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Imaging-Based Subtyping for Psychiatric Syndromes

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INTRODUCTION

In contrast to other areas of medicine, considerable gaps exist between neuroimaging research and clinical practice in psychiatry. Extensive research demonstrates significant alterations captured with multimodal brain imaging in various psychiatric conditions. Along with cognitive and electrophysiological approaches, neuroimaging methods have been central to the neurobiological conceptualization of psychiatric disorders. In fact, imaging research was central to shifts from psychological to biological models in the 1970's and 1980's (Cunningham Owens, Johnstone et al. 1980). Imaging tools provide advantages over other methods in light of their wide availability and ability to provide non-invasive quantitative data on structural, functional and chemical alterations in the brain. Moreover, imaging approaches have demonstrated considerable potential for capturing biologically homogeneous subgroups of patients with complex brain disorders, offering pathways for novel translational and clinical applications (Sun, Lui et al. 2015, Lui, Zhou et al. 2016, Zhang, Xiao et al. 2018).

Nevertheless, despite considerable advances in neuroimaging research, brain imaging is still not a widely used tool in diagnostic algorithms for psychiatric disorders. Multiple hindrances contribute to this persisting research-clinical practice gap, including but not limited to the innate complexity of psychiatric disorders, overwhelming clinical and biological heterogeneity of the current diagnostic constructs, poor diagnostic specificity and lack of established reliability of imaging findings from large scale validation studies, as well as considerable practical demands related to implementation of quantitative neuroimaging

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tools in clinical practice. The developing field of psychoradiology, pioneered by Gong et al (<https://radiopaedia.org/articles/psychoradiology>) (Gong 2016, Lui, Zhou et al. 2016, Huang, Gong et al. 2019), undertakes the challenging task of incorporating radiological approaches into the daily workflow of psychiatry.

With enhanced knowledge of molecular and structural determinants of medical conditions, diagnostic classifications in most fields of medicine have been largely transformed from nosology/symptom-based to biologically-based taxonomies. Yet, diagnostic formulations in psychiatry remain at a far less advanced level. Instead of grouping patients by combined laboratory and clinical evidence into well-validated disease entities that warrant specific treatments, psychiatric diagnoses broadly characterize patients into clinically overlapping and biologically heterogeneous conditions (Cuthbert and Insel 2013). The marked heterogeneity within and across psychiatric syndromes also manifests as discordance between emerging biomarker-informed disease constructs and conventional symptom-based diagnoses (Clementz, Sweeney et al. 2016, Price, Lane et al. 2017, Xia, Ma et al. 2018). This limitation hinders progress in elucidating disease mechanisms, developing biologically-informed methods to predict outcomes, and exploiting novel approaches to advance precision medicine. Most importantly, the lack of biologically-informed disease definitions has been a bottleneck in the development of mechanistic therapeutic targets (Linden 2013, Keshavan, Lawler et al. 2017).

Because biological heterogeneity within psychiatric syndromes is large, brain alterations are similar across diagnoses, and biological mechanisms of illness so poorly understood, the role for diagnostic radiology in relation to psychiatry is complex in relatively novel ways. First, there are no obvious imaging targets suitable for direct clinical translation. While neuroimaging research has identified a wide range of abnormalities in different psychiatric disorders, they often involve relatively modest and widely distributed alterations across the brain that have poor diagnostic specificity. Second, alterations associated with psychiatric disorders are rarely seen on visual inspection, and require fairly complex quantitative analysis of parameters like regional volume, cortical thickness, etc. – none of which are immediately available in clinical practice. Third, syndromal diagnoses need to be parsed into biologically discrete entities as in other fields of medicine. This latter point implies that radiological approaches need to be applied collaboratively with psychiatric researchers in a research context to define biologically homogeneous subgroups of patients within syndromes and to evaluate the utility of imaging data for predicting prognosis and differential treatment response (Insel and Cuthbert 2015, Keshavan, Lawler et al. 2017). However, this is possible based on the psychoradiological hypothesis by Gong et al, in which brain structural alteration leads to clinical syndromes, due to the conjunction impact of the impaired functional connectivity (Lui, Deng et al. 2009, Tregellas 2009, Gong, Lui et al. 2016, Lui, Zhou et al. 2016).

Efforts to develop imaging markers for complex psychiatric syndromes—such as schizophrenia, bipolar disorder and ADHD—have generally failed, largely because of substantial biological heterogeneity of these syndromes (Clementz, Sweeney et al. 2016, Sun, Chen et al. 2018). Success of psychoradiology is more likely to be achieved by demonstrating a unique ability to capture biologically homogenous and specific ‘disease

units' (and corresponding subgroups of patients) based on brain alterations detectable with imaging, despite phenomenological similarities across the subgroups, similar to other medical conditions, e.g., diabetes type I vs. II. Making progress in these directions requires a multidisciplinary effort and a considerable shift in conceptual framework in both psychiatric and radiology research and clinical practice.

In this chapter, we will discuss imaging approaches designed to capture neurobiologically-distinct disease constructs across major psychiatric syndromes. We will present a conceptual review of the most robust and important findings from studies that use imaging methods as subtyping measures for defining distinct disease subtypes, as well as external validators of subtypes derived from other neurobiological measures. We will specifically focus on approaches that have a high relevance to psychiatric disease manifestations, functional outcomes and treatment planning. We will emphasize cross-diagnostic and dimensional approaches. Furthermore, we will discuss current challenges in translating psychiatric imaging into clinical practice and strategies to move forward in the evolution of psychoradiology that will benefit from combined efforts of psychiatry and radiology investigators and clinicians.

SUBTYPING OF PSYCHIATRIC SYNDROMES BASED ON BRAIN IMAGING BIOMARKERS

Various imaging approaches, including structural MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), and MR spectroscopy (MRS), have been utilized to study psychiatric patients. An extensive neuroimaging literature demonstrates considerable heterogeneity of imaging findings *within*, and overlaps *between*, psychiatric syndromes (e.g., McTeague et al., 2017 (McTeague, Huemer et al. 2017)). Therefore, transdiagnostic studies are of great importance as they provide strategies to capture more biologically-homogenous disease units irrespective of or 'masked' by current clinical diagnoses (Clementz, Sweeney et al. 2016, Tamminga, Pearlson et al. 2017).

One neuroimaging approach is to parse biological heterogeneity based on imaging features (e.g. functional connectivity, fractional anisotropy), and then characterize emerging subgroups with respect to relevant symptoms and clinical outcomes (Zhang, Xiao et al. 2018). Hermens et al. (2019) used DTI-based fractional anisotropy (FA) to derive imaging-based subgroups across a broad range of psychiatric diagnoses, including psychotic, affective (depressive, bipolar) and anxiety disorders. They demonstrated three clusters characterized by specific alterations in FA values (Hermens, Hatton et al. 2019). Notably, these clusters did not correspond to clinical diagnoses, and showed similar cognitive and behavioural/symptom abnormalities.

A more sophisticated approach, capturing both biological and behavioural manifestations of psychopathology, is to link specific brain alterations to phenomenological manifestations across multiple diagnostic categories, in order to identify patient groups with distinct 'bio-behavioral' profiles. Stefanik et al. (2018) derived such 'bio-behavioral' constructs integrating cortical thickness, subcortical volume and DTI-based tractography data with cognitive and clinical characteristics across individuals with schizophrenia spectrum

disorders, autism spectrum disorders, bipolar disorder and healthy individuals (Stefanik, Erdman et al. 2018). They identified four novel groups with distinct ‘neural circuit-cognitive’ profiles, and validated these constructs using independent imaging and functional measures. The ‘circuit-cognitive’ constructs demonstrated greater differentiation on structural circuit nodes and social functioning than traditional diagnostic classes. Goodkind et al. (2015) identified a shared pattern of gray matter loss in the anterior insula and dorsal anterior cingulate across six diverse diagnostic groups including schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety (Goodkind, Eickhoff et al. 2015). Furthermore, they demonstrated that the regions involved in this ‘transdiagnostic structural abnormality pattern’ formed an interconnected network during task-based and resting state fMRI, and showed associations with poor cognitive functioning (Goodkind, Eickhoff et al. 2015).

Ivleva et al. (2013) identified broad and overlapping patterns of gray matter volume reductions across the ‘psychosis dimension’ in probands with schizophrenia, schizoaffective and psychotic bipolar disorder (Ivleva, Bidesi et al. 2013). Similar gray matter changes were found in biological relatives of patient probands with mild psychosis manifestations. Lifetime duration of psychosis and psychotic symptom severity inversely correlated with gray matter volumes in several neocortical (e.g., frontal, temporal, insular) and subcortical (thalamus, basal ganglia) regions (Ivleva, Bidesi et al. 2013), suggesting a potential value of MR data for estimating clinical prognosis. Targeting functional brain networks, Xia et al. (2018) identified correlated patterns of functional connectivity and symptom dimensions in a large sample of youth. Using sparse canonical correlation analysis, they revealed four dimensions—‘mood’, ‘psychosis’, ‘fear’, and ‘externalizing behaviour’—which were associated with distinct patterns of functional connectivity (Xia, Ma et al. 2018).

A recent meta-analysis of task-based fMRI studies tracking brain activity during a broad array of sensory, motor and cognitive tasks applied in patients with diverse diagnoses revealed a shared transdiagnostic pattern of regional activation abnormalities localized to prefrontal cortex, anterior insula, intraparietal sulcus and midcingulate/presupplementary motor area (McTeague, Huemer et al. 2017). These regions correspond to the ‘multiple-demand network’ that is critically important for adaptive, flexible cognition.

Dimensionally-focused imaging studies have demonstrated broader overlap spanning not only various disease cohorts but also healthy populations (Gates, Molenaar et al. 2014, Costa Dias, Iyer et al. 2015, Price, Lane et al. 2017). Price et al. (2017) used a fMRI-based connectivity approach to parse functional connectivity profiles across depressed and healthy adults during ‘positive mood induction’ (i.e., exposure to emotionally-positive stimuli). They identified two functional connectivity-based groups-exhibiting hypo- or hyperconnectivity-which spanned the ‘depression-healthy’ dimension (Price, Lane et al. 2017). The subgroup characterized by hyperconnectivity demonstrated higher self-reported depressive symptoms and lower sustained positive mood during the induction. Dias et al. (2015) demonstrated distinct subgroups among typically developed children and children with ADHD based on functional connectivity characteristics within the reward network (Costa Dias, Iyer et al. 2015). Gates et al. (2014) identified five subgroups based on functional connectivity networks in a dimensionally organized sample of ADHD and typically developing children

(Gates, Molenaar et al. 2014). Two of these subgroups were comprised of mainly ADHD cases; however, about a third of ADHD children were spread across three other subgroups, which predominantly contained typically developing children.

Transdiagnostic and dimensional studies are few; nevertheless, neurobiologically-informed disease constructs that have been generated by these studies share critically-important characteristics and teach useful lessons. First, the findings consistently demonstrate that the imaging-based subgroups do not map well onto traditional symptom-based diagnoses. This has important implications for the unlikely success of simple “MR profiles for existing disorders” approaches, which represents the majority of the relevant literature. Second, some imaging-based constructs appear to capture groups of cases with extremes of neural features (Gates, Molenaar et al. 2014, Price, Lane et al. 2017). These subgroups may represent “tipping points” that mark a transition to either a more severe or qualitatively different pathology (Cuthbert and Insel 2013). Identification of such points and examining their relationship with risk and resilience factors are of potential clinical importance (Cuthbert and Insel 2013). Third, dimensional approaches have demonstrated neurobiological overlaps beyond the disease realm, extending to healthy populations. Identifying mechanisms that allow ‘healthy’ individuals to compensate for a biological feature indicative of disease risk may inform paths to individualized treatments and disease prevention.

IMAGING APPROACHES AS INDEPENDENT VALIDATORS OF DISEASE SUBTYPES DERIVED FROM OTHER NEUROBIOLOGICAL MEASURES

Technological advances in clinical neuroscience provide powerful methods (e.g., electrophysiological, neuroimaging) to characterize the neurobiological diversity of psychiatric disorders. However, development of optimal strategies for combining largely variable findings from methodologically diverse studies to inform clinically-translatable knowledge has been challenging. Using these methods for disease subtyping and subsequently validating and extending subtype constructs with neuroimaging methods offers advantages for clinical translation purposes. In this section, we will review studies that use *neuroimaging techniques as independent validators* to capture the biological distinctiveness of experimental disease constructs derived from biomarker-based tools.

To our knowledge, Sun et al. were the first to make effort to subtype psychiatric disorders based on imaging features in conjunction with the unsupervised machine learning technique/algorithm, and they have been able to identify two distinct subtypes of Schizophrenia using diffusion tensor imaging (Sun et al. 2015). This is a milestone from the perspective of imaging-based subtyping as they are the first to make effort to parse the psychiatric disorder subtypes based on neuroimaging and machine learning approaches. Subsequently Drysdale et al. stated to make the first effort for the purpose of defining depression subtypes in individual patients via similar approach (Drysdale et al. 2017).

As a matter of fact, another leading effort which incorporated this strategy—along with broader psychosis biomarker-focused goals—is the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium (Tamminga, Ivleva et al. 2013). The B-SNIP has undertaken a novel strategy of applying a dense biomarker battery to a large,

dimensionally-acquired psychosis sample in order to (i) reduce biological heterogeneity underlying psychotic syndromes, and (ii) identify subgroups of psychosis cases based on their distinctive neurobiological profiles irrespective of clinical diagnosis. In a sample of psychosis probands (including schizophrenia, schizoaffective and psychotic bipolar I disorders, $n=711$), their first-degree relatives ($n=883$), and healthy subjects ($n=278$), Clementz et al. (2016) performed a series of multivariate taxometric analyses to a broad battery of cognitive, eye movement and EEG-based biomarkers, and identified 3 neurobiologically-distinct groups, the “B-SNIP Biotypes” (for details on Biotype development see Clementz et al (Clementz, Sweeney et al. 2016)). Biotype1 cases were characterized by significantly impaired cognitive function and sensorimotor reactivity; Biotype2 cases had reduced cognitive function but exaggerated sensorimotor reactivity, primarily driven by increased intrinsic EEG activity; and Biotype3 cases showed normal cognitive function and only modestly diminished sensorimotor reactivity, compared to healthy controls. Similar, albeit attenuated, neurobiological profiles were observed in relatives consistent with patient biotype classification; this suggests familial and/or heritable characteristics of the Biotypes. Furthermore, conventional diagnoses did not correspond to the Biotypes: all three targeted diagnoses were represented in all Biotype groups, only with a slight predominance of schizophrenia cases in Biotype1 and bipolar cases in Biotype3 (Clementz, Sweeney et al. 2016).

Using a whole brain voxel-wise gray matter density approach, Ivleva et al. (2017) demonstrated extensive and diffuse gray matter reductions (predominant in frontal, temporal and cingulate cortex) in Biotype1. Biotype2 showed intermediate and more localized reductions, with the largest effects in insula and fronto-temporal regions, while Biotype3 showed small, highly localized reductions, mainly in anterior limbic regions (Ivleva, Clementz et al. 2017). Biological relatives grouped by their respective probands’ Biotype demonstrated distinctive regional effects: broadly distributed gray matter reductions in relatives of Biotype1, with the strongest effects in anterior (fronto-temporal, cingulate) regions; predominantly posterior (visual and auditory sensory cortices, cerebellum) reductions in Biotype2 relatives; and normal gray matter structure in Biotype3 relatives. Biotypes showed stronger group separation based on gray matter density characteristics, and were a stronger predictor of gray matter density change, compared to conventional diagnoses (Ivleva, Clementz et al. 2017).

Meda et al. (2016) used resting state fMRI to identify impaired functional connectivity in the Biotypes in 9 functional networks linked to diverse cognitive functions, e.g., cognitive control, working memory, attention, and introspective thought maintenance (Meda, Clementz et al. 2016). All Biotype groups showed reduced connectivity across the networks, except for one: the cuneus-occipital network showed reductions in connectivity in Biotypes1 and 2, but not Biotype3. In addition, Biotype1 and Biotype2 relatives showed reduced connectivity in the fronto-parietal network, compared to controls. Biotypes performed marginally better in discriminating psychosis subgroups compared to conventional diagnoses, based on resting state functional connectivity deficits (Meda, Clementz et al. 2016).

Mothi et al. (2018) investigated the utility of machine learning approaches for delineating psychosis subgroups in the B-SNIP sample (Mothi, Sudarshan et al. 2018). Integrating both

clinical and biomarker-based data (EEG, cognition), they used an unsupervised learning algorithm and identified three distinct clusters. They used brain structure, eye movement and social functioning data as independent validators for the observed subgroups. The greatest cortical thinning was depicted in Group1; Group2 showed milder impairments; while little to no significant differences were observed for Group3, compared to controls. The 3 conventional psychosis syndrome diagnoses were represented in all novel subgroups, again highlighting the non-specificity of imaging findings across conventional diagnoses (Mothi, Sudarshan et al. 2018).

A complimentary approach is to initially parse disease heterogeneity based on clinical features alone (e.g., symptom clusters, lifetime history, disease course), and investigate their biological correlates using neuroimaging approaches. Maglanoc et al. (2018) studied a large sample of individuals with and without lifetime history of depression, and identified five subgroups with distinct depression and anxiety symptom profiles, which cut across diagnostic boundaries (Maglanoc, Landro et al. 2019). Similar to the B-SNIP psychosis Biotype constructs, participants with or without history of depression were represented in all novel subgroups. Furthermore, these subgroups demonstrated distinct resting state functional connectivity patterns, specifically in the fronto-temporal network. These findings demonstrate that data-driven clustering methods, even based on dimensionally-organized symptom data alone, may capture more biologically-relevant disease constructs than conventional diagnoses (Maglanoc, Landro et al. 2019).

Dimensional approaches offer unique advantages in capturing the profound clinical and biological heterogeneity evident not only in disease populations but also in healthy individuals (Van Dam, O'Connor et al. 2017). Van Dam et al. (2017) identified data-driven phenotypes based on behavioural features that represent different functional domains—personality/temperament, symptom features, interpersonal functioning, and behavioural tendencies—in a community-ascertained sample (Van Dam, O'Connor et al. 2017). Using a hybrid hierarchical clustering method, they identified a nested hierarchy of homogenous participant groups. The algorithm identified two groups based on functional adaptiveness: adaptive vs. maladaptive. Moreover, the two groups demonstrated differences in functional connectivity in several networks, including limbic, thalamic, basal ganglia and somatomotor regions (Van Dam, O'Connor et al. 2017).

Taken together, growing evidence indicates the substantial biological heterogeneity associated with current diagnostic formulations of psychiatric syndromes, and that advanced biomarker and computational tools. These strategies may help link different levels of system pathology and elucidate within- and between-level relationships across clinical manifestations, biomarkers and molecular disease markers. Neuroimaging tools, which provide rich structural and functional information through non-invasive approaches, are essential to these efforts, both as a means of disease subtyping and external validators to develop novel, biologically-informed disease formulations.

IMAGING-BASED SUBTYPING RELEVANT TO PROGNOSIS AND TREATMENT OUTCOMES

The majority of available treatments in psychiatry were discovered coincidentally and are not targeting identified disease mechanisms. Treatment approaches informed by objective, measurable brain-based biomarkers are currently lacking.

“Precision medicine” is an emerging concept that aims to incorporate an individual patient’s symptom, biological and environmental factors into clinical decision-making (National Research Council 2011, Fernandes, Williams et al. 2017). While precision medicine approaches have become routine in other fields (e.g., infectious and cardiovascular diseases), they remain at an early stage of development in psychiatry. The ultimate goal of “precision psychiatry” is to identify neural signatures that can inform clinical prognosis and treatment response to particular interventions *a priori*, with a high level of exactness (Insel and Cuthbert 2015, Fernandes, Williams et al. 2017). Implementation of the approach will depend on a challenging task of elucidating mechanisms of psychiatric disorders, or in the absence of full disease mechanisms, identification of outcome predictors or modifiable treatment targets. Similar to other complex disorders with largely unknown mechanisms (e.g., cancer), substantial progress in clinical outcomes can be made via implementation of specific treatments targeting known aspects of the disorder, e.g., herceptin in treatment of HER2 overexpressing breast cancer.

Growing evidence supports neuroimaging as one of the most promising approaches for precision psychiatry (Gong 2016, Sarpal, Lencz et al. 2016, Janssen, Mourao-Miranda et al. 2018). Several recent reviews (e.g., see (Dazzan, Arango et al. 2015, Gifford, Crossley et al. 2017, Fonseca, MacQueen et al. 2018, Janssen, Mourao-Miranda et al. 2018)) outline implication of neuroimaging methods in predicting treatment response, transition to advanced disease stage, and predicting functional outcomes. Various neuroimaging methods have been utilized to identify patterns that predict treatment response, including structural and functional MRI, DTI and MRS (Janssen, Mourao-Miranda et al. 2018). Studies have reported imaging biomarkers of therapeutic response in major depressive disorder (MDD), including structural and functional characteristics within the frontostriatal-limbic network (Fu, Steiner et al. 2013, Fonseca, MacQueen et al. 2018). A recent meta-analysis demonstrated that increased activity in the anterior cingulate cortex was predictive of a higher likelihood of improvement in response to pharmacological and psychotherapy interventions in MDD (Fu, Steiner et al. 2013). Furthermore, two separate meta-analyses (Fu, Steiner et al. 2013, Colle, Dupong et al. 2018); identified reduced hippocampal volume as predictor of poorer treatment response and lower remission rates in individuals with depression. In addition to predictors of pharmacologic treatment response (Gyurak, Patenaude et al. 2016, Liu, Xu et al. 2017, Colle, Dupong et al. 2018, Kraus, Klobl et al. 2019), neuroimaging studies have offered biomarkers of response to neuromodulation (e.g., electroconvulsive therapy (ECT) (Redlich, Opel et al. 2016, Levy, Taib et al. 2019); transcranial magnetic stimulation (TMS) (Avissar, Powell et al. 2017, Drysdale, Grosenick et al. 2017, Weigand, Horn et al. 2018, Fan, Tso et al. 2019)) and psychotherapy (Marwood, Wise et al. 2018) in MDD.

In bipolar disorder, the majority of studies have focused on neuroimaging predictors of treatment response to lithium and other mood stabilizers. Several studies reported associations between increased hippocampal, amygdala and cortical volumes/thickness and good lithium response in individuals with bipolar disorder (for a recent review see Porcu et al (Porcu, Balestrieri et al. 2018)). Structural and functional alterations in emotion processing and broader brain networks have been linked to various mood stabilizer effects and/or treatment response (Porcu, Balestrieri et al. 2018), including in pediatric bipolar samples (Wegbreit, Ellis et al. 2011, Kafantaris, Spritzer et al. 2017, Zhang, Xiao et al. 2018). Machine learning approaches applied to multimodal imaging data have demonstrated high classification accuracies (above 80%) for lithium response in first-episode mania (Fleck, Ernest et al. 2017). Similar approaches in schizophrenia indicated greater ventricular volumes (Lieberman, Chakos et al. 2001), diminished fronto-temporal gray matter volumes (Quarantelli, Palladino et al. 2014), and reduced white matter integrity in various tracts (Zeng, Ardekani et al. 2016, Samanaite, Gillespie et al. 2018) as neuroimaging correlates of poorer response to antipsychotic treatments (for a recent review, see Tarcijonas et al (Tarcijonas and Sarpal 2018)). Although fewer in number, studies in other psychiatric disorders (e.g., ADHD, PTSD (Kim, Sharma et al. 2015, Yang, Allen et al. 2017, Szeszko and Yehuda 2019)) demonstrated the use of neuroimaging biomarkers as predictors of treatment response.

Another rapidly developing and promising area in “precision psychiatry” research is identification of potential neural markers that are predictive of future onset of psychosis in individuals at ‘clinically high risk’ (CHR) (Gifford, Crossley et al. 2017). Regionally-specific alterations in medial temporal lobe and prefrontal cortex volumes and white matter integrity have been associated with psychosis conversion (for a comprehensive review, see Gifford et al (Gifford, Crossley et al. 2017)). Koutsouleris et al. (2018) demonstrated that structural alterations in a broad set of neocortical regions and cerebellum were predictive of functional outcome in CHR individuals (Koutsouleris, Kambeitz-Illankovic et al. 2018). Das et al. (2018) reported that disorganized gyrification network properties predicted transition to psychosis in CHR individuals with higher than 80% accuracy (Das, Borgwardt et al. 2018). Cao et al. (2018), using fMRI data from the North American Prodrome Longitudinal Study (NAPLS), showed significantly increased connectivity in a cerebello-thalamo-cortical circuit in CHR individuals who later developed psychosis (Cao, Cho et al. 2018). Bossong et al. (2019) demonstrated that MRS-based hippocampal glutamate levels were significantly elevated in CHR individuals who subsequently converted to psychosis or had poor functional outcome at follow-up (Bossong, Antoniadis et al. 2019). These studies offer potential strategies towards the identification of specific neural signatures that may inform clinical decision-making in “at risk” individuals with the aim of identifying individuals for intervention to prevent the onset of psychosis.

Considerable limitations, however, warrant caution in interpretation of these early efforts. The substantial clinical and biological heterogeneity of available disease constructs, e.g., MDD or schizophrenia, limit diagnostic specificity of imaging findings. Likewise, other target groups (e.g., CHR samples) are characterized by substantial variability in biological features, disease course and functional outcomes (Nelson, Yuen et al. 2013, Gifford, Crossley et al. 2017). The majority of studies to date are based on small to modest sample

sizes, which may lead to overoptimistic predictor estimates (Janssen, Mourao-Miranda et al. 2018, Varoquaux 2018). Alternative strategies built upon identification of biologically-homogeneous groups in large, transdiagnostic, multimodal datasets, and subsequent investigation of their predictive potential are needed to utilize neural and clinical heterogeneity to increase the accuracy and replicability of precision medicine in psychiatry.

CONCLUSIONS AND FUTURE DIRECTIONS

Parsing disease subtypes based on neuroimaging approaches, within and across complex psychiatric syndromes, can provide more precise diagnostic algorithms and targeted treatments. Progress in research can move the field past early “proof of concept” studies. However, challenges will need to be addressed including advances in psychiatric nosology relying more on brain based features, developing clinically useful and valid uses of biomarkers, and practical limitations. Substantial work is needed to bridge the gap between research and clinical practice to demonstrate the translational applicability of imaging findings in psychiatry. This work is needed to address crucial questions:

- Are imaging-based disease subtypes reproducible in independent research and clinical samples? Do they provide specific targets suitable for clinical translation?
- Do subtypes derived from different imaging modalities correspond to each other? If not, can the information be combined for clinical decision-making?
- Do subtype constructs derived in patients at different disease stages (e.g., early vs. chronic course) correspond to each other? How do psychiatric treatments impact imaging findings?
- Could subtypes derived via sophisticated (and costly) imaging tools be detected by less costly biomarkers?

To begin to tackle these challenges, there is a critical need for replication studies that incorporate multimodal biomarkers. Large-scale biomarker-focused consortia have made progress but more studies along these lines are needed (Tamminga, Ivleva et al. 2013, Cannon, Chung et al. 2015, van Erp, Walton et al. 2018). Future efforts are needed to parse biological heterogeneity of psychiatric syndromes to guide successful clinical translation. Additionally, longitudinal studies are needed to investigate the prognostic value of imaging features. To date, pharmacological target and clinical trial studies incorporating radiology tools are few, and are typically limited by small samples and single imaging modalities (e.g., fMRI or DTI). Furthermore, much more basic work is necessary in linking human *in vivo* biomarkers (e.g., those captured with imaging) to potential molecular targets, e.g., via animal models or live cell studies. Cumulatively, these strategies may move the field closer to elucidating disease mechanisms and exploiting mechanistically-informed therapeutic targets—the bases for successful clinical translation.

Another challenge is the insufficient application of available imaging tools in routine practice of psychiatry. In contrast to many other fields of medicine where radiology tools are the cornerstone of diagnostic algorithms, imaging data are used insufficiently to support psychiatric diagnoses. Experimental research biomarker batteries (e.g., the B-SNIP) are

complex and costly, and require substantial technical and analytic expertise as well as further development in automatic quantification tools. Such tools may be useful not only for clinical practice but also for the pharmacological industry to stratify patients for trials and establish target engagement.

Ultimately, to successfully address the challenging task of establishing clinical utility, the field of psychoradiology will have to bring imaging markers to an individual patient level. This calls for sophisticated computational approaches, which would allow biomarker characterization and 'biotyping' in individual patients, in real time, with subsequent application of these biomarkers as a means to guide clinical decision making. Changes in radiology and psychiatric training, and in insurance policies so they will support objective brain measures as part of routine clinical workup are examples of challenging tasks lying ahead.

To conclude, significant challenges remain for direct clinical translation of neuroimaging research in psychiatry, though none are insurmountable in light of fast progress in other fields of medicine towards similar translational goals. The developing field of psychoradiology offers unique paths to tackle these challenges via multidisciplinary efforts that bridge research and clinical practice (Huang et al. 2019). If successful, these efforts may generate stronger diagnostic algorithms and offer novel therapeutic targets for psychiatric disorders.

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KEY POINTS

1. Major psychiatric syndromes as currently defined are highly heterogeneous and show considerable overlap in clinical features, disease course, neurobiological markers, genetic susceptibility and treatment response.
2. Identifying disease subtypes based on psychoradiology, within and across psychiatric syndromes, offers novel perspectives potentially relevant to development of more precise diagnostic algorithms and targeted treatments.
3. Considerable challenges exist in incorporating research imaging approaches into clinical practice of psychiatry.
4. Multidisciplinary efforts are needed to bridge the gap between research and clinical practice and to demonstrate translational applicability of imaging-based subtyping approaches in psychiatry.

SYNOPSIS

Despite considerable research evidence demonstrating significant neurobiological alterations in psychiatric disorders, incorporating neuroimaging approaches into clinical practice remains challenging. There is an urgent need for biologically-validated psychiatric disease constructs that can inform diagnostic algorithms and targeted treatment development. In this chapter, we present a conceptual review of the most robust and impactful findings from studies that use neuroimaging methods in efforts to define distinct disease subtypes, while emphasizing large-scale cross-diagnostic and dimensional approaches. Additionally, we discussed current challenges in the field of psychoradiology and outline potential future strategies for clinically-applicable translation.

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