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Review

Paradigm shift in translational neuroimaging of CNS disorders

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ABSTRACT

During the last two decades, functional neuroimaging technology, especially functional magnetic resonance imaging (fMRI), has improved tremendously, with new attention towards resting-state functional connectivity of the brain. This development has allowed scientists to study changes in brain structure and function, and probe these two properties under conditions of evoked stimulation, disease and drug administration. In the domain of functional imaging, the identification and characterization of central nervous system (CNS) functional networks have emerged as potential biomarkers for CNS disorders in humans. Recent attempts to translate clinical neuroimaging methodology to preclinical studies have also been carried out, which offer new opportunities in translational neuroscience research. In this paper, we review recent developments in structural and functional MRI and their use to probe functional connectivity in various CNS disorders such as schizophrenia, mood disorders, Alzheimer's disease (AD) and pain.

Contents

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1. Introduction to functional imaging

Neuroimaging techniques have advanced greatly [1,2] and have been an essential component of studying brain structure and function in the diseased state [3,4]. In drug development research, utilizing methodology and results that can be translated from preclinical to clinical platforms can facilitate the identification of effective and ineffective therapeutic compounds to treat CNS diseases. Translational neuroimaging can provide quantitative information on brain morphology and function in preclinical models of CNS diseases, healthy human subjects, and patients.

Among the variety of imaging methods used for understanding and treating brain diseases are positron emission tomography (PET), single photon emission tomography (SPECT), X-ray/computed tomography (CT), near-infrared (NIR) optical imaging and magnetic resonance imaging (MRI). These methods utilize different parts of the electromagnetic spectrum and each has different advantages and disadvantages with respect to (i) temporal resolution, (ii) spatial resolution, (iii) sensitivity and (iv) invasiveness. Fox et al. provide a detailed review of the above modalities in CNS drug discovery [5]. There have been recent developments in terms of utilizing the translational capabilities of these modalities (Fig. 1). For example, MRI techniques have been used to evaluate drug safety [6] and identification of disease biomarkers [7]. Other imaging methods such as optical microscopy and electron microscopy have similarly been used [8]. Nonetheless, MRI is the most commonly used neuroimaging research tool today since it is noninvasive and it can reveal information about both the structure and function of the brain *in vivo*. Since its introduction in 1992 [9–12], developments in fMRI have enabled characterization of functional properties of neuronal substrates and networks. Changes in the hemodynamic responses of the brain during an evoked or stimulated state, which reflect an indirect measure of neuronal activity, can be captured over time by blood oxygen level-dependent (BOLD) fMRI. Moreover, structures of the CNS that are directly or indirectly connected functionally via axonal projections (*functional connectivity*) can also be identified with this technique [9–12].

Recently, BOLD fMRI methodology has been increasingly utilized to investigate different functional brain networks and study the changes of these networks in different brain disorders [13–16]. Among those brain networks, a particular functional network, called the *default mode network* (DMN) [17], has been identified and characterized. Clinical imaging studies have shown promise for classification of subjects that have different brain disorders such as schizophrenia [18], bipolar disorder [18,19] and Alzheimer's disease [15] based on perturbations within the DMN. In general, functional brain networks are emerging as potential neuroimaging biomarkers for various CNS disorders. Developments in functional brain imaging methods have provided new insights into how the functional properties of the brain are affected by different diseases and may have implications in CNS drug development.

In this paper, we review application of structural MRI and fMRI, functional connectivity in CNS, and their application to study various CNS disorders in preclinical and clinical studies. We review the past and current work on how neuroimaging techniques have been used as CNS disease biomarkers, particularly with the application to schizophrenia, mood disorders, AD, and pain.

1.1. Magnetic resonance imaging (MRI)

MRI can be used to selectively image different tissue types such as gray matter, white matter, cerebrospinal fluid (CSF), and axonal tracts, etc. Unlike X-ray or CT, MRI uses no ionizing radiation but rather strong magnetic fields to align the magnetization of certain atoms in the body (usually hydrogen atoms) and radio frequency (RF) pulses to systematically alter the alignment of their magnetization. These alterations produce magnetic precessions

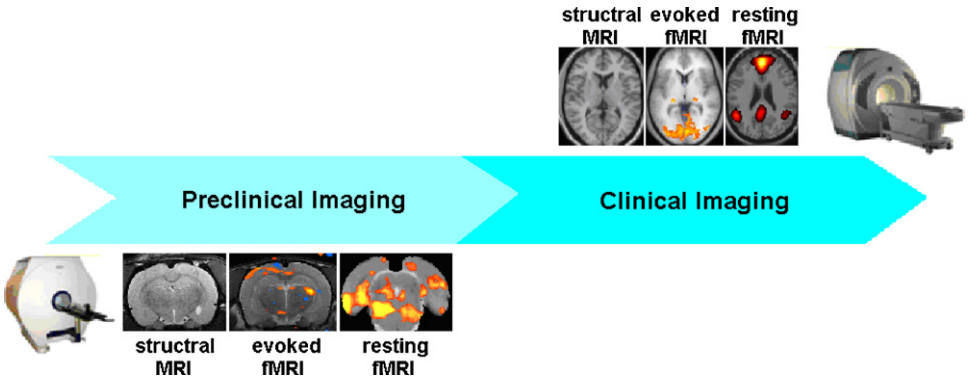

Fig. 1. Structural MRI, task-evoked functional MRI and resting-state functional MRI in preclinical and clinical settings provide the capability of translational neuroimaging.

that can be detected by the scanner and the precession characteristics depend on the tissue type. These precessions can be manipulated by spatially changing magnetic fields in such a way that atoms from different locations carry different RF signatures such as frequency and/or phase, and all this information is used to reconstruct cross-sectional images of the body. MRI provides much greater contrast between soft tissues in the body than CT does, making it very useful for neuroimaging applications, since the brain's white and gray matter structures and CSF produce different MR signals allowing us to identify different brain structures [5].

1.2. Functional magnetic resonance imaging (fMRI)

Structural MRI has been used to detect and diagnose disorders that alter the structure of the brain, e.g. stroke, hemorrhage, atrophy, and tumors. However, assessing brain function is more challenging, especially in disorders which primarily affect brain function rather than structure. For example, psychiatric disorders fall into this category, in which brain function is altered more so than structure. Brain imaging techniques that evaluate functionality by collecting data over time are called functional neuroimaging techniques. To detect functional changes in the brain, a powerful *in vivo* imaging technique which can provide good temporal (preferably milliseconds) and spatial (preferably micrometers) resolution is needed. An advantage of fMRI when compared with other imaging modalities is that multiple whole-brain images can be acquired quickly (<1 s) with sub-millimeter spatial resolution. fMRI thus allows the study of neuronal, physiological, and hemodynamic changes in the brain, making it the best modality to obtain optimal temporal and spatial resolution at the same time. fMRI data, when analyzed, can reveal which parts of the brain are activated during certain tasks, how these activations are altered by various disease, drug and stimulus conditions, and how these alterations change over time. Functional connectivity analysis can reveal which parts of the brain behave as a functional network and provides insight into overall functional connectivity between networks. fMRI data are large; therefore, they come with challenges in terms of amount of data and complexity. Typical fMRI data from a 5-min whole-brain scan can have hundreds of millions of data points. Therefore, analysis techniques which reduce the data into simpler components which explain or "summarize" the data are often employed. These analysis methods are beyond the scope of this review. Van den Heuvel and Hulshoff provide a good review of these methods [20].

fMRI studies have recently been employed in animal imaging studies for all aspects of drug development including safety, efficacy, target validation, target-compound interaction and pharmacodynamics. However, the emerging potential of translational imaging techniques has so far been underutilized. These translational techniques, once applied, can accelerate drug discovery programs and reduce costs associated with drug development.

2. Functional brain networks

In this section we review the brain networks that are active while the brain is at rest. We introduce the DMN, which reflects baseline activity of the brain and its relation to other networks when the brain is activated by a goal-oriented task or other stimuli.

2.1. Intrinsic brain activity and resting-state functional networks

Since its beginning, functional brain imaging has been used to study neuronal responses to external stimuli and to study related functional brain activity while performing the tasks. This type of activity is called *evoked* activity. In contrast, *intrinsic* activity is the ongoing neuronal and metabolic activity that is not directly associated with performing a task, but the activity while the brain is at rest. This intrinsic activity is also called *resting-state* activity. Even at rest, the human brain accounts for ~20% of the energy consumed in the body, despite representing only ~2% of the body weight. Relative to this high level of baseline energy consumption, the additional energy consumption caused by an external task is small, often less than 5% [21,22]. Studying intrinsic brain activity, which accounts for the majority of brain energy consumption, is a key to understanding brain function, but it is challenging. Developments in functional brain imaging methods have provided new insights for understanding this intrinsic activity.

2.2. Default mode network

Observation of the brain's intrinsic activity with neuroimaging methods first occurred after analysis of several PET studies conducted by Shulman et al. [23]. Their key observation was that the activity in specific brain regions during the performance of goal-oriented tasks decreased when compared with passive resting-state conditions. The areas that exhibited consistent decreases were mainly the medial prefrontal cortex, posterior cingulate, and parts of the lateral parietal cortex (see Fig. 2). This finding was soon confirmed by fMRI studies [17,24,25]. These brain areas were collectively referred to as the *default mode* in the seminal 2001 paper by Raichle et al. [17]. The network consisting of these regions has since been referred to as the *default mode network*, or DMN, and it has been shown to decrease activity across a wide variety of goal-oriented tasks when compared with the resting-state conditions. In other words it is negatively correlated with the task-positive networks, which are activated during goal-oriented tasks. To date, many unique features of this network have been studied (see Buckner et al. [26] and Hagmann et al. [27] for detailed findings).

Discovery of the DMN has introduced a paradigm of large-scale organization of intrinsic brain activity. The brain regions that make up the DMN have also been shown to exhibit coherent BOLD fMRI time-activity curves at resting-state, or spontaneous fluctuations [16]. BOLD fMRI, with good temporal and spatial resolution has allowed the study of brain network coherence and functional connectivity. First resting-state fMRI functional connectivity study involved selection of a "seed" region-of-interest (ROI) (e.g. in the somatomotor region) and correlating its ROI-averaged BOLD fMRI signal with the rest of the brain's signals [28]. Distant parts of the brain were observed to exhibit strikingly similar temporal low-frequency (<0.1 Hz) BOLD fMRI fluctuations at rest. This seed-based approach found coherence among the DMN [16] and also for other networks in the human brain [3,29]. In addition to seed-based analysis, exploratory analysis methods such as independent component analysis have revealed similar findings [14,30,31]. Coherent networks at resting-state have been also observed in monkeys [32] and rats [33].

2.3. Interpreting the resting-state fMRI signal

BOLD fMRI signal is complex [4]; it is indirect measurement of neural activity through measuring the hemodynamic response. Therefore, the BOLD fMRI signal also has non-neural components such as physiological sources (e.g. changing cardiac and respiration rate, blood flow, blood volume) as well as noise sources (e.g. subject motion, thermal noise, scanner drifts, magnetic field inhomogeniety). Effects of these confounding signals have been well-studied and various methods have been developed to regress out the effects of these signals. Signal sources like respiration and cardiac pulsing are usually monitored and/or measured during the fMRI experiment and they are filtered out by signal processing techniques. Subject motion can be estimated by motion–detection

algorithms and it can be compensated. Due to these confounding components, caution need to be exercised while interpreting the fMRI signal.

In addition, analysis of resting-state fMRI data also varies in complexity. If a priori knowledge about the region-of-interest is available, analysis using seed voxels is simple yet powerful approach. Otherwise, exploratory or data-driven approaches such as independent or principal component analysis or spectral analysis can be used. However, the DMN can be consistently found using different analysis methods in multi-center, large-cohort studies [34].

Overall, there is great evidence supporting the physiological basis of BOLD signal based on resting-state fMRI of living vs. dead brain of animals [35]. For a comprehensive review of how various confounding components effect the resting-state BOLD fMRI signal, how they can be corrected to a certain degree, and how fMRI is used as evidence supporting the neural basis of BOLD signal, see reference [4].

2.4. Applications of fMRI in translational medicine

Although fMRI is still in the earliest stages of translation from animal imaging to human imaging applications, it is beginning to make meaningful contributions to CNS drug discovery and development [36]. For example, a recent in-house awake rodent imaging study demonstrated its predictive value via identification of the pharmacological action site with $\alpha4\beta2$ nicotinic receptor binding in a dose related manner. Such pharmacological MRI (phMRI) data along with corroborative findings from *ex vivo* autoradiographic binding studies provide evidence of A-85380 and ABT-594s unique central effect [37]. Besides direct assessment of receptor binding via phMRI, treatment effects to the CNS can also be evaluated through an indirect approach. Glial cell line-derived neurotrophic factor (GDNF)-induced functional changes of basal ganglia in hemiparkinsonian monkeys via phMRI to a direct apomorphine challenge has been reported in a recent study. GDNF has been proven to halt or reverse progressive degeneration of the nigrostriatial dopamine system in a model of Parkinson disease. Parkinsonian features were improved and apomorphine-evoked activation in the dopamine denervated putamen was attenuated by the chronic intraputamenal infusion of GDNF [38]. Beyond a few preclinical fMRI applications in CNS drug discovery, application of human fMRI studies for the discovery and development of new therapies are implicated in the following areas: (1) relating molecular target to behavior; for example, addiction; (2) enrichment of study populations with treatment responders; (3) differentiating strong placebo responders; (4) pharmacodynamic markers; (5) pharmacokinetic markers; (6) potentially more sensitive measures of treatment response for example, in analgesia development [36]. However, like any technology, there are limits and caveats that worth noting. How valid is the use of fMRI in CNS drug evaluation? How sensitive and reproducible is this? Is it a population-based approach or an individual approach? Are global or local changes produced by pharmacologic agents altering afferent inputs to the brain, incidental to cardiovascular changes or are they a nonspecific functional response? Standards of subject inclusion criteria, specificity of stimuli, data collection and analysis are needed for advancement of translational neuroimaging [39].

3. Use of functional networks as neuroimaging biomarkers of CNS disorders

3.1. Mood disorders: depression and anxiety

Depression and anxiety are mood disorders during which emotions are disturbed. Major mood disorders can be either unipolar or bipolar, with unipolar depression being the most common mood disorder. Unipolar depression has at least three of the following symptoms: disturbed sleep, diminished appetite, loss of weight, loss of energy, slowing down of thoughts and actions, restlessness, difficulty in concentrating, indecisiveness, decreased sex drive, feelings of guilt, worthlessness, pessimism, and suicidal thoughts. Unipolar depression shows the characteristics of a group of disorders rather than a single disorder and three subtypes are commonly distinguished: melancholic depression, atypical depression, and dysthymia. Bipolar disorder patients experience both manic and depressive episodes. Depressive episodes have symptoms similar to those of unipolar disorder. Manic episodes are characterized by elevated and irritable mood lasting at least seven days with symptoms of increased energy and activity, distractibility, decreased need for sleep, over-eating, over-spending, and in severe cases, hallucinations and delusions. Some patients with bipolar disorder switch between depression and mania within minutes [40].

The brain regions involved in emotional behavior, such as the amygdala, hypothalamus, nucleus accumbens, parts of the brain stem, and parts of the frontal cortex which process and make decisions based on emotions, have been hypothesized to show abnormal activity in mood disorders.

3.1.1. fMRI studies of mood disorders

Patients with unipolar and bipolar mood disorders have functional abnormality in the subgenual prefrontal cortex, especially areas ventral to the genu of the corpus callosum [41]. The activity in this area is decreased and increased during depressive and manic phases of the mood disorders, respectively. These results have been supported by animal studies and are consistent with the above mentioned hypothesis, since the subgenual prefrontal cortex has extensive connections with the regions that are involved in emotional behavior [40]. This is also consistent with the fact that people who have subgenual prefrontal cortex lesions have difficulty processing emotional stimuli and making rational decisions in emotionally elevated cases [42]. The subgenual prefrontal cortex is included in the medial prefrontal cortex, which constitutes the anterior part of the DMN. It was predicted that the DMN should exhibit differences in mood disorders. Greicius et al. found that DMN functional connectivity with subgenual cingulate and thalamus was different in patients with depression, based on independent component analysis of their resting-state fMRI data [43]. Another study by Zhao et al. showed that DMN deactivation among patients with anxiety was significantly different compared to controls when subjects were presented with threatening words. Conversely, no difference was observed when emotionally neutral words were presented [44].

3.2. Schizophrenia

Schizophrenia is a relatively common psychotic disorder which affects about 1% of the world population [45]. Schizophrenia mainly disrupts cognition and is characterized by one or more of the following symptoms: hallucinations, delusion, disorganized speech, thought and behavior, perceptual disturbances, apathy, alogia and avolition [46,47]. It has been shown to impair episodic memory and attention [48], as well as sensorimotor function [49]. A major hypothesis for the pathophysiology of schizophrenia is the "disconnection hypothesis", which states that schizophrenia may be associated with disrupted functional brain connectivity [50].

3.2.1. fMRI and resting-state functional connectivity studies of schizophrenia

Various analysis methods [51,52] have demonstrated functional connectivity differences in schizophrenia [19,53–55]. Some

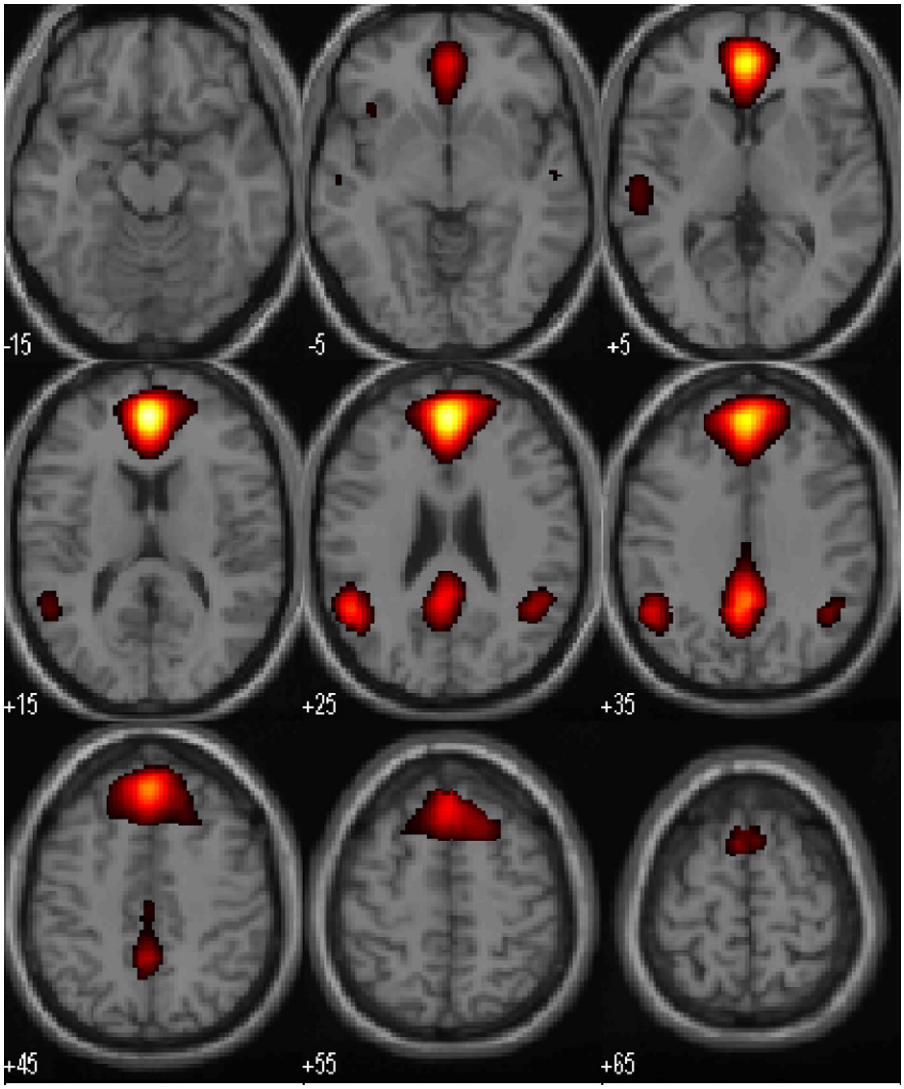

Fig. 2. The default mode network in human brain, depicted by hot colors, overlaid on a grayscale T1-weighted MRI. Hot colors depict the brain areas which are functionally connected, or in other words, inherently coherent, based on independent component analysis of BOLD fMRI data. The network mainly consists of posterior cingulate cortex, medial prefrontal cortex and lateral parietal areas. (http://icatb.sourceforge.net/groupica.htm, developed by Calhoun et al., The Mind Research Network, Albuquerque, NM, USA).

studies suggest that brain function in schizophrenia differs from healthy brain function even for sensorimotor functions, although this may result in part from medication effects [56]. However, the most consistent activation differences in schizophrenia when compared to controls involved DMN. For example, in a group of schizophrenia patients, Zhou et al. showed significantly increased resting-state functional coherence within the DMN and task-positive network, and increased anti-correlations between the two networks [57]. Jafri et al. showed that DMN and other resting-state networks exhibit increased functional connectivity in schizophrenia patients [58]. Garrity et al. showed increased temporal frequency in DMN activity in schizophrenia patients during an auditory oddball task and reported high correlation of positive symptom severity with increased deactivation in the middle frontal gyrus, left middle temporal gyrus and precuneous [13]. Liang et al. [59] and Bluhm et al. [60] also found abnormal low-frequency activity in schizophrenia patients at rest. Öngür et al. found differences in frequency distribution of fluctuations in DMN and dorsomedial prefrontal cortex of schizophrenia patients [61]. Skudlarski et al. studied both structural and functional connectivity and showed decreased correlation between structural and functional connectivity of the posterior cingulate portion of the DMN as well as in the task-positive network in schizophrenia patients performing an auditory task (see Fig. 2).

While the above methods analyzed the functional connectivity of networks during the overall fMRI scan, dynamic (windowed) analysis of functional connectivity has also been assessed. Sakoglu et al. compared the functional connectivity of brain networks in schizophrenic and healthy patients using both static and dynamic functional connectivity analysis methods, and studied how an auditory oddball task modulates functional connectivities between different networks [62–64]. Their dynamic functional connectivity analysis revealed that task-modulation of connectivity between the posterior portion of the DMN and parietal area was greater in schizophrenia patients whereas task-modulation of orbitofrontal–posterior DMN connectivity and temporal–frontal connectivity was greater in healthy controls.

All of these differences that involve DMN are potential biomarkers for schizophrenia; in fact classification attempts have been made based on these fMRI data alone. Calhoun et al. reported successful classification of schizophrenia and bipolar disorder (90% sensitivity, 95% specificity) by combining DMN (see Fig. 3) and temporal lobe functional connectivity differences [19]. Therefore, use of coherent resting-state brain networks may diagnose and

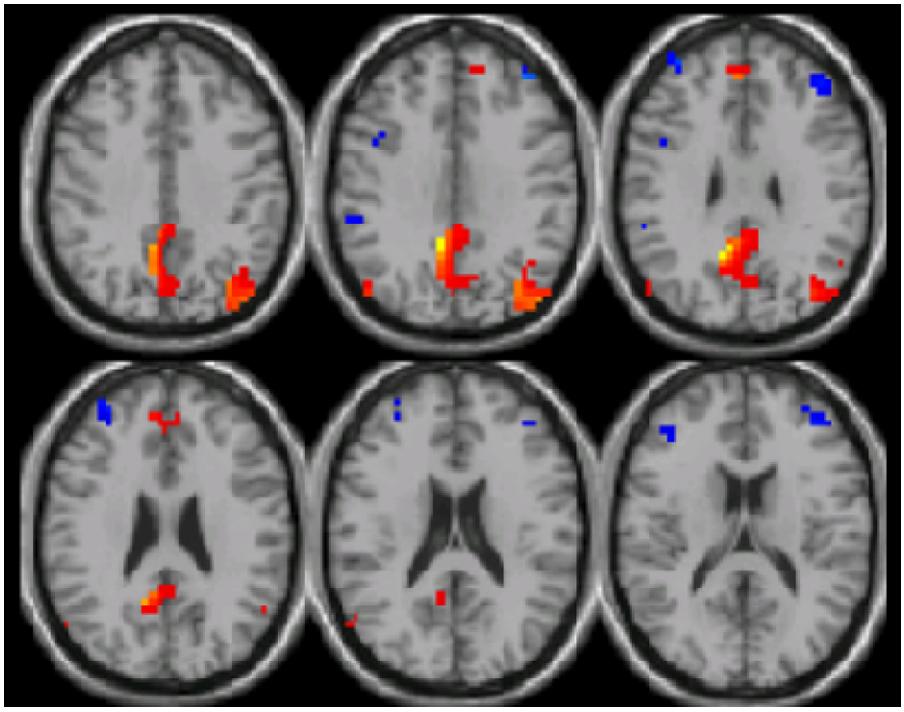

Fig. 3. Regions of the brain in which healthy controls and schizophrenia patients show significant difference in a BOLD fMRI study. Red/hot colors: Functional connectivity of the network for controls > schizophrenia patients. Blue/cold colors: connectivity in schizophrenia patients > controls. Note the significantly stronger DMN functional connectivity in the healthy controls, especially in the posterior part of the DMN (Figure printed with permission from Dr. Vince Calhoun, The Mind Research Network, Albuquerque, NM, USA). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

identify disease state. The combination of two such brain networks shows promise as a potential biomarker for these diseases.

3.3. Animal models of schizophrenia

Schizophrenia is a complex disorder that is thought to be caused by many factors such as multiple susceptibility genes, epigenetic factors, and environmental influences. Although the etiology of this psychiatric disorder remains elusive, several animal models have been developed in an attempt to mimic neurobiological substrates of schizophrenia [65]. In particular, with the advances of molecular genetic and genomic methodologies, genetic mouse models for schizophrenia have been developed, which can be useful tools to study the cellular pathogenesis of disease and potentially allow the evaluation of novel therapeutics. Indeed, multiple genes have recently been associated with schizophrenia, including NGR-1 (Neuregulin-1), DISC-1 (disrupted in schizophrenia-1), AKT, and Dysbindin-1 [66]. Mutant mice heterozygous for either NRG-1 or its receptor ErbB4 display behavioral phenotypes that overlap with mouse models for schizophrenia. Likewise, cognitive deficits have been observed in mice with expressing mutant DISC-1, suggesting a relationship between DISC-1 variants and working memory function. Characterization of brain functional connectivity of these mutant mice may provide insights into specific aspects of psychopathology that might attribute to individual genetic variants and their association with symptom clusters.

To recapitulate behavioral symptoms or neurobiological substrates of schizophrenia, several animal models have been developed and characterized [67,68]. In particular, the prenatal methylazoxymethanol acetate (MAM) treatment has been proposed as a neurodevelopmental model of schizophrenia [69,70], in which structural abnormalities in brain development are produced via the administration of MAM prenatally. By the disruption of cerebral development, dysregulation of sub-cortical dopaminergic activity and cortical atrophy are seen in MAM-exposed animals, as well as behavioral and cognitive deficits that mimic the symptoms observed in schizophrenia [69–71]. Of note, notwithstanding the extensive knowledge gained from these studies, the MAM model is typically validated by behavioral assays or *ex vivo* histological analyses. In order to develop translational imaging biomarkers, we have recently exploited structural MRI and diffusion tensor imaging (DTI) to examine the cytoarchitectural and morphological alterations in MAM-exposed rats. Recent advancements in imaging technology have led to increased adoption of DTI and other structural imaging techniques to characterize white matter pathophysiology in patients with schizophrenia [72]. Our results indicated that enlargement of lateral and third ventricles was evidently shown in MAM-exposed rats, which is consistent with one of the most reproducible pathological findings in schizophrenia patients [73]. In addition, DTI data revealed reduction of diffusion anisotropy was found in corpus callosum and cingulum of MAM-exposed animals (Fig. 4), which was confirmed by demyelination identified by luxol fast blue (LFB) histological staining. The structural abnormalities observed in these white-matter tracts also agree with imaging findings in schizophrenic patients [72,74]. Additionally, several studies have pointed to anomalies in white matter connectivity, specifically patterns of oligodendrocytic loss, which have been implicated in the etiogenesis of schizophrenia [75,76]. While clinical neuroimaging studies have revealed white matter abnormalities in the brains of patients with schizophrenia, it has been a challenge to draw a similar conclusion using imaging studies in animal models of schizophrenia, specifically models that mimic white matter abnormalities in the patient population [72,73,77,78].

The behavioral phenotypes of schizophrenia have been well characterized using animal models generated either following induction of lesions or pharmacological modification [79]. However, the field of schizophrenia research has lacked models that target the white matter abnormalities. Recently, there have

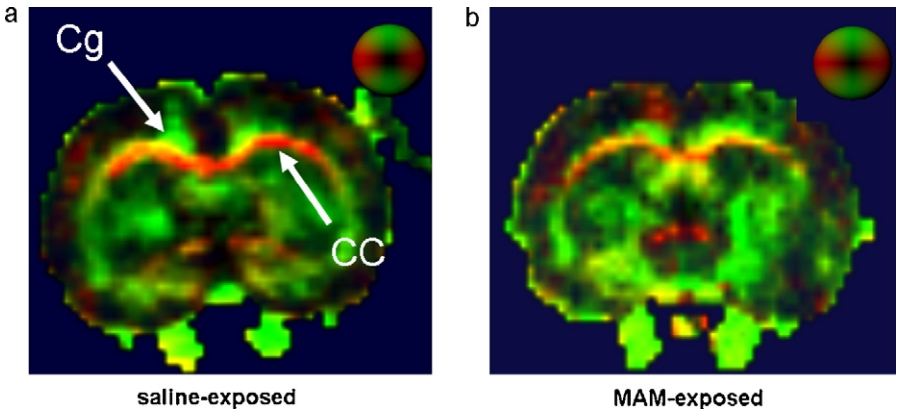

Fig. 4. DTI color-coded images obtained from (a) saline-exposed and (b) MAM-exposed rats (green color indicates rostral/caudal and red color indicates left/right white-matter tract direction. Notably, the saline-exposed animal corpus callosum (CC, red) and cingulum (Cg, green) are readily identified in the DTI data, while the intensity of these white-matter tracts was diminished in the MAM-exposed animal, indicting the reduction of diffusion anisotropy or demyelination. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

been a growing number of studies using cuprizone, a copper chelator to induce oligodendrocytic loss in mice [80,81] that mimics the white matter abnormalities associated with schizophrenia [82–85]. Cuprizone induced demyelination is a standard animal model used to study white matter connectivity loss in multiple sclerosis. Histological and *in vivo* imaging studies in this field have shown demyelination in brain regions such as the corpus callosum, hippocampus, and the cortex [86–89]. These brain regions have also been implicated in schizophrenia pathophysiology. Additionally, the behavioral deficits observed following cuprizone administration can be reversed by first and second generation antipsychotics [83].

Based on this evidence, it is hypothesized that cuprizone-induced demyelination may serve as a good model to study the etiopathogenesis of schizophrenia. Using non-invasive *in vivo* high resolution MRI techniques, we have been able to assess a disruption in white matter connectivity in the cuprizone mouse model (unpublished data). Exposing mice to a cuprizone diet induces a disintegration of the corpus callosum that can be blocked with an atypical antipsychotic, when co-administered with cuprizone (Fig. 5). These imaging data were verified by histological staining with LFB and immunohistochemical staining with myelin basic protein (MBP).

Functional connectivity studies in animal models of schizophrenia have the potential to replicate DMN related changes that have been observed in human. To the best of our knowledge, functional connectivity MRI studies in animal models of schizophrenia have not yet been conducted.

3.4. Alzheimer's disease

Physicians often recommend MRI when investigating whether a person has AD, mainly to rule out other possible causes for cognitive impairment, such as a brain tumor or blood clot. But recent research suggests that MRI (from structural MRI to fMRI to resting-state brain connectivity) could provide prognostic value by revealing changes in the brain even before AD symptoms appear.

3.4.1. Structural MRI in confirmation and diagnosis of AD

In AD, anatomical or structural MRI assessments are part of the routine workup of clinical conformational or differential diagnosis [90]. Anatomical imaging can be used as a tool for differential

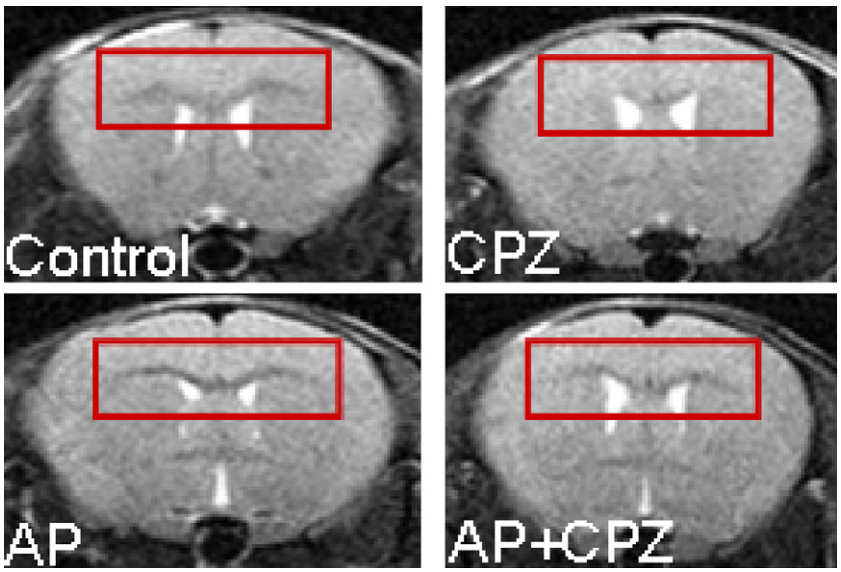

Fig. 5. Representative T2-weighted MRI mouse brain images under four different treatment conditions: control (regular chow diet), cuprizone (CPZ), an atypical antipsychotic (AP) co-administered with CPZ (AP + CPZ), and atypical antipsychotic and regular chow diet (AP). Corpus callosum is highlighted in the boxed region. Clear T2 signal hypointensity observed in control, AP and AP + CPZ treated mice, but not in CPZ treated group.

diagnosis to eliminate other possible causes of cognitive impairment (e.g., hydrocephalus, inflammatory and demyelinating lesions, and other space-occupying lesions), although AD is the most common cause of dementia [91,92].

Structural MRI studies in human subjects diagnosed with AD or mild cognitive impairment (MCI) consistently reveal brain atrophy in the entorhinal cortex and hippocampus [90,93–95]. At autopsy, severity of medial temporal atrophy assessed with anatomical MRI is strongly associated with severity of medial temporal degenerative pathology [94]. Atrophy in the entorhinal cortex and hippocampus on MRI scans predicts future cognitive decline and conversion to AD among individuals with MCI was illustrated in longitudinal studies in the same patients over time [90,95]. In a 3-year longitudinal study of seven members with familial AD history, three subjects who became symptomatic during the follow-up period had faster hippocampal volume reduction (5–10% annual rate) compared with normal controls and those who remained asymptomatic (<4% annual rate) [96]. In another 3-year longitudinal study of hippocampal volume measurements involving 58 controls, 43 patients with MCI, and 28 patients with AD, Jack et al. [97] reported that the annualized rate of hippocampal atrophy was most severe in AD patients. Reduction rate was greatest in AD patients ($3.5 \pm 1.8\%$), followed by those with MCI ($3.0 \pm 1.6\%$), and least in controls ($1.9 \pm 1.1\%$). Recently, an Alzheimer's disease neuroimaging initiative (ADNI) study which consisted of 84 subjects with mild Alzheimer's disease, 175 subjects with mild cognitive impairment, and 139 healthy control subjects over one year observation confirmed the predictive value of AD prognosis by measuring atrophy in the entorhinal cortex and hippocampus [98]. In this study, MCI patients with no initial brain atrophy had entorhinal cortex volume reduction of 0.4% and 0.8% in 6 and 12 months, respectively, while the average reduction rates for MCI patients with initial brain atrophy were 1.2% and 2.0%. The reduction rates in the hippocampus were 0.8% and 1.6% for the former group, and 1.9% and 3.0% for the latter group.

Thus MRI volumetric assessment may have utility in the identification of *in vivo* biomarkers for diagnosis and disease progression in AD and holds the promise to increase the efficiency for clinical trials [90,98]. Nevertheless, structural MRI has been incorporated into many clinical trials which provide complimentary information on the effects of therapy, though negative correlation has been found in a syntethic beta-amyloid (Aβ) antibody (AN1792, Elan Pharmaceuticals) responders [94].

3.4.2. fMRI investigation of AD

It is believed that the pathophysiological process of AD occurs prior to the onset of clinical diagnosis. Therefore, early therapeutic interventions provided during long asymptomatic or minimally symptomatic phase of AD might slow and perhaps ultimately prevent the progression to clinical dementia. fMRI allows *in vivo* visualization of alterations in brain function related to the earliest symptoms of AD, possibly before the development of irreversible structural damage. Many recent fMRI studies of AD focus on subjects at risk for AD by virtue of their genetics or evidence of cognitive impairment [99–101], Bookheimer et al. have investigated whether the neural activation elicited by declarative memory is related to APOE genotype, as well as whether this activation predicts later memory decline. Their results showed that the number of brain voxels that were activated during a memory task with respect to the rest condition in dorsolateral prefrontal, medial temporal and parietal regions were greater in APOE 4 allele carriers than in non-carriers (2.05% vs. 1.25%, 0.8% vs. 0.1% and 0.9% vs. 0.55% for the three regions, respectively), suggesting activation patterns revealed by fMRI may be a predictive marker for memory decline [99,102]. Further, fMRI has been used to study task-related episodic memory, a cognitive function most characteristically impaired in early AD. Sperling et al. have demonstrated that, compared to cognitively normal age-matched controls, AD patients have decreased fMRI activation in the hippocampus and related structures within the medial temporal lobe during the encoding of new memories [103]. Interestingly, several studies have also shown that in the prodromal phase of AD, brain activation might be paradoxically increased, although further longitudinal studies to investigate the pattern of alterations in functional activity over the course of prodromal AD and the relationship to AD pathology are needed [101,103].

3.4.3. Resting-state functional connectivity measurement of AD

Despite the breakthrough made by amyloid imaging in the AD brain *in vivo* (e.g. ^{11}C-labeled Pittsburgh Compound B (PiB)), the functional consequences of amyloid deposition in AD remain unknown [104]. As a noninvasive *in vivo* imaging technique, fMRI has been recognized as a valuable tool to identify brain dysfunction. A distinct advantage of resting-state functional connectivity measurement is that it does not suffer from variability related to task performance in typical fMRI and may be easier to standardize across study sites. This is not trivial since compliance and tolerance for the experimental procedures were much more challenging for probable AD patients with cognitive demand [105]. Despite practical issues, more study results support the hypothesis that disruption of functional connectivity, especially the DMN could be an alternative phenotypic marker for early diagnosis of AD [15]. Using the independent component analysis approach, studies have shown decreased resting-state activity (cluster size) in hippocampus (an area of $\sim$0.9 cm^3 showed decrease, $p < 0.05$) and posterior cingulate cortex ($\sim$50% decrease in activated volume of PCC), suggesting a decreased participation of the DMN in AD [15]. It has been reported that AD patients show decreased deactivation of the DMN in processing of attentional information, suggesting decreased resting-state activity and decreased adaptation of the DMN in comparison to healthy controls [106]. In addition, a resting-state fMRI graph analysis study revealed a decreased overall clustering of the brain network of AD in comparison to age-matched healthy controls, suggesting decreased efficiency of local information processing in AD [107]. These findings are in support of resting-state functional connectivity MEG studies, reporting decreased brain network integrity and efficiency in AD [108]. In prodromal AD, or even cognitively normal subjects, connectivity within the DMN was significantly reduced in the PiB-positive counterparts. Further, the correlation with amyloid deposition seemed specific to DMN, because no significant intergroup (PiB-positive vs. PiB-negative) differences were found in other regions (motor or visual) [109,110]. As it was shown by multiple independent laboratories that amyloid plaques disrupt resting-state DMN connectivity also in cognitively normal elderly, it was suggested that older adults defined as clinically normal by standard neuropsychological tests were not homogenous in DMN function. This should be taken into consideration for patient stratification/subject recruitment in AD clinical trial design [5,111]. Although the causality between amyloid deposition and DMN dysfunction remains to be determined, DMN dysfunction might be one of the principal causes of amyloid deposition. High levels of neural activity can result in amyloid accumulation *in vivo* [112] and nondemented elders with amyloid burden fail to deactivate DMN during memory tasks [113]. Likely, amyloid deposition and DMN dysfunction might aggravate each other in the course of AD.

3.5. Animal models of Alzheimer's disease

3.5.1. Structural MRI in the identification and validation of animal models of AD

Transgenic (Tg) mouse models of AD have become essential for developing and defining optimal pre-clinical imaging approaches

to visualize AD pathology *in vivo* as well as for understanding the genotype–phenotype interaction in this disease [114]. Tg2576 (hAPP695.SWE) and APP London (V717I) mice develop Aβ neuritic plaques [114–116]. P201S Tau transgenic mice develop Tau pathology [114]. APP/Tau mice develop amyloid deposits, NFT, and neuronal loss [117]. The 3xTg-AD mouse model (APP/Tau/PS1) is characterized by both neuritic Aβ plaques and tangles [114].

Despite the sparse application of anatomical MRI to determine brain atrophy in Alzheimer's disease animal models, work is under way in several laboratories to examine the effect of immunotherapy-based approaches to treat AD. Feasibility of screening antibodies *in vivo* with reduced microhemorrhage liability using MR microscopy has been investigated, since an important mechanistic-related safety concern is the risk of exacerbating incidence of microhemorrhages associated with rapid removal of Aβ deposits found in blood vessels or brain parenchyma [118–120]. Several preclinical reports with non-selective antibodies that bind and remove deposited Aβ plaque and soluble Aβ have indicated an increased incidence of microhemorrhages in aged APP transgenic mice using histological techniques [118–120].

In recent studies conducted at Abbott Laboratories [121] we aimed to develop an *in vivo* cerebral microhemorrhage biomarker using MRI and determine the effects of 12 weeks treatment with two anti Aβantibodies, 6G1 and 8F5, compared to PBS control in aged Tg2576 mice. 6G1 is a non-selective antibody that binds soluble and deposited Aβ, whereas 8F5 is a more selective antibody with a lower affinity for deposited Aβ [122]. MRI imaging was performed on a 7T horizontal bore scanner using gradient echo T2*-weighted MR microscopy (100 μm × 100 μm × 400 μm). Cerebral microhemorrages using MRI were quantified at baseline and after 12 and 18 weeks of treatment and compared to histological hemosiderin staining in each animal. Our results show that MRI can reliably detect microhemorrhages of ≥60 μm size at baseline and after 12 and 18 weeks of treatment in the same animals, and significantly correlates with histological results. This provides a new imaging safety biomarker that can be applied to longitudinal preclinical antibody screening. T2*-weighted gradient echo MRI has been used for cerebral microhemorrhage diagnosis in humans [123,124], and our study using an identical imaging contrast provides a straightforward screening platform for a safer vaccine which is translatable to humans. 6G1 and 8F5, however, both increased microhemorrhage incidence when compared to PBS treated Tg2576 mice. A highly selective antibody for soluble Aβ is needed to address the question of whether antibodies that do not bind to deposited Aβ have no microhemorrhage liability.

3.5.2. *fMRI in the identification and validation of animal models of AD*

To examine animal models of AD, brain function in amyloid precursor protein 23 (APP23) transgenic mice that reproduce the neuropathological alterations associated with AD was characterized using CBV-based fMRI [125]. Using a forepaw electrical stimulation paradigm, Mueggler et al. found that the hemodynamic response of APP23 mice decreased with increasing age and stimulus amplitude when compared with wild-type animals, and the observed age-dependent dysfunction in APP23 mice was attributed in part to a compromised cerebrovascular reactivity [125]. Nonetheless, it was conceivable that this might be used for assessment of disease progression and therapy. We have developed a non-invasive model of cerebral vasoactivity using fMRI, which potentially can be used as a biomarker for disease-modifying efficacy of novel small molecule and biologics drugs [126]. We have shown that Aβ (1–40) significantly decreases CBV in a quantifiable, dose-related and region-specific manner (e.g. 9.6% decrease in Hippocampus with a 0.1 mg dose and 4.7% decrease with 0.01 mg dose), while Aβ (40-1) does not elicit any significant change in vascular response. More importantly, these findings demonstrate, for the first time, the feasibility of characterizing pathogenic Aβ (1–40)-induced vascular dysfunction *in vivo* using a non-invasive approach that might ultimately be translatable to AD [126]. It is conceivable that this technique can be readily applied to preclinical screening in a longitudinal manner for novel drugs or antibodies targeting disease modification. Although multiple AD mouse models are available, no AD animal model has been found to recapitulate AD pathophysiology because they emphasize only partial aspects of AD pathology [114]. For example, using a combination of FDG-PET and fMRI, we examined the Tg2576 mouse for global and regional measures of brain glucose metabolism at 7 and 19 months of age. We observed that at younger ages, when some plaque burden and cognitive deficits have been reported, Tg2576 mice showed hypermetabolism as assessed with FDG-PET. This hypermetabolism decreased with age to levels similar to wild type (WT) counterparts such that the 19 months old Tg mice did not differ from age matched WTs. Using cerebral blood volume (CBV) fMRI, we demonstrated that the hypermetabolism observed in Tg mice at 7 months could not be explained by changes in blood volume as no differences were observed when compared to WTs. Taken together, these data identify brain hypermetabolism in Tg2576 mice that can not be accounted for by changes in vascular compliance. Instead the hypermetabolism may reflect a neuronal compensatory mechanism. Our data are discussed in the context of disease biomarker identification and target validation, suggesting little or no utility for translational neuronal metabolism-based studies using Tg2576 mice [127].

3.5.3. *Resting-state functional connectivity measurement in animal models of AD*

Contrary to the limited reports of applying resting-state functional connectivity method in animal models of AD, we have conducted functional connectivity MRI pilot studies, which demonstrate impaired brain functional connectivity in rats with amygdala lesions. Amygdala projections to hippocampus are blocked, resulting in dysfunctional amygdala and hippocampus interaction, which is relevant to memory and emotion problems [128]. Fig. 6(e) shows decreased functional connectivity between amygdala and hippocampus in a lesioned rat vs. a sham rat (correlation coefficient of 0.8 vs. 0.1). Our ongoing studies include: (1) feasibility of detection of functional connectivity MRI in naïve rats in a test-retest paradigm; (2) assessment of deficit in functional connectivity in AD and schizophrenia animal models or changes in brain trajectory via fMRI; (3) detection of pharmacological challenge induced functional connectivity from fMRI signal changes.

3.6. *Pain*

The presence of chronic pain is known to induce morphological and functional plasticity in supraspinal or central nervous system (CNS) networks [129,130]. In acute and chronic pain conditions, supraspinal or CNS networks mediate the various elements of pain perception, be it sensation, motivation or emotion. Thus, measuring functional connectivity in CNS networks such as the somatosensory or reward/aversion networks may offer an objective manner to further characterize how chronic pain functionally modifies CNS circuitry, and also if and how various pain conditions (i.e., fibromyalgia, trigeminal neuralgia or chronic back pain) differentially alter CNS circuitry. Determining how various chronic pain conditions differentially induce plasticity in CNS circuitry may in fact play an important role in defining possible pain phenotypes for distinct pain conditions. Knowledge

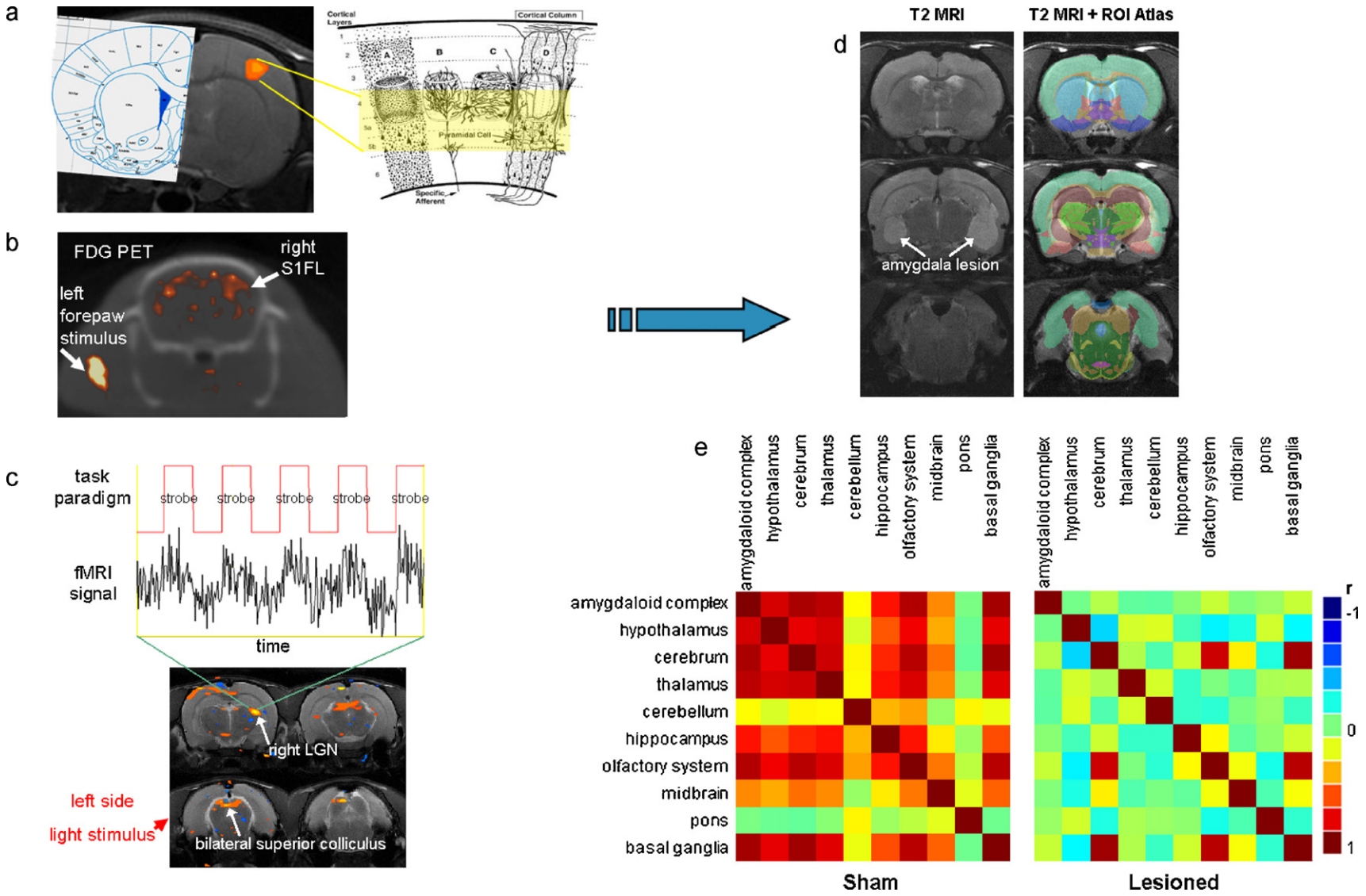

Fig. 6. (a) Activation in the front leg primary somatosensory area (S1FL) of a rat in response to left forepaw electrical stimulation, shown by fMRI. Activation is mostly in cortical layers 4 and 5. (b) Glucose uptake increase in S1FL in another rat imaged by FDG-PET. (c) Time-courses of task paradigm (visual stimulus of the left eye) and the fMRI signal; activation in right lateral geniculate nucleus (LGN) and bilateral superior colliculus in response to the visual stimulus. (d) Structural (T2-weighted) MRI of a rat with amygdala lesion model; a rat atlas consisting of various regions-of-interest (ROIs) coregistered and overlaid on the structural MRI on the right. (e) Functional connectivity among the atlas ROIs in lesioned rat. In the connectivity matrices, warm color ($r > 0$, shades of yellow and red) shows good or positive correlation between ROIs, while cold color ($r < 0$, shades of green and blue) encodes poor or negative correlation. Cold color correlation maps in lesioned rat reflect decreased correlation caused by the amygdala lesion induced impairment on brain functional connectivity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

of such pain phenotypes may improve the therapeutic strategy for different chronic pain diseases.

3.6.1. fMRI and functional connectivity studies in chronic pain

Numerous functional imaging studies have been performed where the CNS response to evoked pain (thermal, mechanical, and electric shock) is measured [131,132]. These studies have shown activity in neuronal structures (thalamus, striatum, anterior cingulate, periaqueductal gray) and networks (somatosensory, limbic, DMN) that mediate pain. Moreover, with resting-state fMRI, it is possible to extract and characterize the same structures and networks even in the absence of evoked pain [133,134]. Therefore, a characterization of the basal activity in CNS circuitry yields a very fundamental measure of how chronic pain alters the brain. Functional connectivity measures may also provide an alternative and objective means for evaluating complex conditions such as spontaneous pain [134]. The implementation of resting-state functional connectivity analysis to comprehend functional changes in chronic pain states has recently been implemented in several diseases. These conditions include chronic back pain [133], fibromyalgia [135] and diabetic neuropathic pain [136]. These and other similar studies demonstrate how resting-state functional connectivity is altered in chronic pain conditions. However, it has yet to be determined if functional connectivity measures are in fact disease biomarkers, where the onset, progression, remission and relapse of chronic pain can be tracked.

Nevertheless, given the current difficulty in obtaining translatable behavioral measures that assess pain in preclinical (i.e. tail flick or paw withdrawal) and clinical (i.e. subjective pain ratings) investigations, CNS activity in the presence of acute or chronic pain may prove to be a more ubiquitous measure across species used in preclinical investigations (e.g., mice, rats and non-human primates) and humans. Thereby, functional neuroimaging techniques and functional connectivity measures may offer complementary information to traditional behavioral endpoints and identify similarities and differences between a preclinical model for chronic pain and actual chronic pain condition in humans. This information may be very important in preclinical pharmacological studies where validation for the use of a particular animal model for pain is vital for appropriate evaluation of a potential analgesic.

3.7. Animal models of pain

There is a high demand for more efficacious analgesics that can overcome the side-effect limitations of many current treatment options such as abuse liability or sedation. Using CNS imaging (PET, SPECT and MR) to assess animal models of pain is powerful objective analysis tool complimentary to behavioral pain modeling which is largely subjective. Detection of direct CNS responses to stimulation during acute or chronic pain conditions using any or all imaging techniques is important for validation; however, these conditions might also cause alterations to DMN connectivity. If changes in the DMN could be detected using fMRI as a result of exposure to a chronic or acute pain modality then a return to baseline or sham conditions could serve as a biomarker for pain and gauge of therapeutic efficacy. Pain imaging studies and the detection of the DMN in animals could therefore serve as a translational indicator from animal to human in the evaluation of novel analgesics.

3.7.1. fMRI investigation of pain in animal models

Magnetic resonance, PET and SPECT imaging have been used to evaluate a number of pain models. Using MRI, zymosan-induced inflammatory hyperalgesia shows a bi-lateral blood-oxygenation-level-dependent (BOLD) signal increase in response to noxious heat in several sub-cortical brain regions associated with pain processing in rats [137]. Similar changes in BOLD activation were observed in the brains of rats using the formalin model of spontaneous pain [138]. An increase in BOLD signal in response to light touch was observed in the lumbar spine of rats using the capsaicin model of hyperalgesia [139]. Animal models of osteoarthritis have also been used to study pain. For example, sodium iodoacetate (MIA) injected into the knee-joint of a rat is an established model of osteoarthritis [140,141]. In one of our recent functional MRI studies of osteoarthritis model in rats, we observed that flexing (1–2 Hz) of the injected knee at day 43 post MIA injection produced an increase in BOLD signal (~4%) in several sub-cortical regions (somatosensory cortex, insula, thalamus, hypothalamus) that are involved in pain signaling. When the flexing was stopped the BOLD signal quickly returned to pre-flexing levels (Fig. 7).

In a rodent model of chronic neuropathic pain, SPECT imaging using annexin V-128 as a marker of cell stress showed increased

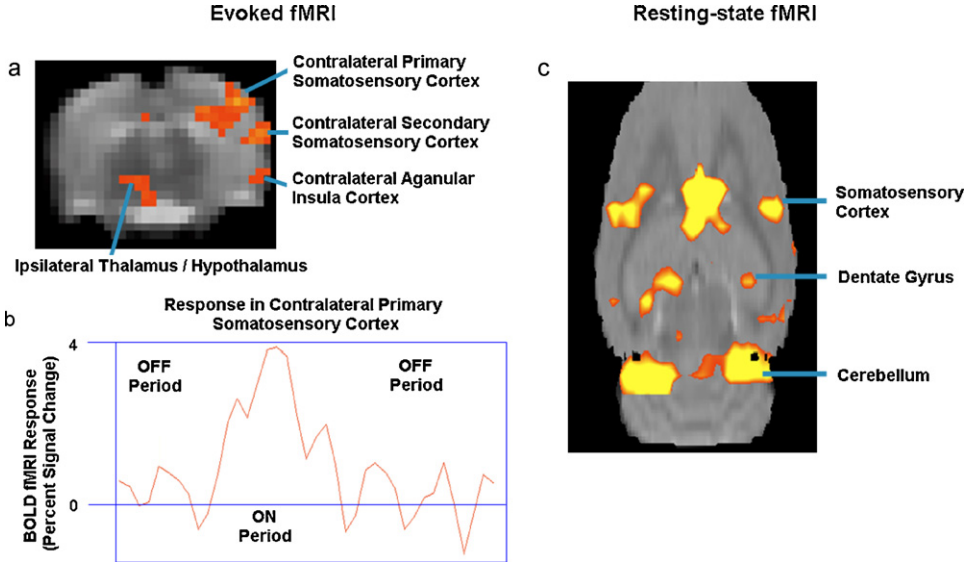

Fig. 7. (a) Average activation map showing evoked BOLD fMRI signal change in rat (Sprague–Dawley). (b) Percentage BOLD signal change over time during rest (OFF) period then evoked (ON) period and a return to rest in the same animal. Rat was anesthetized using ketamine–metatomadine in saline, test preformed at day 43 post unilateral MIA injection (5 μg/50 μl i.a.). (c) Brain regions that have synchronous BOLD oscillations with cingulate cortex in a rat at resting-state in another fMRI study.

uptake of the tracer in the dorsal spine as well as thalamic-hippocampal and sensory cortical regions [142]. The dopaminergic system (dorsal and ventral striatum) has been associated with central processing of pain signaling and [^{11}C]-raclopride, a $D_{2/3}$ antagonist, having been quantified in rats could be used to measure pain signaling [143,144]. The opioid system is well associated with pain transmission and can be investigated using PET imaging and tracers such as [^{11}C]-carfentanil and diprenorphine to measure opioidergic changes in neuronal transmission [145].

The use of imaging modalities such as these can illustrate the involvement of established pain CNS regions. The detection of DMN in rodents and how it might be affected by pain remains to be established. Small brain size and subject motion remain confounding issues in animal neuroimaging which affect detection of resting-state networks such as the DMN. Still a growing amount of evidence suggests that chronic pain can alter cortical networks and might in fact be a mechanism of chronic pain transmission and not just a result [146]. Measures of DMN alteration and their pharmacological manipulation could be a strong early indicator of future efficacy of analgesics in humans.

4. Conclusions

The brain consists of functional networks that exhibit coherent neural activation in response to external stimuli or at rest. This activation can be indirectly detected by functional neuroimaging methods such as fMRI. These functional networks exhibit changes under different CNS disease conditions such as schizophrenia, mood disorders, Alzheimer's disease and pain. Within the last decade many studies have shown that neuroimaging of the resting-state networks, especially the default mode network, has great potential to emerge as biologically-based diagnostic indicators, or biomarkers, for certain CNS disorders. Moreover, resting-state functional networks have recently been observed in animals, which is promising for potential use of resting-state networks for prognosis and diagnosis of these disorders as well as drug development for their treatment. Resting-state fMRI studies and default mode network can provide a new paradigm for understanding and treatment of CNS disorders in CNS drug discovery.

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