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The cortical focus in childhood absence epilepsy; evidence from nonlinear analysis of scalp EEG recordings

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HIGHLIGHTS

- The transition into the absences is dominated by a frontocentral rise in nonlinear synchronisation.
- A dynamic rapidly engaging bilaterally distributed epileptic network highlights typical absences.
- Trails leading to the thalamus relaying homotopic areas to isochronous synchronisation during absences.

ABSTRACT

Objective: To determine the origin and dynamic characteristics of the generalised hyper-synchronous spike and wave (SW) discharges in childhood absence epilepsy (CAE).
Methods: We applied nonlinear methods, the error reduction ratio (ERR) causality test and cross-frequency analysis, with a nonlinear autoregressive exogenous (NARX) model, to electroencephalograms (EEGs) from CAE, selected with stringent electro-clinical criteria (17 cases, 42 absences). We analysed the pre-ictal and ictal strength of association between homologous and heterologous EEG derivations and estimated the direction of synchronisation and corresponding time lags.
Results: A frontal/fronto-central onset of the absences is detected in 13 of the 17 cases with the highest ictal strength of association between homologous frontal followed by centro-temporal and fronto-central areas. Delays consistently in excess of 4 ms occur at the very onset between these regions, swiftly followed by the emergence of "isochronous" (0–2 ms) synchronisation but dynamic time lag changes occur during SW discharges.
Conclusions: In absences an initial cortico-cortical spread leads to dynamic lag changes to include periods of isochronous interhemispheric synchronisation, which we hypothesize is mediated by the thalamus.
Significance: Absences from CAE show ictal epileptic network dynamics remarkably similar to those observed in WAG/Rij rats which guided the formulation of the cortical focus theory.

1. Introduction

Gibbs, in his pioneering work on the newly developed electroencephalogram, described in 1935 the characteristic 3 Hz spike and wave (SW) discharge of "petit mal" (Gibbs and Lennox, 1935). In 1941 Jasper and Kershman on EEGs of patients with "petit mal" seizures reported the abrupt onset and offset of bilateral highly synchronous SW discharges, and postulated a subcortical origin

Abbreviations: CAE, childhood absence epilepsy; EEG, electroencephalogram; ERR, error reduction ratio; GTCS, generalized tonic clonic seizure; ILAE, International League against Epilepsy; OIRDA, occipital intermittent rhythmical delta activity; TV-GFRF, time-varying generalised frequency response function; TV-NARX, time-varying nonlinear autoregressive exogenous model.

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as the generator of the attacks (Jasper and Kershman, 1941). A midline placed pacemaker projecting to both hemispheres could explain both the bilateral synchrony and the generalised onset and termination of the absences. Since then, the electro-clinical characteristics of absence seizures have been the subject of debate (Meeren et al., 2005; Avoli, 2012).

The electroencephalogram (EEG) of a typical absence seizure is characterised by almost identical SW discharges over distant homologous brain areas. In 1954 Pendfield proposed the centrencephalic theory based on the concept of a "centrencephalic integrating system" in the diencephalon and brainstem supposed to control consciousness (Penfield, 1952; Penfield and Jasper, 1954). Buzsaki (1991) refined this concept into the "thalamic clock" hypothesis where a thalamic pacemaker drives the cortical SW discharges. In contrast, Gibbs and Gibbs (1952) proposed the cortex as the region of the generation of the SW discharges and suggested this activity depended on diffuse cortical processes. Injection of pro-convulsive agents into the carotid (supplying the cerebral cortex) has been demonstrated to produce generalised SW discharges. In contrast, such discharges were not reported from injections into the vertebral artery, supplying the brainstem and diencephalon either in patients or cats (Bennett, 1953; Gloor, 1968; Gloor and Testa, 1974). The experiments favoured the cortical theory and provided the basis for Gloor's concept of the cortico-reticular epilepsies (Gloor, 1968), where thalamus/reticular formation and cortex were all important constituents of the epileptic network generating SW discharges.

More recently, the dynamic network mechanisms that generate the SW complexes and the anatomical pathways through which the widespread synchronisation during absence seizures occurs has been studied in WAG/Rij rats (Meeren et al., 2002, 2004, 2005). The requirement for a functionally intact cortex as a prerequisite for SW generation and that the intrathalamic circuitry in isolation is not sufficient for the cortico-thalamic oscillations to occur resulted in the formulation of the cortical focus theory (Meeren et al., 2005). Employing high spatial and temporal resolution, the dynamic spatiotemporal characteristics of the epileptic network during absences, particularly at the transition into an attack were revealed. Cortico-cortical, cortico-thalamic and intrathalamic functional coupling of relevant local field potentials, with a non-parametric nonlinear association method, the "h^2", have been demonstrated. Time lags between the anatomical regions were described, shedding light on the causality, i.e. driver-response interactions, of the various epileptic network constituents in typical absences. Meeren et al. emphasised the significance of nonlinear analysis particularly in detecting cortico-thalamic coupling in absences. They demonstrated that the h^2 nonlinear association coefficient can be significantly higher in comparison to the linear correlation coefficient r^2 and that hence, corticothalamic coupling can have a significant nonlinear component. Noticeably, the two methods could also produce a different direction of the time delay. This consistent direction of the coupling at the beginning of the seizures, the cortex leading the thalamus, would have been missed should a linear association methodology have been implemented (Meeren et al., 2002). The ERR causality test we use in this study has the ability to detect dynamic linear and nonlinear interactions over time, automatically identify the strongest of the two and then estimate synchronisation strength and corresponding time lags between pairs of EEG electrodes. Already at cellular level neurons exhibit dynamic behaviours governed by phenomena of threshold, integration and saturation (Lehnertz, 2008). These physiological facts indicate that nonlinear behaviour is introduced already at a cellular level and is valid to expect that huge neuronal networks also behave in a nonlinear way (Lehnertz, 2008). Epileptic seizures are highly nonlinear phenomena and analysis of ictal and pre-ictal EEG recordings help to better define the spatial and temporal characteristics of an epileptic network in humans (Lehnertz, 1999, 2008; Elger et al., 2000; Lehnertz et al., 2001). Other previous work has also shown that nonlinear phenomena can occur during a seizure (Lopes da Silva et al., 1989) and no assumptions can be made as to the type of interactions (linear vs nonlinear) between different constituents of an epileptic network. Particularly for the generalised epilepsies, the propagation of SW discharges occurs between cortical and thalamic constituents of the epileptic network within milliseconds and only special nonlinear analytical methods were able to determine the initial sequence of events, the cortex leading the thalamus (Stefan and Lopes da Silva, 2013). We have also shown in previous work the importance of nonlinear interactions both in focal (Sarrigiannis et al., 2014) and in generalised epilepsies (Zhao et al., 2012; He et al., 2013; Zhao et al., 2013a,b; Sarrigiannis et al., 2014). All these observations make the case for the fundamental role nonlinear complex signal analysis methods have to play in decoding the dynamic spatiotemporal characteristics of epileptic networks.

In this work we reveal on scalp EEG recordings from children with childhood absence epilepsy (CAE) the most functionally coupled brain areas during absences and show the dynamic fluctuations that take place during the attacks. We measure time lags between homologous and heterologous brain areas, including contiguous EEG recording positions, and discuss the interpretation of dynamic time lags estimates to infer the anatomical pathways involved. Synchronous neuronal activity is the hallmark of absences and we show how a very short-lived rise in nonlinear synchronisation, exclusively seen during the transition period into the absences, can identify the source of SW discharges. We compare our findings to the observations made in the genetic rat model of absence epilepsy that led to the formulation of the cortical focus theory (Meeren et al., 2002) confirmed later by other authors in other rat models of absence epilepsy (Polack et al., 2009; Depaulis et al., 2016).

2. Methods

In this study the terms causality, synchronisation and strength of association are used interchangeably and refer to the degree of phase coupling estimated between various bipolar EEG channel pairs.

2.1. Case selection for analysis

We selected patients with CAE fulfilling the current International League against Epilepsy (ILAE) diagnostic criteria (2016), but additionally excluding patients with photosensitivity. Our case selection was based on the following electro-clinical criteria: normal development, drug naïve, no previous history of generalised tonic clonic seizures (GTCS) and/or myoclonic jerks, age 4–10 years, no clinical or EEG evidence of photosensitivity, a normal background EEG, no consistent focal EEG abnormalities, regular 2.5–4 Hz generalised ictal SW discharges without fragmentations. Fragments of less than 2-second duration of generalised or focal SW abnormalities were allowed in the interictal record. To avoid hyperventilation-induced high amplitude generalised synchronous slow wave activity that could interfere with quantitative EEG (QEEG) analysis, only patients with at least one spontaneous epileptic absence occurring before or 3 or more minutes after the completion of hyperventilation were selected. EEGs recorded at a sampling rate of 500 Hz (i.e. time resolution of 2 ms) were selected.

We searched our EEG database for the term "Childhood Absence Epilepsy" and identified 231 standard EEGs recordings between January 2005 and July 2014. Of those only 17 fulfilled the stringent selection criteria.