

Supplementary online material for:

**ABNORMAL HIPPOCAMPAL STRUCTURE AND FUNCTION IN
JUVENILE MYOCLONIC EPILEPSY AND UNAFFECTED SIBLINGS**

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Running title: Hippocampal abnormalities in JME and siblings

SUPPLEMENTARY MATERIAL 1. Sensitivity analyses for left hippocampal volumetry.

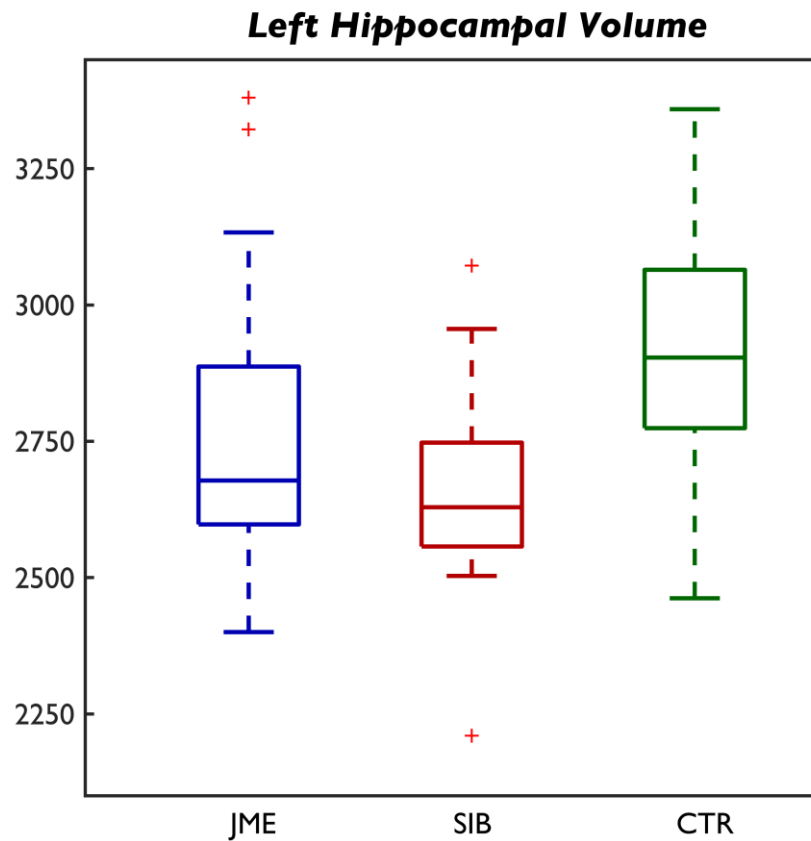
Inspection of Q-Q plots and normality tests revealed normal distribution of hippocampal volumetric data (Shapiro-Wilk test, all $p > 0.05$ for the whole study sample as well for separate analyses in each study subgroup).

For group comparisons of left hippocampal volumes, repeat models using age, gender and handedness produced virtually identical results, and showed convergence of mean hippocampal volume values for patients and siblings [ANCOVA; $F_{(\text{model})}$: 2.7, $p = 0.027$, partial $\eta^2 = 0.17$; $F_{(\text{group})} = 6.01$, $p = 0.004$, partial $\eta^2 = 0.16$; *post-hoc* Bonferroni-adjusted p -values: 0.01/0.006, JME/siblings versus controls; $p = 1.0$, JME versus siblings; estimated marginal means (SD), JME/SIB/CTR: 2731 mm³ (249)/ 2668 mm³ (207)/ 2930 mm³ (216)].

Inspection of boxplots for left hippocampal volumes identified two outliers above the upper quartile in the JME group, along with one above and one below the lower quartile in the sibling group (shown below, *Boxplot 1*). As sensitivity analysis, we thus repeated group comparisons for left hippocampal volume after excluding outliers. Repeat analyses detected a significant effect of group for left hippocampal volume [JME/SIB/CTR, mean (SD): 2709 mm³ (2709)/ 2666 mm³ (144)/ 2907 mm³ (220); one-way ANOVA: $F_{(2,68)} = 8.13$, $p = 0.001$, partial $\eta^2 = 0.20$]. *Post-hoc* Bonferroni-corrected tests showed that both JME patients ($p = 0.002$, Cohen's $d = 0.93$) and their siblings ($p = 0.003$, Cohen's $d = 1.30$) had a smaller left hippocampus than controls. *Post-hoc* comparison of JME and siblings was not statistically significant ($p = 1.0$). Repeat models using age, gender and handedness as covariates again showed virtually identical results [ANCOVA; $F_{(\text{model})}$: 3.94, $p = 0.004$, partial $\eta^2 = 0.24$; $F_{(\text{group})} = 9.14$, $p = 0.0003$, partial $\eta^2 = 0.23$; *post-hoc* Bonferroni-adjusted p -values: 0.001/0.002, JME/siblings versus controls; $p = 1.0$, JME versus siblings; estimated marginal means (SD), JME/SIB/CTR: 2698 mm³ (206)/ 2667 mm³ (204)/ 2928 mm³ (211)].

These results corroborate findings of the main analysis and show further convergence towards similar values for mean hippocampal volume in patients with JME and their siblings.

Boxplot 1. Left hippocampal volume in JME, unaffected siblings and healthy controls.



SUPPLEMENTARY MATERIAL 2. Subgroup discrimination via measures of hippocampal volumetry and positioning.

To complement validation of structural hippocampal anomalies in JME and siblings as endophenotypes, we assessed whether quantitative hippocampal measures would be accurate in achieving subgroup discrimination. Using receiver operating characteristic (ROC) curves, we assessed discrimination accuracy of (1) left hippocampal volume and (2) left hippocampal diameter ratio. The latter was chosen because of the significant group effects in the MANOVA for quantitative traits related to HIMAL and the statistically significant *post-hoc* comparisons for JME and siblings versus controls. We also investigated (3) the role of a combination of volume and positioning via entering the above measures in a principal component analysis. The first principal component obtained from left hippocampal volume and diameter ratio (eigenvalue: 1.38, accounting for 69% of the total variance) was considered as a composite left hippocampal marker. We also repeated all the above models controlling for age, gender and handedness. In the latter case, the first principal component

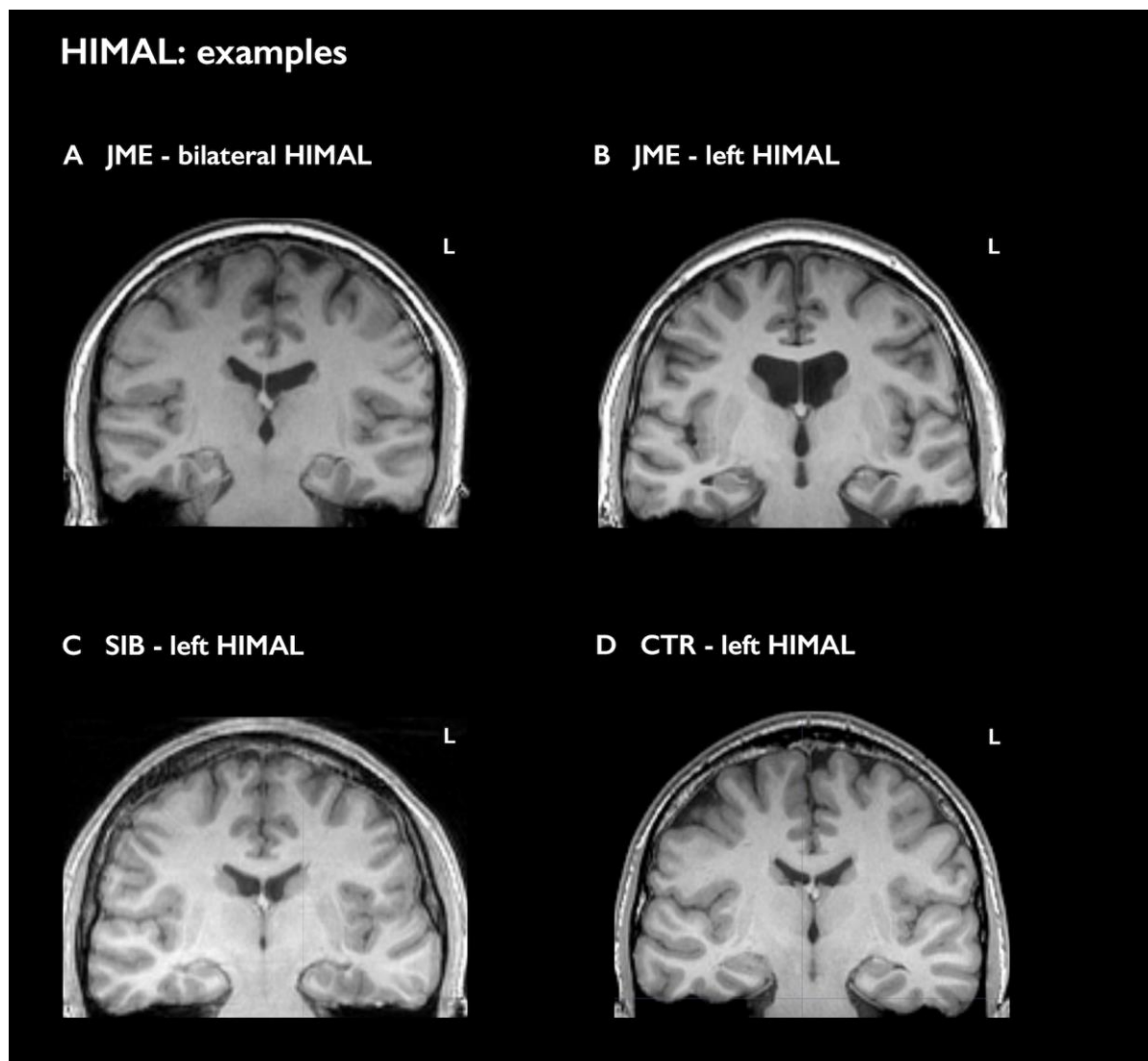
obtained after linear regression of the above covariates from both hippocampal measures had a similar eigenvalue (1.39) and explained an identical proportion of the total variance.

ROC curve analysis identified successful discrimination of patients with JME from controls via left hippocampal volumetric measures and left diameter ratio, with identical accuracy [AUC=0.71, standard error (SE) 0.07, $p=0.01$ equally in both]. Use of a composite marker improved classification accuracy (AUC=0.74, SE=0.07, $p=0.003$). Repeat models accounting for covariates showed higher classification accuracy for all measures, with the composite marker (AUC=0.80, SE=0.07, $p=0.0002$) outperforming individual measures (AUC=0.72/0.77, SE=0.07/0.07, $p=0.007/0.001$ for volume and diameter ratio, respectively).

The above models were also repeated considering JME patients and their siblings as a unitary group. Again, successful group discrimination was achieved for left hippocampal volume and diameter ratio individually (AUC=0.74, SE=0.06, $p=0.002$ equally in both) and for the left hippocampal composite marker (AUC=0.77, SE=0.07, $p=0.0004$). Similarly, models accounting for covariates showed higher discrimination abilities for all measures, and the composite marker (AUC=0.81, SE=0.06, $p<0.0001$) performed better than individual measures (AUC=0.75/ 0.79, SE=0.06/0.06, $p=0.001/0.0002$ for volume and diameter ratio, respectively).

By showing relatively high discrimination of (a) JME patients and (b) a combined JME-sibling group from controls, this supplementary analysis confirms co-segregation of left hippocampal morphological patterns in patients and their relatives, validating the endophenotypic potential of the quantitative markers identified in our study.

SUPPLEMENTARY FIGURE 1. Representative examples of HIMAL.



Abbreviations: CTR = healthy controls; HIMAL = hippocampal malrotation; JME = patient with juvenile myoclonic epilepsy; SIB = unaffected sibling of patient with JME. Examples of subjects with JME and bilateral HIMAL (A) or unilateral (left) HIMAL (B) are presented in the first row. In the second row, panel C, left-hand side, a scan of an unaffected JME sibling is shown, where HIMAL is associated with atypical morphometry of the inferior temporal sulci. Panel D provides an example of HIMAL in a healthy control.

SUPPLEMENTARY TABLE 1. Qualitative and quantitative measures associated with HIMAL

Test	HIMAL	Normal	Test Statistic	P value	Sensitivity*	Specificity*	AUC
Shape (abnormal)	33/35 (94.3%)	2/111 (1.8%)	125.2†	<0.0001	94.3%	98.2%	0.98
Verticalisation of DITS (verticalized)	25/35 (71.4%)	16/111 (14.4%)	52.5†	<0.0001	71.4%	85.6%	0.87
Lateral hippocampal margin (loss of convexity)	27/35 (77.1%)	7/111 (6.3%)	81.9†	<0.0001	77.1%	93.7%	0.93
Hippocampal diameter ratio (%, mean ±SD)	89.6 (12.3)	65.3 (6.7)	230.6^	<0.0001	94.3%	95.5%	0.99
DITS height ratio (%, mean ±SD)	58.9 (14.8)	25.4 (16.5)	115.6^	<0.0001	82.9%	94.6%	0.94
Parahippocampal angle (deg., mean ±SD)	98.5 (9.7)	121.7 (9.8)	150.6^	<0.0001	97.1%	90.1%	0.98

Abbreviations: AUC= area under the curve; deg. = degree; DITS= dominant inferior temporal sulcus. †Pearson's χ^2 ; ^F statistic, ANOVA. *For quantitative morphological criteria, sensitivity and specificity are reported for cut-off values attaining maximal Youden's index: diameter ratio, 75.4; DITS ratio: 46.1; parahippocampal angle: 110.35.

SUPPLEMENTARY TABLE 2. Verbal subsequent memory – fMRI activation coordinates

<i>Region</i>	<i>Left Hemisphere</i>				<i>Right Hemisphere</i>			
	MNI coordinates (x,y,z)	Z-score	P value	Parameter estimate (95% CI)	MNI coordinates (x,y,z)	Z-score	P value	Parameter estimate (95% CI)
<i>All Subjects</i>								
<i>Anterior hippocampus</i>	-21 -19 -20	2.33	0.048	0.28 (0.05–0.52)				
<i>Inferior frontal gyrus</i>	-51 32 10	2.77	0.003	0.34 (0.11–0.57)				
<i>CTR</i>								
<i>Anterior hippocampus</i>	-18 -10 -20	3.23	0.009	0.27 (0.13–0.42)				
<i>Anterior hippocampus</i>	-27 -16 -20	3.20	0.01	0.33 (0.15–0.52)				
<i>Posterior hippocampus</i>					27 -37 1	3.25	0.008	0.17 (0.08–0.26)
<i>Amygdala</i>	-21 -1 -14	2.92	0.019	0.17 (0.04–0.30)				
<i>Parahippocampal gyrus</i>	-30 -22 -20	2.71	0.032	0.29 (0.13–0.45)				
<i>Putamen</i>	-21 8 -5	3.17	0.001	0.24 (0.12–0.37)				
<i>Globus pallidum</i>	-27 2 -8	3.13	0.001	0.29 (0.14–0.43)	24 -5 -2	2.83	0.002	0.24 (0.10–0.38)
<i>Middle temporal gyrus</i>	-51 -43 4	4.27	<0.001	0.21 (0.14–0.28)	54 -46 5	3.21	0.001	0.14 (0.07–0.21)
	-69 -28 -8	3.87	<0.001	0.26 (0.16–0.36)				
	-63 58 10	3.48	<0.001	0.34 (0.18–0.48)				
<i>Anterior medial frontal cortex</i>	-2 59 -11	3.50	<0.001	0.66 (0.36–0.96)				
<i>Supplementary motor area</i>					3 20 64	3.49	<0.001	0.38 (0.21–0.55)
<i>Superior frontal gyrus</i>	-15 41 55	3.46	<0.001	0.34 (0.19–0.50)				
	-6 56 31	3.00	0.001	0.47 (0.21–0.73)	3 56 28	2.98	0.001	0.51 (0.23–0.79)
<i>Middle frontal gyrus</i>	-45 17 55	2.89	0.002	0.17 (0.07–0.26)				
<i>Inferior frontal gyrus</i>	-42 23 -8	3.05	0.001	0.45 (0.21–0.70)	51 17 -11	3.23	0.001	0.41 (0.21–0.61)
	-54 35 13	2.93	0.002	0.28 (0.12–0.43)	54 20 -5	3.07	0.001	0.33 (0.16–0.51)
	-51 17 19	2.82	0.002	0.37 (0.15–0.59)				
<i>Insula</i>	-30 -22 1	2.87	0.002	0.17 (0.07–0.26)				
<i>Precentral gyrus</i>					60 2 31	2.84	0.002	0.20 (0.08–0.32)
					36 -16 64	2.50	0.006	0.19 (0.06–0.33)
<i>Paracentral lobule</i>	-3 16 67	3.25	0.001	0.23 (0.12–0.34)				
<i>Supramarginal gyrus</i>	-60 -28 37	2.72	0.003	0.17 (0.06–0.27)				
<i>Angular gyrus</i>	-39 -70 43	2.65	0.004	0.26 (0.09–0.43)				

<i>Precuneus</i>	-6 -61 31	2.64	0.004	0.40 (0.14–0.66)	3 -67 25	3.03	0.001	0.34 (0.16–0.53)
<i>Inferior occipital gyrus</i>	-42 -88 -8	3.05	0.001	0.25 (0.12–0.38)				
JME								
<i>Anterior hippocampus</i>	-21 -19 -20	1.05	0.19	0.16 (-0.27–0.59)				
<i>Inferior frontal gyrus</i>	-48 32 19	1.91	0.03	0.45 (0.01–0.88)				
SIB								
<i>Anterior hippocampus</i>	-18 -10 -20	2.73	0.031	0.41 (0.14–0.68)				
<i>Parahippocampal gyrus</i>	-18 -4 -35	2.85	0.024	0.52 (0.20–0.85)				
<i>Temporal pole</i>					30 14 -32	2.82	0.002	0.92 (0.41–1.44)
<i>Fusiform gyrus</i>					33 -13 38	2.74	0.003	0.50 (0.21–0.79)
<i>Cerebellum</i>	-24 -64 -23	2.89	0.002	0.49 (0.23–0.75)	36 -49 -29	2.64	0.004	0.55 (0.21–0.89)

Abbreviations: CI = confidence interval; CTR = controls; JME = patients with juvenile myoclonic epilepsy; MNI = Montreal Neurological Institute; SIB = siblings of patients with juvenile myoclonic epilepsy. Coordinates for mesiotemporal and extra-mesiotemporal activations are given in MNI space. When in bold, *P*-values for peak-level mesiotemporal activations are family-wise error rate (FWE) corrected for multiple comparisons using a small volume correction within a 12-mm diameter sphere, centred on the local activation maximum. *P*-values not in bold are uncorrected for multiple comparisons. Parameter estimates (i.e., betas) are reported along with their 95% confidence intervals (CI). For a given anatomical region, statistics are reported for up to three peak-level local activation maxima, ordered by statistical significance. For the JME group, there were no supra-threshold voxels. For completeness, we report coordinates of sub-threshold activation for the two locations showing significant group effects across all subjects (left hippocampus and left inferior frontal gyrus).

SUPPLEMENTARY TABLE 3. Verbal subsequent memory – group comparisons

Region	Left Hemisphere			Right Hemisphere		
	MNI coordinates (x,y,z)	Z-score	P value	MNI coordinates (x,y,z)	Z-score	P value
Group effects (F test)						
<i>Amygdala/anterior hippocampus</i>	-24 -7 -11 (18 -7 17)	2.69 (2.60)	0.031 (0.033)			
<i>Middle temporal gyrus</i>	-64 58 7	3.62	<0.001			
	-54 52 13	3.24	<0.001			
<i>Middle frontal gyrus</i>	-33 8 52	3.64	<0.001	45 20 22	2.95	0.002
	-42 4 37	3.37	<0.001			
	-42 8 43	3.10	<0.001			
<i>Inferior frontal gyrus</i>	-48 17 16	2.93	0.002	54 29 1	3.16	0.001
<i>Superior frontal gyrus</i>	-15 50 37	2.81	0.002	21 56 25	2.80	0.003
<i>Cingulate gyrus</i>	-6 -16 31	3.29	<0.001			
<i>Precentral gyrus</i>				27 -19 49	2.86	0.002
<i>Insula</i>	-39 -4 2	3.04	0.001			
<i>Precuneus</i>	-18 -52 40	2.78	0.003	9 -46 31	2.85	0.002
CTR > JME						
<i>Amygdala/anterior hippocampus</i>	-18 -7 -14	2.79 (2.98)	0.019 (0.007)			
<i>Putamen</i>	-30 -10 1	2.50	0.006			
<i>Middle frontal gyrus (anterior)</i>	-45 20 37	2.63	0.004			
<i>Middle frontal gyrus (posterior)</i>	-24 -10 46	3.45	<0.001			
<i>Rolandic operculum</i>				42 -4 19	2.99	0.001
<i>Precentral gyrus</i>				33 -10 40	2.95	0.002
CTR > SIB						
<i>Amygdala/anterior hippocampus</i>	-24 -7 -11	3.08 (2.67)	0.009 (0.031)			
<i>Anterior hippocampus</i>				30 -10 -17	2.39	0.049
<i>Middle temporal gyrus</i>	-63 58 7	4.16	<0.001	66 -46 -1	2.98	0.001
	-54 -52 13	3.80	<0.001			
<i>Putamen</i>	-30 -7 7	3.04	0.001	-30 -4 7	2.97	0.002
<i>Superior frontal gyrus</i>	-15 50 37	3.36	<0.001	9 50 28	3.10	0.001
<i>Middle frontal gyrus</i>	-33 -8 52	4.13	<0.001			
	-42 8 43	3.66	<0.001			
	-39 26 34	3.34	<0.001			
<i>Inferior frontal gyrus</i>	-38 38 -11	3.03	0.001	54 29 1	3.75	<0.001
				45 20 22	3.54	<0.001
<i>Insula</i>	-39 -4 -2	3.92	<0.001			
<i>Precentral gyrus</i>				54 5 34	3.55	<0.001
<i>Anterior cingulate gyrus</i>	-6 -16 31	3.87	<0.001			
<i>Supramarginal gyrus</i>	-57 -22 -40	3.30	<0.001			
<i>Precuneus</i>	-9 -61 -37	3.32	0.001			
CTR > JME-HIMAL						
<i>Hippocampus (body)</i>	-33 -19 -17	2.63	0.025			

	(2.86)	(0.015)			
<i>Middle frontal gyrus</i>	-39 20 34	3.80	<0.001	42 29 40	3.38 <0.001
	-27 -10 46	3.58	<0.001	27 17 37	2.95 0.002
<i>Superior frontal gyrus</i>				33 5 37	3.28 0.001
	-6 32 43	3.31	<0.001	9 47 42	3.00 0.001
	-18 23 40	3.07	0.001	18 5 49	3.63 <0.001
				18 32 49	3.07 0.001
			21 23 43	3.09 0.001	
<i>CTR > JME-noHIMAL</i>					
<i>Amygdala/anterior hippocampus</i>	-21 -10 -14	2.48	0.035		
		(2.61)	(0.025)		
<i>Rolandic operculum</i>				54 -13 13	2.93 0.002
				42 -10 22	2.90 0.002
<i>JME-noHIMAL > JME-HIMAL</i>					
<i>Middle frontal gyrus</i>	-33 23 34	4.14	<0.001	18 26 34	4.45 0.031
	-21 29 28	3.87	<0.001	42 29 40	3.47 <0.001
	-24 44 28	3.32	<0.001	36 26 28	3.43 <0.001
<i>Superior frontal gyrus</i>	-9 35 43	3.68	<0.001	18 20 46	3.87 <0.001
	-18 29 46	3.66	<0.001	21 41 43	3.39 <0.001
	-9 41 49	3.54	<0.001	3 29 52	3.34 <0.001

Abbreviations: CTR= controls; HIMAL= hippocampal malrotation; JME= patients with juvenile myoclonic epilepsy; MNI= Montreal Neurological Institute; noHIMAL= without hippocampal malrotation. SIB= siblings of patients with juvenile myoclonic epilepsy.

Coordinates of mesiotemporal and extra-mesiotemporal group differences are given in MNI space. *P* values for peak-level mesiotemporal activations, all reported in bold font, are family-wise error rate (FWE) corrected for multiple comparisons (small-volume correction) using a 12-mm diameter sphere centred on the local activation maximum. For group differences regarding left mesiotemporal activation, *Z*-scores and *P* values in brackets refer to repeat models including left hippocampal volume as covariate.

When in bold, *P* values for peak-level extra-mesiotemporal group differences are FWE-corrected for multiple comparisons across the whole brain (e.g. right middle frontal gyrus, JME-noHIMAL vs JME-HIMAL). When not in bold, *P* values for peak-level extra-mesiotemporal differences are uncorrected across the whole brain.

For a given anatomical region, statistics are reported for up to three peak-level local maxima, ordered by statistical significance.

SUPPLEMENTARY TABLE 4. Visual subsequent memory – fMRI activation coordinates

<i>Region</i>	<i>Left Hemisphere</i>				<i>Right Hemisphere</i>			
	MNI coordinates (x,y,z)	Z-score	P value	Parameter estimate (95% CI)	MNI coordinates (x,y,z)	Z-score	P value	Parameter estimate (95% CI)
All Subjects								
<i>Anterior hippocampus</i>	-21 -13 -26	2.48	0.031	0.19 (0.06–0.31)				
<i>Posterior hippocampus</i>	-21 -40 4	2.83	0.013	0.12 (0.03–0.21)				
<i>Parahippocampal gyrus</i>					18 -25 -17	2.44	0.034	0.15 (0.01–0.29)
<i>Fusiform gyrus</i>					42 -46 -26	2.98	0.001	0.14 (0.06–0.24)
<i>Occipital pole</i>					-24 -103 4	2.85	0.002	0.16 (0.05–0.26)
<i>Cerebellum</i>					12 -46 44	2.74	0.003	0.11 (0.03–0.19)
CTR								
<i>Anterior Hippocampus</i>	-21 -13 -23	2.48	0.04	0.23 (0.05–0.41)	24 -13 -23	2.56	0.033	0.18 (0.05–0.31)
<i>Inferior frontal gyrus</i>					48 35 4	2.48	0.007	0.19 (0.05–0.32)
<i>Occipital pole</i>	-24 -103 4	2.67	0.004	0.27 (0.09–0.46)	27 -100 -8	2.62	0.004	0.24 (0.08–0.39)
JME								
<i>Posterior Hippocampus</i>	-33 -31 -5	2.53	0.027	0.16 (0.04–0.29)				
	-21 -40 -4	2.47	0.031	0.19 (0.04–0.34)				
<i>Parahippocampal gyrus</i>					18 -28 -14	3.10	0.006	0.31 (0.12–0.50)
<i>Anterior cingulate gyrus</i>					3 35 -5	2.83	0.002	0.44 (0.16–0.72)
<i>Fusiform gyrus</i>					42 -46 -29	3.32	<0.001	0.25 (0.12–0.37)
<i>Angular gyrus</i>					57 -67 22	2.80	0.003	0.21 (0.07–0.38)
SIB								
<i>Anterior hippocampus</i>					33 -16 -14	1.72	0.043	0.11 (-0.04–0.27)
<i>Posterior hippocampus</i>	-27 -46 -2	2.32	0.04	0.15 (-0.06–0.36)				
<i>Orbitofrontal cortex</i>	-33 -41 2	2.54	0.006	0.14 (0.04–0.24)				
<i>Superior frontal gyrus</i>	-18 32 61	3.27	<0.001	0.24 (0.13–0.35)				
<i>Fusiform gyrus</i>					33 -61 -2	3.64	<0.001	0.13 (0.08–0.18)
<i>Middle occipital gyrus</i>	-42 -67 -13	2.92	0.002	-0.11 (0.05–0.17)				

Abbreviations: CI = confidence interval; CTR = controls; JME = patients with juvenile myoclonic epilepsy; MNI = Montreal Neurological Institute; SIB = siblings of patients with juvenile myoclonic epilepsy. Coordinates for mesiotemporal and extra-mesiotemporal activations are given in MNI space. When in bold, *P*-values for peak-level mesiotemporal activations are family-wise error rate (FWE) corrected for multiple comparisons using a small volume correction within a 12-mm diameter sphere, centred on the local activation maximum. *P*-values not in bold are uncorrected for multiple comparisons. Parameter estimates (i.e., betas) are reported along with their 95% confidence intervals (CI). For a given anatomical region, statistics are reported for up to three peak-level local maxima, ordered by statistical significance. For the SIB group, there were no supra-threshold mesiotemporal voxels. Coordinates of sub-threshold mesiotemporal activation are reported for completeness.

SUPPLEMENTARY TABLE 5. Visual subsequent memory – subgroup analyses

<i>Region</i>	<i>Left Hemisphere</i>			<i>Right Hemisphere</i>		
	MNI coordinates (x,y,z)	Z-score	<i>P</i> value	MNI coordinates (x,y,z)	Z-score	<i>P</i> value
<i>JME-HIMAL > CTR</i>						
<i>Posterior hippocampus</i>	-36 -31 -8	3.08 (2.83)	0.007 (0.013)			
<i>JME-noHIMAL > CTR</i>						
<i>Anterior cingulate gyrus</i>				1 35 1	3.80	<0.001
<i>Frontal pole</i>	-42 53 -8	2.75	0.003			
<i>Middle frontal gyrus</i>	-30 -2 46	2.91	0.002	45 26 31	2.67	0.004
<i>Supramarginal gyrus</i>	-36 -46 37	2.77	0.003			
<i>Angular gyrus</i>	-30 -64 22	3.03	0.001	45 -61 19	3.00	0.001
<i>Middle occipital gyrus</i>	-48 82 16	2.95	0.002	30 -91 28	2.61	0.005
	-30 -94 22	2.79	0.003			
<i>JME-HIMAL > JME-noHIMAL</i>						
<i>Posterior hippocampus</i>	-33 -28 -11	2.44 (2.43)	0.034 (0.036)			

Abbreviations: CTR= controls; HIMAL= hippocampal malrotation; JME= patients with juvenile myoclonic epilepsy; MNI= Montreal Neurological Institute; noHIMAL= without hippocampal malrotation.

Coordinates of mesiotemporal and extra-mesiotemporal group differences are given in MNI space. *P* values for peak-level mesiotemporal comparisons (reported in bold font) are family-wise error rate (FWE) corrected for multiple comparisons using a 12-mm diameter sphere, centred on the local activation maximum. Z-scores and *P*

values in brackets refer to repeat models including left hippocampal volume as covariate. *P* values for peak-level extra-mesiotemporal differences (all not in bold) are reported as uncorrected across the whole brain.

SUPPLEMENTARY TABLE 6. Structure-function relations – fMRI activation coordinates

<i>Region</i>	<i>Left Hemisphere</i>			<i>Right Hemisphere</i>		
	MNI coordinates (x,y,z)	Z-score	P value	MNI coordinates (x,y,z)	Z-score	P value
<i>All subjects</i>						
<i>Hippocampus</i>	-36 -22 -17	3.24	0.005			
<i>Middle frontal gyrus</i>	-30 23 37	3.62	<0.001	27 23 31	3.51	<0.001
	-33 17 46	3.57	<0.001	21 26 46	3.45	<0.001
<i>Superior frontal gyrus</i>	-24 11 37	3.03	0.001	24 38 43	3.23	0.001
	-15 47 40	2.93	0.002	24 29 49	3.38	0.001
<i>JME & SIB</i>						
<i>Hippocampus</i>	-36 -22 -17	2.81	0.015			
<i>Middle frontal gyrus</i>	-33 23 34	3.49	<0.001	24 23 31	3.35	<0.001
	-33 17 46	3.10	0.001	24 38 43	3.15	<0.001
	-24 29 22	3.08	0.001	33 38 40	3.03	0.001
<i>Superior frontal gyrus</i>	-18 35 37	2.72	0.003	24 29 49	2.96	0.002

Abbreviations: JME= patients with juvenile myoclonic epilepsy; MNI= Montreal Neurological Institute; SIB= siblings of patients with juvenile myoclonic epilepsy. Coordinates for mesiotemporal and extra-mesiotemporal correlational effects are given in MNI space. When in bold, *P*-values for peak-level mesiotemporal activations are family-wise error rate (FWE) corrected for multiple comparisons using a 12-mm diameter sphere (small volume), centred on the local activation maximum. *P*-values not in bold are uncorrected for multiple comparisons. For a given anatomical region, statistics are reported for up to three peak-level local maxima, ordered by statistical significance.