Modeling Brain Dysconnectivity in Rodents

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ABSTRACT

Altered or atypical functional connectivity as measured with functional magnetic resonance imaging (fMRI) is a hallmark feature of brain connectopathy in psychiatric, developmental, and neurological disorders. However, the biological underpinnings and etiopathological significance of this phenomenon remain unclear. The recent development of MRI-based techniques for mapping brain function in rodents provides a powerful platform to uncover the determinants of functional (dys)connectivity, whether they are genetic mutations, environmental risk factors, or specific cellular and circuit dysfunctions. Here, we summarize the recent contribution of rodent fMRI toward a deeper understanding of network dysconnectivity in developmental and psychiatric disorders. We highlight substantial correspondences in the spatiotemporal organization of rodent and human fMRI networks, supporting the translational relevance of this approach. We then show how this research platform might help us comprehend the importance of connectional heterogeneity in complex brain disorders and causally relate multiscale pathogenic contributors to functional dysconnectivity patterns. Finally, we explore how perturbational techniques can be used to dissect the fundamental aspects of fMRI coupling and reveal the causal contribution of neuromodulatory systems to macroscale network activity, as well as its altered dynamics in brain diseases. These examples outline how rodent functional imaging is poised to advance our understanding of the bases and determinants of human functional dysconnectivity.

https://doi.org/10.1016/j.biopsych.2022.09.008

STUDYING THE DYSCONNECTED BRAIN

Over the past 3 decades, progress in functional neuroimaging methods such as functional magnetic resonance imaging (fMRI) has been instrumental in assessing the landscape of brain network dysfunction in psychiatric disorders. The recent deployment of computational tools and resources for sharing and processing large datasets has further accelerated the transition from small-scale proof-of-concept studies in selected patient cohorts to initiatives aimed at assessing the extent and manifestation of network dysfunction in larger patient populations. The Autism Brain Imaging Data Exchange (ABIDE) (1), the ADHD-200 Consortium (2), ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) (3), and the UK Biobank (4) are examples of such large-scale endeavors. There is now great hope that these initiatives will help better pinpoint and categorize disruption of brain networks in psychiatric conditions (5), possibly providing objective imaging markers that can distinguish a diseased state from a normal one, a long-term quest of neuropsychiatric imaging (6).

However, understanding the biological and etiopathological significance of aberrant connectivity in mental illnesses is a nontrivial problem that is unlikely to be solved simply by aggregating more and more data. While it has been possible to demonstrate the presence of altered or atypical connectivity in most of these disorders at the population level, albeit with great variability at the individual level, the biological determinants and mechanistic significance of these deficits remain largely unknown. Moreover, human neuroimaging methods provide a snapshot of functional activity at the macroscale but do not allow us to probe pathophysiological mechanisms occurring at a finer investigational scale. This results in a wide explanatory gap between models of brain (dys)function at the cellular mesoscopic scale (i.e., receptor or neuronal dysfunction, excitatory/inhibitory imbalance, miswiring or circuit alterations) and the corresponding system-level measurement of brain function and connectivity. For these reasons, it is not yet clear what it means when specific brain functional connections in a psychiatric condition are weakened, are altered, or deviate from the corresponding measure in healthy control populations. The consequence is that imaging techniques in psychiatric and developmental disorders are still widely regarded as general imaging markers of endophenotypes, often devoid of true diagnostic, etiopathological, or mechanistic significance.

In this review, we argue that investigational approaches that allow for causally testing mechanistic hypotheses and bridging investigational scales beyond what is currently possible in human research can clarify the significance and multifactorial origin of brain dysconnectivity in mental disorders. Preclinical application of fMRI in animal models, such as rodents, gives a chance to fill this gap. By incorporating targeted and causally explainable perturbations into the same fMRI paradigms that are used in human investigations, rodent connectivity mapping is rapidly becoming a key tool for modeling, examining, and comparing network signatures found in human brain disorders (7,8). Furthermore, compared with humans, there is an abundance of high-resolution whole-brain physiological data (9), including direct tract tracing.
axonal connectivity data (10–13), high-resolution gene expression maps (14), and cell density atlases (15,16). This allows examination and comparison of macroscopic network metrics with fundamental biological aspects of the brain, thereby addressing the need to reconcile data on brain cellular mechanisms in rodent models with theories of brain network function from human imaging.

This review is organized as follows. To begin, we briefly go over the technical considerations for acquiring resting-state connectivity fMRI signals in rodents, as well as current initiatives aimed at creating common platforms for data acquisition, processing, and sharing. We discuss strategies for building rodent-to-human translation based on encouraging correspondences in network organization across species. Next, we illustrate how rodent fMRI can be used to generate and test mechanistic hypothesis concerning the origin and significance of functional brain dysconnectivity in psychiatric illnesses. Finally, we review (pre)clinical fMRI research that has looked at ascending neuromodulatory systems (NMSs) and the impact of these systems on brain connectivity by offering the reader insight into how these mechanisms are relevant to the interpretation of connectivity aberrations in mental disorders. Our review is intended for both specialists and nonexperts in the fields of psychiatry, neuroscience, and neuroimaging who want to learn about the outstanding topics that rodent fMRI aims to investigate (Table 1).

Table 1. Technical/Methodological Challenges in the Field of Rodent fMRI

| Key Technical and Methodological Challenges | Translational Implications | Current or Future Workarounds/Mitigation Strategies | Selected References |
|---------------------------------------------|----------------------------|-----------------------------------------------|---------------------|
| Consensus atlas and naming convention of functional networks in the rodent brain | Unclear referencing poses significant limits to studying the physiology of cortical and subcortical networks and extrapolating findings across species | Large data-sharing initiatives toward consensus papers | (24,32,33,149–151) |
| Unclear rodent-human homology across functional networks | Lack of direct correspondence between networks limits application of cross-species fMRI | Standardized analysis tools across species | (9,41,48,152) |
| Use of light anesthesia in rodent imaging | Potential confounding effects on neurovascular coupling | Online monitoring of physiological parameters | (29,33,51,85,96,153) |
| Stress associated with awake procedures | State-dependent connectivity bias between animals and humans | Reliable habituation protocols on multiple days (weeks) | (54,57,63,64,66,67,154) |
| Lack of consensus on rodent and human common data acquisition, preprocessing, and analysis pipelines | Unclear effects of data (pre)processing and acquisition on fMRI connectivity and connectivity changes | Large data sharing initiatives will engage standardization of best practices for acquisition and analyses of datasets | (7,27,33,34,155) |
| Rodent imaging studies tend to be minimally powered owing to strict ethics requirements (3Rs) | May limit reproducibility of rodent research | Multicenter data sharing initiatives | (33,34,86) |
| Unclear physiological meaning of fMRI connectivity changes in animal models | fMRI connectivity changes often relegated to endophenotypes of unknown biological origin in animal studies | Stronger focus on multimodal recordings and manipulations in rodents | (49,86,96,133,139,156) |
| MRI is an expensive and technically challenging method inaccessible to many groups | Limited scope of application of the technique for technical or economic reasons | Increased access to large-scale facilities | (33,34) |

fMRI, functional magnetic resonance imaging.
FUNCTIONAL CONNECTIVITY MRI IN RODENTS:
TECHNICAL CONSIDERATIONS AND PERSPECTIVES

Recent reviews summarizing the history and development of rodent fMRI are an excellent resource for the interested reader (7,17,18). The first attempts to map fMRI connectivity in rodents date back to more than 15 years, and they were met with mixed and often contradictory results (19–22). Leveraging advancements in MR hardware, optimized control of motion artifacts and physiological parameters (23), and improved image analyses pipeline, a second wave of investigations revealed the possibility of reliably mapping networks in rats (24–26) and mice (27–30).

Fast-forward to 2022, the field has matured and begun to provide answers to initial uncertainties. For example, divergences between animal preparation, anesthesia, data acquisition, and processing were found to underlie a number of disagreements within the animal functional neuroimaging community, such as the nature of unilateral versus bilateral resting-state networks (RSNs) in mice (19,27,28,31), or the existence of RSNs of translational relevance, such as plausible rodent homologues of the human default mode network (DMN) and salience network (28,32).

Perhaps one of the community’s most interesting actions occurred 2 years ago when 17 groups around the world openly shared their data in a joint effort to define a common image processing and analysis pipeline for mouse fMRI (33). Despite differences between laboratories in imaging equipment and procedures, this study identified multiple and reproducible large-scale RSNs in mice, including a DMN, in most datasets. This work also described several parameters, animal handling procedures, and equipment that can improve detection of RSNs. The experimental parameters associated with an improved spatial specificity of RSNs and an enhanced reproducibility of the functional connectivity parameter estimation between institutes include the use of dedicated cryoprobes, mechanical ventilation, and light sedation with medetomidine–isoflurane or intrapulmonary administered gaseous anesthetics. This and other initiatives including a similar ongoing effort in rats (34) are critical to guide the design and analysis of future rodent fMRI investigations.

HOMOLOGIES AND DISSIMILARITIES IN RSNs BETWEEN HUMANS AND RODENTS

The discovery of reproducible and consistent RSNs in rodents has sparked fresh ideas about how this information may be exploited to assess commonalities and dissimilarities between animal models of humans and rodents, parallel to fMRI efforts conducted in nonhuman primates. Indeed, the establishment of comparable and homologous brain networks is required for direct comparison of rodent and human fMRI research. Testing this falls within the scope of a novel branch of neuroscience termed comparative functional neuroanatomy, which studies the brain’s organization from an evolutionary perspective (35,36). The initial findings of these investigations revealed that several brain networks in rodents have a homologous architecture similar to that seen in human and primates, such as the salience (37,38), default mode (32,39), motor (40), and limbic (41) networks. Other investigations have expanded these analogies to include hierarchical organization of cortical connectivity as mapped with fMRI connectivity gradients (9,13,42,43) or the coactivation dynamics of blood oxygen level–dependent fMRI signals (44–46).

Indeed, cross-species variation exists in both functional and neuroanatomical network organization. Notably, rodents lack a clear neuroanatomical equivalent of the precuneus in their DMN, which serves as the most prominent hub in the human DMN, and its functional role may be transferred to the retrosplenial cortex (32,47). It is also possible that some of these disparities are the outcome of the evolution of functional networks with particular and distinctive capabilities for humans. For example, Balsters et al. (41) revealed that connectivity from the caudate nucleus and anterior putamen striatal regions in humans and macaques could not be matched to any mouse corticostriatal circuitry. Interestingly, the circuits formed by these areas are related to executive and sociolinguistic function and seem to be specific to nonhuman and human primates.

This information is extremely valuable and can assist the interpretation of connectivity fMRI recordings on animals and their cautious extrapolation to corresponding investigations of network dysconnectivity in humans. We believe that upcoming results from this active field of research will be pivotal in determining the translation potential of rodent models to humans so that the knowledge gained in animal research may be applied to understand the significance of clinical results. A review by Xu et al. (48) covers further outstanding topics and open questions about network homologies and dissimilarities between rodents and humans, from both a methodological and an evolutionary standpoint.

TOWARD AWAKE fMRI MAPPING IN RODENTS

Light anesthesia or sedation is commonly used in rodents to ensure animal immobilization and reduce stress related to image acquisition. Notwithstanding the possible confounding effects of anesthesia, this procedure also comes with a number of possible advantages. For one, optimized anesthesia protocols exist (23,25,29,49), and they enable the reliable detection of translationally relevant RSNs while mitigating physiological artifacts and reducing intersubject variability (50). In contrast, anesthetics may interfere with hemodynamic coupling under some circumstances, as well as regionally alter cortical and subcortical activity [reviewed by (51)], potentially confounding the results of manipulation or recording studies (36,52,53). These effects can be compounded by possible peripheral confounds affecting body temperature, heart rate, blood pressure, and respiratory rate, a set of parameters that can however be tightly controlled and monitored using advanced animal preparations (49,51).

In response to these concerns and in an attempt to increase the direct translatability of connectivity fMRI, the number of studies using fMRI in awake rodents has grown over the past few years (54,55). These investigations have shown the possibility of reliably mapping networks in awake restrained (56) or head-fixed (57) animals, with minimal stress and motion-related artifacts. Notably, closely recapitulating analogous human and primate investigations (58,59), comparisons between network organization in awake and anesthetized rodents have shown that RSN organization is overall preserved across
Biological Psychiatry

Brain Dysconnectivity in Rodents

Disrupted or atypical patterns of functional connectivity have been detected in all major psychiatric and brain disorders (68–70), supporting a conceptualization of brain pathology as the result, at least in part, of impaired brain communication (71–73). However, recent progress in human mapping of fMRI dysconnectivity has not been paralleled by increased knowledge of the mechanistic and etiological significance of these findings. The implementation of fMRI connectivity in rodents can strategically fill this knowledge gap, shedding light on the mechanistic and etiological significance of brain functional dysconnectivity (Figure 1).

Much of the added value of this field of research lies in the possibility of testing (or generating) mechanistically relevant hypotheses under tightly controlled experimental conditions that are unachievable in clinical settings. These include the control of 1) physiological and motion artifacts via sedation or head fixation (23,33,57), 2) environmental variability by breeding mice under controlled laboratory conditions, and 3) genetic variation via the assessment of genetic mutations or pathological determinants with respect to well-defined control groups composed of age- or sex-matched, genetically homogeneous littermate animals. The importance of these factors should not be understated because difficulties in controlling motion-related artifacts and in properly accounting for the genetic and demographic heterogeneity of both control and patient populations are recognized limitations of human fMRI mapping in mental illness (74–76).

Two dominant translational paradigms encompassing the use of rodent fMRI to unravel functional dysconnectivity in mental disorders have emerged over the past few years. The most widely used approach (Figure 1A) relies on the isolation and modeling of disease-relevant genetic alterations in rodents to investigate whether and how these factors affect functional connectivity. The most advanced examples of this method have been described in the field of autism and related developmental disorders, a broad spectrum of conditions marked by high heritability and high genetic heterogeneity (77). Using fMRI in transgenic rodents, many studies have causally linked autism-associated etiological determinants to specific patterns of fMRI hypo/hyperconnectivity. The vast majority of examined factors are genetic mutations in autism risk genes such as Cntnap2 (78,79), Shank3 (80), Tsc2 (81), Fmr1 (82), Nf1 (83), Chd8 (84), and 16p11.2 microdeletion (85).

The translational relevance of this paradigm is high because it can be used to explain findings from clinical populations harboring the corresponding genetic alterations. Bertero et al. (85) used this approach to characterize similar patterns of prefrontal hypoconnectivity in a mouse model and in people with 16p11.2 microdeletion, revealing that this effect is linked to immature thalamoprefrontal wiring and diminished delta band coupling. Similarly, mTOR (mechanistic target of rapamycin)–related synaptic surplus has been shown to produce hyperconnectivity patterns that can be decoded in patients with idiopathic autism (81). Encouraging cross-species correspondences in dysconnectivity have also been reported for Nf1 deficiency (83). In our view, these investigations are critical because they can inform both preclinical and clinical researchers about the relevance of the mechanism studied and the translational value of the animal models used.

When carried out on a large scale, rodent fMRI can also help address fundamental questions related to the significance of functional dysconnectivity in brain disorders. In a recent study (86), we compared connectivity alterations across 16 distinct mouse models of autism, with the goal of assessing whether network alterations in autism converge onto a discrete network...
signature of dysfunction as previously hypothesized (87) or if instead they differ as a result of the etiological heterogeneity of the spectrum. The mouse models chosen for this work were based on 1) genetic modifications that resemble/relate to a genetic alteration found in individuals with autism spectrum disorder as listed in the Simons Foundation Autism Research Initiative (SFARI) gene database and 2) other autism spectrum disorder–associated etiologies such as environmental models or models for idiopathic autism spectrum disorder accompanied by an autistic-like behavioral phenotype. Our mapping revealed a broad array of connectional abnormalities in which diverse, even diverging, connectivity signatures were recognizable across models. These results reconcile highly conflicting findings in clinical populations (88), suggesting that etiological variability is a key determinant of heterogeneous dysconnectivity in autism. Moreover, they support a reconceptualization of autism dysconnectivity as the sum of distinct pathophysiological mechanisms (89). Future extensions of this paradigm to other complex mental disorders can be envisioned.

A second emerging research paradigm (Figure 1B) relies on a broader modeling of basic pathophysiological processes associated with mental illness with the aim of identifying how each of these affects the organization of fMRI connectivity networks. Mechanistically relevant studies that can be ascribed to this category include investigations of the contribution of molecular, cellular, or environmental factors associated with brain disorders, such as impaired developmental pruning (30,90) and maternal immune activation (91), both of which linked synaptic dysfunction to fMRI dysconnectivity, or the role of chronic stress on brain network function (92). While the broad transdiagnostic nature of the mechanisms investigated with this approach prevents direct translation to clinical populations, the benefit of this paradigm ultimately lies in the mechanistic understanding of the cascade linked to altered functional connectivity and the possibility of conceptualizing fMRI dysconnectivity into a set of physiologically dysregulated components that may add and converge to produce clinical dysconnectivity (Figure 1B).

**Figure 1.** Unraveling the determinants of functional dysconnectivity with rodent functional magnetic resonance imaging (fMRI). **(A)** Transgenic models can be used to isolate genetic alterations linked to psychiatric or developmental diseases (here referred to as A, B, and C). Here, rodent fMRI can serve to identify large-scale disconnection patterns associated with these mutations and, if possible, to compare the changes with corresponding human populations (88). This process forms the basis for establishing whether dysconnectivity can be further investigated in the animal model with more invasive or postmortem investigations. **(B)** Rodents can also be used to isolate and map the effects of known molecular, cellular, developmental, or environmental factors on brain-wide patterns of connectivity. These investigations have high mechanistic relevance, and they can help conceptualize human functional dysconnectivity as the complex combination of multiple and distinct pathophysiological mechanisms. **(C)** Acute neuronal manipulation studies using optogenetics, chemogenetics, and concuring neural recordings can similarly help gain a basic understanding of the determinants of functional dysconnectivity in human disorders via a multimodal dissection of the basic cascade of events linking regional patterns of brain activity to brainwide fMRI coupling (98). When linked to appropriate physiological validations and computational modeling, this approach could potentially be used to reverse-translate (or decode) physiologically relevant fMRI signal metrics from patient populations into microcircuitual dysfunction parameters, such as imbalances in excitatory–inhibitory (E:I) ratio (95,99). Brain renderings from panel **(C)** replicate design used in (146).

**DECODING THE SIGNIFICANCE OF DYSCONNECTIVITY VIA MULTIMODAL fMRI**

Importantly, recent extensions of this approach to physiologically decode functional dysconnectivity potentially allow for reverse-translation of human fMRI datasets (Figure 1C). Recent examples of this line of investigation entail the use of chemogenetic manipulations to probe how regional alterations in brain activity affect corresponding brainwide patterns of connectivity (93–95). Three recent studies epitomize the power
of this approach. Rocchi et al. (96), recently showed that chronic or acute chemogenetic inactivation of the mouse cortex can counterintuitively lead to fMRI overconnectivity and increased delta band coupling between the inactivated regions and its terminals as a result of enhanced global oscillatory activity. This result suggests that the fMRI hyperconnectivity and increased delta power often observed in disorders characterized by loss of cortical function (i.e., stroke and degenerative disorders) may mechanistically reflect increased global oscillatory activity as opposed to rerouting of signals as previously hypothesized (97). Importantly, the same study also confirmed the prediction that inverse chemogenetic manipulations, i.e., those leading to increased excitatory-inhibitory ratio (E:I) in cortical areas, would lead to decreased fMRI connectivity via increased gamma and decreased delta activity. Similar results were previously described in another rodent study in which chemogenetically augmented E:I in somatosensory areas was found to reduce cortical fMRI connectivity (95). Notably, in the same study, the authors next trained a classifier on the recorded fMRI signals in mice and showed its ability to accurately classify cortical areas exhibiting increased E:I in a mouse model of autism. These important investigations link E:I imbalance [a postulated physiological correlate of cortical dysfunction in multiple brain disorders (98)] to a characteristic signature of fMRI dysconnectivity, thus offering additional opportunities to infer and possibly decode microcircuit abnormalities from macroscopic fMRI measurements. A compelling demonstration of the translational power of this approach has recently been described by Trakoshis et al. (99). Using chemogenetics to increase or decrease E:I in mouse cortical areas during fMRI recordings, the authors identified a time-series metric called the Hurst index, corresponding to 1/f relationship of blood oxygen level–dependent fMRI signal, that changes significantly in relation to the experimental manipulation. The same parameter could be used to decode regions with imbalanced E:I in a clinical population and revealed impairments in specific social brain regions including the medial prefrontal cortex. This research reveals the possibility, under certain circumstances, of using the fMRI signal to infer microcircuit properties of high pathophysiological significance.

Other important rodent studies have used chemogenetic or optogenetic manipulations to probe the contribution of subcortical NMSs (e.g., noradrenergic, cholinergic, serotonergic, or dopaminergic neurotransmission) to brainwide patterns of connectivity. These investigations may help disambiguate the physiological or maladaptive contribution of specific neurotransmitter systems to brainwide network dynamics with a precision unattainable in pharmacological studies, and they are a key component of research on brain dysconnectivity that we cover in greater detail in the next section.

**NMS Dysfunction and Brain States in Mental Illnesses**

Ascending NMSs form the basis of many cognitive functions and endow the brain’s relatively static structural architecture with flexibility, making it possible to support malleable neural dynamics required for adaptive behavior (100). Therefore, it is not surprising that NMS dysfunction is related to many psychiatric disorders characterized by persistent discomfort when adapting to new environmental, sensory, or social stimuli (101).

Until now, much of the experimental and theoretical work in this area has been devoted to determining how neuromodulatory activity is encoded in the firing patterns of target neurons (102,103). However, far less is known about how changes in single neuron firing pattern characteristics driven by NMSs propagate into large-scale phenomena, such as large-scale fMRI network activity. Recent studies have produced initial evidence that sustained neuromodulatory release exerts a powerful modulatory effect on coordinated neural activity and fMRI connectivity (104–107). In humans, Shine et al. (105) have shown that brainwide fMRI responses across a range of cognitive tasks align with regional differences in the density of neuromodulatory receptors. Based on these findings, they theorized that a key function of NMSs is to coordinate the fluctuations between integration and segregation of functional networks with the aim of optimizing cognitive functioning as a response to a continuously evolving environment (108,109). Accordingly, alterations in NMSs could lead to inability to flexibly switch between states of connectivity, contributing to symptomatology or the emergence of neurological and psychiatric conditions.

Given the high level of interest in these processes coupled with the inability to dissect them in humans, research platforms that allow for controlled manipulation of NMSs are crucial for understanding their contribution to brain (dis)connectivity in brain disorders.

To date, preclinical neuroimaging research has combined fMRI and pharmacological NMS manipulations to examine the effects of various receptor agonists and antagonists on the brain’s neuronal activity (110). This approach, termed pharmacological fMRI, was first used to map broad substrates of the brain that are directly activated by drugs of abuse such as nicotine (111), cocaine (112,113), amphetamine (114), ketamine (115), and psilocybin (116). These studies were later expanded to probe the receptor basis of these responses (112,117), thus laying the foundation for a fertile area of translational research (118–120). Leveraging the sensitivity of this approach, pharmacological fMRI has recently been expanded to study the functional connectivity profiles and substrates engaged by exogenously administered modulatory compounds and neuropeptides such as oxytocin (121,122), ghrelin (123), or orexin (124). Investigations of how drugs affect resting-state fMRI connectivity in rodent models have also been described (115,125). While useful in probing central engagement of drugs of interest in a fashion amenable to clinical translation, the mechanistic specificity of pharmacological fMRI to the investigation of modulatory transmission is inevitably limited by off-target pharmacological effects and possible direct vasoactive contributions of multiple drug agents (126,127). As a result, the central substrates engaged by pharmacological agents can differ from those modulated by endogenous transmitter release.

Optogenetic and chemogenetic tools, combined with advances in rodent imaging capabilities, now enable us to map the functional substrates of endogenous modulatory activity without the inconvenient contribution of vasoactive or peripheral pharmacological effects (Figure 2) (128). For example,
Giorgi et al. showed that cell type–specific chemogenetic activation of 5-HT (serotonin) cells led to a specific pattern of fMRI activation of corticohippocampal, ventrostriatal, and cerebellar areas. In contrast, pharmacologically increasing serotonin levels resulted in widespread fMRI deactivation, reflecting a combination of central and peripheral vasoconstrictive effects (126). Other studies have used similar approaches in animal models to show that manipulation of dopaminergic neurons in the ventral tegmental area and substantia nigra (129–132) and their targets in the striatum (133,134), serotonin neurons in the dorsal raphe nucleus (135), cholinergic neurons in the basal forebrain (128,136,137), and noradrenergic neurons in the locus coeruleus (138,139) can lead to brainwide activity changes measured by cerebral blood volume or blood oxygen level–dependent fMRI, which in turn could alter functional connectivity within specific networks and regions of interest.

One highly relevant mechanism through which NMSs could dynamically shape brainwide functional connectivity is via alterations of spontaneous neuronal ensemble dynamics from a synchronous to an asynchronous state and vice versa. High asynchronous dynamics would lead to lower connectivity but at the same time to stronger brain responses to incoming stimuli as background noise is reduced, thus increasing signal-to-noise ratio. Conversely, a state of high global synchronicity would elevate functional connectivity but at the cost of reducing the selective response to external stimuli. Evidence for this modulatory role has been shown by Lottem et al. (140), who demonstrated that optogenetic activation of the serotonin dorsal raphe nucleus can rapidly inhibit spontaneous fluctuation in the olfactory cortex in mice, effectively increasing activity related to incoming sensory responses. This mechanism would be consistent with the data of Grandjean et al. (135) in which stimulation of dorsal raphe nucleus evoked a reduction in cortical blood volume mirrored by suppression of intrinsic delta oscillations. Other neurotransmitters may act in a similar way. For example, Meir et al. (141) showed that electrical or optogenetic activation of the cholinergic system is able to shift cortical activity to an asynchronous state, which improved sensory responses. These effects of NMSs could at least partially explain the results of a systematic meta-analysis on working memory tasks in patients with schizophrenia or major depressive disorder, which found common stronger fMRI responses in prefrontal and anterior cingulate cortices, 2 regions belonging to the DMN (142). In contrast, 2 independent studies showed that activation of the locus coeruleus–norepinephrine system increases low-frequency synchronous fMRI connectivity within multiple cortical networks, including the DMN (138,139). The strength of this reconfiguration was found to be spatially correlated with $\delta_{1-2}$ and $\beta_1$ adrenergic receptor transcript levels and norepinephrine turnover levels, corroborating the hypothesis from human stress research that locus coeruleus activity and norepinephrine release are causally linked to fMRI network integration (143–145). Overall, these studies show that fMRI connectivity is strongly constrained by underlying neuromodulatory tone. Studying these links is an opportunity to shed light on the elusive contribution of maladaptive NMS function to brain dysconnectivity in psychiatric and neurological disorders.

CONCLUSIONS
fMRI applied to rodents offers a privileged angle of investigation from which to explore the origin and significance of brain dysconnectivity at different levels of inquiry. We urgently need to break fMRI dysconnectivity down into a number of physiological processes that can be mechanically explained, such as the function of NMSs in mental illness. Multimodal imaging must be strongly promoted in this case. We further advise that the field moves toward longitudinal and awake imaging studies to examine the relationships between etiological factors and their chronobiological effects on brain connectivity. In addition, we must keep fostering research domains whereby animal and human networks can be comparable. Understanding which circuits and networks exist in both species is essential for choosing research questions and hypotheses that arise from clinical research on patients. Leveraging emerging correspondences in the organization of fMRI networks across the phylogenetic tree, the impact of this versatile research platform toward a better understanding of human brain function is
substantial, and it is expected to grow rapidly in the coming years. We believe that the current research marks the beginning of a new chapter for functional rodent imaging and that new routes for integrating preclinical and clinical data through direct comparisons or computational models will lead to a better understanding of the mechanism(s) underlying dysconnectivity in mental illness.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Swiss National Science Foundation (Ambizione Grant No. PZ00P3_173984/1 and ECELLENZA Grant No. PCEFP3_203005 [to VZ]), the European Research Council under the European Union’s Horizon 2020 research and innovation program DISCONN (Grant No. 892371 to [AG]), the Brain and Behavior Foundation NARSAD (Independent Investigator Grant No. 25861 [to AG]), the Simons Foundation (Grant No. SFARI 400101 [to AG]), the National Institutes of Health (Grant No. 1R21MH116473-01A1 [to AG]), the Teletfon Foundation (Grant No. GGP19177 [to AG]), and the Uyeltenguison 22q11 Neuropsychiatry program at Stanford University (Grant No. UiH22QEXTFY22-04 [to AG]). We thank Christine Grimm for critically reading this manuscript. The authors report no biomedical financial interests or potential conflicts of interest.

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Received May 26, 2022; revised Aug 19, 2022; accepted Sep 10, 2022.

REFERENCES

1. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, et al. (2013): The autism brain imaging data exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 19:659–667.
2. Milham PM, Damien F, Maarten M, Stewart HM (2012): The ADHD-200 Consortium: A model to advance the translational potential of neuroimaging in clinical neuroscience. Front Syst Neurosci 0:1–5.
3. Hibar DP, Stein JL, Renteria ME, Arias-Vasquez A, Desrivieres S, Jahanshad N, et al. (2015): Common genetic variants influence human subcortical brain structures. Nature 520:224–229.
4. Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, et al. (2016): Multimodal population brain imaging in the UK Biobank: A prospective epidemiological study. Nat Neurosci 19:1523–1536.
5. Deco G, Krügelich ML (2014): Great expectations: Using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron 84:892–905.
6. Turner JA (2014): The rise of large-scale imaging studies in psychiatry. GigaScience 3:29.
7. Mandino F, Cerri DH, Garin CM, Straathof M, van Tilborg GAF, Chakravarty MM, et al. (2019): Animal functional magnetic resonance imaging: Trends and path toward standardization. Front Neuroinform 13:78.
8. Pais-Roldan P, Mateo C, Pan WJ, Acland B, Kleinfeld D, Snyder LH, et al. (2021): Contribution of animal models toward understanding resting state functional connectivity. Neuronology 245:118630.
9. Fulcher BD, Murray JD, Zerbi V, Wang XJ (2019): Multimodal gradients across mouse cortex. Proc Natl Acad Sci U S A 116:4689–4695.
10. Oh SW, Harris JA, Ng L, Winslow B, Cain N, Mihalas S, et al. (2014): A mesoscale connectome of the mouse brain. Nature 508:207–214.
11. Harris JA, Mihalas S, Hirokawa KE, Whitesell JD, Choi H, Bernard A, et al. (2019): Hierarchical organization of cortical and thalamic connectivity. Nature 575:195–202.
12. Hintiryen H, Foster NN, Bowman I, Bay M, Song MY, Lou L, et al. (2016): The mouse cortico-striatal projection. Nat Neurosci 19:1100–1114.
13. Coletta L, Pagani M, Whitesell JD, Harris JA, Bernhardt B, Gozzi A (2020): Network structure of the mouse brain connectome with voxel resolution. Sci Adv 6:eabb7187.
14. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, et al. (2007): Genome-wide atlas of gene expression in the adult mouse brain. Nature 445:168–176.
15. Kim Y, Yang GR, Pradhan K, Venkataraju KU, Bota M, Garcia del Molino LC, et al. (2017): Brain-wide maps reveal stereotyped cell-type-based cortical architecture and subcortical sexual dimorphism, Cell 171:456–469.e22.
16. Erö C, Gewaltig MO, Keller D, Markram H (2018): A cell atlas for the mouse brain. Front Neuroinform 12:84.
17. Markovic M, Savvateev I, Grimm C, Zerbi V (2021): Emerging imaging methods to study whole-brain function in rodent models. Transl Psychiatry 11:457.
18. Gorges M, Roselli F, Müller HP, Ludolph AC, Rasche V, Kassubek J (2017): Functional connectivity mapping in the animal model: Principles and applications of resting-state fMRI. Front Neurol 8:2000.
19. Jonckers E, Van Audekerke J, De Visscher G, Van der Linden A, Vanhoey M (2011): Functional connectivity fMRI of the rodent brain: Comparison of functional connectivity networks in rat and mouse. PLoS One 6:e18875.
20. Hutchison RM, Mirsattari SM, Jones CK, Gati JS, Leung LS (2010): Functional networks in the anesthetized rat brain revealed by independent component analysis of resting-state fMRI. J Neurophysiol 103:3398–3406.
21. Zhang N, Rane P, Huang W, Liang Z, Kennedy D, Fraizer JA, King J (2010): Mapping resting-state brain networks in conscious animals. J Neurosci Methods 190:186–196.
22. Pawela CP, Biswal BB, Cho YR, Kao DS, Li R, Jones SR, et al. (2008): Resting-state functional connectivity of the rat brain. Magn Reson Med 59:1021–1029.
23. Ferrari L, Turini G, Crestan V, Bertani S, Cristofori P, Bifone A, Gozzi A (2012): A robust experimental protocol for pharmacological fMRI in rats and mice. J Neurosci Methods 204:9–18.
24. Lu H, Zou Q, Gu H, Raichle ME, Stein EA, Yang Y (2012): Rat brains also have a default mode network. Proc Natl Acad Sci U S A 109:3979–3984.
25. Pawela CP, Biswal BB, Hudezt AG, Schulte ML, Li R, Jones SR, et al. (2009): A protocol for use of medetomidine anesthesia in rats for extended studies using task-induced BOLD contrast and resting-state functional connectivity. Neuroimage 46:1137–1147.
26. van Meer MAP, Otte WM, van der Marel K, Nijsber CH, Kavelaars A, van der Sprenkel JW, et al. (2012): Extent of bilateral neuronal network reorganization and functional recovery in relation to stroke severity. J Neurosci 32:4495–4507.
27. Zerbi V, Grandjean J, Rudin M, Wenderoth N (2015): Mapping the mouse brain with rs-fMRI: An optimized pipeline for functional network identification. Neuroimage 123:11–21.
28. Sforazzini F, Schwarz AJ, Galbusera A, Bifone A, Gozzi A (2014): Distributed BOLD and CBV-weighted resting-state networks in the mouse brain. Neuroimage 87:403–415.9.
29. Grandjean J, Schroeter A, Batata I, Rudin M (2014): Optimization of anesthesia protocol for resting-state fMRI in mice based on differential effects of anesthetics on functional connectivity patterns. Neuroimage 102:838–847.
30. Zhan Y, Paolicelli RC, Sforazzini F, Weinhard L, Bolasco G, Pagani F, et al. (2014): Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat Neurosci 17:400–406.
31. Mechling AE, Hübner NS, Lee HL, Henning J, von Elverfeldt D, Harris LA (2014): Fine-grained mapping of mouse brain functional connectivity with resting-state fMRI. Neuroimage 96:203–215.
32. Gozzi A, Schwarz AJ (2016): Large-scale functional connectivity networks in the rodent brain. Neuroimage 125:497–509.
Brain Dysconnectivity in Rodents

33. Grandjean J, Camella C, Anckaerts A, Ayaranci G, Bougacha S, Bienert T, et al. (2020): Common functional networks in the mouse brain revealed by multi-centre resting-state fMRI analysis. NeuroImage 205:116278.

34. Grandjean J (2022): StandardRat: A multi-center consensus protocol to enhance functional connectivity specificity in the rat brain. bioRxiv. https://doi.org/10.1101/2022.09.006.

35. Grimm C, Balsters JH, Zerbi V (2021): Shedding light on social reward circuitry: (un)common blueprints in humans and rodents. Neuroscientist 27:159–183.

36. Thiebaut de Schotten M, Croxson PL, Mars RB (2019): Large-scale comparative neuroimaging: Where are we and what do we need? Cortex 118:189–202.

37. Mandino F, Vroon RM, Foo HE, Yeow LY, Bolton TAW, Salvan P, et al. (2022): A triple-network organization for the mouse brain. Mol Psychiatry 27:865–872.

38. Tsai PJ, Keeley RJ, Carmack SA, Vendruscolo JCM, Lu H, Gu H, et al. (2020): Converging structural and functional evidence for a rat salience network. Biol Psychiatry 86:867–878.

39. Stafford JM, Jarrett BR, Miranda-Dominguez O, Mills BD, Cain N, Mihalas S, et al. (2014): Large-scale topology and the default mode network in the mouse connectome. Proc Natl Acad Sci U S A 111:18745–18750.

40. Sierakowiak A, Monnot C, Aski SN, Uppman M, Li TQ, Damberg P, Brené S (2015): Default mode network, motor network, dorsal and ventral basal ganglia networks in the rat brain: Comparison to human networks using resting-state-fMRI. PLoS One 10:e0120345.

41. Balsters JH, Zerbi V, Sallet J, Wenderoth N, Mars RB (2020): Primate homologs of mouse cortico-striatal circuits. eLife 9:e53680.

42. Bergmann E, Gofman X, Kavushansky A, Kahn I (2020): Individual functional connectivity hubs of the mouse brain. NeuroImage 115:281–291.

43. Gutierrez-Barragan D, Singh NA, Alvino FG, Coletta L, Rocchi F, De Guzman E, et al. (2022): Unique spatiotemporal fMRI dynamics in the awake mouse brain. Curr Biol 32:631–644.e6.

44. Battfeld P, Uhlig L, Sitt JD, Sigman M, Jarraya B, Dehaene S (2015): Signature of consciousness in the dynamics of resting-state brain activity. Proc Natl Acad Sci U S A 112:887–892.

45. Demertzi A, Tagliazucchi E, Dehaene S, Deco G, Battfeld P, Raimondo F, et al. (2019): Human consciousness is supported by dynamic complex patterns of brain signal coordination. Sci Adv 5:e187603.

46. Liu Y, Perez PD, Ma Z, Ma Z, Dopfel D, Cramer S, et al. (2020): An open database of resting-state fMRI in awake rats. NeuroImage 220:117094.

47. Gutierrez-Barragan D, Singh NA, Alvino FG, Coletta L, Rocchi F, De Guzman E, et al. (2022): Unique spatiotemporal fMRI dynamics in the awake mouse brain. Curr Biol 32:631–644.e6.

48. Battfeld P, Uhlig L, Sitt JD, Sigman M, Jarraya B, Dehaene S (2015): Signature of consciousness in the dynamics of resting-state brain activity. Proc Natl Acad Sci U S A 112:887–892.

49. Liang Z, Liu X, Zhang N (2015): Dynamic resting state functional connectivity in awake and anesthetized rodents. NeuroImage 104:89–99.

50. Liang Z, King J, Zhang N (2012): Intrinsic organization of the anesthetized brain. J Neurosci 32:10183–10191.

51. Chelini G, Zerbi V, Cinino L, Grigoli A, Markicevic M, Libera F, et al. (2019): Aberrant somatosensory processing and connectivity in mice lacking Engrailed-2. J Neurosci 39:1525–1538.

52. King JA, Garelick TS, Brevard ME, Chen W, Messenger TL, Duong TQ, Ferris CF (2005): Procedure for minimizing stress for fMRI studies in conscious rats. J Neurosci Methods 148:154–160.

53. Mandular D, Mathieu AP, Kumaragamage C, Reynolds LM, Near J, Flores C, Rajah MN (2017): A non-invasive restraining system for awake mouse imaging. J Neurosci Methods 287:53–57.

54. Yoshida K, Mimura Y, Ishihara R, Nishida H, Komaki Y, Minakuchi T, et al. (2016): Physiological effects of a habituation procedure for functional MRI in awake mice using a cryogenic radiofrequency probe. J Neurosci Methods 274:38–48.

55. Chang PC, Procsis D, Bao G, Centeno MV, Baria A, Akparan AV (2016): Novel method for functional brain imaging in awake minimally restrained rats. J Neurophysiol 116:61–80.

56. Russo G, Helluy X, Behroozi M, Manahan-Vaughan D (2021): Gradual restraint habituation for awake functional magnetic resonance imaging incorporating combined with a sparse imaging paradigm reduces motion artifacts and stress levels in rodents. Front Neurosci 15:805679.

57. Di Martino A, O’Connor D, Chen B, Alaerts K, Anderson JS, Asfat M, et al. (2017): Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. Sci Data 4:170010.

58. Wang L, Alpert KI, Calhoun VD, Cobia DJ, Keator DB, King MD, et al. (2016): SchizConnect: Mediating neuroimaging databases on schizophrenia and related disorders for large-scale integration. NeuroImage 124:1155–1167.

59. Corbetta M, Ramsook-Labadie S, Collejas A, Baldassare A, Hacker CD, Siegel JS, et al. (2015): Common behavioral clusters and subcortical anatomy in stroke. Neuro 85:927–941.

60. Vasa RA, Mostofsky SH, Even JB (2016): The disrupted connectivity hypothesis of autism spectrum disorders: Time for the next phase in research. Biol Psychiatry Cogn Neuroimaging 1:245–252.

61. Fortino A, Zalesky A, Breakspear M (2015): The connectomics of brain disorders. Nat Rev Neurosci 16:159–172.

62. Stam CJ (2014): Modern network science of neurological disorders. Nat Rev Neurosci 15:683–695.

63. Arian RD, Vogelstein JT, Pillai JJ, Caffo B, Pekar JJ, Sair HI (2016): Factors affecting characterization and localization of interindividual differences in functional connectivity using MRI. Hum Brain Mapp 37:1986–1997.

64. Gao W, Elton A, Zhu H, Alcauter S, Smith JK, Gilmore JH, Lin W et al. (2019): Awake mouse imaging: From two-photon microscopy to awake mouse brain. Curr Biol 32:631–644.e6.

65. Dejardins M, Klögl K, Thunemann M, Mateo C, Holland D, Ferri CGL, et al. (2019): Awake mouse imaging: From two-photon microscopy to blood oxygen level-dependent functional magnetic resonance imaging. Biol Psychiatry Cogn Neurosci Neuroimaging 4:533–542.
78. Lisa A, Bertero A, Gomolka R, Sabbioni M, Galbusera A, Barsotti N, et al. (2018): Homozygous loss of autism-risk gene CNTNAP2 results in reduced local and long-range prefrontal functional connectivity. Cereb Cortex 28:1141–1153.

79. Zerbi V, Ielacqua GD, Markicevic M, Haberl MG, Elliotson MH, A-Bhaskaran et al. (2018): Dysfunctional autism risk genes cause circuit-specific connectivity deficits with distinct developmental trajectories. Cereb Cortex 28:2495–2506.

80. Pagani M, Bertero A, Lisa A, Galbusera A, Sabbioni M, Barsotti N, et al. (2019): Deletion of autism risk gene Shank3 disrupts prefrontal connectivity. J Neurosci 39:S529–S531.

81. Pagani M, Barsotti N, Bertero A, Trakoshis S, Ulysse L, Locarno A, et al. (2022): mTOR-related synaptic pathology causes autism spectrum disorder-associated functional hyperconnectivity. Nat Commun 12:6084.

82. Haberl MG, Zerbi V, Velten A, Ginger M, Heerschap A, Frick A (2015): Chronic psychosocial stress in mice leads to synapse density and disrupts hippocampal connectivity in offspring. NeuroImage 220:117088.

83. Shofty B, Bergmann E, Zur G, Asleh J, Bosak N, Kavushansky A, et al. (2019): Autism-associated Nf1 deficiency disrupts cortico-cortical and corticostriatal functional connectivity in human and mouse. Neurobiol Dis 130:104479.

84. Suettler P, Hurley S, Mohan C, Riemann K, Pagani M, Caruso A, et al. (2018): Altered neocortical gene expression, brain overgrowth and functional over-connectivity in Chd8 haploinsufficient mice. Cereb Cortex 28:2192–2208.

85. Bertero A, Lisa A, Pagani M, Parolisi R, Masferrer ME, Gritti M, et al. (2018): Autism-associated 16p11.2 microdeletion impairs prefrontal functional connectivity in mouse and human. Brain 141:2055–2065.

86. Zerbi V, Pagani M, Markicevic M, Matteoli M, Pozzi D, Fagioli M, et al. (2021): Brain mapping across 16 autism mouse models reveals a spectrum of functional connectivity subtypes. Mol Psychiatry 26:7610–7620.

87. Holiga S, Hipp JF, Chatham CH, Garces P, Spooren W, D’Arduy XL, et al. (2019): Patients with autism spectrum disorders display reproduced functional connectivity alterations. Sci Transl Med 11:eaat9223.

88. He Y, Byrne L, Kennedy DP (2020): Nonreplication of functional connectivity differences in autism spectrum disorder across multiple sites and denoising strategies. Hum Brain Mapp 41:1334–1350.

89. Hong SJ, Vogelstein JT, Gozzi A, Bernhardt BC, Yeo BTT, Milham MP, Di Martino A (2020): Toward neurosubtypes in autism. Biol Psychiatry 88:111.

90. Filippello F, Morini R, Corradini I, Zerbi V, Canzi A, Michalski B, et al. (2018): The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. Immunity 48:979–991.e8.

91. Milrabella F, Desiato G, Mancinelli S, Fossati G, Rasile M, Morini R, et al. (2021): Prenatal interleukin 6 elevation increases glutamatergic synapse density and disrupts hippocampal connectivity in offspring. Immunity 54:2611–2631.e8.

92. Grandjean J, Azzinnari D, Seuven A, Signor H, Seifritz E, Pryce CR, Rudin M (2016): Chronic psychosocial stress in mice leads to changes in brain functional connectivity and metabolite levels comparable to human depression. NeuroImage 142:544–552.

93. Tu W, Ma Z, Ma Y, Doppelf D, Zhang N (2021): Suppressing anterior cingulate cortex modulates default mode network and behavior in awake rats. Cereb Cortex 31:312–323.

94. Peeters LM, Ho R, Detrez JR, Missault S, De Vos WH, Verhoeye M, et al. (2020): Chemogenetic silencing of neurons in the mouse anterior cingulate area modulates neuronal activity and functional connectivity. NeuroImage 220:117088.

95. Markicevic M, Fulcher BD, Lewis C, Helmchen F, Rudin M, Zerbi V, Wendener N (2020): Cortical excitation/inhibition imbalance causes abnormal brain network dynamics as observed in neurodevelopmental disorders. Cereb Cortex 30:4922–4937.

96. Rocchi F, Canella C, Noell S, Gutierrez-Barragan D, Coletta L, Galbusera A, et al. (2022): Increased fMRI connectivity upon chemogenetic inhibition of the mouse prefrontal cortex. Nat Commun 13:1056.

97. Hillary FG, Grafman JH (2017): Injured brains and adaptive networks: The benefits and costs of hyperconnectivity. Trends Cogn Sci 21:385–401.

98. Sohal VS, Rubenstein JLR (2019): Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. Mol Psychiatry 24:1248–1257.

99. Trakoshis S, Martinez-Cañada P, Rocchi F, Canella C, You W, Chakrabarti B, et al. (2020): Intrinsic excitation-inhibition imbalance affects medial prefrontal cortex differently in autistic men versus women. eLife 9:e55684.

100. McCoy MC, Kircmar JL (2017): Neuromodulatory systems and their interactions: A review of models, theories, and experiments. Front Neural Circuits 11:108.

101. Coplan JD, Aronson CJ, Panthangi V, Kim Y (2015): Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches. World J Psychiatry 5:366–378.

102. Marder E (2012): Neuromodulation of neuronal circuits: Back to the future. Neuron 76:1–11.

103. Lee SH, Dan Y (2012): Neuromodulation of brain states. Neuron 76:219–222.

104. Breakspear M (2017): Dynamic models of large-scale brain activity. Nat Neurosci 20:340–352.

105. Shine JM, Breakspear M, Bell PT, Egozto Martens KA, Shine R, Koyejo O, et al. (2019): Human cognition involves the dynamic integration of neural activity and neuromodulatory systems. Nat Neurosci 22:259–296.

106. Shine JM, van den Brink RL, Hemaus D, Nieuwenhuis S, Poldrack RA (2018): Catecholaminergic manipulation alters dynamic network topology across cognitive states. Nat Neurosci 2:381–396.

107. Bradley C, Nydam AS, Dux PE, Mattingly JB (2022): State-dependent effects of neural stimulation on brain function and cognition. Nat Rev Neurosci 23:459–475.

108. Murn B, Müller EJ, Wainstein G, Shine JM (2021): The ascending arousal system shapes low-dimensional neural dynamics to mediate awareness of intrinsic cognitive states. Neuroscience 2:6016.

109. Shine JM, Aburn MJ, Breakspear M, Poldrack RA (2018): The modulation of neural gain facilitates a transition between functional segregation and integration in the brain. eLife 7.

110. Schwarz AJ, Gozzi A, Reese T, Bifone A (2007): In vivo mapping of functional connectivity in neurotransmitter systems using pharmacological MRI. Neuron 34:1627–1636.

111. Gozzi A, Schwarz AJ, Reese T, Bertani S, Crestan V, Bifone A (2006): Region-specific effects of nicotine on brain activity: A pharmacological MRI study in the drug-naïve rat. Neuripsychopharmacology 31:1690–1703.

112. Choi JK, Chen YI, Hamel E, Jenkins BG (2006): Brain hemodynamic changes mediated by dopamine receptors: Role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. NeuroImage 30:700–712.

113. Gozzi A, Tissari M, Dacone L, Agosta F, Lepore S, Lanzoni A, et al. (2011): Neuroimaging evidence of altered fronto-cortical and striatal function after prolonged cocaine self-administration in the rat. Neuripsychopharmacology 36:2431–2440.

114. Schwarz A, Gozzi A, Reese T, Bertani S, Crestan V, Hagan J, et al. (2004): Selective dopamine D3 receptor antagonist SB-277011-A potentiates pMRI response to acute amphetamine challenge in the rat brain. Synapse 54:1–10.

115. Montani C, Canella C, Schwarz AJ, Li J, Gilmour G, Galbusera A, et al. (2021): The M1/M4 preferring muscarinic agonist xanomeline modulates functional connectivity and NMDAR antagonist-induced changes in the mouse brain. Neuripsychopharmacology 46:1194–1206.

116. Grandjean J, Buehlmann D, Buere A, Signor H, Seifritz E, Vollenweider FX, et al. (2021): Psychobehavior exerts distinct effects on resting state networks associated with serotonin and dopamine in mice. NeuroImage 225:117456.

117. Gozzi A, Herdon HE, Trakoshis S, Bertani S, Crestan V, Turrini G, Bifone A (2008): Pharmacological stimulation of NMDA receptors via co-agonist site suppresses fMRI response to phencyclidine in the rat. Psychopharmacol (Berl) 210:273–284.
Brain Dysconnectivity in Rodents

118. De Simoni S, Schwarz AJ, O’Daly OG, Marquand AF, Brittain C, Gonzales C, et al. (2013): Test–retest reliability of the BOLD pharmacological MRI response to ketamine in healthy volunteers. Neuroimage 64:75–90.

119. Doyle OM, De Simoni S, Schwarz AJ, Brittain C, O’Daly OG, Williams SCR, Mehta MA (2013): Quantifying the attenuation of the ketamine pharmacological magnetic resonance imaging response in humans: A validation using antipsychotic and glutamatergic agents. J Pharmacol Exp Ther 345:151–160.

120. Javitt DC, Carter CS, Krystal JH, Kantrowitz JT, Girgis RR, Doyle OM, De Simoni S, Schwarz AJ, Brittain C, O’Daly OG, Williams SCR, Mehta MA (2013): Quantifying the attenuation of the ketamine pharmacological magnetic resonance imaging response in humans: A validation using antipsychotic and glutamatergic agents. J Pharmacol Exp Ther 345:151–160.

121. Fennis CF, Yee JR, Kenkel WM, Dumas KM, Moore K, Veenea AH, et al. (2015): Distinct BOLD activation profiles following central and peripheral oxytocin administration in awake rats. Front Behav Neurosci 9:245.

122. Pagani M, De Felice A, Montani C, Galbusera A, Papaleo F, Gozzi A (2020): Acute and repeated intranasal oxytocin differentially modulate brain-wide functional connectivity. Neuroscience 445:83–94.

123. Wellman PJ, Clifford PS, Rodriguez JA, Hughes S, Di Francesco C, Melotto S, et al. (2012): Brain reinforcement system function is ghrelin dependent: Studies in the rat using pharmacological fMRI and intracranial self-stimulation. Addict Biol 17:908–919.

124. Gozzi A, Turnini G, Piccoli L, Massagrande M, Amantini D, Antolini M, et al. (2011): Functional magnetic resonance imaging reveals different neural substrates for the effects of Orexin-1 and Orexin-2 receptor antagonists. PLoS One 6:e18408.

125. Gass N, Schwarz AJ, Sartorius A, Schenker E, Risterucci C, Linden A (2016): Cholinergic and serotonergic modulations differen- tially affect large-scale functional networks in the mouse brain. Brain Struct Funct 221:3067–3079.

126. Ioanas HI, Saab BJ, Rudin M (2022): Whole-brain opto-fMRI map of mouse VTA dopaminergic activation reflects structural projections with small but significant deviations. Transl Psychiatry 12:60.

127. Holohan S, Poplawsky AJ, Kim SG, Moghaddam B (2017): Unexpected global impact of VTA dopamine neuron activation as measured by opto-fMRI. Mol Psychiatry 22:585–594.

128. Grimm C, Frässle S, Steiger C, von Ziegler L, Sturman O, Shemesh N, et al. (2021): Optogenetic activation of striatal D1R and D2R cells differentially engages downstream connected areas beyond the basal ganglia. Cell Rep 37:110161.

129. Lee HJ, Weitz AJ, Bemm-Arias D, Duffy BA, Choy M, Kravitz AV, et al. (2016): Activation of direct and indirect pathway medium spiny neurons drives distinct brain-wide responses. Neuron 91:412–424.

130. Grandjean J, Corcoba A, Kahn MC, Upton AL, Deneris ES, Sefrit E, et al. (2019): A brain-wide functional map of the serotonergic responses to acute stress and fluoxetine. Nat Commun 10:3350.

131. Naef J, Klaiassen A, Arato J, Vyssotski AL, Harvey M, Rainer G (2018): Basal forebrain contributes to default mode network regulation. Proc Natl Acad Sci U S A 115:1352–1357.

132. Turchi J, Chang C, Ye FQ, Rusa BE, Yu DK, Cortes CR, et al. (2018): The basal forebrain regulates global resting-state fMRI fluctuations. Neuron 97:940–952.e4.

133. Zerbi V, Floriou-Servou A, Markicievic M, Vermeiren Y, Sturman O, Privitera M, et al. (2019): Rapid reconfiguration of the functional connectome after chemogenetic locus coeruleus activation. Neuron 103:702–718.e5.

134. Oyarzabal EA, Hsu LM, Das M, Chao T-HH, Zhou J, Song S, et al. (2022): Chemogenetic stimulation of tonic locus coeruleus activity strengthens the default mode network. Sci Adv 8:eabm9898.

135. Lottem E, Lörincz ML, Mainen ZF (2016): Optogenetic activation of dorsal raphe serotonin neurons rapidly inhibits spontaneous but not odor-evoked activity in olfactory cortex. J Neurosci 36:7–18.

136. Meir I, Katz Y, Lamb L (2018): Membrane potential correlates of network decorrelation and improved SNR by cholinergic activation in the somatosensory cortex. J Neurosci 38:10692–10708.

137. Zhang W, Liera A, Hashemi MM, Kaldewaij R, Koch SBJ, Beckmann CF, et al. (2020): Discriminating stress from rest based on resting-state connectivity of the human brain: A supervised machine learning study. Hum Brain Map 41:3089–3099.

138. Botzel RF (2021): Network neuroscience and the connectomics rev-olution. In: Horn A, editor. Connectomic Deep Brain Stimulation. Amsterdam: Elsevier, 25–58.

139. Hersmans EJ, Van Marie HJF, Oesewaarde L, Henckens MJAG, Qin S, Van Kesteren MTR, et al. (2011): Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. Science 334:1151–1153.

140. Mars RB, Sotiropoulos SN, Passingham RE, Sallet J, Verhagen L, Mars RB, Gladwin TE, Neubert FX, Beckmann CF, et al. (2020): Discriminating stress from rest based on resting-state connectivity of the human brain: A supervised machine learning study. Hum Brain Map 41:3089–3099.

141. Meir I, Katz Y, Lamb L (2018): Membrane potential correlates of network decorrelation and improved SNR by cholinergic activation in the somatosensory cortex. J Neurosci 38:10692–10708.