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Altered relationship between thickness and intrinsic activity amplitude in generalized tonic–clonic seizures

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Abstract A thinner cortex has higher potential for binding GABA receptor A which is associated with larger amplitudes of intrinsic brain activity (iBA). However, the relationship between cortical thickness and iBA is unknown in intact and epileptic brains. To this end, we investigated the relationship between cortical thickness measured by high-resolution MRI and surface-based iBA derived from resting-state functional MRI in normal controls ($n = 82$) and patients with generalized tonic–clonic seizures (GTCS) only ($n = 82$). We demonstrated that the spatial distribution of cortical thickness negatively correlated with surface-based iBA amplitude at both whole-brain and within independent brain functional networks. In GTCS patients, spatial coupling between thickness and iBA amplitude decreased in the default mode, dorsal attention, and somatomotor networks. In addition, the vertex-wise across-subject thickness–iBA amplitude correspondence altered in the frontal and temporal lobes as well as in the precuneus in GTCS patients. The relationship between these two modalities can serve as a brain-based marker for detecting epileptogenic changes.

SPECIAL TOPIC: Mapping the Human Brain Function In Vivo

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1 Introduction

Generalized tonic–clonic seizure (GTCS) is a common subtype of generalized seizures [1]. GTCS patients typically exhibit bursts of bilaterally synchronous generalized spike-wave discharges on routine electroencephalogram (EEG) [2].

Advanced quantitative magnetic resonance imaging (MRI) of GTCS has revealed subtle neuroanatomical abnormalities in cortical and subcortical structures [3, 4]. Voxel-based morphometry studies of GTCS have reported decreased [5–7] or normal [8] thalamic volumes. Widespread fronto-central cortical thinning was observed in GTCS [9, 10]. Thus, surface-based morphometry (e.g., cortical thickness) with respect to the folded cortical surface can provide a direct quantitative index of cortical morphology [11].

Resting-state functional MRI studies of GTCS have revealed abnormal local and distant connectivity in thalamocortical circuits [12–16]. Epileptic events or paroxysms increase blood oxygenation level-dependent fluctuations [17]; the amplitude of low-frequency fluctuation (ALFF) has been identified as abnormal intrinsic brain activity (iBA) at rest in epileptic patients [3, 18]. In our previous studies, volume-based ALFF analyses of GTCS patients revealed abnormal iBA in the thalamus and prefrontal cortex [19, 20]. However, surface-based detection of brain activity is more sensitive and reliable than volume-based measurements [21, 22]. There have been no studies to date using surface-based ALFF with minimum inter-subject variability [23, 24] to identify iBA alterations in GTCS.

Structure–function relationships are dynamic and pleiotropic in the healthy as well as in the pathological brain [25]. A negative correlation exists between cortical thickness and brain activation during tasks; that is, a thinner cortex is more strongly activated than a thicker one [26, 27]. In the absence of a stimulus (i.e., in the resting state), cortical thickness is negatively correlated with $GABA_A$ receptor binding potential in temporal and occipital lobes [28, 29]. However, higher $GABA_A$ receptor binding potential and glucose metabolism have been linked to proportionally larger iBA amplitudes at rest, suggesting that energy-efficient synaptic neurotransmission may consume most of the brain's energy [30–32]. Recently, Qing and Gong [33] have found an evidence of a strong association between brain size/volume and volume-based iBA amplitudes, suggesting that the structural substrates underlie the iBA in the human brain. It is unclear how cortical thickness is correlated with iBA, since studies on inter-individual variability of surface-based iBA and its relationship to morphological features are spares. The association between surface-based cortical morphology and local intrinsic functional connectivity has a neurobiological significance that is likely determined by anatomical factors [24]. Clarifying this relationship can enable a more sensitive detection of subtle brain abnormalities.

In this study, we investigated the relationship between cortical thickness measured by high-resolution MRI and surface-based iBA derived from resting-state fMRI in intact and epileptic brains. Given the variability in morphometric observations resulting from different sample sizes and methodologies [3], we examined a large cohort of GTCS patients. In addition, given that surface-based iBA measured by ALFF is more sensitive and reliable than volume-based measurements, we identified alterations in surface-based iBA in GTCS at rest. Finally, we examined the association between cortical thickness and surface-based iBA to bridge the gap between them. Anatomical-functional connectivity was disrupted in GTCS [34, 35]. Based on the existed evidence, we therefore investigate whether and where the morphometric–functional relationship was altered in the GTCS to provide a repertoire of cross-modal relationships disrupted by epileptic diseases.

2 Materials and methods

2.1 Participants

Patients were consecutively enrolled at Jinling Hospital, Nanjing, China from December 2009 to January 2013 and were diagnosed according to criteria of the International League Against Epilepsy 2001 classification. Inclusion criteria for patients were as follows: (1) manifestation of typical clinical symptoms, including tonic extension of the limbs, followed by a clonic phase of rhythmic jerking of the extremities, loss of consciousness during seizures without precursory symptoms of partial epilepsy or aura; (2) no evidence of causing secondary generalized seizures, such as trauma, tumor, and intracranial infection; (3) no abnormalities in structural MRI; (4) presence of generalized spike-wave discharges on the video-EEG; and (5) right-handedness. A total of 97 patients with GTCS only met these criteria. Exclusion criteria were as follows: (1) self-reported falling asleep during resting-state fMRI scanning; (2) head translation or rotation parameters exceeding ± 1.5 mm or $\pm 1.5°$. Based on these criteria, 82 patients with GTCS only were ultimately included in the study. Sixty patients took antiepileptic drugs of valproic acid; a part of them additionally took other medications,