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Neuroanatomical Correlates of Cognitive Phenotypes in Temporal Lobe Epilepsy

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Abstract

Background—Previous research characterized three cognitive phenotypes in temporal lobe epilepsy; each associated with different profiles of clinical seizure and demographic characteristics, total cerebral (gray, white, CSF) and hippocampal volumes, and prospective cognitive trajectories. The objective of this investigation is to characterize in detail the specific neuroanatomical abnormalities associated with each cognitive phenotype.

Methods—High resolution MRI scans from healthy controls (n=53) and temporal lobe epilepsy patients (n=55), grouped by cognitive phenotype (minimally impaired; memory impaired; memory, executive and speed impaired) are examined in regard to patterns of gray matter thickness throughout the cortical mantle as well as volumes of subcortical structures, corpus callosum, and regions of the cerebellum.

Results—Increasing abnormalities in temporal and extratemporal cortical thickness, volumes of subcortical structures (hippocampus, thalamus, basal ganglia), all regions of the corpus callosum, and bilateral cerebellar gray matter distinguish the cognitive phenotypes in a generally step-wise fashion. The most intact anatomy is observed in the minimally impaired epilepsy group and the most abnormal anatomy is evident in the epilepsy group with impairments in memory, executive and speed.

Conclusion—Empirically derived cognitive phenotypes are associated with the presence, severity, and distribution of anatomic abnormalities in widely distributed cortical, subcortical, callosal, and cerebellar networks.

Keywords

Cluster analysis; neuropsychological tests; MRI; seizures; cognition; cortical thickness

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Introduction

Neuropsychological impairment is an important co-morbidity of chronic epilepsy [1]. A rich literature has characterized the relationship between cognitive impairment and clinical seizure features such as seizure type, seizure frequency or severity, age of onset and duration of epilepsy, and antiseizure medications [2-7]. In addition, descriptive cognitive profiles have been reported for various epilepsy syndromes which emphasize the link between the primary epileptogenic region and its major corresponding cognitive consequences, such as episodic memory in temporal lobe epilepsy and executive function in juvenile myoclonic epilepsy [1, 8-11]. While these syndrome-specific structure-function associations are helpful, comprehensive characterization of neuropsychological status may actually demonstrate cognitive disruption to exist outside the confines of the primary epileptogenic region [12,13].

In the case of chronic mesial temporal lobe epilepsy, a pattern of relatively generalized cognitive impairment has been reported which raises the possibility that anatomic abnormality may exist outside the bounds of the mesial temporal lobe [12,14,15]. This inference has been supported by findings of diffuse temporal and extratemporal abnormalities in cortical thickness, cortical complexity, and gyral and sulcal curvature that are present both contralateral as well as ipsilateral to the side of seizure onset [16-20], along with atrophy of multiple subcortical structures and the cerebellum [21-23]. These anatomic abnormalities could be due to any number of factors including but not limited to the neurodevelopmental consequences of an early initial precipitating injury, the effects of recurrent seizures and their treatment on brain development, and/or the result of decades of medication resistant seizures [24].

A persisting limitation of modal cognitive profiles is that they fail to reflect the degree of variability exhibited by *individuals* with any one epilepsy syndrome, including mesial temporal lobe epilepsy, cognitive variability which is quite evident in clinical settings. To that end, we attempted to identify *cognitive phenotypes* of temporal lobe epilepsy [25]. Specifically, adjusted (age, gender, education) cognitive domain scores were derived (intelligence, language, perception, immediate and delayed memory, executive function, motor/psychomotor speed) and subjected to cluster analysis. Three distinct groups were identified (see Figure 1). Cluster 1 (47% of subjects) exhibited the most intact cognition and were minimally impaired compared to healthy controls, Cluster 2 (27% of subjects) presented with primary impairments in immediate and delayed memory function, while Cluster 3 (24% of subjects) exhibited generalized cognitive compromise with particularly severe impairments in memory, executive function, and motor/psychomotor speed. These groups were found to be associated with different clinical and demographic characteristics, increasing abnormalities in total cerebral gray and white matter and hippocampal volumes, and increasingly abnormal prospective (4 year) cognitive trajectories [25].

The volumetric measurements examined in that investigation were extremely broad and nonspecific in nature (total cerebral gray, white matter, CSF, and hippocampus). The nature of the neuropsychological abnormalities would suggest that increasingly severe and distributed structural abnormalities would be associated with the cognitive phenotypes. In this paper we present the results of a reanalysis of the MRI data using an analytic system that provides a comprehensive characterization of cortical thickness and volumes of multiple subcortical structures, regions of the corpus callosum, and the cerebellum. This reanalysis provides very detailed and thorough information regarding the neuroanatomic abnormalities associated with these important cognitive phenotypes of temporal lobe epilepsy.

Methods

Subjects

Research participants were patients with temporal lobe epilepsy ($n = 55$) and healthy controls ($n = 53$). Selection criteria for epilepsy participants have been described in detail previously [16]. Briefly, epilepsy and control subjects were between 14-59 years of age with WAIS-III Full Scale > 69 . Patients suffered from long standing temporal lobe epilepsy confirmed by ictal monitoring or consensus conference review of clinical data (history, seizure semiology, MRI, interictal EEG). Controls were a friend or relative of epilepsy participants.

All described previously [25], participants were administered a comprehensive test battery that included standard clinical measures of intelligence, language, perception, verbal and visual memory, executive function, and motor and psychomotor speed. *Raw scores* for all measures were converted to adjusted (age, gender, years of education) z-scores (mean = 0, sd = 1) using multiple regression techniques. Cognitive domain scores were created by computing the average adjusted z-scores of tests falling within the designated cognitive domains, and the resulting cognitive domain scores were subjected to cluster analysis and the three previously described cognitive phenotype groups were identified (Figure 1).

MRI Procedures

MRI Acquisition—Images were obtained on a 1.5 T GE Signa MR scanner. Sequences acquired for each participant included: (i) T1-weighted, three-dimensional SPGR acquired with the following parameters: TE = 5, TR = 24, flip angle = 40, NEX = 1, slice thickness = 1.5 mm, slices = 124, plane = coronal, FOV = 200, matrix = 256×256; (ii) proton density (PD) and (iii) T2-weighted images are acquired with the following parameters: TE = 36ms (for PD) or 96 msec (for T2), TR = 3000 ms, NEX = 1, slice thickness = 3.0 mm, slices = 64, slice plane = coronal, FOV = 200, matrix = 256×256.

All MR images are inspected prior to image processing. Image quality was rated on a five point scale as described at, (http://www.psychiatry.uiowa.edu/mhcrc/IPLpages/qa_main.htm). We required a minimum of Quality 3 or better for the scan to be included in this analysis.

MRI Processing—Images were transferred to a Mac OSX computer for processing with the FreeSurfer image analysis suite which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). FreeSurfer is a set of software tools for the study of cortical and subcortical anatomy. The T1 volumetric MRI scan was used for cortical reconstruction and volumetric segmentation. The technical details of these procedures are described in prior publications [26-37]. Briefly, this processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure [37], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles)[30,31] intensity normalization [38], tessellation of the gray matter white matter boundary, automated topology correction [29,39] and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [26-28]. After creation of the white matter and pial surfaces the cortical thickness is calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface [28]. Surface curvature is also calculated delineating gyral and sulcal features. Comparison of surface measures across subjects is possible after surface inflation [32], and registration to a spherical atlas which utilizes individual cortical folding patterns to match cortical geometry across subjects [33]. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved.

Mean thickness differences between groups can then be displayed on the pial surface of the standard atlas. An automatic parcellation of the cerebral cortex into units based on gyral and sulcal structure [34,40] results in 34 neuroanatomical regions per hemisphere (4 medial temporal, 5 lateral temporal, 11 frontal, 5 parietal, 4 occipital, and 4 cingulate). Average thickness measures are produced for each of the parcellation ROIs. These 34 regions were combined into 6 lobar regions per hemisphere for initial analyses. The average thickness for each lobe was calculated as the areal weighted average of the lobes constituent regions.

The reported data was produced using the FreeSurfer **4.0.4** default processing stream (recon-all -all). Data were visually inspected, and manual interventions were performed when the automated steps reported errors. These included manual alignment to the Talairach template in cases where automated registration was poor, and adjustments to the watershed threshold to restore areas of the brain that were erroneously removed during skull stripping. Occasional editing of the gray matter and white matter segmentation image was completed when defects were evident.

Analyses

The analytic plan was as follows. Mean cortical thickness data were first addressed by analysis of the six major left and right hemisphere regions characterized by FreeSurfer (frontal, medial temporal, lateral temporal, parietal, cingulate, occipital) using multivariate analysis of covariance (MANCOVA) with age as the covariate. Subsequent examination of lobe-specific subregions was pursued only for those lobes where MANCOVA identified a significant group effect. Volumetric data (hippocampus, amygdale, thalamus, caudate, putamen, cerebellum, corpus callosum) were analyzed by MANCOVA using age and ICV as covariates. The regions of interest were limited to areas reported to be abnormal in temporal lobe epilepsy.

A full characterization of the adjusted means for all regions of interest (cortical thickness and volume) is provided in the supplemental table. The Results section provides summary figures depicting the anatomic areas where significant univariate effects of group were obtained with accompanying bar graphs summarizing the findings for each cognitive phenotype group compared to the controls. The bar graphs are presented in terms of percent reduction in thickness or volume compared to healthy controls which thereby allows all data to be considered on the same metric. Finally, a summary of the salient post-hoc pair-wise contrasts across cognitive phenotype groups is presented in the text.

Results

Cortical thickness

The overall MANCOVA examining cortical thickness across the 12 lobar regions was significant ($F=2.4$, $df=12,94$, $p=.009$). Univariate results were significant for the left frontal lobe ($F=1.9$, $df=3$, 103 , $p=.037$), left lateral temporal ($F=3.5$, $df=3$, 103 , $p=.018$), left parietal ($F=6.4$, $df=3$, 103 , $p<.001$), right parietal ($F=4.5$, $df=3$, 103 , $p=.005$), left occipital ($F=4.0$, $df=3$, 103 , $p=.009$), and right occipital ($F=7.69$, $df=3$, 103 , $p<.001$) lobes; but not right lateral temporal ($F=2.2$, $df=3$, 103 , $p=.09$), right frontal ($F=1.9$, $df=3$, 103 , $p=.65$), left cingulate ($F=.25$, $df=3$, 103 , $p=.86$), right cingulate ($F=.55$, $df=3$, 103 , $p=.65$), left medial ($F=2.29$, $df=3$, 103 , $p=.08$) or right medial ($F=.65$, $df=3$, 103 , $p=.59$) regions.

Figures 2 and 3 summarize the results of analyses of specific cortical regions for those lobes where a significant group effect was obtained. Figure 2 characterizes those areas where significant cortical thinning was detected *bilaterally*. The affected areas include the cuneus and precuneus as well as the pericalcarine, postcentral, inferoparietal, superoparietal, and supramarginal gyri. The bar graph in Figure 2 indicates a general pattern of increasing cortical

thinning from the most intact (Cluster 1) to the most impaired (Cluster 3) cognitive phenotypes. The results of the pair-wise comparisons will be provided below. Percent reduction is calculated as the average of the left and right hemisphere reduction for each region.

Figure 3 depicts cortical regions where a significant group effect was detected unilaterally *unilaterally*. Areas affected in the left hemisphere include the caudal-middle-frontal gyrus, inferior temporal and middle temporal gyri, pars opercularis, pars orbitalis, and transverse temporal gyri. Areas affected in the right hemisphere included the right isthmus cingulus, lateral occipital gyrus, lingual gyrus, pars triangularis, and rostral middle frontal regions.

The bar graph in Figure 3 indicates a pattern of increasing cortical thinning from the most intact (Cluster 1) to the most impaired (Cluster 3) cognitive phenotypes. The results of the pair-wise comparisons follow below.

Subcortical and cerebellar volumes—The overall MANCOVA examining targeted subcortical, cerebellar, and corpus callosum was significant ($F=5.8$, $df=20, 85$, $p<.001$). Univariate effects (all $df=3,102$) were significant for left ($F=3.5$, $p<0.02$) and right cerebellar cortex ($F=3.3$, $p=.023$) but not the left ($F=.83$, $p=.48$) or right ($F=1.06$, $p=.37$) cerebellar white matter; left ($F=7.6$, $p<.001$) and right ($F=5.2$, $p=.002$) thalamus; left ($F=7.1$, $p<.001$) and right ($F=5.2$, $p=.002$) hippocampus; left ($F=3.5$, $p=.019$) and right ($F=3.1$, $p=.029$) caudate; but not left ($F=1.0$, $p=.38$) or right ($F=2.1$, $p=.10$) amygdala; or left ($F=.03$, $p=.99$) or right ($F=.09$, $p=.97$) putamen. All regions of the corpus callosum were affected including anterior ($F=3.9$, $p=.01$), mid-anterior ($F=5.6$, $p=.001$), central ($F=3.8$, $p=.013$), mid-posterior ($F=5.9$, $p=.001$), and posterior ($F=8.7$, $p<.001$) areas.

Figure 4 depicts the subcortical and cerebellar regions that differed significantly across the cognitive phenotypes and the associated bar graph summarizes the percent reductions for these regions across the cognitive phenotypes, again with a consistent pattern of increasing atrophy from the most intact (Cluster 1) to the most impaired (Cluster 3) cognitive phenotypes.

Figure 5 summarizes the volumetric reductions in regions of the corpus callosum including posterior, mid posterior, central, mid anterior and anterior regions where again there is increasing volumetric loss from the most intact (Cluster 1) to the most impaired (Cluster 3) cognitive phenotypes.

Finally, figure 6 provides a subtraction map of the healthy controls compared to each of the cognitive phenotypes. The increasing degree and distribution of cortical thinning can be appreciated in these images.

Pair-wise comparisons across measures of cortical thickness and volume

Cluster 3 compared to healthy controls and other epilepsy groups—Cluster 3 was clearly the most affected group compared both to controls and other epilepsy cognitive phenotype groups. Compared to controls, Cluster 3 exhibited significant cortical thinning across all 14 bilateral regions indicated in Figure 2 (all p 's $<.04$), all regions of the corpus callosum (all p 's $<.002$); the left and right thalamus (p 's $<.002$), caudate (p 's $<.04$), and cerebellum (p 's $<.007$); and the left (.036) but not right (.10) hippocampus. Cluster 3 exhibited significant cortical thinning compared to Cluster 1 across 12 of the 14 areas including the left and right cuneus (p 's $<.003$), precuneus (p 's $<.01$), superiorparietal (p 's $<.04$) and supramarginal (p 's $<.04$), inferiorparietal (p 's $<.03$) regions; and the right ($p=.05$) but not left pericalcarine gyrus (.187), and left (.02) but not right (.51) postcentral gyrus. Cluster 3 also exhibited significantly lower volume compared to Cluster 1 across all regions of the corpus callosum (all p 's $<.02$) and the left and right thalamus (p 's $<.002$); the right (.04) but not left (.94) cerebellum, the left (.001) but not right (.66) hippocampus, and neither caudate (p 's $>.9$)

Clusters 1 and 2 compared to controls—Compared to controls, Cluster 1 showed few significant differences with thinner cortex only in the left pericalcarine gyrus (.019), left and right caudate (p 's <.009), and left transverse temporal gyrus (.02). Compared to controls, Cluster 2 showed thinner cortex in the left cuneus (.01), left inferiorparietal (.05), left middle temporal (.009), right pericalcarine (.02), right precuneus (.04), left frontal pole (.012), right isthmus cingulate (.04), left rostral middle frontal (.03), right hippocampus (.05), and posterior corpus callosum (.04).

Cluster 1 versus 2—Cluster 2 exhibited thinner cortex in the right precentral (.04), left frontal pole (.03), and left and right hippocampus (p 's <.02).

Discussion

One reasonable way to anticipate and conceptualize the cognitive correlates of specific epilepsy syndromes is through their primary underlying pathophysiology, that is, memory impairment characterizing temporal lobe epilepsy, executive impairment prominent in frontal lobe epilepsies, and attentional problems dominating in absence epilepsy [1,8]. Memory problems can certainly be documented in temporal lobe epilepsy as would be expected given the primary neuropathology (hippocampal sclerosis) [41], but when characterized in a comprehensive fashion, cognitive abnormalities appear more distributed and generalized than expected [12, 14,15]. While this “average cognitive profile” provides a somewhat different view of the neuropsychological consequences of temporal lobe epilepsy, clinical experience suggests that not all patients actually exhibit such a profile. That is, individual patients with mesial temporal lobe epilepsy may range from rather unscathed to severely affected mental status. Somewhat the same might be said regarding the structural abnormalities reported to be associated with temporal lobe epilepsy, abnormalities that have been found to extend beyond the epileptogenic hippocampus to affect a diversity of temporal and extratemporal lobe regions both ipsilateral as well as contralateral to the side of seizure onset [16-21,23]. It has been our hypothesis that non-overlapping groups of patients may be identified who present with varying cognitive profiles and associated anatomic abnormality, findings that would identify important phenotypes for future research.

To address this issue, we adjusted (age, gender, education) cognitive test scores based on a healthy control population, derived cognitive domain scores, and used cluster analysis to determine whether meaningful profiles of cognitive status could be identified. Specific “cognitive phenotypes” were identified (Figure 1) with associated clinical seizure and demographic characteristics, increasing abnormalities in summary volumetric measures of total cerebral gray and white matter and hippocampi, and increasingly abnormal prospective (4 year) cognitive trajectories [25]. Here we take advantage of sophisticated postprocessing techniques to comprehensively examine patterns of abnormality in cortical thickness and volumes of subcortical structures, callosal, and cerebellar regions across these cognitive phenotypes. The results are noteworthy for the regularity of evident neuroanatomic abnormality across the cognitive phenotypes, and perhaps surprising for the distribution and degree of abnormality.

First, the cognitive phenotypes were distinguished by abnormalities across very diverse cortical regions (left frontal lobe, left lateral temporal lobe, left and right parietal lobe, left and right occipital lobe), subcortical structures (bilateral hippocampus, thalamus, caudate, and gray matter of the cerebellum), and white matter (all regions of the corpus callosum). Second, the pattern of abnormality in all these abnormal regions was quite uniform in that those patients with the most impaired cognition (Cluster 3) exhibited the most significant cortical thinning (5 to 8%) and volumetric reductions across all subcortical (10 to 18%), cerebellar gray matter (14%) and white matter regions of interest (17 to 26%). These same anatomic measures were

least abnormal in the most cognitively intact temporal lobe epilepsy group (<1 to 4% for cortical thinning, 4 to 10% for subcortical structures, 4 to 5% for cerebellar gray matter, 5 to 8% for regions of the corpus callosum). This symmetry between cognitive profile and brain structure speaks to the importance of underlying neuroanatomic abnormalities in the etiology of cognitive impairment compared to what might be considered to be more transient factors (e.g., epilepsy medications, epileptiform spike frequency) or clinical seizure characteristics (e.g., seizure frequency), although these variables certainly play a role. Third, the patterns of abnormality were often bilateral in nature affecting both cortical regions (Figure 2), subcortical structures (thalamus, hippocampus, caudate), and cerebellar gray matter (Figure 4), in conjunction with substantial white matter abnormality (Figure 5). That there can be such widely distributed pathology in a localization related form of epilepsy is both surprising as well as a finding of concern. Fourth, cortical thinning was especially evident in posterior brain regions including parietal, occipital, posterior temporal and sensorimotor regions. We would have anticipated more anterior and frontal abnormalities, but these regions did not distinguish the clusters in a broad fashion, although there were unilateral frontal lobe differences. Abnormalities in these posterior regions have been reported in recent studies of cortical thickness in temporal lobe epilepsy [17-20] and are found here to especially characterize the more cognitively impaired cohort (Cluster 3). Executive and motor functions are especially affected in Cluster 3 and it is possible that executive function is disrupted predominantly by abnormalities in subcortical structures known to be an intrinsic component of fronto-striatal systems that mediates these abilities [42,43]. Finally, prior neuroimaging studies have presented modal profiles of structural abnormalities in temporal lobe epilepsy. As is the case for cognition, these modal profiles do not reflect the substantial degree of variability that may be present across patients. The interesting diversity of anatomic abnormality speaks to this underlying individual variability with clear implications for cognition.

Overall, these findings help characterize the neuroanatomic status of cognitive phenotypes that have associated patterns of prospective cognitive courses. As we have reported previously, the clinical and demographic features are not that strikingly different compared to the divergent nature of the cognitive and imaging results [25]. Interestingly, despite the fact that these epilepsy patients were recruited from tertiary care centers that tend to care for more adversely affected patients, the largest cohort of patients (Cluster 1, 47% of subjects) exhibited comparatively intact cognition and the least affected brain structure, despite a prolonged course of epilepsy.

While we have presented considerable information regarding the identification of cognitive phenotypes; their clinical, demographic, and structural features as well as their prospective cognitive course, critical issues remain to be clarified regarding the origin, etiology, and epigenetics of these groups.

The limitations of this investigation should be recognized. The number of subjects is modest, we are not able to examine cognitive and structural patterns by lateralization of temporal lobe epilepsy, and as we are examining only patients with temporal lobe epilepsy the degree to which these phenotypes may be represented in other forms of epilepsy cannot be addressed. Future research should replicate these clusters and their associated features in a larger sample of patients.

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Figure 1. Cognitive phenotypes

Figure 2. Bilateral reductions in cortical thickness across cognitive phenotypes

Unilateral left

- Rostral middle frontal
- Pars opercularis
- Middle temporal
- Inferior temporal

Unilateral right

- Precentral
- Lateral occipital
- Lingual

Figure 3. Unilateral reductions in cortical thickness across cognitive phenotypes

Hippocampus
Thalamus
Caudate
Cerebellum

Figure 4. Volumetric reductions in subcortical and cerebellar regions

Figure 5. Volumetric reductions of the corpus callosum across cognitive phenotypes

Figure 6. Thickness difference images across cognitive phenotypes

Table 1

Demographic and clinical characteristics

Clusters	1	2	3
Age (yrs)	33.6	37.9	41.8
Gender (% F)	63	72	65
Education (yrs)	13.4	13.1	12.4
Age of onset (yrs)	15.6	15.6	12.9
Duration (yrs)	17.5	21.7	27.7
AEDs	1.6	1.7	2