BJR https://doi.org/10.1259/bjr.20190093

Received: 25 January 2019 | Revised: 18 June 2019 | Accepted: 24 June 2019

Cite this article as:
Sugrue LP, Desikan RS. Precision neuroradiology: mapping the nodes and networks that link genes to behaviour. *Br J Radiol* 2019; **92**: 20190093.

ADVANCES IN NEURODEGENERATIVE AND PSYCHIATRIC IMAGING SPECIAL FEATURE: REVIEW ARTICLE

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

[1]LEO P. SUGRUE, MD, PhD and [1,2]RAHUL S. DESIKAN, MD, PhD

[1]Departments of Radiology and Biomedical Imaging, University California, San Francisco, USA
[2]Department of Neurology, University California, San Francisco, USA

Address correspondence to: Dr. Leo P. Sugrue
E-mail: *leo.sugrue@ucsf.edu*

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.

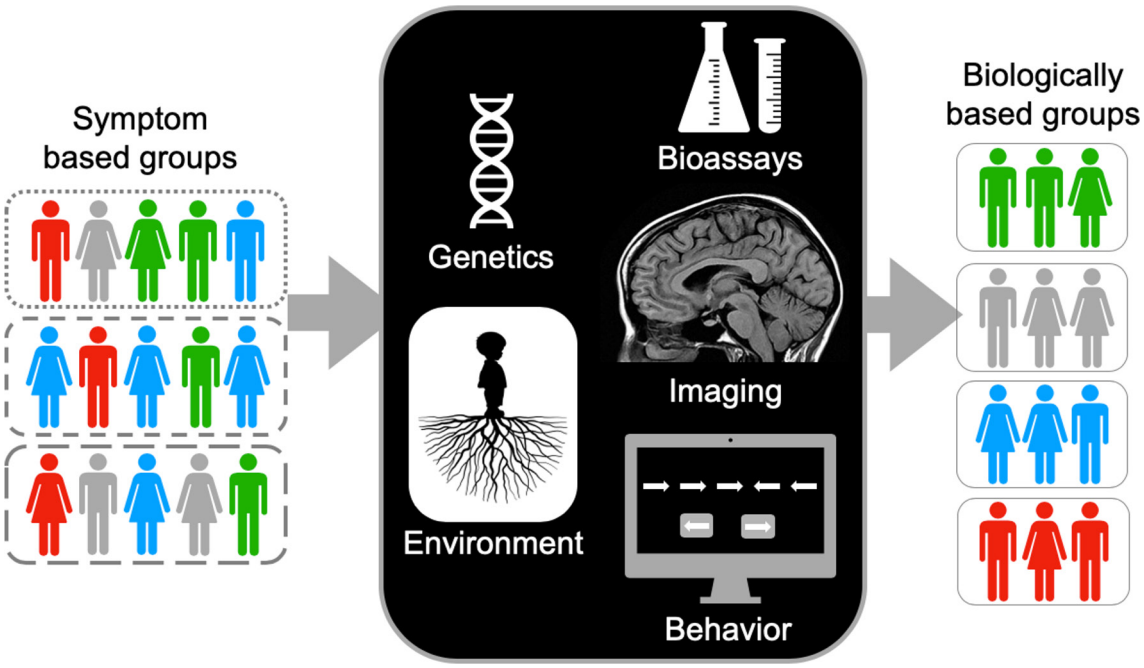
The payoff is that these changes will align neuroradiology with the emerging field of precision psychiatry, which promises to replace symptom-based diagnosis and trial-and-error treatment of psychiatric disorders with diagnoses based on quantifiable genetic, imaging, physiologic, and behavioural criteria 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.[1] 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.[2,3] 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.[4] 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)[5] 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[6] (Figure 1).

Developing a pathophysiologically based classification system to facilitate this transition is a central goal of the NIMH Research Domain Criteria Initiative[7] 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.[8,9] 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.[10] At the systems level, meanwhile, a central goal of the NIH *BRAIN Initiative*[11,12] is to develop new tools and brain-machine-interface

Figure 1. Precision Medicine in Psychiatry. The goal is to use empirical methods, including genetics and imaging, to stratify patients with psychiatric disease into subgroups that have greater biological validity than those derived from traditional, purely symptom based, diagnostic criteria.



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.[13,14] 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%.[14,15]

The biggest challenge in the genetics of psychiatric disease is translating genetic findings into mechanistic understanding about underlying disease biology.[13] 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[15] 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.[16]

Approximately 50% of individuals with TSC fulfill criteria for autism spectrum disorder (ASD), making TSC one of the most common monogenic causes of ASD.[17] However, the pathogenesis of ASD in the TSC population is not well understood. Using human expression data from the Allen Brain Sciences Institute[18,19] and Human Brain Transcriptome databases,[20,21] our group has investigated regional gene expression of *TSC1* and *TSC2* (the genes responsible for TSC[22] with the goal of leveraging patterns of gene expression to better understand the TSC phenotype.[23] During mid-fetal development, we find that *TSC1*

and *TSC2* expression is elevated in the cortical plate, a developmental 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 function[25–27] and the development of neuropsychiatric conditions such as ASD.[17,27] 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,[28,29] 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 person[34,35] that distills their individual disease risk into a single number. Accurate, generalizable, polygenic risk scores have the potential to broadly impact medical practice.[35] 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]

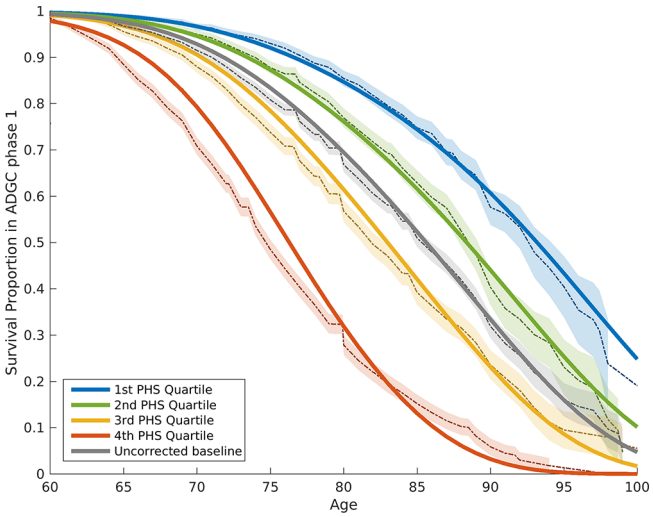
In psychiatry, polygenic scores may provide a basis for more biologically valid diagnosis and prognosis. For example, Allardyce and colleagues recently showed that a PRS derived from a large schizophrenia GWAS[38] could distinguish between patients with subtypes of bipolar disorder with and without psychotic 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) dementia[40,41] (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 aphasia

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.



following injury to the inferior frontal gyrus,[44] and Penfield's later delineation of topographic motor and sensory representations along the pre- and post-central gyrus.[45] The development of functional MRI in the 1990s[46–48] 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 function.[49,50] However, in the past decade modern neuroscience has recognized the limitations of this approach and that most complex cognitive and behavioural functions result from the coordinated activity of spatially distributed brain networks, a shift that inspired the 'circuit-based' perspective of precision psychiatry.

As with the shift in genetics from single genes to gene networks and polygenic/pleiotropic inheritance, the shift in neuroscience from individual neurons and brain areas to neural circuits and brain networks requires new tools and approaches. As previously mentioned, developing these tools is a central goal of the NIH *BRAIN Initiative*[11,12] which seeks to develop new techniques for studying how complex neural circuits interact in time and space and new technologies for 're-tuning' these circuits when they malfunction. Below we discuss some of the major challenges and opportunities posed by this goal, including the development of noninvasive imaging techniques capable of measuring the activity and connectivity of brain networks with the necessary spatial and temporal sensitivity to target and monitor such interventions.

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[51] and are disrupted in Parkinson's disease (PD) due to loss of midbrain dopaminergic input,.[52,53] We owe our understanding of this network to the work of DeLong and colleagues in the early 90's who used the 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.[54–56] 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).[52,53]

The success of DBS in treating PD and other movement disorders prompted excitement that 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.[57–60] We also know that these representations appear to contribute to healthy decison-making through the activity of neurons within a group of frontal cortical regions that includes orbitofrontal[61–63] and anterior cingulate cortex[64–66] (OFC/ACC) and that damage to these areas results in disruptions in emotional and cognitive function.[67–71] Various researchers have proposed models of decision making and behavioural control based on these findings,[72,73] 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,[74,75] two multicenter randomized controlled trials failed to show an effect.[76,77] 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.[77,78] 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.[79] 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.[80,81] 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

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'.[82] 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.[83,84] 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,[85] 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.[86] 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.[87,88]

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,[89] 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,'[90] 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.[91] This idea was elaborated in 2003 when Greicius and colleagues[92]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.[93] 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[94–96]) 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[97]) and prompting investigators to propose disruption in the normal anticorrelation between the DMN and 'task positive' networks as a signature of mood disorders.[97,98]

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.[99,100] Functional connectivity fingerprints appear to stabilize during adolescent development,[101] and there is evidence that both delayed stabilization and particular patterns of whole-brain connectivity are associated with certain cognitive-affective traits[102] and psychiatric disorders.[103] 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[104] – putative endophenotypes. One of the most studied non-invasive methods for modulating neural circuits is transcranial magnetic stimulation (TMS) (reviewed in[105]) 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.[106] High-frequency ('excitatory') TMS of the left dorsolateral prefrontal cortex (DLPFC) has been approved by the FDA for treatment of major depression.[107] 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.[104]

Finally, in elegant work relating resting-state functional-connectivity maps to the efficacy of brain stimulation, Fox and colleagues[108] examined results from studies across a wide range

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.[109] Epilepsy has extremely high comorbidity with psychiatric disorders in general, and depression/anxiety in particular.[110,111] 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.

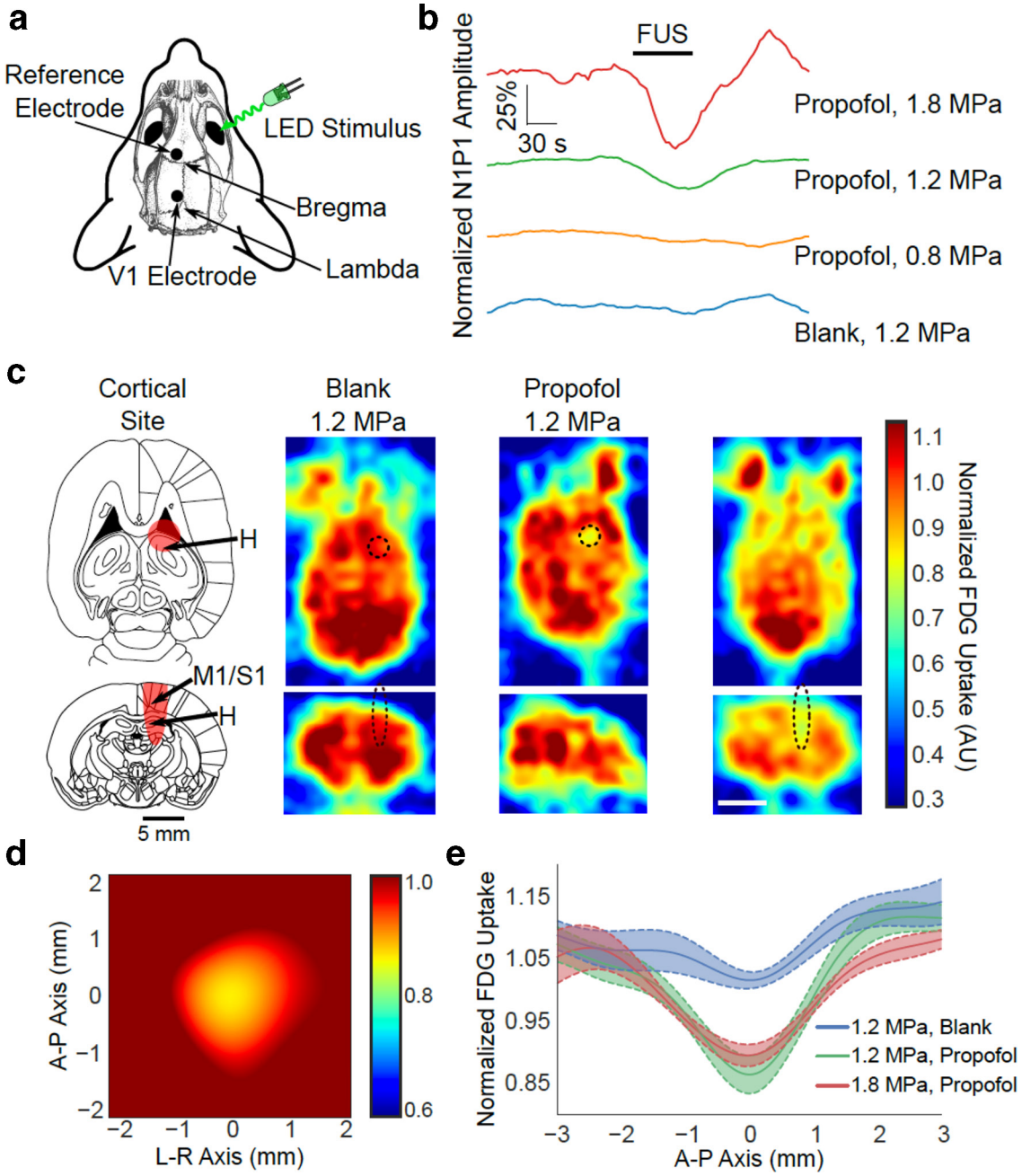
In patients with moderate-severe baseline assessments of depression the authors found that low-frequency (4–12 Hz) iEEG power recorded from lateral OFC negatively correlated with natural fluctuations in mood (*i.e.* lower power = more positive mood assessments). Intriguingly, stimulation of lateral OFC 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.[112,113] 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,[114–116] by opening the blood brain barrier to mediate drug delivery,[117] or through the local uncaging of psychoactive drugs.[118,119]

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.[120] 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

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.



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

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.

REFERENCES

1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015; **372**: 793–5. doi: https://doi.org/10.1056/NEJMp1500523
2. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 2014; **371**: 2189–99. doi: https://doi.org/10.1056/NEJMoa1406498
3. Su MY, Fisher DE. Immunotherapy in the Precision Medicine Era: Melanoma and Beyond. *PLoS Med* 2016; **13**: e1002196. doi: https://doi.org/10.1371/journal.pmed.1002196
4. Knowles JW, Ashley EA. Cardiovascular disease: The rise of the genetic risk score. *PLoS Med* 2018; **15**: e1002546. doi: https://doi.org/10.1371/journal.pmed.1002546
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*: American Psychiatric Pub; 2013: 991.
6. Insel TR, Cuthbert BN. Medicine. Brain disorders? Precisely. *Science* 2015; **348**: 499–500. doi: https://doi.org/10.1126/science.aab2358
7. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010; **167**: 748–51. doi: https://doi.org/10.1176/appi.ajp.2010.09091379
8. Servick K. Human brain samples yield a genomic trove. *Science* 2018; **362**: 1227. doi: https://doi.org/10.1126/science.362.6420.1227
9. .PsychENCODE Consortium. Revealing the brain's molecular architecture. *Science* 2018; **362**: 1262–3. doi: https://doi.org/10.1126/science.362.6420.1262
10. Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, et al. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* 2018; **362**: eaat8127. doi: https://doi.org/10.1126/science.aat8127
11. Bargmann CI, Newsome WT. The Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) initiative and neurology. *JAMA Neurol* 2014; **71**: 675–6. doi: https://doi.org/10.1001/jamaneurol.2014.411
12. Insel TR, Landis SC, Collins FS. Research priorities. The NIH BRAIN Initiative. *Science* 2013; **340**: 687–8. doi: https://doi.org/10.1126/science.1239276
13. Gandal MJ, Leppa V, Won H, Parikshak NN, Geschwind DH. The road to precision psychiatry: translating genetics into disease mechanisms. *Nat Neurosci* 2016; **19**: 1397–407. doi: https://doi.org/10.1038/nn.4409
14. Smoller JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS. Psychiatric genetics and the structure of psychopathology. *Mol Psychiatry* 2019; **24**: 409–20. doi: https://doi.org/10.1038/s41380-017-0010-4
15. Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. *Neuron* 2016; **89**: 248–68. doi: https://doi.org/10.1016/j.neuron.2015.12.008
16. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. *Cell* 2017; **168**: 960–76. doi: https://doi.org/10.1016/j.cell.2017.02.004
17. Sundberg M, Sahin M. Cerebellar Development and Autism Spectrum Disorder in Tuberous Sclerosis Complex. *J Child Neurol* 2015; **30**: 1954–62. doi: https://doi.org/10.1177/0883073815600870
18. Hawrylycz M, Miller JA, Menon V, Feng D, Dolbeare T, Guillozet-Bongaarts AL, et al. Canonical genetic signatures of the adult human brain. *Nat Neurosci* 2015; **18**: 1832–44. doi: https://doi.org/10.1038/nn.4171

19. Allen Institute for Brain Science. Allen Human Brain Atlas [Internet]. Available from: http://human.brain-map.org/
20. Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, Li M, et al. Spatio-temporal transcriptome of the human brain. *Nature* 2011; **478**: 483–9. doi: https://doi.org/10.1038/nature10523
21. Department of Neurobiology and Kavli Institute for Neuroscience,Yale University. Human Brain Transcriptome.. Available from: http://hbatlas.org/.
22. Sampson JR, Harris PC. The molecular genetics of tuberous sclerosis. *Hum Mol Genet* 1994; **3 Spec No**(suppl_1): 1477–80. doi: https://doi.org/10.1093/hmg/3.suppl_1.1477
23. Li Y, Barkovich MJ, Karch CM, Nillo RM, Fan C-C, Broce IJ, et al. Regionally specific TSC1 and TSC2 gene expression in tuberous sclerosis complex. *Sci Rep* 2018; **8**: 13373. doi: https://doi.org/10.1038/s41598-018-31075-4
24. Willsey AJ, Sanders SJ, Li M, Dong S, Tebbenkamp AT, Muhle RA, et al. Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. *Cell* 2013; **155**: 997–1007. doi: https://doi.org/10.1016/j.cell.2013.10.020
25. Bodranghien F, Bastian A, Casali C, Hallett M, Louis ED, Manto M, et al. Consensus Paper: Revisiting the Symptoms and Signs of Cerebellar Syndrome. *Cerebellum* 2016; **15**: 369–91. doi: https://doi.org/10.1007/s12311-015-0687-3
26. Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 2013; **80**: 807–15. doi: https://doi.org/10.1016/j.neuron.2013.10.044
27. Reeber SL, Otis TS, Sillitoe RV. New roles for the cerebellum in health and disease. *Front Syst Neurosci* 2013; **7**: 83. doi: https://doi.org/10.3389/fnsys.2013.00083
28. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci* 2005; **23**(2-3): 183–7. doi: https://doi.org/10.1016/j.ijdevneu.2004.09.006
29. Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, et al. Consensus paper: pathological role of the cerebellum in autism. *Cerebellum* 2012; **11**: 777–807. doi: https://doi.org/10.1007/s12311-012-0355-9
30. Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, et al. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature* 2012; **488**: 647–51. doi: https://doi.org/10.1038/nature11310
31. Reith RM, McKenna J, Wu H, Hashmi SS, Cho S-H, Dash PK, et al. Loss of Tsc2 in Purkinje cells is associated with autistic-like behavior in a mouse model of tuberous sclerosis complex. *Neurobiol Dis* 2013; **51**: 93–103. doi: https://doi.org/10.1016/j.nbd.2012.10.014
32. Truillet C, Cunningham JT, Parker MFL, Huynh LT, Conn CS, Ruggero D, et al. Noninvasive Measurement of mTORC1 Signaling with ^{89}Zr-Transferrin. *Clin Cancer Res* 2017; **23**: 3045–52. doi: https://doi.org/10.1158/1078-0432.CCR-16-2448
33. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature* 2016; **530**: 177–83. doi: https://doi.org/10.1038/nature16549
34. Chatterjee N, Shi J, García-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nat Rev Genet* 2016; **17**: 392–406. doi: https://doi.org/10.1038/nrg.2016.27
35. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet* 2018; **19**: 581–90. doi: https://doi.org/10.1038/s41576-018-0018-x
36. Seibert TM, Fan CC, Wang Y, Zuber V, Karunamuni R, Parsons JK, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. *BMJ* 2018; **360**: j5757. doi: https://doi.org/10.1136/bmj.j5757
37. Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL, et al. Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. *JAMA Oncol* 2016; **2**: 1295–302. doi: https://doi.org/10.1001/jamaoncol.2016.1025
38. .Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**: 421–7. doi: https://doi.org/10.1038/nature13595
39. Allardyce J, Leonenko G, Hamshere M, Pardiñas AF, Forty L, Knott S, et al. Association Between Schizophrenia-Related Polygenic Liability and the Occurrence and Level of Mood-Incongruent Psychotic Symptoms in Bipolar Disorder. *JAMA Psychiatry* 2018; **75**: 28–35. doi: https://doi.org/10.1001/jamapsychiatry.2017.3485
40. Desikan RS, Fan CC, Wang Y, Schork AJ, Cabral HJ, Cupples LA, et al. Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLoS Med* 2017; **14**: e1002258: e1002258: . doi: https://doi.org/10.1371/journal.pmed.1002258
41. Tan CH, Hyman BT, Tan JJX, Hess CP, Dillon WP, Schellenberg GD, et al. Polygenic hazard scores in preclinical Alzheimer disease. *Ann Neurol* 2017; **82**: 484–8. doi: https://doi.org/10.1002/ana.25029
42. Tan CH, Fan CC, Mormino EC, Sugrue LP, Broce IJ, Hess CP, et al. Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition. *Acta Neuropathol* 2018; **135**: 85–93. doi: https://doi.org/10.1007/s00401-017-1789-4
43. Kauppi K, Fan CC, McEvoy LK, Holland D, Tan CH, Chen C-H, et al. Combining Polygenic Hazard Score With Volumetric MRI and Cognitive Measures Improves Prediction of Progression From Mild Cognitive Impairment to Alzheimer's Disease. *Front Neurosci* 2018; **12**: 260. doi: https://doi.org/10.3389/fnins.2018.00260
44. Dronkers NF, Plaisant O, Iba-Zizen MT, Cabanis EA. Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong. *Brain* 2007; **130**(Pt 5): 1432–41. doi: https://doi.org/10.1093/brain/awm042
45. Penfield W, Boldrey E. Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation. *Brain* 1937; **60**: 389–443. doi: https://doi.org/10.1093/brain/60.4.389
46. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 1990; **87**: 9868–72. doi: https://doi.org/10.1073/pnas.87.24.9868
47. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci U S A* 1992; **89**: 5951–5. doi: https://doi.org/10.1073/pnas.89.13.5951
48. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A* 1992; **89**: 5675–9. doi: https://doi.org/10.1073/pnas.89.12.5675
49. Szaflarski JP, Gloss D, Binder JR, Gaillard WD, Golby AJ, Holland SK, et al. Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the

American Academy of Neurology. *Neurology* 2017; **88**: 395–402. doi: https://doi.org/10.1212/WNL.0000000000003532
50. Black DF, Vachha B, Mian A, Faro SH, Maheshwari M, Sair HI, et al. American Society of Functional Neuroradiology-Recommended fMRI Paradigm Algorithms for Presurgical Language Assessment. *AJNR Am J Neuroradiol* 2017; **38**: E65–E73. doi: https://doi.org/10.3174/ajnr.A5345
51. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; **9**: 357–81. doi: https://doi.org/10.1146/annurev.ne.09.030186.002041
52. Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron* 2013; **77**: 406–24. doi: https://doi.org/10.1016/j.neuron.2013.01.020
53. Wichmann T, Delong MR. Anatomy and physiology of the basal ganglia: relevance to Parkinson's disease and related disorders. *Handb Clin Neurol* 2007; **83**: 1–18. doi: https://doi.org/10.1016/S0072-9752(07)83001-6
54. Mitchell SJ, Richardson RT, Baker FH, DeLong MR. The primate globus pallidus: neuronal activity related to direction of movement. *Exp Brain Res* 1987; **68**: 491–505. doi: https://doi.org/10.1007/BF00249793
55. Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* 1991; **547**: 140–4. doi: https://doi.org/10.1016/0006-8993(91)90585-J
56. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 1990; **249**: 1436–8. doi: https://doi.org/10.1126/science.2402638
57. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* 1997; **275**: 1593–9. doi: https://doi.org/10.1126/science.275.5306.1593
58. Tremblay L, Schultz W. Relative reward preference in primate orbitofrontal cortex. *Nature* 1999; **398**: 704–8. doi: https://doi.org/10.1038/19525
59. Padoa-Schioppa C, Assad JA. Neurons in the orbitofrontal cortex encode economic value. *Nature* 2006; **441**: 223–6. doi: https://doi.org/10.1038/nature04676
60. Sugrue LP, Corrado GS, Newsome WT. Choosing the greater of two goods: neural currencies for valuation and decision making. *Nat Rev Neurosci* 2005; **6**: 363–75. doi: https://doi.org/10.1038/nrn1666
61. Padoa-Schioppa C, Conen KE. Orbitofrontal Cortex: A Neural Circuit for Economic Decisions. *Neuron* 2017; **96**: 736–54. doi: https://doi.org/10.1016/j.neuron.2017.09.031
62. Murray EA, O'Doherty JP, Schoenbaum G. What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. *J Neurosci* 2007; **27**: 8166–9. doi: https://doi.org/10.1523/JNEUROSCI.1556-07.2007
63. Wallis JD. Orbitofrontal cortex and its contribution to decision-making. *Annu Rev Neurosci* 2007; **30**: 31–56. doi: https://doi.org/10.1146/annurev.neuro.30.051606.094334
64. Shenhav A, Cohen JD, Botvinick MM. Dorsal anterior cingulate cortex and the value of control. *Nat Neurosci* 2016; **19**: 1286–91. doi: https://doi.org/10.1038/nn.4384
65. Kolling N, Wittmann MK, Behrens TEJ, Boorman ED, Mars RB, Rushworth MFS. Value, search, persistence and model updating in anterior cingulate cortex. *Nat Neurosci* 2016; **19**: 1280–5. doi: https://doi.org/10.1038/nn.4382
66. Ebitz RB, Hayden BY. Dorsal anterior cingulate: a Rorschach test for cognitive neuroscience. *Nat Neurosci* 2016; **19**: 1278–9. doi: https://doi.org/10.1038/nn.4387
67. Rolls ET, Hornak J, Wade D, McGrath J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J Neurol Neurosurg Psychiatry* 1994; **57**: 1518–24. doi: https://doi.org/10.1136/jnnp.57.12.1518
68. Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Exp Brain Res* 1970; **11**: 376–86. doi: https://doi.org/10.1007/BF00237911
69. Rolls ET. The orbitofrontal cortex and reward. *Cereb Cortex* 2000; **10**: 284–94. doi: https://doi.org/10.1093/cercor/10.3.284
70. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994; **50**(1-3): 7–15. doi: https://doi.org/10.1016/0010-0277(94)90018-3
71. Bechara A, Damasio H, Damasio AR, Emotion DAR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 2000; **10**: 295–307. doi: https://doi.org/10.1093/cercor/10.3.295
72. Gunaydin LA, Kreitzer AC. Cortico-Basal Ganglia Circuit Function in Psychiatric Disease. *Annu Rev Physiol* 2016; **78**: 327–50. doi: https://doi.org/10.1146/annurev-physiol-021115-105355
73. Kelley WM, Wagner DD, Heatherton TF. In search of a human self-regulation system. *Annu Rev Neurosci* 2015; **38**: 389–411. doi: https://doi.org/10.1146/annurev-neuro-071013-014243
74. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005; **45**: 651–60. doi: https://doi.org/10.1016/j.neuron.2005.02.014
75. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nat Neurosci* 2007; **10**: 1116–24. doi: https://doi.org/10.1038/nn1944
76. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017; **4**: 839–49. doi: https://doi.org/10.1016/S2215-0366(17)30371-1
77. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 2015; **78**: 240–8. doi: https://doi.org/10.1016/j.biopsych.2014.11.023
78. Dobbs D. Why a "Lifesaving" Depression Treatment Didn't Pass Clinical Trials. *The Atlantic* 2018.
79. Widge AS, Sahay A. Closing the Loop in Deep Brain Stimulation for Psychiatric Disorders: Lessons from Motor Neural Prosthetics. *Neuropsychopharmacology* 2016; **41**: 379–80. doi: https://doi.org/10.1038/npp.2015.241
80. Lo M-C, Widge AS. Closed-loop neuromodulation systems: next-generation treatments for psychiatric illness. *Int Rev Psychiatry* 2017; **29**: 191–204. doi: https://doi.org/10.1080/09540261.2017.1282438
81. Widge AS, Malone DA, Dougherty DD. Closing the Loop on Deep Brain Stimulation for Treatment-Resistant Depression. *Front Neurosci* 2018; **12**: 175. doi: https://doi.org/10.3389/fnins.2018.00175
82. Van Essen DC, Smith SM, Barch DM, Behrens TEJ, Yacoub E, Ugurbil K, et al. The WU-Minn Human Connectome Project: an overview. *Neuroimage* 2013; **80**: 62–79. doi: https://doi.org/10.1016/j.neuroimage.2013.05.041
83. Malone DA, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN,

et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009; **65**: 267–75. doi: https://doi.org/10.1016/j.biopsych.2008.08.029
84. Greenberg BD, Gabriels LA, Malone DA, Rezai AR, Friehs GM, Okun MS, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry* 2010; **15**: 64–79. doi: https://doi.org/10.1038/mp.2008.55
85. Makris N, Rathi Y, Mouradian P, Bonmassar G, Papadimitriou G, Ing WI, et al. Variability and anatomical specificity of the orbitofrontothalamic fibers of passage in the ventral capsule/ventral striatum (VC/VS): precision care for patient-specific tractography-guided targeting of deep brain stimulation (DBS) in obsessive compulsive disorder (OCD. *Brain Imaging Behav* 2016; **10**: 1054–67Available fromp. . doi: https://doi.org/10.1007/s11682-015-9462-9
86. Fenoy AJ, Schulz PE, Selvaraj S, Burrows CL, Zunta-Soares G, Durkin K, et al. A longitudinal study on deep brain stimulation of the medial forebrain bundle for treatment-resistant depression. *Transl Psychiatry* 2018; **8**: 111. doi: https://doi.org/10.1038/s41398-018-0160-4
87. Liebrand LC, Caan MWA, Schuurman PR, van den Munckhof P, Figee M, Denys D, et al. Individual white matter bundle trajectories are associated with deep brain stimulation response in obsessive-compulsive disorder. *Brain Stimul* 2019; **12**: 353–60. doi: https://doi.org/10.1016/j.brs.2018.11.014
88. Baldermann JC, Melzer C, Zapf A, Kohl S, Timmermann L, Tittgemeyer M, et al. Connectivity Profile Predictive of Effective Deep Brain Stimulation in Obsessive-Compulsive Disorder. *Biol Psychiatry* 2019; **85**: 735–43. doi: https://doi.org/10.1016/j.biopsych.2018.12.019
89. Sejnowski TJ, Churchland PS, Movshon JA. Putting big data to good use in neuroscience. *Nat Neurosci* 2014; **17**: 1440–1. doi: https://doi.org/10.1038/nn.3839
90. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003; **160**: 636–45. doi: https://doi.org/10.1176/appi.ajp.160.4.636
91. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995; **34**: 537–41. doi: https://doi.org/10.1002/mrm.1910340409
92. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 2003; **100**: 253–8.
93. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A* 2001; **98**: 676–82. doi: https://doi.org/10.1073/pnas.98.2.676
94. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol* 2013; **34**: 1866–72. doi: https://doi.org/10.3174/ajnr.A3263
95. Raichle ME. The restless brain. *Brain Connect* 2011; **1**: 3–12. doi: https://doi.org/10.1089/brain.2011.0019
96. Snyder AZ, Raichle ME. A brief history of the resting state: the Washington University perspective. *Neuroimage* 2012; **62**: 902–10. doi: https://doi.org/10.1016/j.neuroimage.2012.01.044
97. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol* 2012; **8**: 49–76. doi: https://doi.org/10.1146/annurev-clinpsy-032511-143049
98. Buckner RL, Krienen FM, Yeo BTT, . Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci* 2013; **16**: 832–7. doi: https://doi.org/10.1038/nn.3423
99. Airan RD, Vogelstein JT, Pillai JJ, Caffo B, Pekar JJ, Sair HI. Factors affecting characterization and localization of interindividual differences in functional connectivity using MRI. *Hum Brain Mapp* 2016; **37**: 1986–97. doi: https://doi.org/10.1002/hbm.23150
100. Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci* 2015; **18**: 1664–71. doi: https://doi.org/10.1038/nn.4135
101. Kaufmann T, AlnÃ¦s D, Doan NT, Brandt CL, Andreassen OA, Westlye LT. Delayed stabilization and individualization in connectome development are related to psychiatric disorders. *Nat Neurosci* 2017; **20**: 513–5. doi: https://doi.org/10.1038/nn.4511
102. Leyton M, Kennedy SH. Neuroimaging tests for clinical psychiatry: Are we there yet? *J Psychiatry Neurosci* 2017; **42**: 219–21. doi: https://doi.org/10.1503/jpn.170109
103. Barch DM. Resting-State Functional Connectivity in the Human Connectome Project: Current Status and Relevance to Understanding Psychopathology. *Harv Rev Psychiatry* 2017; **25**: 209–17. doi: https://doi.org/10.1097/HRP.0000000000000166
104. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* 2017; **23**: 28–38. doi: https://doi.org/10.1038/nm.4246
105. Dougherty DD, Widge AS. Neurotherapeutic Interventions for Psychiatric Illness. *Harv Rev Psychiatry* 2017; **25**: 253–5. doi: https://doi.org/10.1097/HRP.0000000000000174
106. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat Neurosci* 2013; **16**: 838–44. doi: https://doi.org/10.1038/nn.3422
107. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010; **67**: 507–16. doi: https://doi.org/10.1001/archgenpsychiatry.2010.46
108. Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. *Proc Natl Acad Sci U S A* 2014; **111**: E4367–E4375. doi: https://doi.org/10.1073/pnas.1405003111
109. Rao VR, Sellers KK, Wallace DL, Lee MB, Bijanzadeh M, Sani OG, et al. Direct Electrical Stimulation of Lateral Orbitofrontal Cortex Acutely Improves Mood in Individuals with Symptoms of Depression. *Curr Biol* 2018; **28**: 3893–902. doi: https://doi.org/10.1016/j.cub.2018.10.026
110. Shorvon S. What epilepsy comorbidities are important to model in the laboratory? Clinical perspectives. *Adv Exp Med Biol* 2014; **813**: 265–71. doi: https://doi.org/10.1007/978-94-017-8914-1_21
111. Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet* 2013; **382**: 1646–54. doi: https://doi.org/10.1016/S0140-6736(13)60899-5
112. Jolesz FA, McDannold NJ. Magnetic resonance-guided focused ultrasound: a new technology for clinical neurosciences. *Neurol Clin* 2014; **32**: 253–69. doi: https://doi.org/10.1016/j.ncl.2013.07.008

113. Piper RJ, Hughes MA, Moran CM, Kandasamy J. Focused ultrasound as a non-invasive intervention for neurological disease: a review. *Br J Neurosurg* 2016; **30**: 286–93. doi: https://doi.org/10.3109/02688697.2016.1173189
114. Fry FJ, Ades HW, Fry WJ. Production of reversible changes in the central nervous system by ultrasound. *Science* 1958; **127**: 83–4. doi: https://doi.org/10.1126/science.127.3289.83
115. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, et al. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat Neurosci* 2014; **17**: 322–9. doi: https://doi.org/10.1038/nn.3620
116. Lee W, Lee SD, Park MY, Foley L, Purcell-Estabrook E, Kim H, et al. Image-Guided Focused Ultrasound-Mediated Regional Brain Stimulation in Sheep. *Ultrasound Med Biol* 2016; **42**: 459–70. doi: https://doi.org/10.1016/j.ultrasmedbio.2015.10.001
117. McDannold N, Zhang Y, Power C, Arvanitis CD, Vykhodtseva N, Livingstone M, Targeted LM. Targeted, noninvasive blockade of cortical neuronal activity. *Sci Rep* 2015; **5**: 16253. doi: https://doi.org/10.1038/srep16253
118. Airan RD, Meyer RA, Ellens NPK, Rhodes KR, Farahani K, Pomper MG, et al. Noninvasive Targeted Transcranial Neuromodulation via Focused Ultrasound Gated Drug Release from Nanoemulsions. *Nano Lett* 2017; **17**: 652–9. doi: https://doi.org/10.1021/acs.nanolett.6b03517
119. Airan R. Neuromodulation with nanoparticles. *Science* 2017; **357**: 465. doi: https://doi.org/10.1126/science.aao1200
120. Wang JB, Aryal M, Zhong Q, Vyas DB, Airan RD. Noninvasive Ultrasonic Drug Uncaging Maps Whole-Brain Functional Networks. *Neuron* 2018; **100**: 728–38. doi: https://doi.org/10.1016/j.neuron.2018.10.042
121. Jha S, Topol EJ. Information and Artificial Intelligence. *J Am Coll Radiol* 2018; **15**(3 Pt B): 509–11. doi: https://doi.org/10.1016/j.jacr.2017.12.025