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Review article

Multimodal neuroimaging as a window into the pathological physiology of schizophrenia: Current trends and issues

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ABSTRACT

Visualizing the detailed brain anatomy of individuals with schizophrenia has been made possible by recent advances in magnetic resonance imaging (MRI). Although structural MRI cannot be currently used to diagnose schizophrenia, multimodal MRI can reveal insightful information on key clinical aspects of the pathological physiology of schizophrenia. However, in this regard, the number of multimodal MRI studies is still limited and definitely required. In this review, we discuss how classical and popular theories on the pathological physiology of schizophrenia can be re-examined using neuroimaging studies, and also discuss how multimodal MRI studies may provide additional findings. The pathological hypotheses examined include the "progressive brain disease hypothesis" and "disconnection hypothesis". This article is discussed mainly based on recent findings published by our research group.

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1. Introduction

In research settings, a dataset consisting of multiple imaging modalities can be obtained from a single magnetic resonance imaging (MRI) scanning session, including structural, diffusion tensor, and functional MR images. Whereas MRI analysis using a single data processing method can capture a certain pathological aspect of schizophrenia, the combined application of multiple imaging modalities with multiple image processing protocols may elucidate a far more comprehensive understanding of its nature (Sui et al., 2012) (Fig. 1). Representative multi-modal MRI studies on schizophrenia offer an opportunity to reappraise common beliefs of schizophrenia pathology, yet are still limited (Table 1). In this paper, we reexamine some of the major hypotheses and beliefs from the viewpoint of neuroimaging, and discuss the future direction of multimodal MRI studies.

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Table 1
Multimodal neuroimaging studies of schizophrenia.

Study	Subjects	Modalities	Findings
Calhoun et al. (2006)	15 chronic SZ, 15 HC	GM, task fMRI	Group differences in bilateral parietal and frontal as well as posterior temporal regions in GM were associated with bilateral temporal regions activated by the auditory oddball target stimuli
Miyata et al. (2007)	40 SZ and 36 HC	WM, DTI	SZ showed smaller anterior/total CC length and area rates
Schlosser et al. (2007)	18 chronic SZ, 18 HC	DTI, task fMRI	DTI analyses revealed reductions of FA in the right medial temporal lobe adjacent to the right parahippocampal gyrus, and fMRI revealed prefrontal, superior parietal and occipital relative hypoactivation in SZ
Seok et al. (2007)	30 chronic SZ, 22 HC	WM, DTI	In SZ groups, FA was significantly decreased in the left superior longitudinal fasciculus, whereas WM density was significantly increased in the left inferior longitudinal fasciculus. The mean FA value of the left frontal part of the SLF was positively correlated with the severity of auditory hallucination in the hallucinating group
Correa et al. (2008)	37 chronic SZ, 36 HC	GM, task fMRI	Canonical correlation analysis results show a correlation between fMRI and GM, with SZ showing more functional activity in motor areas and less activity in temporal areas associated with less GM as compared to HC
Michael et al. (2010)	70 chronic SZ, 70 HC	GM, task fMRI	HC have stronger correlations between GM and fMRI than SZ. Significant structural MRI–fMRI inter-regional links are detected, with regions in the cerebellum showing more positive correlations with functional regions in HC, compared with SZ
Moriya et al. (2010)	19 first episode SZ, 19 HC	GM, WM, DTI	SZ demonstrated a significant increase in the MD of the left parahippocampal gyrus, left insula, and right anterior cingulate gyrus compared with HC. No significant difference was observed in the correlation between the GM/WM volume and FA
Skudlarski et al. (2010)	27 chronic SZ, 27 HC	DTI, resting state fMRI	SZ had lower anatomical connectivity and lower coherence between DTI and resting fMRI. Although anatomical connectivity nearly uniformly decreased, FC in SZ was lower for some connections and higher for others. Within the default mode network, SZ showed decoupling between structural connectivity and FC
Camchong et al. (2011)	29 chronic SZ, 29 HC	DTI, resting state fMRI	SZ demonstrated altered functional and anatomical connectivity in medial frontal and anterior cingulate gyri. In addition, frontal connectivity in SZ was positively associated with symptoms as well as with general cognitive ability measures
Koch et al. (2011)	19 chronic SZ, 20 HC	DTI, task fMRI	Decision-making under uncertainty was associated with a significantly decreased activation in a fronto-striato-cingulate network in SZ. Structurally, they exhibited increased radial diffusivity in temporal WM that was negatively correlated with activation in parts of the fronto-striato-cingulate network.
Liu et al. (2011)	10 chronic SZ, 10 HC	DTI, resting state fMRI	Decreased FC to many regions was found in SZ compared to HC; while decreased FA values in the left superior cerebellar peduncle were found in SZ. HC showed significant correlation between the FC from cerebellum and the FA values of the middle cerebellar peduncle
Marenco et al. (2012)	9 chronic SZ, 18 HC	DTI, task fMRI	SZ showed reduced total connectivity of the thalamus to the lateral frontal cortex (LPFC). The total thalamo-cortical connectivity to the LPFC predicted working memory performance and also correlated with LPFC BOLD activation, and the correlation with BOLD activation of LPFC was accentuated in SZ
Michael et al. (2011)	100 chronic SZ, 100 HC	GM, task fMRI	The whole brain correlation histograms for GM–fMRI overlapped for several load levels of the working memory task in HC, but no overlap was found in SZ for any of the load levels. GM–fMRI differential correlation clusters included the left and right superior temporal gyri and anterior cingulate. Inter-cluster GM–fMRI correlations for medium load were positive in HC but negative in SZ
Sui et al. (2011)	54 chronic schizophrenia and 48 bipolar patients, 62 HC	DTI, task fMRI	Both patient groups shared significant dysfunction in dorsolateral prefrontal cortex and thalamus, as well as reduced WM integrity in anterior thalamic radiation and uncinate fasciculus. SZ and bipolar subjects were separated by functional differences, as well as WM tracts. There were different group trends for age effects on loading parameters in motor cortex and multiple WM regions
Venkataraman et al. (2012)	19 chronic SZ, 19 HC	DTI, resting state fMRI	Our model identifies significant increases in FC between the parietal/posterior cingulate region and the frontal lobe and reduced FC between the parietal/posterior cingulate region and the temporal lobe in SZ
Sugranyes et al. (2012)	22 chronic SZ, 19 HC	DTI, task fMRI	Conventional unimodal analyses revealed both functional and structural deficits in SZ. The fMRI source implicated SZ showed hypoactivation in the regions including the anterior cingulate cortex, and hyperactivation in the frontopolar cortex. The DTI source localized reduced FA in SZ in the splenium and posterior cingulum
Zhang et al. (2012)	8 chronic SZ, 10 HC	DTI, resting state fMRI	Significant increased FCs were detected for cortico-subcortical connections between cortical ROIs and subcortical regions, and the strength of FC was mostly higher in SZ. The cortical ROIs with increased FC are localized in frontal and parietal lobes. No significant difference in the structural connectivity was found between SZ and HC
Du et al. (2013)	23 chronic SZ, 22 HC	MTR, DTS	The MTR was significantly reduced in SZ, suggesting reduced myelin content. By contrast, the apparent diffusion coefficient of N-acetylaspartate (NAA) was significantly elevated, suggesting intra-axonal abnormalities