Gray Matter Loss and Related Functional Connectivity Alterations in a Chinese Family With Benign Adult Familial Myoclonic Epilepsy

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Abstract: Benign adult familial myoclonic epilepsy (BAFME) is a nonprogressive monogenic epilepsy syndrome. So far, the structural and functional brain reorganizations in BAFME remain uncharacterized. This study aims to investigate gray matter atrophy and related functional connectivity alterations in patients with BAFME using magnetic resonance imaging (MRI).

Eleven BAFME patients from a Chinese pedigree and 15 matched healthy controls were enrolled in the study. Optimized voxel-based morphometric and resting-state functional MRI approaches were performed to measure gray matter atrophy and related functional connectivity, respectively. The Trail-Making Test-part A and part B, digit symbol test (DST), and verbal fluency test (VFT) were carried out to evaluate attention and executive functions.

The BAFME patients exhibited a significant gray matter loss in the right hippocampus, right temporal pole, left orbitofrontal cortex, and left dorsolateral prefrontal cortex. With these regions selected as seeds, the voxelwise functional connectivity analysis revealed that the right hippocampus showed significantly enhanced connectivity with the right inferior parietal lobule, bilateral middle cingulate cortex, left precuneus, and left precentral gyrus. Moreover, the BAFME patients showed significant lower scores in DST and VFT tests compared with the healthy controls. The gray matter densities of the right hippocampus, right temporal pole, and left orbitofrontal cortex were significantly positively correlated with the DST scores, and the gray matter density of the right hippocampus was significantly negatively correlated with the duration of illness in the patients.

The current study demonstrates gray matter loss and related functional connectivity alterations in the BAFME patients, perhaps underlying deficits in attention and executive functions in the BAFME.

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INTRODUCTION

The core symptoms of benign adult familial myoclonic epilepsy (BAFME), a nonprogressive monogenic epilepsy syndrome, include nonrhythmic myoclonus and distal subtle tremor, with or without generalized tonic-clonic seizure (GTCS). 2–4 Electrophysiology studies showed that the myoclonus or tremor originated from the cortex. To date, around 100 families with this rare form of epilepsy were reported worldwide, most of which were in Japan and Europe.5–9 Previous studies reported that mental retardation and cognitive impairments such as visuospatial impairment, executive and attention deficits were observed in some pedigrees.5,10–12 However, the pathophysiology of this intriguing disease remains unclear.

In the past decades, several neuroimaging studies attempted to explore the structural or functional brain abnormalities underlying the pathophysiology of BAFME. van Rooijelaar et al. 13 used simultaneously electromyograms and functional MRI recordings to directly relate hyperkinetic movements to brain activity in BAFME. 1H-MR spectroscopy was used to demonstrate prominent cerebellar dysfunction in BAFME. 14,15 A diffusion tensor imaging study reported decreased cerebellar fiber density in BAFME, 16 and a case study found pontocerebellar dysfunction in type 3 BAFME during aging using single photon emission computed tomography. 17 It seems that cerebellar atrophy is a convergent finding in BAFME patients.4,12,18 However, perhaps due to the infrequency and limited sample with the VFT scores, and the gray matter density of the right hippocampus was significantly negatively correlated with the duration of illness in the patients.
sizes, the gray matter and functional connectivity reorganizations of the brains of BAFME patients thus far remain uncharacterized.

Due to the potential genetic heterogeneity of different pedigrees, using subjects from the same pedigree may be of benefit to neuroimaging studies by restricting (narrowing) the risk of genetic heterogeneity. Thus, we included 11 BAFME patients from the same Chinese pedigree in the present study. The previous studies have identified 4 different disease loci in the BAFME, suggesting genetic heterogeneity of this rare disorder, but there are no studies discovering causative genes.

The genetic testing of this Chinese BAFME pedigree has been conducted before, but the results revealed absence of linkage to $q$23.3–q24.1 and $p$11.1–2.2 in this Chinese pedigree, and further genetic studies such as linkage analysis and exon sequencing are ongoing. Additionally, 15 matched healthy controls were also recruited. All of the subjects underwent both structural MRI and blood-oxygen-level-dependent functional MRI (BOLD-fMRI). We first used the structural MRI to explore gray matter density alterations in the BAFME patients relative to the healthy controls. Then, using the clusters with significant gray matter changes as regions of interest (ROIs), we used seed-based analyses to investigate gray matter atrophy-associated functional connectivity changes in the BAFME patients.

METHODS

Subjects

The participants included 11 patients with BAFME from a previously reported pedigree and 15 demographically matched healthy controls recruited via advertisements. All of the patients were right-handed and were native Chinese speakers. All of the patients received an electroencephalography (EEG) examination, and the somatosensory evoked potentials (SEPs) and long-loop reflexes were also recorded. The BAFME patients were diagnosed according to the diagnostic criteria described in previous studies. Exclusion criteria included acute physical illness, substance abuse or dependence, a history of head injury resulting in the loss of consciousness. Similar exclusion criteria were adopted for healthy control subjects with no history of neurological or psychiatric diseases. Three patients received antiepileptic treatments (Valproic acid for one patient and Phenobarbital for the other 2 patients). No subjects were removed due to excessive motion (>2 mm translation and >2 degree rotation). The Unified Myoclonus Rating Scale (UMRS) and Fahn-Tolosa-Marin Tremor Rating Scale (FTRS) were used by 2 professional clinicians in the Department of Neurology of Xiangya Hospital to assess the myoclonus and tremor severity. Several neuropsychological assessments were carried out by 2 experienced neuropsychologists, who were blinded to the grouping of subjects. We evaluated executive and attention functions using the following assessments: Trail-Making Test (Part A and Part B (TMTA, TMTB), digit symbol test (DST), and verbal fluency test (Animal Naming) (VFT)). Only 1 patient could not complete TMTA, TMTB, or DST tests due to binocular blindness. The Clinical and Demographic Characteristics of the Subjects were presented in Table 1. This study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of Xiangya Hospital of the Central South University, and all participants provided written informed consent. The methods were carried out in accordance to the approved guidelines.

Data Acquisition

All images of the patients and controls were acquired using a 3-T Trio Tim scanner (Siemens, Erlangen, Germany). To reduce head movement, the subjects’ heads were fixed using foam pads with a standard 12-channel phased-array birdcage head coil. Structural data used a high-resolution multi-echo T1-weighted, magnetization-prepared gradient-echo image: repetition time/echo time/inversion time = 1900/ 3.41/ 900 ms; flip angle = 9 degree; field of view = 230 × 230 mm; image matrix = 256 × 256; slice thickness = 1.0 mm; slices = 160; and no gap.

In the resting experiments, subjects were simply instructed to keep their eyes closed, to relax, to remain awake, and not to perform a specific cognitive exercise. All fMRI images of the patients and controls were collected using a gradient-echo echo-planar pulse sequence sensitive to BOLD contrast: repetition time/echo time = 2000/30 ms; field of view = 256 × 256 mm; flip angle = 90 degree; matrix = 64 × 64; slice thickness = 4 mm; slices = 32; and no gap. Each subject underwent 2 resting-state fMRI runs, and each run lasted 6 minutes and 40 seconds (200 frame points).

Image Preprocessing

We did not observe any artifacts or structural abnormalities in the structural MRI data by visual inspection. The structural MRI images were preprocessed using the previously described procedures (SPM8) (Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm): segmentation with new segmentation procedure; template generation with DARTEL technique; spatial normalization into the Montreal Neurological Institute (MNI) space; smoothing with a 6-mm full-width half-maximum (FWHM) Gaussian kernel. Finally, a mask covering voxels with values >0.2 was generated and then applied to all of the gray matter images.

The BOLD-fMRI data were preprocessed using the previously described procedures. We discard the first 5 frames of each run to allow T1-equilibration effects. Then we performed slice timing, motion correction, normalization (3-mm isotropic voxels in the MNI space), spatial smoothing (6-mm FWHM Gaussian kernel), linear detrending and 0.01 to 0.08 Hz temporal filtering. Finally, we regressed out the 6 head motion parameters, global signal, ventricular and white matter signals, and the first temporal derivatives of all of the above. The residuals of the regressions were used for functional connectivity analyses.

Gray Matter Analysis

Two-tailed 2-sample $t$ tests were conducted in SPM to compare the voxel-wise gray matter density between the BAFME patients and the healthy controls (voxel-wise $P < 0.001$ in conjunction with cluster-wise $P < 0.05$ to correct for multiple comparisons based on Gaussian random field theory: cluster size $\geq 50$ voxels). Due to limited sample size, 2-sample Kolmogorov-Smirnov test, a nonparametric statistical test, was used to confirm the findings in the 2-sample $t$ tests. Furthermore, we conducted clinical correlation analysis with Spearman rank correlation coefficient between the gray matter density of the significant clusters and clinical variables including the duration of illness, age at onset, UMRS, and FTRS scores in the BAFME patients ($P < 0.05$, uncorrected): $R(X, Y) = cov(X, Y)/\sqrt{var(X)\cdot var(Y)}$, where ranks $X$ and $Y$ were converted from the $N$ (sample size) raw gray matter
density and clinical variable, and \( \text{cov} \) is the covariance, and \( \text{var} \) is the variance. Additionally, we performed correlation analysis with Spearman rank correlation coefficient between the gray matter density of the significant clusters and neuropsychological assessment scores with significant group differences in all subjects.

### Functional Connectivity Analysis

Considering the clusters with significant gray matter density changes as ROIs, the averaged BOLD time courses of all voxels within each ROI were obtained for each subject. In the present study, we used Pearson correlation coefficient to evaluate functional connectivity:

\[
R(T, S) = \frac{\text{cov}(T, S)}{\sqrt{\text{var}(T) \times \text{var}(S)}},
\]

where \( T \) and \( S \) denote 2 time courses, and \( \text{cov} \) is the covariance, and \( \text{var} \) is the variance. Then, gray matter atrophy-related voxel-wise functional connectivity maps were calculated for each ROI, and were converted to \( z \)-maps by using Fisher \( r \)-to-\( z \) transformation.

To explore any gray matter atrophy-related functional connectivity differences between the patient and healthy control groups, 1-sample \( t \) tests \((P < 0.05, \) false discovery rate corrected, cluster size \( \geq 20 \) voxels) were conducted for the \( z \)-maps of each ROI within the patient and control groups, respectively. A spatial \( z \)-map mask of a given ROI was then obtained by combining the spatial maps of the 2 groups together, and 2-tailed 2-sample \( t \) tests were finally performed on the individual \( z \)-maps in a voxel-wise manner by applying the spatial \( z \)-map masks \((\text{voxel-wise } P < 0.001 \text{ in conjunction with cluster-wise } P < 0.05 \text{ to correct for multiple comparisons based on Gaussian random field theory; cluster size } \geq 10 \text{ voxels}).\)

Similar to gray matter analysis, we used Kolmogorov-Smirnov tests to confirm the findings in the 2-sample \( t \) tests of functional connectivity. Furthermore, we conducted clinical correlation analysis with spearman’s rank correlation coefficient between the functional connectivity of the significant clusters and clinical variables including the duration of illness, age at onset, UMRS, and FTRS scores \((P < 0.05, \) uncorrected). Additionally, we performed correlation analysis with Spearman rank correlation coefficient between the functional connectivity of the significant clusters and neuropsychological assessment scores with significant group differences in all subjects.

### RESULTS

#### Clinical and Demographic Characteristics of the Subjects

All of the patients exhibited nonrhythmic cortical myoclonus and distal subtle tremors in their upper limbs. GTCS occurred in 2 patients, and 1 patient presented with frequent episodes \((2–3 \text{ attacks per year})\) of GTCS. None exhibited...
ataxia. The EEGs, SEPs, and long-loop reflexes indicated evidence of cortical reflex myoclonus in all of the patients. The sex \( (P = 0.851, \text{Pearson } \chi^2 \text{ test}) \), age \( (P = 0.797, 2\text{-sample } t \text{ test}) \) and education \( (P = 0.471, 2\text{-sample } t \text{ test}) \) were matched between the patient and control groups. The DST and VFT scores of the patients were significantly lower than those of the healthy controls with \( P \) values of 0.019 and 0.048 (2-sample \( t \) test), respectively, but there was no significant difference in TMTA and TMTB scores between the 2 groups \( (P = 0.399 \text{ and } 0.169, \text{respectively}) \). Additionally, no significant difference was observed in the mean motion between the 2 groups \( (0.078 \pm 0.051 \text{ mm for the patients, } 0.072 \pm 0.025 \text{ mm for the controls, } P = 0.720, 2\text{-sample } t \text{ test}) \).30

### Gray Matter Results

Relative to the healthy controls, the BAFME patients exhibited significantly reduced gray matter density in the right hippocampus, left orbitofrontal cortex (OFC, Brodmann area [BA] 11), right temporal pole (BA 38), and left dorsolateral prefrontal cortex (DLPFC, BA 10), as shown in Table 2 and Figure 1. Due to limited sample size, we used 2-sample Kolmogorov-Smirnov tests to confirm the current findings. The results revealed that the group differences demonstrated by 2-sample \( t \) tests were also significant in the 2-sample Kolmogorov-Smirnov tests \( (P < 0.001) \).

#### Functional Connectivity Results

The right hippocampus, left OFC, right temporal pole, and left DLPFC, all of which displayed significant gray matter atrophy, were selected as ROIs, and whole-brain voxel-wise functional connectivity z-maps were calculated. The group-level comparison analysis revealed that the right hippocampus showed significantly enhanced functional connectivity with the right inferior parietal lobule (IPL, BA 40), bilateral middle

| Anatomical Region          | BA | Cluster Size, Voxels | MNI Coordinates (x, y, z) | \( T \) Value |
|----------------------------|----|----------------------|---------------------------|--------------|
| Hippocampus (R)            | 141| 38, -14, -12         | -4.70                     |
| Orbitofrontal cortex (L)   | 11 | 111                  | -20, 26, -21              | -4.60        |
| Temporal pole (R)          | 38 | 200                  | 45, 17, -35               | -5.51        |
| Dorsolateral prefrontal (L)| 10 | 87                   | -35, 45, 21               | -4.34        |

A significance threshold with voxel-wise \( P < 0.001 \) in conjunction with cluster-wise \( P < 0.05 \) to correct for multiple comparisons based on Gaussian random field theory and a cluster size \( \geq 50 \) voxels were used. BA = Brodmann area, L/R = left/right, MNI = Montreal Neurological Institute.

**FIGURE 1.** Anatomical regions with significant gray matter atrophy in benign adult familial myoclonic epilepsy. A significance threshold with voxel-wise \( P < 0.001 \) in conjunction with cluster-wise \( P < 0.05 \) to correct for multiple comparisons based on Gaussian random field theory and a cluster size \( \geq 50 \) voxels were used.
cingulate cortex (MCC, BA 31), left precuneus (BA 7), and left precentral gyrus (BA 6) in the BAFME patients, as shown in Table 3 and Figure 2. No significant hippocampal functional connectivity reduction was observed in the BAFME patients. No significant functional connectivity differences were detected to relate to the 3 other ROIs between the 2 groups. Due to limited sample size, we used 2-sample Kolmogorov-Smirnov tests to confirm the current findings. The results revealed that the group differences demonstrated by 2-sample $t$ tests were also significant in the 2-sample Kolmogorov-Smirnov tests ($P < 0.001$).

**Clinical Correlation Results**

The gray matter density of the right hippocampus was significantly correlated with the DST ($R = 0.66, P < 0.001$) and duration of illness ($R = -0.81, P = 0.003$), respectively (Figure 3). And the gray matter density of the right temporal pole was significantly correlated with the DST ($R = 0.64, P < 0.001$) and VFT ($R = 0.45, P = 0.023$), respectively (Figure 3). In addition, the gray matter density of the left OFC was significantly correlated with the DST ($R = 0.52, P = 0.008$, Figure 3). No significant correlation was detected between the clinical variables and functional connectivity of the aforementioned regions with significant functional connectivity alterations.

**DISCUSSION**

In this study, we investigated gray matter and functional connectivity alterations in patients with BAFME using MRI and observed significant gray matter loss in the right hippocampus, right temporal pole, left OFC, and left DLPFC and significantly enhanced hippocampal functional connectivity with the right IPL, bilateral MCC, left precuneus, and left precentral gyrus in the BAFME patients compared with the healthy controls. The findings may shed new light on the pathophysiology of BAFME and may help to interpret how BAFME patients exhibit mild cognitive impairment in daily life.

Hippocampal formation has been demonstrated to play an important role in some aspects of spatial coding and control of attention. In this study, gray matter loss of the right hippocampus was observed in the BAFME patients, and the regional gray matter density was significantly positively correlated with the DST scores, which were significantly lower in the patients than those in the healthy controls. A previous study reported that signs of slight cognitive impairment, such as short-term memory and attention deficits, were seen in a Dutch BAFME pedigree. Suppa et al demonstrated that verbal memory and executive functions were moderately impaired in BAFME, in addition to visuospatial impairment. The current results may suggest that the right hippocampal gray matter loss was associated with the low DST performance in the BAFME patients. In addition, the functional connectivity of the right hippocampus was enhanced in the right IPL, bilateral MCC, left precuneus, and left precentral gyrus in the BAFME patients. The precuneus, together with the precentral gyrus, has been suggested to be involved in visuospatial mental operations. It is possible that the enhanced functional connectivity may compensate for the gray matter atrophy of the hippocampus in the BAFME patients. However, no significant correlation was detected between the clinical variables and functional connectivity of the aforementioned regions in the BAFME patients, so the compensation effect needs to be confirmed with further evidence. Note that the left and right hippocampus exhibited asymmetries in the BAFME patients. Asymmetries in the morphology and connectivity of the left and right hippocampus have been observed in epilepsy in previous studies. As for memory processing, episodic memory is more associated with the left hippocampus, whereas the use of the right hippocampus is dominant during spatial memory tasks. Memory was not evaluated in the present study, but the finding of asymmetries may provide new insight into the distinct role of hippocampus in BAFME.

| Anatomical Region | BA   | Cluster Size, voxels | MNI Coordinates (x, y, z) | $T$ Value |
|-------------------|------|----------------------|--------------------------|-----------|
| Inferior parietal lobule (R) | 40   | 24                   | 42, –27, 30              | 4.71      |
| Middle cingulate cortex (L) | 15   | 15                   | –21, –24, 48             | 5.69      |
| Middle cingulate cortex (R) | 31   | 22                   | 6, –18, 48               | 4.35      |
| Precuneus (L) | 7    | 24                   | –6, –60, 60              | 5.34      |
| Precentral gyrus (L) | 6    | 10                   | –30, –6, 57              | 4.73      |

A significance threshold with voxel-wise $P < 0.001$ in conjunction with cluster-wise $P < 0.05$ to correct for multiple comparisons based on Gaussian random field theory and a cluster size $\geq 10$ voxels were used.

**TABLE 3. Functional Connectivity Alterations of the Right Hippocampus in Benign Adult Familial Myoclonic Epilepsy**
Gray matter reduction was also observed in the right temporal pole and left OFC in the BAFME patients relative to healthy controls. Relative to healthy controls, the BAFME patients showed lower scores in the VFT test. The temporal pole is involved in the relationship of emotion/mood to visceral function,\(^{41,42}\) whereas the medial parts of the OFC are related to the monitoring and learning.\(^{43}\) We observed that the gray matter density of the left OFC was significantly positively correlated with the DST scores, and that the gray matter density of the right temporal pole was significantly positively correlated with the DST and VFT scores, respectively, suggesting that gray matter loss from these two regions may be related to some slight cognitive deficits observed in BAFME patients.\(^{4,11,12}\) In addition, the left DLPFC also exhibited reduced gray matter density in the BAFME patients. The DLPFC is a critical region in the frontoparietal control network, which is involved in working memory and cognitive control function.\(^{44}\) The previous neuroimaging studies suggested that structural or functional alterations of DLPFC might underlie deficits in working memory and executive function in epilepsy.\(^{45-47}\) In addition, impaired executive functions were observed in BAFME patients in previous studies.\(^ {12}\) The current results may suggest that the gray matter loss in the left DLPFC is associated with executive function impairments in BAFME.

There are several limitations in the present study. First, there are limitations related to the lack of a large independent dataset with which to confirm the findings. Because BAFME is a rare form of epilepsy, we only included 11 BAFME patients from 1 Chinese pedigree in the study. To corroborate the correlation between the gray matter density of right hippocampus and duration of illness in the patients, we conducted stepwise linear regression additionally. The results revealed that the correlation is significant with a \(P\) value of 0.003, consistent with the results of Spearman rank correlation analysis. There are around 100 BAFME families reported worldwide, but they are mainly in Japan and Europe. The family we enrolled in this study is likely the first one in China. There may be genetic heterogeneity between different pedigrees, so it is valuable and informative to study a Chinese family with BAFME. Notably, an expansion of this sample is ongoing. Second, 3 patients received antiepileptic treatments (Valproic acid for 1 patient and Phenobarbital for the other 2 patients). Because the drug valproic acid and Phenobarb might reduce cortical volume, we conducted control analyses in which the patient in use of Valproic Acid and Phenobarb was excluded, respectively. The results revealed that the gray matter differences were still significant in the four aforementioned regions between the patient and control groups (\(P < 0.001\), 2-sample \(t\) test; \(P < 0.01\), 2-sample Kolmogorov-Smirnov test). Thus, we could conclude that the effect of Valproic Acid and Phenobarb was limited in this study. However, one should still interpret the results with caution, given the history of these medications. Third, there are several studies indicating that the genetic abnormality may translate to the cerebellar pathological changes and cortical excitability.\(^{5,8}\) However, so far, there is no direct evidence that affirms the relationship between the genetic abnormality and brain structural abnormalities in BAFME. The structural abnormalities may derive from either genetic factor or acquired disposition (such as long-term cortical excitability). But we could not conclude that the genetic abnormality translates to the current structural abnormalities. Further studies are needed to address the relationship between genetic abnormality and brain structural abnormalities. Fourth, we only investigated gray matter atrophy-related functional connectivity alterations in the BAFME patients. Thus, some other ROIs with a stronger a priori hypothesis could be explored in the future. Finally, though the current results suggest that the decrease in cortical volume may be compensated by an increase in functional connectivity, it remains unclear how long this compensatory mechanism will last since a decline in cognitive function was observed. Thus, a longitudinal work is necessary to analyze cognitive aspects, clinical features, and neuroimaging findings over the years with the same family in the future.
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REFERENCES

1. Yasuda T. Benign adult familial myoclonic epilepsy (BAFME). Kawasaki Med J. 1991;17:1–13.

2. Ikeda A, Kakigi R, Funai N, et al. Cortical tremor: a variant of cortical reflex myoclonus. Neurology. 1990;40:1561–1565.

3. de Falco FA, Striano P, de Falco A, et al. Benign adult familial myoclonic epilepsy. Genetic heterogeneity and allelism with ADCME. Neurology. 2003;60:1381–1385.

4. van Rootselaar A-F, van Schaik IN, van den Maagdenberg AMJM, et al. Familial cortical myoclonic tremor with epilepsy: a single syndrome classification for a group of pedigrees bearing common features. Mov Disord. 2005;20:665–673.

5. Guerrini R, Bonanni P, Patrignani A, et al. Autosomal dominant myoclonic epilepsy (ADME) with complex partial and generalized seizures: a newly recognized epilepsy syndrome with linkage to chromosome 3q26.32-3q28. Eur J Hum Genet. 2001;3:2459–2475.

6. Okuma Y, Shimo Y, Shimura H, et al. Familial cortical tremor with epilepsy: an under-recognized familial tremor. Clin Neurol Neurosurg. 1998;100:75–78.

7. Regragui W, Gerdelat-Mas A, Simonetta-Moreau M. Cortical tremor (FCMTE: familial cortical myoclonic tremor with epilepsy). Neurophysiol Clin. 2006;36:345–349.

8. Striano P, Zara F, Striano S. Autosomal dominant cortical tremor with epilepsy: many syndromes, one phenotype. Acta Neurol Scand. 2005;111:211–217.

9. Uyama E, Tokunaga M, Murakami T. Familial adult myoclonus epilepsies: a new phenotype of autosomal dominant myoclonic epilepsy. Ann Neurol. 1996;40:505.

10. van Rootselaar A-F, Callenbach PM, Hottenga JJ, et al. A Dutch family with ‘familial cortical tremor with epilepsy’: clinical characteristics and exclusion of linkage to chromosome 8q23.3-q241. J Neurol. 2002;249:829–834.

11. Elia M, Musameci SA, Ferri R, et al. Familial cortical tremor, epilepsy, and mental retardation: a distinct clinical entity? Arch Neurol. 1998;55:1569–1573.

12. Suppa A, Berardelli A, Brancati F, et al. Clinical, neuropsychological, neuropsychiologic, and genetic features of a New Italian pedigree with familial cortical myoclonic tremor with epilepsy. Epilepsia. 2009;50:1284–1288.

13. van Rootselaar A-F, Maurits NM, Renken R, et al. Simultaneous EMG-functional MRI recordings can directly relate hyperkinetic movements to brain activity. Hum Brain Mapp. 2008;29:1430–1441.

14. Striano P, Caranci F, Benedetto RD, et al. 1H-MR spectroscopy indicates prominent cerebellar dysfunction in benign adult familial generalized seizures. Neurology. 2008;71:1491–1497.

15. Long L, Song Y, Zhang L, et al. A case-control proton magnetic resonance spectroscopy study confirms cerebellar dysfunction in benign adult familial myoclonic epilepsy. Neupropsychiatr Dis Treat. 2015;11:485–491.

16. Buijnk AWG, Caan MWA, Tijsjen MAJ, et al. Decreased cerebellar fiber density in cortical myoclonic tremor but not in essential tremor. Cerebellum. 2013;12:199–204.

17. Magnin E, Vidalhiet M, Ryff I, et al. Fronto-striatal dysfunction in type 3 familial cortical myoclonic tremor epilepsy occurring during aging. J Neurol. 2012;259:2714–2719.

18. Carr JA, van der Walt PE, Nakayama J, et al. FAME 3-A novel form of progressive myoclonus and epilepsy. Neurology. 2007;68:1382–1389.

19. Depienne C, Magnin E, Bouteiller D, et al. Familial cortical myoclonic tremor with epilepsy The third locus (FCMTE3) maps to 5p. Neurology. 2010;74:2000–2003.

20. Madia F, Striano P, Bonaventura CD, et al. Benign adult familial myoclonic epilepsy (BAFME): evidence of an extended founder haplotype on chromosome 2p11.1-q12.2 in five Italian families. Neurogenetics. 2008;9:139–142.

21. Mori S, Nakamura M, Yasuda T, et al. Remapping and mutation analysis of benign adult familial myoclonic epilepsy in a Japanese pedigree. J Hum Genet. 2011;56:742–747.

22. Yeetong P, Ausavarat S, Bhiyayasri R, et al. A newly identified locus for benign adult familial myoclonic epilepsy on chromosome 3q26.32-3q28. Eur J Hum Genet. 2013;21:225–228.

23. Deng FY, Gong J, Zhang YC, et al. Absence of linkage to 8q23.3-q24.1 and 2p11.1-q12.2 in a new BAFME pedigree in China: Indication of a third locus for BAFME. Epilepsy Res. 2005;65:147–152.

24. Fucht SJ, Leurgans SE, Hallett M, et al. The unified myoclonus rating scale. Adv Neurol. 2002;89:361–376.

25. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. Baltimore, MD: Williams & Wilkins; 1993.

26. Sterling NW, Du G, Lewis MM, et al. Striatal shape in Parkinson’s disease. Neurobiol Aging. 2013;34:2510–2516.

27. Yamall A, Archibald N, Burn DJ. Parkinson’s disease. Mov Disord. 2012;40:529–535.

28. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999;14:167–177.

29. Zeng L-L, Shen H, Liu L, Fang P, Liu Y, Hu D. State-dependent and trait-related gray matter changes in nonreferred depression. NeuroReport. 2015;26:57–65.

30. Zeng L-L, Wang D, Fox MD, et al. Neurobiological basis of head motion in brain imaging. Proc Natl Acad Sci USA. 2014;111:6058–6062.

31. Forman SD, Cohen JD, Fitzgerald M, et al. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of cluster-size threshold. Magn Reson Med. 1995;33:636–647.

32. Moser MB, Moser EI. Functional differentiation in the hippocampus. Hippocampus. 1998;8:608–619.

33. Anderson P, Morris R, Amaral D, et al. The hippocampus book. 1st ed. New York: Oxford University Press; 2007.

34. Oshio R, Tanaka S, Sadato N, et al. Differential effect of double-pulse TMS applied to dorsal premotor cortex and precuneus during internal operation of visuospatial information. NeuroImage. 2010;49:1108–1115.

35. Zaied DW, Esifi MM, Ozbury JM. Sex-related asymmetries in the hippocampus: a follow-up study on epileptic patients. J Neurol. 1994;241:620–623.

36. Pereira FR, Alessio A, Sercelli MS, et al. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. BMC Neurosci. 2010;11:66.

37. Fang P, An J, Zeng L-L, et al. Multivariate pattern analysis of 114 epileptic patients. J Neurol. 1994;241:620–623.

38. Burgess N, Maguire EA, O’Keefe J. The human hippocampus and spatial and episodic memory. Neuron. 2002;35:625–641.

39. Igloi K, Doeller CF, Berthoz A, et al. Lateralized human hippocampal activity predicts navigation based on sequence or place memory. Proc Natl Acad Sci USA. 2010;107:14466–14471.
40. Maguire EA, Frackowiak RS, Frith CD. Recalling routes around London: activation of the right hippocampus in taxi drivers. J Neurosci. 1997;17:7103–7110.

41. Ding SL, Van Hoesen GW, Cassell MD, et al. Parcellation of human temporal polar cortex: a combined analysis of multiple cytoarchitectonic, chemoarchitectonic, and pathological markers. J Comp Neurol. 2009;18:595–623.

42. Zeng L-L, Shen H, Liu L, et al. Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. Brain. 2012;135:1498–1507.

43. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol. 2004;72:341–372.

44. Vincent JL, Kahn I, Snyder AZ, et al. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol. 2008;100:3328–3342.

45. Wandschneider B, Thompson PJ, Vollmar C, et al. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data. Epilepsia. 2012;53:2091–2098.

46. Wei HL, An J, Zeng LL, et al. Altered functional connectivity among default, attention, and control networks in idiopathic generalized epilepsy. Epilepsy Behav. 2015;46:118–125.

47. Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. Epilepsy Res. 2012;98:1–13.