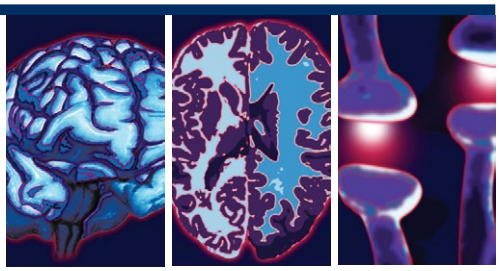
Review



Schizophrenia-Like Psychosis of Epilepsy: From Clinical Characters to Underlying Mechanisms

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Abstract

Epilepsy is associated with an increased prevalence of mental health disorders compared with general population. Psychiatric comorbidity in epilepsy is a non-negligible issue in pursuit of high life quality in patients with epilepsy. This review mainly discussed the clinical characters; diagnose approaches, and predisposing factors of schizophrenia-like psychosis in epilepsy (SLPE), which is one of the most severe comorbidity in epilepsy. Furthermore, a disconnection hypothesis underlying both schizophrenia and SLPE is proposed by accumulating evidences of abnormal large-scale brain networks in these two disorders. With the development of clinical technologies, this review also suggested more resting-state and cognition-related brain networks studies should be conducted in the upcoming future.

Keywords

Comorbidity, Schizophrenia-like psychosis of epilepsy (SLPE), Temporal lobe epilepsy (TLE), Disconnection hypothesis

Psychiatric Comorbidity in Epilepsy

According to International League Against Epilepsy (ILAE), epilepsy is defined as a brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, which is called epileptic seizures [1]. Patients with epilepsy living with sporadic seizures always suffer psychological distress [2]. A long-term of uncontrolled seizures can lead to a chronic psychotic state in more than 5% of patients, often with psychiatric symptoms of paranoid delusions and hallucinations [3]. The most frequent psychiatric diagnoses reported in people with epilepsy include psychoses, neuroses, mood disorders (e.g. depression), personality disorders and behavioural problems [4].

Psychiatric symptoms in epilepsy can be classified according to their temporal relationship with the seizure occurrence into periictal symptoms (when the symptoms occur precede/ follow/ or during the seizure occurrence), and interictal symptoms (when the symptoms occur independently of the seizure occurrence) [5]. The former often provides additional information for epileptiform zone localization, and the later substantially impairs the quality of life in patients with epilepsy. On the other hand, periictal psychosis can be prevented with seizure control, but chronic interictal psychoses require multidisciplinary and psychopharmacologic management [6]. In that case, differences between periictal and interictal psychiatric symptoms implicate different prognoses and treatments.

Periictal psychoses include pre-ictal, ictal, and post-ictal periods [5]. Ictal psychosis usually represents a complex partial status of temporal lobe origin [3]. Postictal psychoses are also significantly correlated with temporal lobe

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epilepsy, complex partial seizures, and magnetic resonance imaging (MRI) temporal plus extra-temporal structural lesions [7,8], and usually lasting for 1-6 days [9,10].

Chronic interictal psychoses are presumed to occur more often (in 20% of the psychoses in epilepsy) [11], which is 6 to 12 times more likely to occur in patients with epilepsy than in the general population [12]. Approximately 7% of patients with epilepsy develop chronic interictal schizophrenia-like psychotic syndromes [13,14], which is also known as the schizophrenia-like psychosis of epilepsy (SLPE) [15]. A more recently cohort study based on 2.27 million people reveals an increased risk of SLPE of 2.93% in people with a history of epilepsy [16]. SLPE is defined as a neuropsychiatric disorder that clinically mimicks schizophrenia, which is accompanied a paranoid-hallucinatory syndrome along with other psychopathological disturbances and cognitive dysfunctions in patients with epilepsy [15]. SLPE distinguishes itself from schizophrenia by a relative absence of negative symptoms and better premorbid as well as long term functioning [16,17].

Diagnose Approaches of SLPE

Schizophrenia is a severe mental disorder with an estimated life-time prevalence of 1%. The disorder is characterized by psychotic symptoms (delusions, hallucinations), negative symptoms (flattening of affect, apathy), and disorganization of thought and behavior (DSM-IV). SLPE has some atypical features different from those in classic schizophrenia, such as the lack of negative symptoms (i.e., preservation of warm affect), adequate or even well-preserved personalities and social functions [15,18-25]. Early studies also suggested a high frequency of delusions and religious, mystical experiences, and paranoid-hallucinatory in patients with SLPE [15,18-24,26].

Considering the clinical differences between SLPE and schizophrenia, the appropriate diagnose approaches for SLPE are discussed for years. Early studies often looked at the presence or absence of a history of psychiatric treatment or hospitalization, because of the lack of standardized methods [5]. Later on, some studies conducted self-report measures (e.g. the Beck Depression Inventory, Minnesota Multiphasic Personality Inventory) and while others relied on rating scales specifically developed for patients with epilepsy (e.g. Bear-Fedio Inventory, Washington Psychosocial Seizure Inventory) [24]. Some other study use Clinical Interview Schedule (CIS) [27,28] or General Health Questionnaire (GHQ) [29,30]. Nowadays, as the Diagnostic and Statistical Manual (DSM) of Mental Disorders criteria is the international standard with respect to classification of mental disorders, most of the studies use structured psychiatric interviews based on DSM [31,32] in addition with Positive and Negative Syndrome Scale.

Predisposing Factors of SLPE

Not all patients with epilepsy suffer with SLPE. Various studies attempt to analyse and identify the predisposing factors that may contribute to psychiatric symptoms. The most popular factor is whether temporal lobe epilepsy (TLE) is involved. Previous studies have reported an increased rate of psychiatric disturbances in patients with TLE, compare to patients with epilepsy outside temporal lobe [33-46]. As temporal lobe is the major involvement of the limbic system regulating affect and mood, some authors emphasize the role of the right hemisphere, which is suggested to have more effective limbic networks than the left hemisphere [47,48]. However, the majority of the studies implicate the left hemisphere [32,46,49-51], or find no effect of lateralization [30,52-59].

The fact that patients with TLE experience more psychiatric disorders compared to patients with extra-TLE might be correlated with the structures characterizing in schizophrenia. The relationship between temporal lobe and psychosis is supported by both clinical and neuroimaging findings [60,61].

Other predisposing factors are also involved in SLPE. SLPE group usually had a later epilepsy age of onset with more complex partial seizures, more with auras, and fewer with generalized epilepsy [51]. Neuropathology studies suggest that TLE patients with 'alien tissue' (tumors, hamartomas, gangliogliomas, focal dysplasia) have higher risks in SLPE [62,63]. A history of febrile seizure is associated with an increased risk of SLPE [64]. Antiepileptic drugs can be either negative as well as positive [65,66]. Some studies reveal that there might be common gene defects between schizophrenia and epilepsy [67,68], suggesting a genetic factor involved in psychiatric comorbidity in epilepsy.

Do Schizophrenia and SLPE Shared Common Bio-marks?

The semiology similarities between schizophrenia and SLP imply there might exist common underlying mechanisms. A previous study suggests dysfunctions of GABA receptor in both epileptic and schizophrenic patients [69]. As epilepsy is often correlated with an imbalance between excitatory and inhibitory neuronal networks, GABAergic interneurons play a critical role in maintaining this balance by modulated the spike timing and the neuronal oscillations [70-72]. These evidences raise a question about whether the abnormality of neuronal synchrony is one of the probable mechanisms underlying both schizophrenia and SLP.

Synchronization of neural responses plays an essential role in information processing, for that the temporal patterning of interactions between distant brain areas are crucial for normal cognitive functions. Uhlhaas and Singer [73] have suggested the possibility of pathological synchrony in brain-related disorders such like schizophrenia, epilepsy, autism, and Alzeimer's disease, which all exist cognitive impairments.

The disconnection hypothesis of schizophrenia has already been proposed for twenty years [74]. The subsequent researches support the hypothesis by showing white matter damages [67,75-78], and reductions of brain network synchrony [69,79-83] in people with diagnose of schizophrenia. More specifically, the abnormalities of the myelin, which could contribute to the white matter impairment, are also found to be relevant with schizophrenic symptoms [12,84,85]. These findings suggest that the deficits of synchrony between brain areas might be vital for schizophrenic psychoses.

Do reductions of synchrony exist in epilepsy? Traditionally, epileptiform activity was assumed to result from too high and too extended neural synchronization [86,87]. However, recent studies have shown that although the synchrony increase in local epileptic zones [88,89] the synchrony would rather reduce between distant brain areas [88,90]. Likewise, a DTI study reported that patients with epilepsy had reduced anatomical connectivity between distant cortical areas [91].

Would the dysconnetivities in epilepsy act a vital role in SLPE? To answer this question, data between epileptic patient with or without psychoses should be compared. More than twenty years ago, a clinical study has revealed that patients with epilepsy with SLP were distinguished from those without SLP by perivascular white-matter softening [92]. More recently, this finding is confirmed by a DTI study which shows white matter structural abnormalities in SLPE [93]).

Particularly, some recent studies suggest an abnormities of connectivity's between frontal and temporal lobes in SLPE. Neuroimaging studies have revealed a dysfunction mainly localized to temporal and frontal regions [60,93-95]. A magneto encephalography study have found working memory-related dysfunction localized to the prefrontal and left temporal cortex in patients with SLPE [96]. Using EEG technology, Canuet *et al.* [97] compare the resting-state EEG oscillations and functional connectivity between patients with schizophrenia-like psychosis of epilepsy (SLPE) and non-psychotic patients with epilepsy. The results showed the increased theta oscillations in the default mode network and increased β temporo-prefrontal connectivity in the hemisphere with predominant seizure focus in the psychotic patients and the later were correlated with positive symptoms. On the other hand, auditory evoke P300, which is generally correlated with high order cognitions, was reduced in both schizophrenic and SLEP patients [98]. One possible interpretation of these findings is that impaired connectivity between higher-order cognition cortices (e.g. frontal lobe) and lower-order sensory cortices (e.g. temporal lobe) leads to the disjoints of the society and dysfunction of perception (e.g. hallucination).

Conclusion and Future Directions

Psychiatric comorbidity in epilepsy is a long-term issue which significantly affect the quality of life in patients with epilepsy and thus cannot be ignored. Although psychiatric comorbidity has been described for half a century, the underlying neural mechanisms are still unclear. Series of recent studies suggest neural synchrony impairments in both psychiatric and epileptic disorders, which further develop a disconnection hypothesis, but whether the abnormities in large-scale cortical connections is the common mechanism is still under debate. For that psychiatric and epileptic disorders often exhibit cognitive impairments, both resting-state and task-state brain networks should be studied in future studies.

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