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Functional neuroimaging abnormalities in idiopathic generalized epilepsy

Megan L. McGill, Orrin Devinsky, Xiuyuan Wang, Brian T. Quinn, Heath Pardoe, Chad Carlson, Tracy Butler, Ruben Kuzniecky, Thomas Thesen*

Comprehensive Epilepsy Center, Department of Neurology, New York University School of Medicine, New York, NY 10016, USA

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ABSTRACT

Magnetic resonance imaging (MRI) techniques have been used to quantitatively assess focal and network abnormalities. Idiopathic generalized epilepsy (IGE) is characterized by bilateral synchronous spike–wave discharges on electroencephalography (EEG) but normal clinical MRI. Dysfunctions involving the neocortex, particularly the prefrontal cortex, and thalamus likely contribute to seizure activity. To identify possible morphometric and functional differences in the brains of IGE patients and normal controls, we employed measures of thalamic volumes, cortical thickness, gray–white blurring, fractional anisotropy (FA) measures from diffusion tensor imaging (DTI) and fractional amplitude of low frequency fluctuations (fALFF) in thalamic subregions from resting state functional MRI. Data from 27 patients with IGE and 27 age- and sex-matched controls showed similar thalamic volumes, cortical thickness and gray–white contrast. There were no differences in FA values on DTI in tracts connecting the thalamus and prefrontal cortex. Functional analysis revealed decreased fALFF in the prefrontal cortex (PFC) subregion of the thalamus in patients with IGE. We provide minimum detectable effect sizes for each measure used in the study. Our analysis indicates that fMRI-based methods are more sensitive than quantitative structural techniques for characterizing brain abnormalities in IGE.

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1. Introduction

Idiopathic generalized epilepsy (IGE) is characterized by bilateral spike–wave epileptiform discharges on electroencephalography (EEG), and recurrent generalized seizure types including absence, myoclonic, and/or generalized tonic–clonic seizures (GTCS). The classical EEG abnormalities simultaneously involve widespread, bilateral brain networks. IGE syndromes are defined primarily by predominant seizure types and age of onset. These include childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy (JME), and generalized tonic–clonic seizures (GTCS). While classification systems emphasize differences between IGE subtypes, many phenotypic features are shared, most notably EEG features, and coexistence of multiple seizure types. For example, ~85% of JME and ~50% of absence epilepsy cases develop GTCS (Mehndiratta and Aggarwal, 2002). Some patients begin with one syndrome (e.g., childhood absence) and later evolve into another syndrome (e.g., JME), while others straddle syndromes (e.g., JME and GTCS). All exhibit normal brain morphology on visual inspection of clinical magnetic resonance imaging (MRI).

While normal clinical MRI is typically required for a diagnosis of IGE, emerging quantitative MRI analysis techniques have shown subtle structural changes between patients with IGE and controls in cortical and subcortical structures, though the findings are inconsistent among studies. Thalamic volumes in IGE patients have been shown to be decreased (Bernhardt et al., 2009; Lin et al., 2009; Kim et al., 2014; Chan et al., 2006; Ciumas and Savic, 2006), increased (Betting et al., 2006) or normal (Bernasconi et al., 2003; Natsume et al., 2003). Similarly, cortical thickness or volume in IGE has been shown to be increased (Lin et al., 2009; Kim et al., 2007; Biswal et al., 2010), decreased (Bernhardt et al., 2009) or normal (Bernasconi et al., 2003; Natsume et al., 2003). To a degree, these variable findings may be explained by the use of different sample sizes and different methodologies such as voxel based or deformation-based morphometry, or manual tracing.

In contrast to uncertainty concerning subtle structural brain abnormalities in IGE, there is an extensive body of research indicating abnormal *function* of frontal and thalamic brain regions in IGE (van Diessen et al., 2013). Electrophysiology studies first demonstrated frontal lobe dysfunction in IGE (Marcus and Watson, 1966). Aberrant thalamic activity and specific cortical changes occurring primarily in the frontal lobe suggest that dysregulated thalamo-cortical interactions generate or propagate seizures (Avanzini et al., 1993). The synchronous EEG activity underlying spike–wave discharges correlates with oscillatory patterns involving interconnected cortical and thalamic neurons (Avanzini et al., 2000). Debate continues whether seizures in people with IGE arise

* Corresponding author. Tel.: +1 917 829 2016.
E-mail address: thomas.thesen@med.nyu.edu (T. Thesen).

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from the cortex, subcortex (e.g., thalamus) or simultaneously in a cortical–subcortical network.

More recent work has applied new techniques such as blood oxygen level dependent (BOLD) functional MR imaging (fMRI) to understanding the basis of IGE. Analysis of low frequency oscillations of the BOLD signal in the 0.01–0.08 Hz range from fMRI reliably assesses the resting state, when cognitive and physical demands are removed. This time course correlates synchronous, spontaneous activity that underlies strengthened synaptic connectivity between distant brain regions (Biswal et al., 1995; Berg et al., 2010). Using resting state functional connectivity (RSFC), we showed that the anterior medial prefrontal cortex (amPFC) was abnormally integrated in the default mode network in IGE patients (McGill et al., 2012). While the majority of RSFC studies focus on correlations in the time course of low frequency oscillations across brain regions, it is also possible to interrogate regional brain function by quantifying the *amplitude* of these oscillations to identify abnormal activity at rest that disrupts functional architecture (Biswal et al., 1995; Zang et al., 2007). The amplitude of low frequency fluctuations (ALFF) has a neuronal basis and is decreased in disorders that arise from a localized abnormality (e.g., temporal lobe epilepsy (TLE)) (Zhang et al., 2010) and the more widespread disorders (e.g., attention deficit hyperactivity disorder (ADHD)) (Tian et al., 2006). Abnormalities of the ALFF have been shown in thalamic and prefrontal cortex in IGE (Wang et al., 2014). The fractional ALFF, or fALFF, is used to study the proportional decrease of BOLD fluctuations in the low frequency band, which is thought to reflect spontaneous activity underlying stable, functional connections between distinct brain regions (Zou et al., 2008).

For this study, we sought to identify functional abnormalities in IGE patients as compared to normal controls using fALFF. We also apply quantitative structural neuroimaging analyses including volumetric, cortical thickness, gray–white contrast and diffusion tensor imaging (DTI) to enable function/structure correlations. Given strong prior evidence for frontal–thalamic abnormalities in IGE (Kim et al., 2014), we focus on these regions of interest, though also assess whole-brain effects. This study combines structural and functional data to characterize focal and network abnormalities in IGE. We hypothesized that morphologic abnormalities would be restricted to the frontal lobes, specifically the amPFC, while abnormal anatomic connections characterized by decreased integrity of white matter tracts on DTI would exist between the frontal lobes and the thalamus. Finally, we hypothesized that decreased fALFF in thalamic areas would be identified in dysregulated thalamocortical circuitry with the frontal lobe. In order to assist future MRI-based studies of IGE, we used power analysis methods to estimate the minimum detectable effect size for each of the methods (structural and functional) used in this study.

2. Methods

2.1. Participants

Twenty-seven patients with IGE were recruited from the New York University Comprehensive Epilepsy Center (12 women, age range 19.9–49.6 years, mean age 32.2 years) and were age- and sex-matched with 27 normal control subjects recruited from the general population (12 women, age range 20.9–48.6 years, mean age 32.1 years). Patients met criteria for IGE and had no history of developmental delay or structural brain abnormalities. Standard, diagnostic structural imaging studies were normal. Electrophysiologic evaluation with interictal, and in most patients, ictal EEG demonstrated typical generalized epileptiform spikes. Patients with focal epileptiform discharges or focal slowing on EEG were excluded. People with IGE were classified according to the International League Against Epilepsy (ILAE) classification as having absence seizures (37%), myoclonic seizures (59%), or generalized tonic–clonic seizures (78%) (Table 1). All of the study participants diagnosed with IGE were under medical treatment at the time of study, and all gave their written informed consent to participate in this study, which was approved by the Institutional Review Board of NYU Langone School of Medicine.

2.2. MRI scanning

Subjects underwent scanning on a Siemens Allegra 3 T scanner at New York University Center for Brain Imaging. All fifty-four participants had a T1-weighted MRI sequence optimized for gray–white matter contrast (TR = 2530 ms, TE = 3.25 ms, T1 = 1100 ms, flip angle = 7°, field of view (FOV) = 256 mm, matrix = 256 × 256 × 192, voxel size = 1 × 1.33 × 1.33 mm). Images were corrected for nonlinear warping caused by non-uniform fields created by the gradient coils. Image intensities were further normalized and made uniform with the FreeSurfer (4.0.2) software package. Fifteen people with IGE (8 women, mean age 30.13 years) and 15 age- and sex-matched control subjects (8 women, mean age 29.8 years) underwent resting state scans. We collected 197 contiguous echo planar imaging functional volumes for each subject (TR = 2000 ms; TE = 25 ms; flip angle = 90°, 39 slices, matrix = 64 × 64; FOV = 192 mm; acquisition voxel size = 3 × 3 × 3 mm). All participants were instructed to lie as still as possible with their eyes closed for the duration of the 6 min, 38 s scan. Eighteen people with IGE (8 women, mean age 31.71 years) and 18 age- and sex-matched normal control subjects (8 women, mean age 31.55 years) also had DTI scans. Diffusion-weighted echo-planar MRI were acquired by applying diffusion gradients along 64 directions (b value = 1000 s/mm^2) with the following parameters during the 6-min, 3 s scan (TR = 5500 ms, TE = 86 ms, FOV = 240 mm, slice thickness = 2.5 mm, voxel size = 2.5 × 2.5 × 2.5 mm).

2.3. Image processing and analysis

2.3.1. Functional: fractional amplitude of low frequency fluctuation analysis

Preprocessing steps were carried out using SPM8, (http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF) V2.0 Basic Edition (Chao-Gan and Yu-Feng, 2010). The first 10 of 197 time points were removed and slice-timing correction for interleaved acquisition was performed. The volumes were all realigned and linearly normalized to their standard MNI template in 3 mm space. To control for the effects of motion, as well as normal physiologic processes such as cardiac and respiratory rhythms, each participant's 4-dimensional (4-D) preprocessed volume was regressed on 9 predictors that modeled nuisance signals from white matter, cerebrospinal fluid and the global signal and 6 motion parameters. Correction for time series autocorrelation (prewhitening) was performed. The images were smoothed with a full-width half maximum Gaussian kernel of 4 mm. The data were then detrended. The time series was transformed to the frequency domain with a fast Fourier transform to obtain the power spectrum.

2.3.1.1. Voxelwise fALFF analysis. We compared the amplitude of the BOLD signal in the bandpass of the power spectrum between 0.01 and 0.08 Hz in patients with IGE and normal control subjects. This bandpass is often used to look at spontaneous neural activity that, when in temporal synchrony with other distinct regions, suggests functional connectivity. The fractional amplitude of the low frequency bandpass at each voxel was calculated by dividing the amplitude of the BOLD signal at the specified bandpass (0.01–0.08 Hz by the amplitude of the entire BOLD signal at that voxel (0.01–0.25 Hz)) (Zou et al., 2008).

2.3.1.2. Region-of-interest fALFF analysis. Because there is strong evidence for thalamic dysfunction in IGE, we focused specifically on this region. To determine what specific parts of the thalamus show differences in spontaneous activity at this meaningful frequency, we compared the fALFF in bilateral thalamic subregions and entire thalami. Thalamic subregions were determined from the thalamic atlas in FSL (Behrens et al., 2003) thresholded at 50%. Subregions of the thalamus that correspond

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