ADVANCES IN NEURODEGENERATIVE AND PSYCHIATRIC IMAGING SPECIAL FEATURE: REVIEW ARTICLE

Precision neuroradiology: mapping the nodes and networks that link genes to behaviour

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ABSTRACT

What is the future of neuroradiology in the era of precision medicine? As with any big change, this transformation in medicine presents both challenges and opportunities, and to flourish in this new environment we will have to adapt. It is difficult to predict exactly how neuroradiology will evolve in this shifting landscape, but there will be changes in both what we image and what we do. In terms of imaging, we will need to move beyond simply imaging brain anatomy and toward imaging function, both at the molecular and circuit level. In terms of what we do, we will need to move from the periphery of the clinical enterprise toward its center, with a new emphasis on integrating imaging with genetic and clinical data to form a comprehensive picture of the patient that can be used to direct further testing and care.

The payoff is that these changes will align neuroradiology with the emerging field of precision psychiatry, which promises to replace symptom-based diagnosis and trial-and-error treatment of psychiatric disorders with diagnoses based on quantifiable genetic, imaging, physiologic, and behavioural criteria and therapies targeted to the particular pathophysiology of individual patients. Here we review some of the recent developments in behavioural genetics and neuroscience that are laying the foundation for precision psychiatry. By no means comprehensive, our goal is to introduce some of the perspectives and techniques that are likely to be relevant to the precision neuroradiologist of the future.

PRECISION PSYCHIATRY

At its core precision medicine is about tailoring diagnosis and treatment to the particular genetic, environmental, and lifestyle factors that influence the pathophysiology of disease in individual patients. The approach is already having clinical impact in oncology where the specific molecular signature of a patient’s tumour is being used to predict treatment response for certain cancers such as melanoma. It may soon become common in other fields of medicine such as cardiology through the incorporation of an individual patient’s genetic risk into treatment and prevention decisions.

In psychiatry, meanwhile, the application of precision medicine is in its infancy, but its goal is ambitious: To replace the old symptom-based system of diagnosis detailed in the Diagnostic and Statistical Manual for Mental Disorders (DSM) with one that uses empirical methods – including genetics, imaging, biosamples, and behavioural measures – to stratify patients with psychiatric disease into subgroups with greater biological validity and meaning (Figure 1).

Developing a pathophysiology-based classification system to facilitate this transition is a central goal of the NIMH Research Domain Criteria Initiative which reimagines mental disorders as brain-circuit disorders, or ‘circuitopathies’, and emphasises the development of new diagnostic categories and therapeutic approaches to modulate these circuits. At the genomic level initiatives such as the NIMH funded PsychENCODE Consortium are mapping the regional expression of genes and genomic elements (those that function to control the expression of protein coding genes) across the brain at different times during brain development. Investigators are already using the PsychENCODE transcriptome atlas to explore the molecular architecture of psychiatric disease, discovering networks or ‘modules’ of functionally related regulatory genes that tend to be expressed together, and examining how such co-expression modules differ in brains from individuals with psychiatric disease. At the systems level, meanwhile, a central goal of the NIH BRAIN Initiative is to develop new tools and brain-machine-interface
technologies to study brain function at the level of networks of neurons and brain areas, and new treatment approaches capable of ‘re-tuning’ activity across disordered brain circuits. Below we expand on some of the developments in genetics and neuroscience that are making precision psychiatry a reality and explore how they might be incorporated into precision neuroradiology.

**PRECISION PSYCHIATRY AND GENETICS**

Studies of twins and families provided the first evidence that psychiatric disorders were highly heritable, and that relatives of an affected individual were at increased risk not only for the same disorder but for psychiatric disorders more generally. In recent years, large genome-wide association studies (GWAS) have shown that common genetic variation at the population level also accounts for substantial psychiatric disease risk and that psychiatric disorders are both highly polygenic (with hundreds to thousands of variations contributing to genetic risk for a given disorder) and highly pleiotropic (with many genetic variants contributing risk to more than one disorder). For many psychiatric conditions estimates of heritability based on this common variation are in the range of 10–20%.

The biggest challenge in the genetics of psychiatric disease is translating genetic findings into mechanistic understanding about underlying disease biology. For example, GWAS can link specific regions of the genome to disease risk, but identifying the particular causal variant or gene responsible for that risk signal and discerning its biological significance remains an enormous challenge. Here we review three different ways in which knowledge about the genetics of psychiatric disease can be linked to the underlying molecular, cellular, and circuit-level processes that ultimately drive pathophysiology.

Single gene disorders – a window into brain wiring and development

Common psychiatric disorders are highly polygenic, however, some rare developmental disorders with characteristic neuropsychiatric symptoms result from mutations in a single gene. The relatively simple genetics of these disorders presents an opportunity to explore how patterns of regional gene expression guide brain development and to study broader gene-behaviour relationships in a simplified context that may have relevance to the pathobiology of conditions with more complex genetic associations. Among such single gene disorders are the neurocutaneous syndromes – including Neurofibromatosis 1 (NF1) and Tuberous Sclerosis Complex (TSC) – conditions familiar to most radiologists because of their association with tissue overgrowth in multiple organ systems. The protein products of the genes mutated in both NF1 and TSC normally function as inhibitors of the AKT/PI3K/mTOR signaling pathway, a critical determinant of cellular growth and differentiation, whose dysregulation has been implicated in autism as well as several neurodegenerative diseases.

Approximately 50% of individuals with TSC fulfill criteria for autism spectrum disorder (ASD), making TSC one of the most common monogenic causes of ASD. However, the pathogenesis of ASD in the TSC population is not well understood. Using human expression data from the Allen Brain Sciences Institute and Human Brain Transcriptome databases, our group has investigated regional gene expression of TSC1 and TSC2 (the genes responsible for TSC) with the goal of leveraging patterns of gene expression to better understand the TSC phenotype. During mid-fetal development, we find that TSC1...
and TSC2 expression is elevated in the cortical plate, a development zone that shows enriched expression of gene networks implicated in ASD.24 Meanwhile, during childhood and adult life, expression of TSC1/2 (and other mTOR pathway genes) is markedly elevated in the neo-cerebellum. Interestingly, in parallel morphometric analysis of structural brain MRIs we find that children with TSC have increased cerebellar volumes compared to controls, providing an imaging correlate for this regional pattern of TSC gene expression.

These findings add to growing evidence that the cerebellum does much more than coordinate motor function. The cerebellum projects extensively to association cortex including prefrontal regions implicated in cognitive control and is hypothesized to play an important role in both normal cognitive function25,27 and the development of neuropsychiatric conditions such as ASD.15,27 In the case of ASD and TSC, cerebellar Purkinje cells, the output cells of the cerebellar cortex, appear to be particularly important: Neuropathological studies show loss of Purkinje cells in individuals with ASD,29,30 and mice with selective deletion of TSC1 or TSC2 from Purkinje cells develop an autistic phenotype that can be prevented through treatment with the mTOR inhibitor Rapamycin.30,31 Together these results suggest that TSC1/2 and the AKT/Pi3K/mTOR signaling pathway may play a role in the development of the cortico-cerebellar networks that link association cortex to the neo-cerebellum and whose disruption may contribute to the cognitive impairment, including the high incidence of ASD, observed in TSC. Molecular imaging agents that target abnormal mTOR pathway activity may soon allow us to test these hypotheses.32

Schizophrenia - from GWAS to underlying biology
In the case of highly polygenic disorders such as schizophrenia, recent breakthrough work by Sekar and colleagues has forged the first direct link between genetic risk for the disease, identified through large GWAS, and its underlying biology. To do this these investigators showed that a known association between schizophrenia and a large stretch of DNA on Chromosome six called the major histocompatibility complex (MHC) was driven by variation in number and isotype of the immune system complement genes C4A and C4B.33 They found that schizophrenia risk increased linearly with increased relative expression of C4A, that C4A expression is elevated in post mortem brain samples from patients with schizophrenia, and that C4 expression in the human brain localizes to neuronal synapses and dendrites. Finally, in a mouse model, they showed that C4 expression is upregulated during a period of post-natal development important for synaptic pruning in the maturing visual system and this pruning is disrupted in C4 deficient mice.

In humans synaptic pruning continues well into young adulthood in late maturing regions of the brain such as prefrontal cortex. While much work still needs to be done, these findings provide a plausible biological mechanism linking genetics to neural circuitry in Schizophrenia whereby increased C4A expression may lead to inappropriate pruning of cortical synapses during late adolescence and young adulthood, the time when symptoms of schizophrenia first become manifest.

Polygenic scores - empowering imaging through patient stratification
Directly linking GWAS findings to causal biological mechanisms as Sekar and colleagues have done is a challenging task. Less direct, data driven approaches, are also showing promise as tools for exploring the underlying biology of psychiatric disorders. For example, a novel type of genetic measure known as a ‘polygenic risk score’ (PRS), is being used to classify psychiatric disorders based on shared genetic architecture and to stratify patients according to disease risk.

Developed using data from large GWAS, polygenic scores reflect the cumulative risk derived from aggregating the many DNA variants associated with a particular trait or disease. In practice, each variant is assigned a weight based on its magnitude of effect and the weighted variants are combined in a statistical model to derive a polygenic score for a single person34,35 that distills their individual disease risk into a single number. Accurate, generalizable, polygenic risk scores have the potential to broadly impact medical practice.36 Their incorporation into clinical decision making is already being advocated in many fields, from assessing cardiovascular disease risk,4 to developing intelligent screening strategies that stratify patients according to their individual cancer risk.36,37

In psychiatry, polygenic scores may provide a basis for more biologically valid diagnosis and prognosis. For example, Allardyce and colleagues recently showed that a PRS derived from a large schizophrenia GWAS38 could distinguish between patients with subtypes of bipolar disorder with and without psychotic features,39 conditions with very different prognosis and treatment. Their results suggest that certain patients with bipolar disorder may share not only symptoms but also underlying genetics with patients with schizophrenia, and highlight how polygenic hazard scores might be used as a tool to dissect clinical and biological heterogeneity within and across disorders.

Polygenic scores may also replace or supplement existing disease biomarkers. For example, in our own work we have shown that an Alzheimer’s polygenic score that quantifies individual age-specific risk for Alzheimer’s disease (AD) dementia40,41 (Figure 2) can predict existing disease markers including imaging-based assessments of brain atrophy, PET imaging of amyloid burden, and CSF markers of amyloid and tau pathology.42,43 The score also adds additional predictive power when included with these other markers in models that predict cognitive decline in older adults or the burden of amyloid or neurofibrillary tangles (the pathological hallmarks of AD) in post-mortem brains. This suggests that polygenic scores may be useful in identifying high risk individuals for trials of early therapeutic interventions and in increasing the positive and negative predictive value of other tests and markers. In neuroradiology an early application of polygenic scores would be to identify patients who might benefit most from a particular type of advanced imaging.

PRECISION PSYCHIATRY AND NEUROSCIENCE
Localizing function in the brain has a rich history in neuroscience stretching back to Broca’s first descriptions of aphasis
following injury to the inferior frontal gyrus, and Penfield’s later delineation of topographic motor and sensory representations along the pre- and post-central gyrus. The development of functional MRI in the 1990s launched a golden age of neural cartography, as researchers used the tiny magnetic fluctuations caused by changes in hemoglobin oxygenation – the blood oxygen level-dependent (BOLD) signal – to infer where in the brain neurons were active in response to particular task events or conditions. The approach even translated from the lab to the clinic in the form of fMRI for presurgical mapping of language areas, enabling functional localization of motor and sensory representations in patients undergoing brain surgery. As researchers used the tiny magnetic fluctuations along the pre- and post-central gyrus, they were able to infer the location of motor and sensory representations in patients undergoing brain surgery.

Figure 2. Alzheimer disease (AD) Polygenic hazard score (PHS) quantifies an individual’s relative age-specific risk for developing AD. Survival analysis using both Kaplan–Meier estimates (dashed lines) and Cox proportional hazard model fits (solid lines) from the ADGC (Alzheimer’s Disease Genetics Consortium) Phase one case–control dataset shows how PHS quartiles capture differences in age-specific genetic risk for AD. Figure reproduced from Reference 41 under creative commons license.

Modulating brain networks - Lessons from DBS

Arguably the best understood brain circuit or network is the set of parallel pathways between the basal ganglia and cortex that function to facilitate normal movement and are disrupted in Parkinson’s disease (PD) due to loss of midbrain dopaminergic input. We owe our understanding of this network to the work of DeLong and colleagues in the early 90’s who used selective dopamine neurotoxin MPTP to develop a nonhuman-primate model of PD, and leveraged this model to study the nodes and connections that comprise this circuit. This basic knowledge, in turn, made it possible to rationally translate deep brain stimulation (DBS) to the clinic to recalibrate activity across this network and restore motor function in PD patients (reviewed in).

The success of DBS in treating PD and other movement disorders prompted excitement that the technique might be similarly effective in recalibrating brain networks thought to be disrupted in psychiatric disease. However, in contrast to movement disorders, in the case of psychiatric disorders such as major depression, at present we have neither good animal models nor the most rudimentary wiring diagram of the underlying circuits. We do know from electrophysiological studies in non-human primates that dopamine neurons in the Ventral Tegmental Area (VTA) which project to the ventral striatum and prefrontal cortex appear to shape representations of value in the brain. We also know that these representations appear to contribute to healthy decision-making through the activity of neurons within a group of frontal cortical regions that includes orbitofrontal and anterior cingulate cortex and damage to these areas results in disruptions in emotional and cognitive function. Various researchers have proposed models of decision making and behavioural control based on these findings, however, currently there is little direct evidence to support any specific proposal.

Attempts to treat treatment-resistant depression (TRD) with DBS directed towards parts of this frontal network provide a cautionary tale. While small open-label trials showed initial promise, two multicenter randomized controlled trials failed to show an effect. Reasons for this failure, and attempts to reconcile it with the technique’s early successes, have been extensively discussed in both the scientific and popular press.

Aside from methodological problems with the trials themselves, at least two factors are likely to be important. The first is related to the technology itself. Current DBS systems operate ‘open-loop’ with no ability to monitor or respond to activity in the circuit that they are attempting to modulate. Developing ‘closed-loop’ systems that can both stimulate and record, and thereby tailor their stimulation to achieve a desired electrophysiological effect, is clearly an important next step. The second is related to target selection in individual patients. Implicit in the network perspective of brain function is the idea that similar cognitive, emotional, or behavioural problems can result from dysfunction at different points or nodes across the responsible network. This means that patients with the same set of symptoms may have dysfunction at very different locations in the brain. To date most DBS approaches have targeted the same anatomically specific region.
defined location in all patients; without a means of identifying subject-specific targets it is perhaps not surprising that outcomes have been so wildly variable.

Targeting neuromodulation - current imaging approaches

In the past several years, new techniques have been developed to noninvasively image physical and functional connections in the living brain, the so-called neural ‘connectome’. When the goal of neuromodulation is to stimulate a specific white matter tract, structural imaging methods such as diffusion tensor imaging (DTI) –which measures the diffusion of water molecules to infer the course and caliber of large axonal connections between brain areas– have the potential to localize the target tract(s) in individual patients. For example, the ventral aspect of the anterior limb of the internal capsule has become a common target for DBS to treat multiple psychiatric disorders, including treatment resistant depression (TRD) and obsessive-compulsive disorder. However, the ventral capsule is a crossroads for numerous white matter pathways connecting diverse cortical and thalamic regions as well as more remote structures such as the ventral tegmental area, moreover, there is extensive individual variability in the exact location of these pathways within the ventral capsule. One of the pathways that traverses the ventral capsule is the medial forebrain bundle (MFB), a white matter tract that connects midbrain dopamine neurons to the ventral striatum and prefrontal cortex. This pathway is thought to be critical to motivated behaviour and has been proposed as a logical DBS target for TRD. In a recent preliminary study Fenoy and colleagues used DTI to map the MFB in individual patients prior to DBS implantation for TRD, and to assess electrode placement with respect to the tract’s location after implantation. In this small sample, the approach showed encouraging results with rapid sustained antidepressant effects in 5 of 6 patients; moreover, in the patient who experienced poor clinical response, DTI showed suboptimal electrode placement. Other recent studies have used DTI to explore the relationship between individual white matter tract trajectories within the ventral capsule and DBS response in OCD.

When the goal of neuromodulation is to change activity across a distributed brain network by modulating one or more of its constituent nodes, the task of targeting becomes even more challenging. An ideal method would permit non-invasive imaging of neural activity across distributed brain networks with high spatial and temporal resolution, allowing us to precisely localize participating nodes and decide which to target in an individual patient. That technology does not currently exist. However, an fMRI technique called resting-state functional-connectivity MRI (rs-fcMRI) shows promise in meeting these goals even though it relies on the BOLD signal with its limited spatial and temporal resolution. First, whole-brain maps of functional connectivity have been proposed as imaging markers, or endophenotypes, that can be used to reliably identify biologically relevant subgroups of patients. Analogous to polygenic scores, such imaging endophenotypes have the potential to function as surrogates for the as-yet-unknown genetic or molecular biology of a disease. Second, measuring the functional connectivity between the nodes of specific networks has been proposed as a means of identifying the site of network dysfunction for targeting neuromodulatory therapies in individual patients.

In 1995 Biswal and colleagues first described how spontaneous low frequency (<0.1 Hz) temporal fluctuations in the BOLD signal measured while subjects simply rested with their eyes closed were highly correlated between homologous regions of somatomotor cortex on opposite sides of the brain, correlations they interpreted as reflecting underlying ‘functional connectivity’ between these areas. This idea was elaborated in 2003 when Greicius and colleagues demonstrated similar spontaneous temporal correlations in low-freq BOLD among a network of midline brain regions previously hypothesized to form a ‘default mode network’ (DMN) because it showed greater metabolic activity (measured through FDG-PET) during rest than during task performance. In the intervening years, researchers have used resting-state BOLD correlations to uncover a family of such networks thought to reflect the brain’s underlying functional architecture (reviewed in) and have begun to explore how this functional architecture changes in the context of neuropsychiatric disease. In the case of major depressive disorder (MDD) early work emphasized the importance of the DMN, showing hyperactivity/failed suppression of the DMN during task performance in patients with MDD (reviewed in and prompting investigators to propose disruption in the normal anticorrelation between the DMN and ‘task positive’ networks as a signature of mood disorders.

More recently, it has been shown that the pattern of functional connectivity across an individual’s brain represents a unique neuronal ‘fingerprint’ that can be used to identify that individual from within a large group and remains stable across time and testing conditions. Functional connectivity fingerprints appear to stabilize during adolescence development, and there is evidence that both delayed stabilization and particular patterns of whole-brain connectivity are associated with certain cognitive- affective traits and psychiatric disorders. For example, in a large sample of over 1,100 patients with depression, Drysdale and colleagues recently showed that distinct patterns of functional connectivity across limbic and frontostriatal networks could be used to group patients with depression into four subtypes with different clinical-symptom profiles – putative endophenotypes. One of the most studied non-invasive methods for modulating neural circuits is transcranial magnetic stimulation (TMS) which applies a rapidly changing magnetic field to the scalp to induce currents that can either excite or inhibit the underlying cortex depending on the frequency of stimulation. High-frequency (‘excitatory’) TMS of the left dorsolateral prefrontal cortex (DLPFC) has been approved by the FDA for treatment of major depression. Adding support to the endophenotype status of these functional-connectivity subtypes, Drysdale and colleagues found that a patient’s subtype predicted their clinical response to left DLPFC TMS.

Finally, in elegant work relating resting-state functional-connectivity maps to the efficacy of brain stimulation, Fox and colleagues examined results from studies across a wide range of psychiatric disorders. This work has revealed links between endophenotypes and measures of brain stimulation treatment response.
of disorders (from PD, to pain, to MDD) in which treatment with invasive (DBS) or non-invasive (e.g. TMS) stimulation has been attempted. Using resting-state functional-connectivity data from a large sample of 1,000 normal subjects these authors showed that when multiple sites have been proposed as effective stimulation targets for a given disorder these sites correspond to nodes in a common functional connectivity network that can be defined by rs-fcMRI. Moreover, the sign of a particular node’s correlation with other nodes in the network predicted whether excitatory or inhibitory stimulation was clinically effective at that site. Together these results point to the potential utility of rs-fcMRI, both in defining functional connectivity fingerprints as possible ‘endophenotypes’ for particular patient subgroups, and in mapping functional networks for targeting neuromodulatory treatments.

Targeting neuromodulation - New approaches for mapping brain circuits

Fox and colleagues work supports the idea that brain stimulation is a network phenomenon and that we can begin to characterize the relevant networks in a clinically relevant way, even with imperfect techniques such as rs-fcMRI. Two very recent studies suggest that our repertoire of techniques for studying brain function at the circuit level, developing imaging-based biomarkers, and targeting neuromodulatory treatments may be about to expand considerably, and offer a glimpse into the future of precision psychiatry.

In the first, Rao and colleagues directly explore the mechanism by which brain stimulation alters underlying neural activity to influence cognitive and emotional states through simultaneous electrophysiological recording and stimulation in the brains of epilepsy patients implanted with intracranial electrodes for the purpose of seizure localization. Epilepsy has extremely high comorbidity with psychiatric disorders in general, and depression/anxiety in particular. This was true of the 25 patients in this study, about half of whom had moderate-to-severe baseline scores on the Beck Depression Inventory. By serially assessing mood in these patients while recording intracranial encephalography (iEEG) over a period of days from electrodes that covered a broad set of limbic and paralimbic structures – including OFC, ACC, insula, amygdala, and hippocampus– the authors were able to study how neural activity in these regions correlated with variability in mood and how electrical stimulation of OFC (a prefrontal region although to be central to reward and affective processing) influenced both mood assessments and neural activity.

In patients with moderate-severe baseline assessments of depression the authors found that low-frequency (4–12 Hz) iEEG power recorded from lateral OFC negatively correlated with natural fluctuations in mood (i.e. lower power = more positive mood assessments). Intriguingly, stimulation of lateral OFC produced suppression in low-frequency power in OFC during stimulation and potentiation of microstimulation evoked responses after stimulation. Moreover, in patients with moderate-severe baseline depression scores, stimulation of lateral OFC produced acute dose-dependent improvement in mood. Finally, the suppression in low-frequency iEEG power seen during lateral OFC stimulation extended to other non-stimulated areas – including anterior cingulate and insular cortex – that are known to be highly connected to OFC. This study provides some of the first direct evidence that OFC stimulation may function to normalize pathologic activity within circuits that are thought to mediate natural mood variation and shows the power of combined recording-stimulation techniques. These results are the product of a relatively rare opportunity to study patients implanted with electrodes for seizure localization. However, in the future, as more patients are implanted with chronic closed-loop stimulation devices capable of both recording and stimulating brain activity our access to such data will increase dramatically. This will mean increasing opportunities to study the relationship between stimulation and underlying neural activity and to correlate real-time high-spatiotemporal electrophysiological recordings of neural activity with rs-fcMRI and other noninvasive imaging measures, vastly increasing our ability to map the brain's functional architecture.

The second recent study also involves neuromodulation, not by electrical stimulation, but by the application of focused ultrasound, a new technique that has the potential to impact a diverse range of basic and clinical neuroscience research. In contrast to the high intensity focused ultrasound used for thermal ablation, applications of focused ultrasound for neuromodulation employ lower intensity sonication, often in conjunction with injected pharmacologic or nanoparticle constructs, to achieve a variety of spatially localized effects within the brain. Focused ultrasound is being explored as a method of modulating neural activity at high temporal and spatial resolution either directly, by opening the blood brain barrier to mediate drug delivery, or through the local uncaging of psychoactive drugs. In a groundbreaking work, Wang and colleagues have now shown that focused ultrasound can be used to non-invasively modulate brain activity by uncaging neuromodulatory drugs in a spatially and temporally specific manner within the living brain. These investigators loaded ultrasound-sensitive nanoparticles with the GABA-agonist anesthetic Propofol and administered them intravenously into the systemic circulation of rats. They show that the Propofol is only released within the brain at sites of sonication, from where the drug exerts an exquisitely local effect, silencing neural activity in a dose dependent manner with a temporal resolution of 10 sec (determined by the half life of the drug) and a spatial resolution of a few millimeters (determined by the sonication field) (Figure 3). Furthermore, using FDG-PET they show that higher ultrasound intensities produce secondary changes in brain activity at distant brain areas that are functionally connected to the sonication target, producing a map of the ‘network-effect’ that results from the local action of Propofol at the target site.

Importantly, the same nanoparticles that these investigators used to encapsulate Propofol can be used to encapsulate and release a wide variety of lipophilic drugs – a class that includes most currently used psychoactive medications, the particles
themselves are made up of components already approved for human administration in other contexts, and the sonication parameters are similar to commercial ultrasound systems currently in clinical use. This means that the translation of this powerful technology to human clinical application may be closer than we might think. Guided by real-time MRI or by neuronavigation systems, focused-ultrasound uncaging of neuromodulatory drugs has the potential to play a crucial role in circuit-based treatments – as a means of validating targets in individual patients prior to implantation of neuromodulatory

Figure 3. Neuromodulation via in-vivo ultrasonic drug uncaging in a rodent model. A. Schematic shows recording electrode in primary visual cortex (V1) and LED light stimulus for visual evoked potential (VEP) experiments. B. Running average of the VEP following sonication (‘FUS’, horizontal black line) applied to V1, normalized by the response 60 s prior to FUS administration shows transient inhibition of VEP when sonication is applied in conjunction with administration of propofol-loaded nanoparticles. C. Left: Cortical sonication target (red) for PET experiments. Right: axial and coronal PET images acquired following sonication in conjunction with administration of blank or propofol-loaded nanoparticles (black dashed ellipse = expected sonication target; Color bar = normalized FDG uptake). D. Average normalized spatial effect on FDG uptake at the sonication site for 1.2 MPa sonication with propofol-loaded nanoparticles. E. Group level averages of FDG uptake across a sagittal slice centered at the sonication site for each condition. Figure courtesy of Dr. Raag Airan, Stanford University.
devices, or of testing the action of a particular psychoactive drug on a specific brain area or network prior to the initiation of systemic therapy.

CONCLUSIONS

We have sought to explore the future of neuroradiology from the perspective of the emerging field of precision psychiatry. In the past decade, genetics and neuroscience have undergone parallel transformations, shifting emphasis from single genes and specific brain locations to a polygenic/pleiotropic model of inheritance and a circuit/network model of brain function. These new perspectives are changing our understanding of psychiatric disease, reimagining psychiatric disorders as ‘circuitopathies’ caused by interactions between complex polygenic and environmental factors. Uncovering the underlying molecular and circuit level mechanisms of psychiatric disease will require new tools to explore the brain’s genetic, molecular, and functional architecture.

In the meantime, genetic tools such as polygenic scores may soon allow us to better stratify patients into subgroups that share common biology or have greater or lesser genetic risk for a given disorder. Similarly, tools based on existing and emerging neurotechnologies may allow us to image and modulate brain function at the network level, providing imaging endophenotypes for diagnosis, and new methods for targeting circuit level therapies in individual patients. Together these developments promise a new convergence of neuroradiology and psychiatry, two disciplines that previously had little in common.

To be an effective partner in this new landscape of precision psychiatry neuroradiology must adapt and begin to focus on integrating imaging with genetic and clinical data to form a comprehensive picture of the patient with which to direct further testing and care.121 Our job description and training will need to change accordingly. We will need to become proficient in methods for studying the genetic and molecular architecture of disease, including polygenic hazard scores, transcriptome atlases, and molecular signaling pathways. We will need to develop new techniques to map the molecular pathways and brain networks that link genes to behaviour and leverage artificial intelligence and other data science tools to harness the power of these multivariate methods. These changes will be disruptive to our current model of neuroradiology, as similar changes have been to the traditional model of psychiatry, but if we navigate them successfully they have the potential to launch a new and vital era of precision neuroradiology.

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