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Grey matter anomalies in drug-naïve childhood absence epilepsy: A voxel-based morphometry study with MRI at 3.0 T

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ABSTRACT

Background: Little is known, so far, about the cerebral structural abnormalities in drug-naïve patients with childhood absence epilepsy (CAE). We aimed to investigate regional grey matter (GM) volume differences using voxel-based morphometry (VBM) in patients and closely matched healthy control subjects.
Methods: Twenty drug-naïve patients diagnosed with CAE and 20 age- and gender-matched healthy subjects were recruited. All participants underwent structural MRI scans with a 3.0 T MR system. The differences in regional GM volumes between the two groups were determined by VBM analysis. Additional regression analyses were performed to identify any associations between regional GM volume and clinical seizure variables.
Results: Compared with controls, the patients with CAE showed less GM volume in the bilateral thalami. Furthermore, the GM volume in the bilateral thalami was negatively correlated with disease duration and age of onset in the CAE group.
Conclusions: By excluding the potential effect of medication on brain structures, our study demonstrates less GM volume in the bilateral thalami in drug-naïve patients with idiopathic CAE. Our study further provides structural neuroimaging evidence on the pathophysiology of absence seizures.

1. Introduction

Childhood absence epilepsy (CAE) is one of the most common forms of pediatric epilepsy (Berg et al., 1999). CAE is characterized by short impairments of consciousness concomitant with a typical electroencephalographic (EEG) pattern of generalized 3 Hz spike-and-wave discharges (SWD) with normal background activity (Matricardi et al., 2014; Sadleir et al., 2006). It has been demonstrated that CAE is linked to a broad spectrum of comorbidities, such as cognitive, behavioral and emotional disorders as well as linguistic deficits, which can have a serious impact on children's lives (Caplan et al., 2008; Vega et al., 2011). The disorder is likely to be multifactorial, resulting from interactions between genetic and acquired factors (Matricardi et al., 2014). However, the underlying pathophysiology remains incompletely understood (Matricardi et al., 2014). Advances in magnetic resonance imaging (MRI) techniques have made tremendous progress in understanding the pathophysiology of CAE. Many studies have reported anatomical and functional brain abnormalities, most often in the cortico-thalamo-cortical circuitry (Berman et al., 2010; Carney et al., 2010; Masterton et al., 2012; Matricardi et al., 2014; Pardoe et al., 2008; Yang et al., 2014, 2012), in patients with CAE compared to healthy controls.

To date, brain structural abnormalities by morphological studies in patients with CAE are mixed. One study using region of interest (ROI) analysis revealed significantly smaller grey matter (GM) volumes of the left orbital frontal gyrus as well as both left and right temporal lobes in patients with CAE (Caplan et al., 2009). Another ROI study did not identify any significant amygdala volume differences between the CAE and normal groups (Schreibman Cohen et al., 2009). In contrast, voxel-based morphometry (VBM) studies show a GM decrease in the thalamus (Chan et al., 2006; Pardoe et al.,

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2008), and subcallosal gyri (Chan et al., 2006), and a GM increase in the pallidum (Chan et al., 2006) in patients with CAE relative to healthy controls. A study (Tosun et al., 2011) utilizing a surface-based morphometry method further identified that children with CAE did not demonstrate the normal age-related changes involving a decrease in cortical thickness and increase in sulcal depth in the frontal, parietal, and temporal lobes. Extending to absence epilepsy (AE), two studies by Betting et al. demonstrated increased anterior thalamic volumes with the ROI method (Betting et al., 2006b), and increased grey matter concentration in the superior mesiofrontal region extending from the frontal to the parietal lobe by VBM in patients with AE (Betting et al., 2006a). In contrast, loss of volume in the bilateral thalami, putamen, and pallidum was found with the ROI method in patients with absence seizures including nine patients with CAE and two patients with juvenile absence epilepsy (Luo et al., 2011). These inconsistent results across studies were partly due to potential confounders associated with substantial methodological differences, duration of illness, and heterogeneous patients, and differences in medications. For example, valproate, one of the first line antiepileptic drugs (AEDs) for CAE, has been associated with cerebral atrophy and cognitive decline in structural neuroimaging studies (Fleisher et al., 2011; Guerrini et al., 1998; Lovett et al., 2014; Pardoe et al., 2013).

VBM, a powerful tool in vivo based on MRI scans, is being increasingly used to investigate the cerebral anatomical changes in patients with epilepsy (Ashburner and Friston, 2000; Yasuda et al., 2010). To the best of our knowledge, no experiments using VBM to explore whole brain GM anomalies in drug-naïve patients with CAE have been carried out. Such studies are not only important as a starting point for evaluating the progression of brain alterations before they can be influenced by potential confounders, but they are also critical for providing novel information relevant to the underlying mechanisms.

Thus, the primary aim of the present work was to explore the GM changes in drug-naïve patients with CAE compared to healthy controls using VBM. In addition, the relationship between the clinical features (age of onset and disease duration) and GM changes was further addressed.

2. Methods and materials

2.1. Subjects selection

Diagnosis of CAE was determined according to the criteria by the International League Against Epilepsy in 2001 (Engel, 2001). All patients and healthy controls were evaluated with the Wechsler Intelligence Scale for Children China-Revised (WISC-CR), Full Scale Intelligence Quotient (FSIQ) (Gong and Cai, 1993). The patients underwent a detailed history survey (including their first-degree relatives), physical examination, neuropsychological assessment, conventional brain structural MRI and 24 h video EEG. Exclusion criteria included: atypical spike and wave complexes; mixed seizure disorder; history of neurological (other than CAE) and psychiatric disease such as affective/anxiety disorders and attention deficit hyperactivity disorder; metabolic disorders; existence of organic brain disorder; and abnormalities in brain MRI scans. None of the patients received any AEDs before MR scanning.

Twenty patients diagnosed with CAE who were not given any AEDs were recruited (8 males, 12 females, mean age 8.65 ± 0.98 years, range 6.50–10.25 years). The mean age of onset and duration of illness in the CAE group were 6.74 ± 0.61 and 1.86 ± 0.81 years, respectively. The control group comprised 20 age- and gender-matched healthy subjects with no history of neurologic or psychiatric diseases (8 males and 12 females; mean age 8.83 ± 0.92 years). This study was approved by the local ethics committee, and all participants and their parents signed the informed consent forms.

2.2. MRI scans and VBM

High resolution T1-weighted images were acquired with a 3.0 T MRI system (Signa HDxt, General Electric Medical Systems, Waukesha, WI, USA) with a volumetric three-dimensional spoiled gradient recall sequence using an eight-channel phase array head coil producing 156 contiguous coronal slices (TR = 8.5 ms, TE = 3.4 ms, flip angle = 12°, slice thickness = 1.0 mm, gap = 0, matrix size = 256×256, field of view = $240 \times 240\ mm^2$, in-plane resolution = $0.47 \times 0.47\ mm^2$). The scan protocol was identical for all subjects.

Data processing and analysis were performed with the VBM8 of the Statistical Parametric Mapping 8 package (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running under Matlab R2010b (The Mathworks, Natick, MA, USA). All imaging analysis processes were conducted as described in detail in the VBM Tutorial (http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf). The process is briefly summarized as follows: (1) each image was inspected for reconstruction artifacts; (2) the image origin was set to the anterior commissure; (3) the T1-weighted images were normalized to the same stereotaxic space generated from the complete data set using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) registration scheme that significantly reduces the imprecision of inter subject registration; (4) the images were segmented into white matter (WM), GM and non-brain voxels (CSF, skull); (5) all images were "modulated" to weight voxel-wise values by local volume change by the Jacobian determinants; and (6) GM images were smoothed by convolution with an isotropic Gaussian kernel of 8 mm full-width at half maximum for statistical analyses. Global differences in GM, WM and CSF volumes were tested by comparing values computed from non-normalized partitions for each participant.

2.3. Statistical analyses

Statistical analyses of demographic and neuropsychological data and the volume of global GM, WM, CSF, and total intracranial volume (TIV) were performed with SPSS 17.0 software for Windows (SPSS, Chicago, Illinois, USA). Demographic and clinical variables were compared between groups using an independent two-sample *t*-test analysis for continuous variables and χ^2 tests for dichotomous variables.

Voxel-wise comparisons of the GM volume were performed between groups with SPM8 by using a general linear model. Age, gender, and TIV were included as nuisance covariates. The significance of group differences was estimated with the theory of random Gaussian fields, and significance levels were set at $p < 0.05$ (whole brain FDR corrected) while the cluster size was set at >100 voxels. The threshold was also set to $p < 0.001$ (uncorrected) to evaluate the extent of any observed clusters. Additionally, Pearson correlation analyses between the regional brain GM volume and mean age of onset, duration of illness and the scores on the WISC-CR FSIQ test were computed in the CAE group. XjView 8 (http://www.alivelearn.net/xjview8/) was used to determine the coordinates of local T-maxima.

3. Results

Age, gender and the scores on the WISC-CR FSIQ did not differ between the two groups (all $p > 0.05$). Clinical and demographic characteristics of the samples and levels of significance of the clinical variables are shown in Table 1.