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REVIEW

The involvement of limbic structures in typical and atypical absence epilepsy

Filiz Yılmaz Onat[a,*], **Gilles van Luijtelaar**[b], **Astrid Nehlig**[c], **O. Carter Snead III**[d,e]

[a] *Marmara University, School of Medicine, Department of Pharmacology, Istanbul, Turkey*
[b] *Biological Psychology, Donders Centre for Cognition, Radboud University Nijmegen, Nijmegen, The Netherlands*
[c] *INSERM U 666, Strasbourg, France*
[d] *Neuroscience and Mental Health Program, Faculty of Medicine, University of Toronto; The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8*
[e] *Division of Neurology, Hospital for Sick Children, Faculty of Medicine, University of Toronto; The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8*

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Summary Typical and atypical seizures of absence epilepsy are thought to be generated by a rhythmogenic interplay between the cortex and the thalamus. However, the question remains as to which other subcortical and extrathalamic structures are involved in the pathophysiology of typical and atypical absence epilepsy. Limbic structures are not thought to be involved in typical absence seizures, since in animal models and human patients there is no evidence for the occurrence of spike-and-wave discharges of absence seizures in the limbic regions. However, there are a number of observations from animal models of absence epilepsy that point to a possibly important link between absence seizure mechanisms and limbic structures. Atypical absence seizures are distinct in many ways from typical absence seizures although they bear considerable clinical, EEG, and pharmacological resemblance to typical absence seizures. The differences between typical and atypical seizures of absence epilepsy appear to be circuitry dependent. While both typical and atypical absence seizures involve the cortico-thalamo-cortical circuitry, they each engage different neuronal networks within that circuitry. This review examines the involvement of limbic structures in typical and atypical absence seizures, shows that limbic circuitry forms an integral component of the absence epilepsy network and concludes that further knowledge of this component is important for understanding the complex relationships involved in absence epilepsy.

* Corresponding author at: Marmara University, School of Medicine, Department of Pharmacology and Clinical Pharmacology, Istanbul 34668, Turkey. Tel.: +90 216 349 2816; fax: +90 216 347 5594.
E-mail addresses: fonat@marmara.edu.tr, fonatmarmara@gmail.com (F.Y. Onat).

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Introduction

Epilepsies have been defined as generalized or localization-related (focal), on the basis of their clinical and electroencephalographic (EEG) features. The prototypical idiopathic generalized epilepsy (IGE), childhood absence epilepsy, is characterized by multiple daily episodes of typical absence seizures which consist of a brief, intermittent impairment of consciousness associated with a brief interruption of behavior and a simultaneous, time-locked EEG finding of bilateral, synchronous, and symmetrical 2.5—4 Hz spike-and-wave discharges (SWDs) (Niedermeyer, 1993; Panayiotopoulos et al., 1989; Panayiotopoulos, 1999; Crunelli and Leresche, 2002; Leresche et al., 2012).

The interconnected circuitry of the cortex and the thalamus is recognized as playing a crucial role in the typical absence seizures that characterize childhood absence epilepsy (Avanzini et al., 1992; McCormick and Contreras, 2001; Snead, 1995; Steriade and Contreras, 1995, 1998). The typical absence seizures of childhood absence epilepsy are considered to be generated by a rhythmogenic interplay between the cortex and the thalamus. Recent data indicate that SWDs may emerge from bilateral frontal lobe circuitry (Bai et al., 2011; Gupta et al., 2011; Holmes et al., 2004; Killory et al., 2011; Lüttjohann et al., 2011; Meeren et al., 2002; Polack et al., 2007; Stefan et al., 2009). It has generally been accepted that limbic structures are not involved in typical absence seizures, since in animal models and human patients there is no evidence for SWD activity in the limbic regions, nor is there synchronized unit activity in these regions along with the cortical SWDs (Inoue et al., 1993). In contrast to this, cortico-thalamo-cortical neurons show increased firing rates most often preceding or during the spike of the SWD (Vergnes et al., 1990; Seidenbecher et al., 1998; Pinault et al., 1998, 2001; Pinault, 2003). However, recent observations in models of absence epilepsy have pointed to a possibly important link between typical absence epilepsy and limbic structures.

Atypical absence seizures share the same anticonvulsant drug pharmacology as typical absence seizures but differ in semiology, associated EEG abnormalities, severity, refractoriness to medical therapy, co-morbid cognitive impairment, and association with the catastrophic pediatric epilepsy syndrome of Lennox—Gastaut (Nolan et al., 2005; Markand, 2003). These differences between typical and atypical absence seizures appear to be circuitry dependent. While both involve the cortico-thalamo-cortical circuitry, they each engage different neuronal networks within that circuitry (Perez Velazquez et al., 2007).

This review is concerned with the involvement of limbic structures in typical and atypical absence seizures and epilepsy.

General features of absence epilepsy; clinical, EEG, and pharmacological features of typical and atypical absence epilepsy

Epilepsies and/or epileptic syndromes have been placed in two major classes as generalized and localization-related (focal) according to the topical (or spatial) distribution of ictal discharges. According to previous classifications, the epilepsies and/or epileptic syndromes were further subcategorized into idiopathic, symptomatic and cryptogenic according to etiology by the Classification and Terminology Commission of the International League Against Epilepsy (ILAE) (Epilepsia, 1981, 1989). The ILAE Commission has recently revised concepts and terminology for classifying seizures and forms of epilepsy as a result of the impressive advances in the neurophysiology and molecular biology of the epilepsies and as a result, a new system of classification is under consideration (Berg et al., 2010; Berg and Scheffer, 2011).

Generalized tonic—clonic, myoclonic and absence seizures are the major seizure types seen in IGE. Either one or more of those three major seizure types may be seen in all IGE syndromes which are named according to the major seizure type, or types, present in that particular syndrome and to the age-range of onset, like, 'childhood absence epilepsy', or, 'juvenile myoclonic epilepsy'. Childhood absence epilepsy occupies a prominent position in the IGEs because they are quite common, accounting for 10—17% of all cases of epilepsy diagnosed in school-aged children (Berg et al., 2000). The typical absence seizure