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Review article

Dynamic functional disturbances of brain network in seizure-related cognitive outcomes

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ABSTRACT

Epilepsy is a prevalent neurologic disorder affecting approximately 50 million people worldwide. Cognitive dysfunction induced by seizures is one of the severe comorbidities of epilepsy and epileptic syndrome, which has a negative impact on epileptic patients' quality of life. Several mechanisms may be associated with cognitive impairment in patients with epilepsy. Here, we review how the dynamic functional alterations of brain network influence seizure-related cognitive outcomes.

1. Introduction

Epilepsy is a paroxysmal neurological disorder characterized by recurrent and unprovoked seizures. Cognitive dysfunction characterized by mood and behavioral problems is a very common and severe comorbidity of epilepsy with poor social outcomes in epileptic patients (Austin, 2009). Traditional views hold that active epilepsy with recurrent seizures is the major origin of the mental and behavioral problems seen with epilepsy (Holmes, 2013). However, according to recent reviews, objective cognitive impairments are frequently present already at the onset of epilepsy or even before, which suggests seizures and impaired cognition must be considered as symptoms or expressions of a common underlying pathology (Helmstaedter et al., 2014; Helmstaedter and Witt, 2017). Although these two views are still debatable, it is generally accepted that cognition in epilepsy is multifactorially determined.

It is of note that static and dynamic factors can synergistically affect cognition in patients with epilepsy. Static factors primarily refer to the presence of acquired cerebral lesions. In the other hand, dynamic factors such as electrophysiological and metabolic changes in the brain, might be involved in seizure-related cognitive impairment (Elger et al., 2004; Helmstaedter and Witt, 2012). Neuronal oscillations and synchronization, spikes, as well as blood oxygen level-dependent alterations are the main features of epilepsy. These dynamic functional changes during seizures might cause disruptions in local connectivity and brain network which eventually result in cognitive and behavioral dysfunction (van Diessen et al., 2013). Conversely, abnormal excessive firing and synchronization of neuronal populations can contribute to repetitive seizures (Jiruska et al., 2013; Lee et al., 2013). However, the overall relationship between dynamic functional brain network and impaired cognition associated with seizures has not been clearly delineated. In this review, we will discuss dynamic changes related to neuronal oscillation and synchronization, interictal epileptiform discharges, peri-rolandic spikes, and blood oxygen level-dependent (BOLD) signals, with aim to help better understand the possible roles of functional brain network responsible for seizure-related cognitive outcomes.

2. Neuronal oscillations and synchronization

Physiologically, neuronal synchronization has been associated with cognition, perception, motor control and sleep, which is depicted by identifiable EEG patterns ranging from gamma to delta oscillations (Avoli, 2014; Ibrahim et al., 2014). Alteration in neuronal oscillations

Abbreviations: BOLD, blood oxygen leveldependent; HFO, high frequency oscillation; FCD, focal cortical dysplasia; IEDs, interictal epileptiform discharges; TCI, transient cognitive impairment; EE, epileptic encephalopathy; NCSE, non-convulsive status epilepticus; ELS, early life seizures; BCECTS, benign childhood epilepsy with centro-temporal spikes; NREM, non-rapid eye movements; AED, anti-epileptic drug; SE, status epilepticus; ESES, electrical status epilepticus during sleep; PPR, photoparoxysmal response; ADSHE, autosomal dominant sleep-related hypermotor epilepsy

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and synchronization involving different brain regions is a hallmark of epileptic activity and diverse epileptic types, including both generalized and focal epileptic disorders (Avoli, 2014; Doesburg et al., 2013), and also contributes to cognitive impairment (Holmes, 2015). Indeed, excessive high frequency oscillations (HFOs; > 80 Hz) may be a biomarker of epileptogenic cortex (Akiyama et al., 2011; Jacobs et al., 2008; Ochi et al., 2007). Moreover, epilepsy has been identified to be associated with atypical oscillatory dynamics in some other frequency ranges, such as gamma oscillations below the HFO range (Ibrahim et al., 2012; Wilke et al., 2011). This kind of oscillations (> 30 Hz) are thought to be important for information processing (Jensen et al., 2007), perception(Ribary, 2005), motor control (Schnitzler and Gross, 2005), sensorimotor integration (Llinas et al., 2005), and the maturation of functional networks underlying cognitive development (Uhlhaas and Singer, 2011) and learning difficulties (Benasich et al., 2008).

As a specific example, we turn to the seizures involving the Rolandic cortex and motor function. Seizure-induced alterations in oscillatory synchronization involving the Rolandic cortex, characterized by excessive gamma-band responses, are associated with motor impairment in children with intractable epilepsy due to focal cortical dysplasia (FCD) (Doesburg et al., 2013; Ibrahim et al., 2012). Abnormal responses in the motor cortex have also been associated with ictal desynchronization of oscillations within the Rolandic cortex, suggesting that ictal disruption of motor networks may be responsible for an altered functional response in the motor cortex, and motor function impairment (Doesburg et al., 2013). A local decrease in inter-electrode phase synchrony in the gamma bands during ictal periods, relative to interictal periods, within the motor cortex has been inferred to clinical motor weakness (Ibrahim et al., 2012). In fact, gamma-band ictal desynchronization might be a predictor of deficits than the presence of the seizure-onset zone or lesion within the motor cortex (Ibrahim et al., 2012).

3. Spikes

3.1. Interictal epileptiform discharges (IEDs)

IEDs are defined as spikes or spike-wave complexes which occur in isolation or serially (in runs) without evidence of a seizure (Ebus et al., 2012; Ung et al., 2017). It arises from the synchronous activation of neurons in the underlying cortex (Tao et al., 2007), and may influence distributed cortical networks (Gotman, 2008), then interfering with cognition(Kleen et al., 2010). Generally the occurrence of IEDs is rarely observed in healthy volunteers without a history of seizures, and the rate of IEDs in healthy people is different between children (0%–5.6%) and adults (0%–6.6%) (So, 2010). Patients with some acute or progressive brain disorders except epilepsy showed higher IEDs occurrence range from 2% to 12% (So, 2010). IEDs can be detected in 60% of patients with autism spectrum disorders without history of seizures or EEG abnormality (Chez et al., 2006).

Neurophysiological and functional neuroimaging evidence suggests that IEDs may impact cognition through either transient effects on brain processing mechanisms, or through more long-lasting effects leading to prolonged inhibition of brain areas distant from but connected to the epileptic focus (i.e. a remote inhibition effect) (Shamshiri et al., 2017; Ung et al., 2017; Van Bogaert et al., 2012). Experimental study on rats also suggested that, spikes of IEDs are necessary to guide axon sprouting during development (Carmichael and Chesselet, 2002). These spikes may lead newly sprouting axon terminals to form recurrent excitatory connections with other neurons in the same network (Staley et al., 2005). Spikes influence widespread cortical networks and interfere with normal cognition (Galanopoulou and Moshe, 2009; Kleen et al., 2010). In addition, focal neocortical IEDs during adolescence have been associated with long-lasting alterations in short-term plasticity (STP), which underlies information processing and synaptic filtering important for cognition in the prefrontal cortex (PFC) networks (Jaaskelainen et al., 2011; Rotman et al., 2011).

The disruptive effect of IEDs on cognition is supported by a wide range of observations, such as the concept of transient cognitive impairment (TCI) during an IED, cognitive deficits in epileptic encephalopathy (EE), the natural course of epileptic syndromes with continuous spike and wave activity during slow sleep, autistic regression related to epileptiform activity, the cognitive profile of benign Rolandic epilepsy, and the cognitive impact of non-convulsive status epilepticus (NCSE) (Garcia-Penas, 2011). Overall, the characteristics of IEDs, including the frequency, localization, the appearance time and duration of serial spike-wave complexes (i.e. runs of spike-wave discharges), may have different effects on cognition. In this subsection, we discuss each of these characteristics in turn.

First, with respect to the frequency of spikes, in children with short non-convulsive seizures, the occurrence of IEDs in more than 1% of the time during neuropsychological testing is associated with slowing of information processing (Aldenkamp and Arends, 2004). A high IED index may be associated with the slowing of central information processing speed and impairment of short-term verbal memory and visual-motor integration (Ebus et al., 2012).

Second, for spike localization, left-sided IEDs are associated with poor language abilities whereas right-sided or occipital IEDs are associated with poor visuo-spatial information processing (Bedoin et al., 2006; Glennon et al., 2016; Kasteleijn-Nolst Trenite et al., 1990; Piccirilli et al., 1994; Wolff et al., 2005). Furthermore, patients with left lateralized seizure onset zones, spikes outside the seizure onset zone impacted memory encoding, whereas those within the seizure onset zone did not, suggesting IEDs might disrupt cognitive processes via outside seizure onset zone (Ung et al., 2017). In general, IEDs located in the non-dominant hemisphere are associated with worse visuo-spatial function and long-term visuo-spatial memory in children (Ebus et al., 2012). Furthermore, specialization of a hemisphere may be affected by unilateral IEDs (Riva et al., 1993). Focal IEDs may exert a deleterious effect on behavior and cognition in children and adults (Hu et al., 2016; Van Bogaert et al., 2012). In one study, cognitive deficits have been observed to be independent of the lateralization of the spike focus (Volkl-Kernstock et al., 2006). A multifocal/generalized distribution of IEDs is also associated with impaired cognition when examined as a separate variable. Moreover, the association between frequent generalized early life seizures (ELS) and hippocampus-dependent cognition is well studied in rodent models and supports the view that IEDs may disrupt normal development of hippocampal networks (Chang et al., 2005; Huang et al., 1999; Huang et al., 2002; Liu et al., 1994). Hippocampal IEDs occurring in the memory retrieval period decrease the likelihood of a correct response when these are contralateral to the seizure focus or bilateral (Kleen et al., 2013). Bilateral IEDs during the memory maintenance period have a similar effect, particularly with spike-wave complexes of longer duration (Kleen et al., 2013). In humans, hippocampal IEDs may disrupt memory maintenance and retrieval but not encoding (Kleen et al., 2013). Recent clinical data suggest that, epileptiform changes in temporolimbic structures may be related to psychopathological symptoms related to stress (Bob et al., 2012). This is consistent with findings that temporal lobe epileptiform activity may provoke various somatic, sensory, behavioral, and memory disturbances similar to temporolimbic seizures and may lead to focal impaired awareness seizure-like symptoms, which are significantly associated with stress-related psychopathology (Bob et al., 2012). Moreover, experiments performed on the IEDs rat model suggest that prefrontal IEDs during development might be associated with deficits in working memory, attention, and sociability (Hernan et al., 2014). We note that these observations in rats should be considered with care, as they only resemble and offer insights into the partial and core features of human epilepsy. More evidence and better disease models are needed to elucidate how IEDs from different localization affect diverse aspects of cognitive impairment.

Third, spike-wave complexes, especially serial complexes, may have more impact than isolated spikes. When examined using spike-triggered