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Individual-specific Analysis for Psychoradiology

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INTRODUCTION

Advancements in numerous radiological modalities such as functional magnetic resonance imaging have provided insight regarding the mechanisms of mental disorders. Indeed, these neuroimaging methods have contributed to a robust body of literature concerning potential neural substrates of mental disorders, and in particular, the development of Psychoradiology as an emerging subspecialty of neuroradiology, began to show potential to play role in guiding diagnostic decision and therapeutic planning in psychiatric patients (Huang et al, 2019; Port, 2018; Sun et al, 2018). However, the neural mechanisms for most psychiatric disorders remain very obscure. Currently, there is contention surrounding the ideal criteria for the clinical diagnosis of psychiatric disorders and whether the current guidelines are suitable for practical use (Cuthbert & Insel, 2013; Frances, 2013). Whether psychiatrists and researchers transition from a strictly categorical approach based on symptoms to one that also considers dimensions derived from neuroimaging data will hypothetically have large implications on future clinical practice in psychiatry. This progression will require further developments in neuroimaging techniques to enable accurate characterization of the individual subject's brain. The following seeks to address how individual-specific analysis impacts psychiatric research and how it may be used as a component of psychoradiology in the future.

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WHY INDIVIDUAL-SPECIFIC ANALYSIS IS IMPORTANT

Recent advancements in technical and analytical brain imaging tools have allowed researchers to investigate subjects at the individual level, opening the door for personalized medicine and treatment. These investigations are fairly new, and in the field of psychiatry, studies that aim to find group-level inferences are the gold standard, whether that be case control studies, cohort studies, or randomized control trials. These types of investigations are prevalent because they are often relatively straightforward, and significant findings can potentially be generalized to large populations. Indeed, most neuropsychiatric research involves investigating group differences in brain characteristics between patients and healthy control subjects. Even before individual-specific analysis was feasible, researchers emphasized the importance of personalized investigations (Miller & Van Horn, 2007; Van Horn, Grafton, & Miller, 2008), and attempts to interpret results derived from individualized analysis has increased within the last few years.

Interest in investigating individual differences is not unfounded. Every individual is unique, and this is exemplified by the considerable interindividual variability in neural activity and structural neuroanatomy in human brains. This interindividual variability is often reflected in individual differences in behavior and cognition, such as delay discounting (Shamosh et al., 2008), emotion regulation (Lee, Heller, van Reekum, Nelson, & Davidson, 2012), intelligence (Song et al., 2008), and visual working memory (Luck & Vogel, 2013). Nonetheless, traditional neuroimaging studies have often attempted to compare and interpret data drawn from two different populations -- usually from a patient group and a healthy control group -- despite the significant heterogeneity within both groups. This simplistic approach has substantial implications on the interpretation of results that are derived from these studies. Namely, by averaging large quantities of data at the group or population level, researchers may average out effects that are present in a subset of the group under investigation, effects which could be meaningful for treatment development and research. For instance, Braga and Buckner (2017) investigated the functional network organization of four healthy individuals by scanning each subject twenty-four times. They found that simply investigating the commonalities between the subjects by evaluating the data as a group resulted in a loss of notable organizational characteristics that could be used in psychiatric applications (Braga & Buckner, 2017). Braga and Buckner's work raises concerns regarding the reliability and practicality of group-averaged data. In a similar thought, Fisher and colleagues' recent work argues that future investigators should categorically analyze the ergodicity of the processes being studied by comparing the mean and variance of the inter- and intra-individual distributions, citing the potential for cases of improper statistical inference (Fisher et al., 2018). They contend that similar to how a cross-sectional sample must be representative of a population before a generalizable claim can be made, the data derived from within an individual must also be representative of the individual's data over a time period before an inference can be established. Evaluating the inter- and intra-individual distributions of six different samples, they found that the central tendency values only agreed in four of the nine comparisons they tested, and that the variance within individuals was up to four times larger than within groups. This finding raises the possibility that some inferences derived from group-based analyses cannot be generalized to the individual,

potentially jeopardizing the credibility of numerous findings concerning brain organization, development of disorders, and treatments. In other words, it is plausible that the findings from studies that have used aggregated data may be less compelling than originally regarded. Fisher and colleagues' study should serve to remind researchers in the future to be cautious about extrapolating data and findings observed at the group level onto the individual. A better method to construct group-level inferences could be to comprehensively investigate phenomena at the individual level before generalizing those findings to the population it aims to describe.

Although individual variability provided incentives for the rapid development of individual-specific approaches, individual-level analysis was previously deemed impractical due to a number of validity and reliability concerns (Dubois & Adolphs, 2016). In functional magnetic resonance imaging (fMRI), the blood oxygen level-dependent (BOLD) signal is a direct measure of neural activity, and there are concerns as to whether the BOLD fMRI signal accurately measures neural activity and if these signals, when derived from different individuals, are functionally homologous and comparable. Also, misalignment of structural and functional maps and differences in physiology that result in differences in the way blood flows through the brain (mainly affected by aging and disease) are common issues associated with validity. On the other hand, reliability is concerned with the stability of derived measures, and is mostly affected by noise. Head motion, physiology, vasomotion, baseline physiological state, neuromodulators, and vasoactive substances are common factors that affect the signal to noise ratio (Dubois & Adolphs, 2016). Simply having food or caffeine can even contribute to fluctuations of fMRI measures (Poldrack et al., 2015). As a result, the field has been under scrutiny for having a "replicability crisis", the observation that the findings of a large number of studies are not corroborated by other or follow-up studies. It is difficult to determine the main source of the irreproducibility, whether that be improper study design, low power, sample size, or other factors. However, recent advancements in neuroimaging approaches have to an extent addressed the concerns of individual-specific analysis delineated above. For instance, Danhong Wang et al. (2015) have demonstrated that functional brain organization may be reliably mapped over time within individuals. Finn et al. (2015) illustrated that individual functional connectivity can act as a fingerprint for each subject, suggesting that the inter-individual variability is robust, stable, and reproducible. Similarly, Tavor et al. (2016) demonstrated that it is possible to predict the brain activity of unseen individuals using a model that is based on individual variability in brain connectivity, further highlighting the intrinsic link between neural organization and function (Tavor et al., 2016). As a powerful device that can sufficiently account for individual differences, individual-specific analysis can be an exceptionally useful tool in the field of psychoradiology for reasons that will be discussed below.

INVESTIGATING THE PROGRESSION OF DISORDERS

Many findings in the current literature with regard to psychiatric disorders are nonconverging, such as in autism (Vissers, Cohen, & Geurts, 2012), depression (Gong & He, 2015), dementia (Stam, 2014), obsessive-compulsive disorder (Brennan, Rauch, Jensen, & Pope, 2013; Milad & Rauch, 2012), and schizophrenia (Fitzsimmons, Kubicki, & Shenton, 2013). With the development of individual level analysis, conducting longitudinal studies

whilst employing individual specific methods could provide a mechanism to unambiguously investigate the natural progression of disorders.

Although longitudinal studies do have a number of disadvantages, namely being difficult to implement, have high costs, often experience subject participation attrition, and can be unpredictable (Anstey & Hofer, 2004), they are superior to cross-sectional studies in a multitude of ways. For instance, longitudinal studies often avoid potential confounding variables, sample selection bias, and are flexible. More importantly, they can illustrate an individual's trends in disease progression and provide more accurate and credible representations of behavior. Taken together, longitudinal studies that use individual-specific analysis theoretically have the potential to provide great insight regarding the progression and development of psychiatric disorders. Indeed, two recent studies have already explored individual-specific analysis in healthy individuals using fMRI (Laumann et al., 2015; Poldrack et al., 2015). Poldrack et al. (2015) investigated the brain connectivity of a healthy individual over 532 days. Using mainly functional and structural magnetic resonance imaging, they found a number of dynamic functional connectivity patterns over the eighteen-month time frame, such as the observation that dorsal attention, somatomotor, and visual networks were the most variable across scanning sessions and that most brain networks were generally stable. In their proof of concept study, the researchers also concluded that structural and functional connectivity are systematically related, and the characterization of psychological brain function using longitudinal studies should be expanded, particularly for psychiatric disorders because for certain illnesses, there is fluctuation in mental function over different time scales.

The findings of these studies suggest that use of individual-specific longitudinal studies should be expanded to both healthy people and people with or are at risk of developing brain disorders. First, investigating the brains of additional healthy subjects is a necessity because novel findings must be corroborated. For instance, if a certain part of the brain in a healthy patient appears to be abnormal, following scans must support that assertion before it is declared as such. More importantly, studying the inter-individual differences between healthy subjects and patients with disorders not only characterizes physiological differences, but can also be used to explore the underlying circuitry responsible for behavior or illness (Kanai & Rees, 2011). Through this approach, it is also plausible that various biomarkers for disease will be uncovered, potentially identifying high-risk patients, differentiating subjects with brain disorders from healthy populations (Rashid, Damaraju, Pearlson, & Calhoun, 2014), identifying populations that may benefit from specific interventions (Avissar et al., 2017), and recognizing populations who may require preventative care (Lui, Zhou, Sweeney, & Gong, 2016). Thus, individual-specific analysis, when employed in longitudinal studies, has the potential to greatly contribute to our understanding of the development of psychiatric disorders.

INVESTIGATING INDIVIDUAL-SPECIFIC TREATMENTS

Among the total health expenditures spent by the United States population, annual spending on mental health disorders ranks above all other conditions, estimated to be \$201 billion in 2013 (Roehrig, 2016). Though the monetary value is high when taken at face value, the

number could very well be an underestimate due to the stigma and social pressure against seeking treatment for mental illnesses. Recent evidence suggests that the efficacy of brain disorder drugs is not ideal (Leucht, Hierl, Kissling, Dold, & Davis, 2012). For depression related disorders, the leading cause for disability for individuals ages 15 to 44, Shilyansky et al. (2016) found that cognitive impairments were persistent after an eight-week treatment for each of the three most commonly prescribed antidepressants, suggesting that many methods of treatment mainly treat the symptoms of the disorder, but not the underlying pathology. Overall, the current state of the art clinical methods to treat psychiatric disorders have great room for improvement. There is evidence that suggests suboptimal performance of contemporary treatments for mental illness is rooted in individual differences.

First, individual differences are intrinsic to the human brain, and the variability in behavior, which is linked with the variability in the human brain, can also be extended to patients' sensitivity to treatment. It has been observed that individual differences may be correlated with vulnerability to drug addiction (Piazza, Deminiere, Le Moal, & Simon, 1989) and responses to drugs or treatment (Buisman-Pijlman et al., 2014), suggesting that different individuals diagnosed with the same disorder may in fact benefit the most from different interventions. For instance, cognitive-behavioral therapy (CBT) is a psychosocial intervention that focuses on influencing attitudes, beliefs, and thoughts as a mechanism to manipulate emotions, feelings, and behavior, and is utilized to treat a vast array of psychiatric disorders. The effect sizes are considerable for many of the populations that are aided by it (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). However, there is evidence that suggests children and adolescents who demonstrate patterns of amygdala hyperreactivity benefit the most from CBT (McClure et al., 2007). Another example of individual variability is treatment response to neuromodulation. FDA approved as an intervention for treatment resistant depression in 2008, rTMS has been also studied as a potential method to treat other disorders such as amyotrophic lateral sclerosis (ALS), chronic pain, schizophrenia, and stroke. Though it offers great promise as a viable treatment for these diseases (O'Reardon et al., 2007; Trevizol et al., 2016), a number of studies have found the standard application of rTMS to be suboptimal (Fregni & Pascual-Leone, 2007; Luber et al., 2017; Padberg & George, 2009). Fox and colleagues observed that there is notable heterogeneity in patients with depression regarding functional connectivity, and ideal rTMS targets can be generated for each individual rooted on these individual differences (Fox, Liu, & Pascual-Leone, 2013). Moreover, alternative investigations have found that a number of factors predict response to rTMS, including comorbidity with anxiety disorders (Lisanby et al., 2009), duration of disease (Lisanby et al., 2009), increased connectivity between subgenual anterior cingulate cortex (sgACC) and regions in the central-executive network (CEN) and default network (DN) (Liston et al., 2014), and resistance to prior treatments (Lisanby et al., 2009). Taken together, these results suggest that individual-specific analysis can play a sizable role in improving the efficacy of contemporary psychiatric treatments. Other than the potential to uncover specific and significant targets for treatments such as in neuromodulation, individual-level analysis can be practical for treatment selection. Individuals with brains that are characteristic of those that benefit from a certain intervention can be given those treatments instead of following a trial and error approach. Similarly, exploratory studies may be able to identify other biomarkers that

predict successful treatment response. At a minimum, individualized target approaches show potential and may be applicable to other disorders. Improved technology to map out circuits will allow better target circuitry for every individual.

CLASSIFICATION OF PSYCHIATRIC DISORDERS

Currently, there are two primary diagnostic systems used for clinical psychiatry (Cuthbert & Insel, 2013). The first is the Statistical Manual of Mental Disorders (DSM) and is published by the American Psychiatric Association. First published in 1952, the original goal of the DSM was to provide a comprehensive classification system that provided standardized nomenclature for psychiatrists to use, following the discovery of many psychiatric disorders. Now onto its fifth edition, the DSM has undergone a number of revisions in an attempt to accurately reflect the progress in research in psychiatry. Similarly, the International Classification of Diseases (ICD), which is published by WHO, was originally created to provide an exhaustive classification system that linked a wide variety of factors to each disease. Though both have been exceptionally useful, have been used extensively in psychiatry, and have shown to be reliable for certain diagnoses (Regier et al., 2013), recent research suggests that a diagnostic system that exclusively relies on heterogeneous categories of symptom clusters for diagnosis has many limitations that stagnate research and confound clinical outcomes (Casey et al., 2013; Cuthbert & Insel, 2013; Frances, 2013). Instead, it has been hypothesized that a system that considers both categorical and dimensional components is ideal for modern psychiatry (Casey et al., 2013).

First, DSM and ICD's categorical approach has a number of limitations regarding patient diagnosis. Because the categories are not always clear (Frances, 2013), there is a probability that a number of diagnoses will be false positives, resulting in unnecessary treatment for the patient. More importantly, different psychiatrists may diagnose the same patient with different outcomes because the guidelines for diagnosis are subjective. This could be a reason why research has found populations with the same psychiatric disorders to have considerable heterogeneity. McTeague and colleagues observed that patients diagnosed with post-traumatic stress disorder (PTSD) can be separated into groups at polar opposites on the scale for reactivity (McTeague & Lang, 2012), suggesting that the disease encompasses two distinct disorders with divergent biological mechanisms. Recently, a study demonstrated that individuals diagnosed with depression can be subdivided into four biotypes by identifying intrinsic irregularities in limbic and fronto-striatal functional connectivity networks in the brain (Drysdale et al., 2017). Different groups responded differently to rTMS, suggesting that each biotype may have a different underlying pathology and requires different treatment. Moreover, it is well known that multiple diseases seem to share mechanistic deficits. For instance, bipolar disorder (BP) and schizophrenia (SZ) have considerable overlap in clinical symptoms, neural characteristics, and risk genes (Rashid et al., 2014). Anxiety disorders, when developed during adolescence, appear to increase risks of addictive disorders and major depressive disorder (MDD), and the comorbidity suggests that the mechanisms underlying these disorders are similar or linked (Hirschfeld, 2001; Regier, Rae, Narrow, Kaelber, & Schatzberg, 1998). Importantly, Ruscio and colleagues found that 90% of their OCD participants qualified for another DSM-IV or Composite International Diagnostic Interview (CIDI) disorder (Ruscio, Stein, Chiu, & Kessler, 2010). Starting with

the disorders with the most comorbidity with OCD, anxiety disorders ranked first (75.8%), mood disorders were second (63.3%), followed by impulse-control disorders (55.9%), and substance use disorders was fourth (38.6%). The extensive comorbidity of disorders and the number of disorders that are comorbid with OCD supports the idea that their underlying mechanisms are similar or linked but also highlights the significant variability in the heterogeneous populations. Taken together, these findings suggest that the current criteria for psychiatric diagnosis is not sufficient for practical use. Disorders with distinct biological mechanisms may share the same diagnosis simply because they demonstrate similar symptoms. Conversely, different illness categories that selectively affect the same networks may elicit a diverse range of symptoms because they differ in the severity of brain damage.

Second, DSM and ICD critically restrict the ability for researchers to investigate several psychiatric disorders. Due to the reasons for potential misdiagnosis above, recruiting patients with any psychiatric disorder under the current guidelines will likely result in a heterogeneous sample of individuals with a wide range of illnesses. Thus, findings obtained from cross-sectional studies are unlikely to be generalizable to both the individual and the population because they are not ergodic, which may have contributed to the replicability crisis experienced in the field.

For these reasons, a diagnostic criterion that also considers dimensions should be beneficial, and the Research Domain Criteria project (RDoC), published by The National Institute of Mental Health (NIMH), is an example of one that incorporates both categories and dimensions. Though it hypothetically should be a superior system than the diagnostic guidelines currently in place, RDoC in its current state is also not without flaws. For instance, it has been suggested that RDoC has an overreliance on the biological level and does not sufficiently consider measurement error, that endophenotypes must be empirically validated, that the RDoC's limits need to be considered, and that there is great importance for the discrimination between biological predispositions and the behavior that is demonstrated (Lilienfeld, 2014). Another concern is that with so many dimensions, RDoC will have a large number of phenotypes that may be difficult to map neatly into diagnostic clusters that will be practical for clinical use, or in other words, the opposite of the problem that DSM and ICD have (Casey et al., 2013). Despite these concerns, recent literature has demonstrated that RDoC is feasible as a clinical tool. For instance, studies have demonstrated that the RDoC framework can be meaningfully used for research involving disorders such as depression (Woody & Gibb, 2015). Recently, due to an immense increase in interest regarding the sequencing of the whole human genome, significant progress has been made in the identification of the components underlying many disorders on the genetic front (Lander, 2011). Approximately 2,500 disease genes for rare Mendelian and 1,100 loci for polygenic diseases have been identified, and these findings have been critical for both clinicians and researchers. Many risk alleles for diseases have been identified via genetic approaches, but only recently have potential biomarkers been identified for psychiatric disorders, mainly because genetic findings only provide statistical estimations of risk and current studies report group-level inferences that cannot be attributed to individuals. Individual-specific analysis can be used to address some of these concerns. As mentioned above, individual-specific analysis can be used to accurately identify potential biomarkers for mental illnesses, and these findings can contribute to RDoC's matrices. Wang and

colleagues demonstrated that by analyzing individual-specific resting-state fMRI data of individuals with schizoaffective disorder (SZA) and bipolar disorder, it is possible to predict positive and negative symptom domains of the participants when considered independently (D. Wang et al., 2018). Similarly, Brennan and colleagues, also using resting-state fMRI data, identified potential connectivity biomarkers that were able to predict pre- and post-treatment scores on various OCD scales, as well as the connectivity changes that followed treatment (Brennan et al., 2019). Moreover, connectivity in the OFC appeared to strongly predict global OCD symptoms. With a sufficient number of trials, other biomarkers for brain disorders may be discovered, and the updated literature ideally will allow researchers to draw subjects from normalized samples that hopefully will be homogenous enough to be generalizable to the populations they aim to describe, providing novel insight into the biological mechanisms, generalizable observations, and clarifications to guidelines for psychiatric diagnosis.

POTENTIAL IMPLICATIONS ON DRUG DEVELOPMENT

In recent years, many pharmaceutical companies are allocating additional resources to non-psychiatric drug development whilst depreciating resources from psychiatric drug efforts. Given the efficacy of current state of the art psychiatric drugs, the reduction in the investment of drugs for mental disorder creates an unmet need (Insel et al., 2013). Presumably, heterogeneous populations, seemingly arbitrary diagnoses, and unsuccessful clinical trials have contributed to this decrease (Casey et al., 2013). Coupled with the lack of validated biomarkers and increased societal expectations (Woodcock & Woosley, 2008), companies may find the risks of psychiatric drug development to be too challenging to overcome.

Currently, the lack of validated biomarkers is arguably the largest roadblock in drug development. Biomarkers are particularly important because they are supposed to provide insight regarding the efficacy of drugs, treatment, or therapy on the targets they were intended for and offer predictive value of clinical effects, such as diagnosing a disorder or predicting an outcome from treatment (Frank & Hargreaves, 2003). This enables proof of concept studies involving humans to be prioritized. Additionally, it has been observed that inter-subject functional connectivity variability is correlated with evolutionary cortical expansion, suggesting that some of the assumptions regarding the relevance of animal models may not be valid and generalizable to human subjects, especially in the cognitive domain (Mueller et al., 2013). Thus, efforts to identify valid, novel biomarkers for psychiatric disorders must be initiated. Overall, the field has seen some progress in uncovering group-level inferences. Unfortunately, factors such as heterogeneous disorder populations and lack of generalizability to the individual cause the findings in the literature to be limited to group-level inferences. Investigations using individual-specific analysis should be critical in future research involving biomarkers and targets. With optimism, the transition from the usage of DSM and ICD to a system such as RDoC will homogenize many of the disorder groups, increasing the efficacy of clinical trials involving those populations.

FINAL REMARKS, FUTURE CONSIDERATIONS, AND SUBSEQUENT GOALS

The current state of psychiatry has provided a considerable amount of knowledge and contributed immensely to what we currently know about psychiatric disorders. However, the gold standard for study design and diagnostic guidelines no longer fit contemporary needs and restricts the ability of current investigators to meticulously investigate brain disorders in great detail. Individual-specific analysis should address many of the concerns with the current methods of investigation, and should be a core component of psychoradiology in the future. Moreover, by employing longitudinal studies and homogeneous disorder populations, potential findings will provide higher clinical value for each patient, identify subtypes of patients for different interventions, and quantify the utility of the provided treatments, hopefully expediting the process of finding novel biomarkers, unique targets, and revitalize investment in drug, treatment, and therapy development.

References

- Anstey KJ, & Hofer SM (2004). Longitudinal designs, methods and analysis in psychiatric research. *Aust N Z J Psychiatry*, 38(3), 93–104. doi:10.1080/j.1440-1614.2004.01343.x [PubMed: 14961925]
- Avisar M, Powell F, Ilieva I, Respingo M, Gunning FM, Liston C, & Dubin MJ (2017). Functional connectivity of the left DLPFC to striatum predicts treatment response of depression to TMS. *Brain Stimul*, 10(5), 919–925. doi:10.1016/j.brs.2017.07.002 [PubMed: 28747260]
- Braga RM, & Buckner RL (2017). Parallel Interdigitated Distributed Networks within the Individual Estimated by Intrinsic Functional Connectivity. *Neuron*, 95(2), 457–471 e455. doi:10.1016/j.neuron.2017.06.038 [PubMed: 28728026]
- Brennan BP, Rauch SL, Jensen JE, & Pope HG Jr. (2013). A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder. *Biol Psychiatry*, 73(1), 24–31. doi:10.1016/j.biopsych.2012.06.023 [PubMed: 22831979]
- Brennan BP, Wang D, Li M, Perriello C, Ren J, Elias JA, ... Liu H (2019). Use of an Individual-Level Approach to Identify Cortical Connectivity Biomarkers in Obsessive-Compulsive Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging*, 4(1), 27–38. doi:10.1016/j.bpsc.2018.07.014 [PubMed: 30262337]
- Buisman-Pijlman FT, Sumracki NM, Gordon JJ, Hull PR, Carter CS, & Tops M (2014). Individual differences underlying susceptibility to addiction: Role for the endogenous oxytocin system. *Pharmacol Biochem Behav*, 119, 22–38. doi:10.1016/j.pbb.2013.09.005 [PubMed: 24056025]
- Casey BJ, Craddock N, Cuthbert BN, Hyman SE, Lee FS, & Ressler KJ (2013). DSM-5 and RDoC: progress in psychiatry research? *Nat Rev Neurosci*, 14(11), 810–814. doi:10.1038/nrn3621 [PubMed: 24135697]
- Cuthbert BN, & Insel TR (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*, 11, 126. doi:10.1186/1741-7015-11-126 [PubMed: 23672542]
- Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, ... Liston C (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med*, 23(1), 28–38. doi:10.1038/nm.4246 [PubMed: 27918562]
- Dubois J, & Adolphs R (2016). Building a Science of Individual Differences from fMRI. *Trends Cogn Sci*, 20(6), 425–443. doi:10.1016/j.tics.2016.03.014 [PubMed: 27138646]
- Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, ... Constable RT (2015). Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci*, 18(11), 1664–1671. doi:10.1038/nn.4135 [PubMed: 26457551]
- Fisher AJ, Medaglia JD, & Jeronimus BF (2018). Lack of group-to-individual generalizability is a threat to human subjects research. *Proc Natl Acad Sci U S A*, 115(27), E6106–E6115. doi:10.1073/pnas.1711978115 [PubMed: 29915059]

- Fitzsimmons J, Kubicki M, & Shenton ME (2013). Review of functional and anatomical brain connectivity findings in schizophrenia. *Curr Opin Psychiatry*, 26(2), 172–187. doi:10.1097/YCO.0b013e32835d9e6a [PubMed: 23324948]
- Fox MD, Liu H, & Pascual-Leone A (2013). Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. *Neuroimage*, 66, 151–160. doi:10.1016/j.neuroimage.2012.10.082 [PubMed: 23142067]
- Frances A (2013). The new crisis of confidence in psychiatric diagnosis. *Ann Intern Med*, 159(3), 221–222. doi:10.7326/0003-4819-159-3-201308060-00655 [PubMed: 23685989]
- Frank R, & Hargreaves R (2003). Clinical biomarkers in drug discovery and development. *Nat Rev Drug Discov*, 2(7), 566–580. doi:10.1038/nrd1130 [PubMed: 12838269]
- Fregni F, & Pascual-Leone A (2007). Technology insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. *Nat Clin Pract Neurol*, 3(7), 383–393. doi:10.1038/ncpneuro0530 [PubMed: 17611487]
- Gong Q, & He Y (2015). Depression, neuroimaging and connectomics: a selective overview. *Biol Psychiatry*, 77(3), 223–235. doi:10.1016/j.biopsych.2014.08.009 [PubMed: 25444171]
- Hirschfeld RM (2001). The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. *Prim Care Companion J Clin Psychiatry*, 3(6), 244–254. [PubMed: 15014592]
- Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, & Fang A (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res*, 36(5), 427–440. doi:10.1007/s10608-012-9476-1
- Huang X, Gong Q, Sweeney JA, Biswal BB (2019). Progress in psychoradiology, the clinical application of psychiatric neuroimaging. *Br J Radiol*. Epub 2019 6 21:20181000.
- Insel T, Voon V, Nye J, Brown VJ, Altevogt B, Bullmore E, ... Malloch G (2013). Innovative solutions to novel drug development in mental health. *Neuroscience & Biobehavioral Reviews*, 37(10), 2438–2444. [PubMed: 23563062]
- Kanai R, & Rees G (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nat Rev Neurosci*, 12(4), 231–242. doi:10.1038/nrn3000 [PubMed: 21407245]
- Lander ES (2011). Initial impact of the sequencing of the human genome. *Nature*, 470(7333), 187–197. doi:10.1038/nature09792 [PubMed: 21307931]
- Laumann TO, Gordon EM, Adeyemo B, Snyder AZ, Joo SJ, Chen MY, ... Petersen SE (2015). Functional System and Areal Organization of a Highly Sampled Individual Human Brain. *Neuron*, 87(3), 657–670. doi:10.1016/j.neuron.2015.06.037 [PubMed: 26212711]
- Lee H, Heller AS, van Reekum CM, Nelson B, & Davidson RJ (2012). Amygdala-prefrontal coupling underlies individual differences in emotion regulation. *Neuroimage*, 62(3), 1575–1581. doi:10.1016/j.neuroimage.2012.05.044 [PubMed: 22634856]
- Leucht S, Hierl S, Kissling W, Dold M, & Davis JM (2012). Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. *Br J Psychiatry*, 200(2), 97–106. doi:10.1192/bjp.bp.111.096594 [PubMed: 22297588]
- Lilienfeld SO (2014). The Research Domain Criteria (RDoC): an analysis of methodological and conceptual challenges. *Behav Res Ther*, 62, 129–139. doi:10.1016/j.brat.2014.07.019
- Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, ... George MS (2009). Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*, 34(2), 522–534. doi:10.1038/npp.2008.118 [PubMed: 18704101]
- Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, ... Dubin MJ (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry*, 76(7), 517–526. doi:10.1016/j.biopsych.2014.01.023 [PubMed: 24629537]
- Luber BM, Davis S, Bernhardt E, Neacsu A, Kwapil L, Lisanby SH, & Strauman TJ (2017). Using neuroimaging to individualize TMS treatment for depression: Toward a new paradigm for imaging-guided intervention. *Neuroimage*, 148, 1–7. doi:10.1016/j.neuroimage.2016.12.083 [PubMed: 28062252]

- Luck SJ, & Vogel EK (2013). Visual working memory capacity: from psychophysics and neurobiology to individual differences. *Trends Cogn Sci*, 17(8), 391–400. doi:10.1016/j.tics.2013.06.006 [PubMed: 23850263]
- Lui S, Zhou XJ, Sweeney JA, & Gong Q (2016). Psychoradiology: The Frontier of Neuroimaging in Psychiatry. *Radiology*, 281(2), 357–372. doi:10.1148/radiol.2016152149 [PubMed: 27755933]
- McClure EB, Adler A, Monk CS, Cameron J, Smith S, Nelson EE, ... Pine DS (2007). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology (Berl)*, 191(1), 97–105. doi:10.1007/s00213-006-0542-9 [PubMed: 16972100]
- McTeague LM, & Lang PJ (2012). The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. *Depress Anxiety*, 29(4), 264–281. doi:10.1002/da.21891 [PubMed: 22511362]
- Milad MR, & Rauch SL (2012). Obsessive-compulsive disorder: beyond segregated corticostriatal pathways. *Trends Cogn Sci*, 16(1), 43–51. doi:10.1016/j.tics.2011.11.003 [PubMed: 22138231]
- Miller MB, & Van Horn JD (2007). Individual variability in brain activations associated with episodic retrieval: a role for large-scale databases. *Int J Psychophysiol*, 63(2), 205–213. doi:10.1016/j.ijpsycho.2006.03.019 [PubMed: 16806546]
- Mueller S, Wang D, Fox MD, Yeo BT, Sepulcre J, Sabuncu MR, ... Liu H (2013). Individual variability in functional connectivity architecture of the human brain. *Neuron*, 77(3), 586–595. doi:10.1016/j.neuron.2012.12.028 [PubMed: 23395382]
- O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, ... Sackeim HA (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*, 62(11), 1208–1216. doi:10.1016/j.biopsych.2007.01.018 [PubMed: 17573044]
- Padberg F, & George MS (2009). Repetitive transcranial magnetic stimulation of the prefrontal cortex in depression. *Exp Neurol*, 219(1), 2–13. doi:10.1016/j.expneurol.2009.04.020 [PubMed: 19409383]
- Piazza PV, Deminiere JM, Le Moal M, & Simon H (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science*, 245(4925), 1511–1513. [PubMed: 2781295]
- Poldrack RA, Laumann TO, Koyejo O, Gregory B, Hover A, Chen MY, ... Mumford JA (2015). Long-term neural and physiological phenotyping of a single human. *Nat Commun*, 6, 8885. doi:10.1038/ncomms9885 [PubMed: 26648521]
- Port JD (2018). Diagnosis of Attention Deficit Hyperactivity Disorder by Using MR Imaging and Radiomics: A Potential Tool for Clinicians. *Radiology*; 287: 631–632. [PubMed: 29668406]
- Rashid B, Damaraju E, Pearson GD, & Calhoun VD (2014). Dynamic connectivity states estimated from resting fMRI Identify differences among Schizophrenia, bipolar disorder, and healthy control subjects. *Front Hum Neurosci*, 8, 897. doi:10.3389/fnhum.2014.00897 [PubMed: 25426048]
- Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, & Kupfer DJ (2013). DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *Am J Psychiatry*, 170(1), 59–70. doi:10.1176/appi.ajp.2012.12070999 [PubMed: 23111466]
- Regier DA, Rae DS, Narrow WE, Kaelber CT, & Schatzberg AF (1998). Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. *Br J Psychiatry Suppl*(34), 24–28. [PubMed: 9829013]
- Roehrig C (2016). Mental Disorders Top The List Of The Most Costly Conditions In The United States: \$201 Billion. *Health Aff (Millwood)*, 35(6), 1130–1135. doi:10.1377/hlthaff.2015.1659 [PubMed: 27193027]
- Ruscio AM, Stein DJ, Chiu WT, & Kessler RC (2010). The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*, 15(1), 53–63. doi:10.1038/mp.2008.94 [PubMed: 18725912]
- Shamosh NA, Deyoung CG, Green AE, Reis DL, Johnson MR, Conway AR, ... Gray JR (2008). Individual differences in delay discounting: relation to intelligence, working memory, and anterior prefrontal cortex. *Psychol Sci*, 19(9), 904–911. doi:10.1111/j.1467-9280.2008.02175.x [PubMed: 18947356]

- Shilyansky C, Williams LM, Gyurak A, Harris A, Usherwood T, & Etkin A (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *Lancet Psychiatry*, 3(5), 425–435. doi:10.1016/S2215-0366(16)00012-2 [PubMed: 26995298]
- Song M, Zhou Y, Li J, Liu Y, Tian L, Yu C, & Jiang T (2008). Brain spontaneous functional connectivity and intelligence. *Neuroimage*, 41(3), 1168–1176. doi:10.1016/j.neuroimage.2008.02.036 [PubMed: 18434203]
- Sun H, Chen Y, Huang Q, et al., (2018). Psychoradiologic Utility of MR Imaging for Diagnosis of Attention Deficit Hyperactivity Disorder: A Radiomics Analysis. *Radiology*. 287(2):620–630. [PubMed: 29165048]
- Stam CJ (2014). Modern network science of neurological disorders. *Nat Rev Neurosci*, 15(10), 683–695. doi:10.1038/nrn3801 [PubMed: 25186238]
- Tavor I, Parker Jones O, Mars RB, Smith SM, Behrens TE, & Jbabdi S (2016). Task-free MRI predicts individual differences in brain activity during task performance. *Science*, 352(6282), 216–220. doi:10.1126/science.aad8127 [PubMed: 27124457]
- Trevizol AP, Shiozawa P, Cook IA, Sato IA, Kaku CB, Guimaraes FB, ... Cordeiro Q (2016). Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: An Updated Systematic Review and Meta-analysis. *J ECT*, 32(4), 262–266. doi:10.1097/YCT.0000000000000335 [PubMed: 27327557]
- Van Horn JD, Grafton ST, & Miller MB (2008). Individual Variability in Brain Activity: A Nuisance or an Opportunity? *Brain Imaging Behav*, 2(4), 327–334. doi:10.1007/s11682-008-9049-9 [PubMed: 19777073]
- Vissers ME, Cohen MX, & Geurts HM (2012). Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. *Neurosci Biobehav Rev*, 36(1), 604–625. doi:10.1016/j.neubiorev.2011.09.003 [PubMed: 21963441]
- Wang D, Buckner RL, Fox MD, Holt DJ, Holmes AJ, Stoecklein S, ... Li K (2015). Parcellating cortical functional networks in individuals. *Nature neuroscience*, 18(12), 1853. [PubMed: 26551545]
- Wang D, Li M, Wang M, Schoeppe F, Ren J, Chen H, ... Liu H (2018). Individual-specific functional connectivity markers track dimensional and categorical features of psychotic illness. *Mol Psychiatry*. doi:10.1038/s41380-018-0276-1
- Woodcock J, & Woosley R (2008). The FDA critical path initiative and its influence on new drug development. *Annu Rev Med*, 59, 1–12. doi:10.1146/annurev.med.59.090506.155819 [PubMed: 18186700]
- Woody ML, & Gibb BE (2015). Integrating NIMH Research Domain Criteria (RDoC) into Depression Research. *Curr Opin Psychol*, 4, 6–12. doi:10.1016/j.copsyc.2015.01.004 [PubMed: 25642446]

KEY POINTS

- Advancements in numerous radiological modalities such as functional magnetic resonance imaging have provided insight regarding the mechanisms of mental disorders.
- The current state of psychiatry has provided a considerable amount of knowledge and contributed immensely to what we currently know about psychiatric disorders.
- The gold standard for study design and diagnostic guidelines no longer fit contemporary needs and restricts the ability of current investigators to meticulously investigate brain disorders in detail.
- Individual-specific analysis should address many of the concerns with the current methods of investigation and should be a core component of psychoradiology in the future.

SYNOPSIS

Group-level neuroimaging investigations have been immensely useful in identifying core components of neurological and psychiatric disorders. One of the major problems in group-level imaging analyses is the heterogeneity that is observed both within subjects and between subjects. Individuals grouped within the same diagnosis category show high variability in the symptoms they present, in their response to various treatments, as well as in their functional and structural brain organization. Thus, averaging data at the level of the group results in the blurring of potentially meaningful individual differences. Here, we advocate for a more widespread use of an individual-specific approach, which involves a more thorough investigation of each individual in a group, and characterization of idiosyncrasies at the level of behavior, cognition, and symptoms, as well as at the level of brain organization. We hope that such an approach, focused on individuals, will provide convergent findings which will help identify the underlying pathology in various psychiatric disorders and help in the development of personalized treatment.