduce a quantitative measure of depression severity¹⁵. The response from early trials is encouraging, but significant effort is needed to understand interactions in the complex parameter space involving MRI sequence options, brain targets, the various analytical methods used to compute the feedback signal, and the diversity of psychiatric disorders. Combining therapy with biotype detection may provide a way to optimize these parameters systematically.

Validating machine learning approaches in psychiatry

Many publications apply machine learning to brain imaging data in psychiatry. However, in the absence of published models and validation of these models on new data, evaluating their generalization potential in new practical situations (e.g., different scanner, different pulse sequence, different participant pools) is difficult, if not impossible. Open machine learning challenges, such as the Netflix prize for content recommendation and the software competitions hosted at Kaggle.com, alter this landscape, allowing consolidation of both models and rigorous validation in a controlled setting. These competitions have enabled a new scalable and collaborative approach to solving practical problems using machine learning and generated new algorithms and software. In brain imaging and psychiatry, there are only a handful examples of software competitions focused on a few isolated disorders: ADHD¹⁶, schizophrenia¹⁷, autism¹⁸, and major depression¹⁹. These competitions help reduce overfitting – i.e. the tendency of any one model or algorithm to perform well initially but then fail to generalize, a common occurrence in machine-learning publications – by holding out test data to validate the models.

Aggregating data to enhance clinical use and develop new technologies

To understand human variation across psychiatric disorders and treatment response and to apply machine learning to psychiatry, there needs to be a continuous supply of cross-sectional and longitudinal data. There have been significant efforts in pooling data, both open-access and restricted-access, in Autism²⁰ and ADHD¹⁶, and the upcoming releases of Connectomes for Disease²¹. Efforts such as ENIGMA²² and GENUS²³ have focused on academic collaborations to scale sample sizes, but such consortia are still generally focused on specific mental illnesses and are not generally accessible for crowdsourcing exploration. Even with these efforts and the number of individuals being imaged across the planet in various research and clinical studies, there are no large-scale databases of neuroimaging data across psychiatric disorders that match their prevalence, and open sources of longitudinal data are rarer still. This limits the possibilities enabled by a plethora of modern machine learning tools, and more importantly limits reproducibility and validation of current models. But sharing data is but a starting point to engage communities to work together to build better clinical tools that leverage current advances in statistical learning and new methods that will need to be created to address the many challenges with these data. These data will come from different scanners and sequences, with each scanning site contributing some combination of neuroimaging, cognitive and neuropsychological assays, and genetic information. As such, there may not be consistency across all

samples, but integrating information across sparse data is a current data science challenge. Given current directions in data protection, there need to be mechanisms and policies in place that ensure that such data can be used, while respecting individual privacy. Simply building walls around data are an insufficient approach to solving a pressing health problem.

The need for computational models when imaging complex systems

Combining multiple imaging modalities and analytical pipelines, the field is now able to generate hundreds of thousands of features, far exceeding the number of samples in some of the largest datasets in existence. This requires development of computational models²⁴ that can help guide the selection of features, predict observations in neuroimaging studies, and create a computational basis for symptoms associated with psychiatric disorders. Our ability to synthesize information from these neuroimaging studies into computational models of psychiatric disorders has lagged the more general growth in brain imaging studies. Such models will serve as essential links between psychiatric disorders and recently identified interacting physiological processes such as inflammation, the microbiome, and others²⁵. Computational models, just like statistical learning models, require data to validate. Thus, even these models will improve with greater sharing of data.

Integrating neuroimaging with other phenotyping approaches and genomics at scale

Mental illnesses are complex. No single modality, whether genomics, neuroimaging, neuropsychological assessments, or other forms of phenotyping (e.g., wearables, voice, and language), is likely to provide robust markers of disease or pathways to treatment. Except in a few disorders, most studies have focused on one of these modalities. For example, voice analysis has been linked to suicide²⁶ and depression²⁷ and gait abnormalities have been noted in depression²⁸ and autism²⁹. Very few efforts have tried to combine information across assays and disorders. Efforts such as ABCD³⁰ to collect longitudinal imaging, behavioral, and clinical data at scale have only just started, but is focused primarily substance abuse.

There is a need to integrate genomics, brain imaging, and other digital phenotyping to create as complete a picture as possible. This integration will require new technologies and models to be developed and validated, with cooperation at a global scale. Mental illness as a human problem needs to be studied across languages and cultures. If certain groups of individuals show lower incidence rates given a consistent diagnostic criterion, it would be very useful to understand why there are differences in incidence rates, whether our symptomatic understanding needs modification, or whether there are genetic and/or cultural traits that make individuals in such groups more or less susceptible to mental illnesses.

Summary

Neuroimaging provides visibility to and quantification of mental illnesses that go beyond symptomatic understanding. However, such measures are in their infancy and still have limited clinical utility. The emergence of machine learning methods alongside the growth of neuroimaging datasets offers an unprecedented opportunity to move beyond classical diagnoses and improve prognosis. Neuroimaging can help create a set of biologically derived subtypes that respond better to specific treatment options and can itself serve a novel therapeutic role via neurofeedback. Using neuroimaging, alongside clinical practice, and coupling with other emerging areas such as digital phenotyping and genotyping may provide the contextual integration necessary to create tools for clinical use. As the future of psychiatry continues to evolve toward the ideals of precision medicine over the next decade, we expect neuroimaging to emerge as an integral component of that future.

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