The Emerging Architecture of Neuropsychological Impairment in Epilepsy

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A rich literature dating back to the early twentieth century has characterized the cognitive morbidity associated with the epilepsies and the association of this morbidity with the cause, course, and treatment of the disorder. Critical reviews over the decades have cataloged the links between cognitive disorders and specific clinical features of the epilepsies including their etiology; seizure frequency and severity; complications of the disorder (e.g. status epilepticus); antiseizure medications; and electroencephalographic abnormalities, such as the type, frequency, and distribution of interictal epileptiform and slow wave activity.[1–6]

The understanding of the neuropsychological consequences of the epilepsies evolved in concert with advancements in the wider worlds of cognitive psychology and epilepsy. First, early studies were typically but not exclusively limited to the evaluation of intelligence. Assessment of higher cognitive functions was in its formative years[7] and with the introduction of the Binet-Simon scales, and especially their adaption for use in the United States (eg, the early Vineland translation and the later Stanford-Binet revision), characterization of intellectual status in epilepsy followed quickly.[8] As a deeper understanding of human cognition developed, and newer tests and measures became available to assess those concepts, appreciation of the cognitive correlates of epilepsy expanded apace. Second, much of the early literature came from very limited segments of the population of people with epilepsy, typically from specialized institutions (or colonies) serving the more complicated and severely affected individuals.[3] Over time more representative portions of the population were sought out and investigated, which yielded a less biased but still imperfect characterization of the relationship between epilepsy and intelligence and broader cognitive status.[2,9,10] The focus of research has continued to be on persons with epilepsy presenting to specialized tertiary care medical centers, although more representative population-based studies of cognition are available, particularly

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among children with epilepsy.[11–14] Third, classification and taxonomy of the epilepsies developed from early rudimentary systems to the evolving and increasingly sophisticated international classification of epileptic seizures and syndromes.[15,16] The neuropsychological features of these syndromes and their primary cognitive signatures have developed accordingly.[6,11,17–20] Finally, as medical technology evolved patients with epilepsy have been studied with increasing sophistication to understand the underlying neurobiology of cognitive impairment in epilepsy, a primary focus of this article.

A critical and fundamental feature of the neuropsychology of epilepsy literature is that throughout its history a primary focus has been the relationship of cognition and cognitive disorders to core clinical features of the epilepsies including but not limited to the age of onset of epilepsy, etiology, seizure type and syndrome, medications, duration of epilepsy, and electroencephalographic features.[21–26] Unequivocal associations between these clinical characteristics and neuropsychological impairments have been reported and repeatedly replicated through the decades, but the neurobiologic mechanisms through which they exert their effects have been investigated less intensively. A new literature is now under way, one linking cognitive abnormalities directly to indices of structural, functional, metabolic, and other neurobiological markers of cerebral integrity, independent of their association with clinical epilepsy characteristics. These trends are reviewed in the material to follow. The initial focus is on temporal lobe epilepsy (TLE) as a model with which to address the core points, because this form of localization-related epilepsy has been very carefully studied from both a cognitive and imaging standpoint. Some pertinent historical issues are touched on first, followed by more detailed reviews of the cognitive and neuroimaging abnormalities that have been found in TLE, followed by an overview of studies examining direct structure-function relationships in TLE and other epilepsies.

THE UNIQUE CONTRIBUTION OF TLE

Psychomotor epilepsy or TLE has provided an especially important window into the neuropsychology of epilepsy. The term "psychomotor epilepsy" was used beginning in the 1930s to describe relatively poorly understood spells that some had called psychic equivalents. [27,28] The early electroencephalographic features were characterized in the context of clinical attacks wherein "….the patient, though he may perform apparently conscious acts, is not subject to command; he may exhibit involuntary tonic movements; he may display psychomotor disturbances….and on recovery he has complete amnesia for the events which occurred in the attack."[27,29,30] These seizures were later found to be associated with an anterior temporal lobe spike focus,[30,31] and consideration of epilepsy surgery for these "nonlesional" patients developed early on in Chicago[32] and Montreal.[33]

Early surgical centers routinely incorporated cognitive assessments in their evaluations, which were performed under the supervision of Donald Hebb[34] and Brenda Milner[35,36] at the Montreal Neurological Institute, Ward Halstead[37] at the University of Illinois, and Victor Meyer at the Maudsley Hospital.[38,39] The neuropsychology of epilepsy benefitted enormously from these early opportunities to assess patients before and after surgery and to correlate cognitive changes with detailed preoperative histories, well-characterized surgical resections, careful neuropathologic examinations of resected tissue, and eventually quantitative neuroimaging.[5]

THE PALM DESERT CONFERENCES ON EPILEPSY SURGERY AND THE NEUROPSYCHOLOGY OF EPILEPSY

Important events for the neuropsychology of TLE were the Palm Desert Conferences on Epilepsy Surgery.[40] Before these international conferences there were varying opinions

regarding the operational definition of surgical candidacy. Various reasonable criteria were proposed, including seizure frequency and severity, the number of failed medications, or the degree of social and occupational disability; but consensus remained to be achieved. At the second Palm Desert Conference a focus was placed on "surgically remediable syndromes," among which mesial TLE (mTLE) was prominent.[40] If a syndrome was surgically curable, it should be identified and treated with minimal delay.[41]

This conceptualization had an important impact not only on the thinking regarding optimal patient selection and surgical timing, but it also facilitated increasingly careful characterization of mTLE.[42] At that time details regarding the neuropsychological features of mTLE were few in number and the primary cognitive correlates were viewed as largely linked to material-specific memory impairment demonstrated either through formal cognitive assessment or the Wada Test. A stated contraindication to the syndrome of mTLE was the presence of generalized cognitive compromise, all of this was a reasonable early characterization.[41] For neuropsychologists who saw a steady stream of surgical candidates with well characterized mTLE, however, the neuropsychological correlates were viewed as considerably more complex. Memory asymmetry was indeed seen in a proportion of patients, an asymmetry linked to the degree of neuronal loss and sclerosis in the affected hippocampus,[43] but this pattern often occurred in the context of more distributed cognitive impairment. Formal investigations of the ability of neuropsychological tests to localize and lateralize the ictalonset area revealed variable discriminatory power[44] and these results were viewed by some as indicative of the limitations of neuropsychological assessment. The material to follow, however, provides an overview of the distributed nature of cognitive abnormality in mTLE in the context of the distributed nature of identified structural abnormalities in mTLE, and their important associations.

THE DISTRIBUTED NATURE OF COGNITIVE IMPAIRMENT IN MTLE

By definition the syndrome of mTLE is a disorder of childhood-adolescent onset.[45] A core finding, clear from some of the earliest cognitive studies and routinely reported through the decades, is that an early age of onset of recurrent seizures is associated with a pernicious impact on a broad array of cognitive functions. This effect was reported as early as 1924[46] and subsequently confirmed in studies of adult patients with diverse seizure types,[10,47–50] and even reported in neuropsychological studies of younger patients with complex partial and other types of seizures.[51–53]

When the comprehensive neuropsychological status of patients with mTLE with confirmed hippocampal sclerosis was examined compared with healthy controls or patients with other TLE syndromes, such as so-called "MRI-negative TLE," mTLE patients exhibited a pattern of distributed cognitive impairment affecting not only memory, but also intelligence quotient (IQ), executive functions, language, sensorimotor, and other abilities (Fig. 1).[54–57]

This average profile of distributed neuropsychological impairment in mTLE, obtained in the context of a focal epileptogenic lesion whose resection results in excellent outcome, was unexpected. The testable hypothesis was that just as memory impairment was related to neuropathology in the hippocampus, perhaps the more widespread neuropsychological abnormalities might be secondary to more diffusely existing neuroanatomic abnormality that could be detected by quantitative neuroimaging techniques, and that individual variability in neuropsychological abnormalities might be associated with individual patterns of anatomic abnormality.[54]

THE DISTRIBUTED NATURE OF ANATOMIC ABNORMALITIES IN CHRONIC TLE

The cumulative neuroimaging literature, focusing here on structural neuroimaging, has shown that anatomic abnormalities in mTLE can be extensive. For reasons that remain to be understood, mTLE seems to be associated with abnormalities in surprisingly diverse neuronal systems, a pattern consistent with the generalized and distributed average neuropsychologic profile of TLE (see Fig. 1).

Initial quantitative MRI volumetric and voxel-based morphometry (VBM) studies identified atrophy of the hippocampus,[58–61] along with reports of abnormalities in related structures including entorhinal cortex,[60–63] fornix,[64] parahippocampal gyrus,[61] amygdala,[60,61] basal ganglia,[65,66] and thalamus.[65,67,68] More distant extrahippocampal temporal lobe[58,69–72] and extratemporal lobe regions[69,73] were implicated including the lateral temporal cortex, frontal lobe, and the cerebellum.[74,75] With this degree of distributed atrophy, it is not surprising that reductions in overall total cerebral tissue volume were reported.[56,69,70,76–78]

With few exceptions[68,79] most of the early volumetric investigations examined one or a limited number of structures rather than characterizing a broad and diverse range of regions as to the presence and degree of abnormality. Examination of several regions in the same patient group facilitated appreciation of the distribution and relative degree of structural burden carried by many patients.[68,79] In that regard, a very helpful summary of the presence and distribution of structural abnormality associated with TLE is provided by Keller and Roberts.[80] In their review they surveyed 26 brain regions examined in VBM investigations of TLE compared with healthy controls. Their summary (Fig. 2) demonstrates the proportion of studies revealing abnormalities in mesial, extramesial temporal lobe, subcortical, and extratemporal lobe cortical regions. The presence and distribution of these abnormalities would suggest that cognitive abnormalities might extend beyond memory to involve diverse cognitive abilities.

DISTRIBUTED ABNORMALITIES IN CORTICAL SURFACE FEATURES IN TLE

Another example of the potential structural consequences of mTLE is provided by quantitative characterization of the cortical mantle, including indices of gyrification, cortical depth, and surface area. These indices provide important information concerning normal and abnormal brain development, the effects of normal aging, and disease impact.

Lee and colleagues[70] were among the first to examine cortical surface features (sulcal curvature) in unilateral TLE, the bulk of evidence awaiting the development of more sophisticated image processing systems. Accumulating evidence has shown that patients with unilateral TLE exhibit bilateral and diffuse abnormalities in sulcal and gyral curvature, cortical depth, and cortical complexity.[56,81–84]

Oyegbile and colleagues[56] examined cortical surface features in an initial cohort of 96 patients with TLE and 82 healthy controls. They found patients with unilateral TLE to exhibit abnormalities in whole-brain gyral and sulcal curvature with increased surface cerebrospinal fluid (CSF) volume. These cortical surface feature abnormalities were generalized in nature and evident both contralateral and ipsilateral to the side of temporal lobe seizure onset.

Lin and colleagues[85] examined cortical thickness and cortical complexity in an extremely carefully defined patient cohort. Their cohort of patients exhibited at least three ictally monitored seizures demonstrating unilateral temporal lobe onset, hippocampal sclerosis demonstrated by histopathology, and class 1 outcome 2 years following surgery. Comparing 15 left and 15 right mTLE patients with 19 healthy controls, they found both left and right

mTLE groups to have regions with up to 30% bilateral decrease in average cortical thickness, with significant thinning of the bilateral frontal poles, frontal operculum, orbitofrontal, lateral temporal, and occipital regions, right angular gyrus, and primary sensorimortor cortex surrounding the central sulcus (Fig. 3). Examining cortical complexity, the left TLE group showed significantly reduced complexity across all left and right hemisphere lobes except the right frontal lobe. The right TLE group exhibited significantly reduced cortical complexity across all lobes except the right frontal and parietal lobes. A very diffuse and bilateral pattern of abnormality was therefore evident in the cortical mantle in patients with unilateral mTLE.

Subsequent studies have elaborated and extended these findings. Bernhardt and colleagues[83] examined 110 patients with TLE (56 left, 54 right) and 45 controls, and Fig. 4 summarizes the findings. Thinning was evident in bilateral frontocentral (superior, middle, and medial frontal gyrus; precentral gyrus; paracentral lobule); cingulate; and contralateral medial occipitotemporal regions. The most severe frontal thinning occurred in the ipsilateral precentral regions. In addition, there was severe cortical thinning in the hippocampus and parahippocampal regions ipsilateral to side of seizure onset. Contralateral to the seizure focus, there was cortical thinning in the medial occipitotemporal gyrus. In right TLE the severity of atrophy was similar and the pattern resembled that found in left TLE, but less widespread.

McDonald and colleagues[82] compared 21 patients with TLE with 21 healthy controls. Bilateral cortical thinning (5%–15%) was reported in the lateral temporal lobes (Heschl's gyrus) and frontal lobes (precentral, paracentral, pars opercularis). Unilateral cortical thinning was evident in the left superior temporal gyrus and sulcus and medial orbital cortex; and the right middle temporal gyrus and lateral orbitofrontal cortex. If analyses were restricted to mTLE patients, then the parietal cortex was also affected.

Mueller and colleagues[84] used 4-Tesla MRI and examined 35 controls and 15 patients with mTLE and 16 non-mTLE patients. Both groups exhibited widespread temporal and extratemporal cortical thinning. The mTLE group showed significant thinning in ipsilateral temporal lobe (entorhinal cortex, parahippocampal fusiform gyrus, temporopolar–anterior superior temporal region, retrosplenial region) and bilateral precentral-postcentral regions, superior frontal, transverse temporal, precuneus, and prestriate regions.

In summary, widespread temporal and extratemporal lobe abnormalities in cortical surface features seem present, both contralateral and ipsilateral to the side of seizure onset, in mTLE in particular and TLE more generally.

DISTRIBUTED ABNORMALITIES IN WHITE MATTER AND WHITE MATTER TRACTS IN TLE

In addition to gray matter abnormalities, a decrease in white matter volume is present in chronic TLE. Traditional volumetric studies have demonstrated distributed cerebral white matter abnormalities in patients with unilateral TLE, with abnormalities evident both contralateral and ipsilateral to the side of seizure onset, affecting temporal and extratemporal regions.[86] Whole-brain VBM analyses have also demonstrated temporal and extratemporal abnormalities, although the findings are much less extensive and consistent when compared with gray matter VBM studies. McMillan and coworkers[87] found that left TLE patients had reduced white matter volume in the left temporal lobe, corpus callosum, and bilateral prefrontal cortex. In patients with right TLE, only right temporal lobe and fornix showed decreased volume. Bernasconi and colleagues[88] found that both right and left TLE individuals had reduced white matter volume in the temporal lobes, ipsilateral to side of seizure onset and the body of the corpus callosum. The right TLE individuals had additional white matter reduction in the postcentral regions. Their study did not, however, reveal frontal lobe white matter abnormalities.

Although these white matter volumetric studies further elucidate the widespread structural abnormalities in TLE, they do not provide measures of specific white matter tract coherence or the overall integrity of networks connecting different brain regions. Recent compelling evidence from functional imaging, lesional, and behavioral studies suggest that widespread and coordinated networks are required for complex cognitive function.[89] These distributed networks are linked by projection, association, and commissural white matter fiber tracts that connect cortical-subcortical, cortical-cortical, and interhemispheric regions.[90]

In macaque monkeys, interrupting major afferent pathways from the basal forebrain to the temporal lobe, without removal of the medial temporal structures, produces severe amnesia. [91] In addition, simply disconnecting the parietal lobe from the frontal lobe functionally, as can be done by white matter stimulation during surgery, leads to profound neglect in humans.[92] In certain cases, loss or disruption of cerebral connections can produce a greater magnitude of deficits than localized lesions, suggesting the importance of an integrated structural network in normal cognitive functions. This concept has led to a unifying hypothesis that disconnection between important cortical and subcortical regions impairs information transfer and contributes to cognitive impairments.[93] Indeed, such disconnection models can now be tested, using quantitative imaging techniques, such as diffusion tensor imaging (DTI), to interrogate the integrity of white matter tracts.[94]

In DTI, the primary measure of white matter integrity is fractional anisotropy (FA), which is determined by the directional magnitude of water diffusion in three-dimensional space.[95] Tightly packed white matter fascicles provide structural coherence, which results in water diffusion in a preferred direction (high FA). In contrast, white matter fascicles that have poor structural organizations allow water to diffuse more randomly (low FA). Other measures of white matter integrity include mean diffusivity (MD) or apparent diffusion coefficient, which calculates bulk water diffusion characteristic in the intracellular and extracellular water compartments.[96] Using these water diffusion parameters, studies have evaluated the coherence of specific white matter tracts and whole-brain white matter connectivity.

Initial DTI studies used a region of interest approach to investigate specific white matter tracts in the limbic network. One of the first DTI tractography studies evaluated the integrity of fornix and cingulum in patients with mTLE. In these fiber tracts, Concha and colleagues[97] observed diffusion abnormalities ipsilateral and contralateral to the side of seizure onset. Postulating a more diffuse epileptogenic network in TLE, other investigations have extended this initial finding to frontal-temporal (uncinate fasciculus and arcuate fasciculus),[98−100] temporal-occipital (inferior longitudinal fasciculus),[101] frontal-occipital (inferior frontal occipital fasciculus),[101] and interhemispheric (corpus callosum) connections.[102−104] Parallel to the gray matter region of interest studies, these DTI studies have also shown extensive bilateral abnormalities in cortical-cortical, cortical-subcortical, and interhemispheric connections, despite unilateral seizure onset.

More recently, whole-brain voxelwise analysis techniques of DTI data have been developed. These analyses allow mapping of white matter profiles and delineate systemic differences between TLE patients and healthy individuals, without a priori bias for specific tracts or brain regions. DTI data have poor anatomic resolution, which makes spatial matching across multiple subjects particularly challenging. Two methods have been developed to overcome these technical difficulties: VBM and tract-based spatial statistics. In patients with mTLE, both methods revealed extensive bilateral white matter diffusion abnormalities, particularly in the temporal and frontal lobes ipsilateral to the side of seizure onset.[105−107] Tract-based spatial statistics seemed to be more a sensitive method by detecting more extensive white matter changes when compared with traditional VBM methods in the same patient population.[106]

TLE: A LOCALIZATION-RELATED DISORDER?

The essential theme is that although the primary epileptic zone may be contained within the confines of the hippocampus and temporal lobe, considerable anatomic abnormality exists outside this region affecting a myriad of cortical, subcortical, and cerebellar regions and their direct and indirect connectivity. Importantly, the sum of these distributed structural abnormalities, not to mention associated abnormalities in other aspects of brain integrity, such as metabolism and blood flow, may result in a cumulative cognitive and behavioral burden that may be substantial on average, but with a mosaic that may be highly individualized depending on the underlying architecture of a given patient's structural and functional pathology.

LINKING DISTRIBUTED COGNITIVE IMPAIRMENTS WITH DISTRIBUTED NEUROIMAGING ABNORMALITIES:THE MOSAIC OF STRUCTURE-FUNCTION RELATIONSHIPS IN CHRONIC TLE

A developing literature has begun to characterize the links between cognition and the diverse regions of anatomic abnormality in TLE. This section touches on representative examples of these links. Although the focus is on associations between cognition and structural abnormalities, additional investigations albeit smaller in number have examined associations between cognition and behavior with other measures of brain integrity (eg, metabolism, functional MRI [fMRI] activation), and a few representative examples of those studies are included.

Hippocampus

Early studies demonstrated the expected relationship between memory performance and hippocampal pathology characterized by neuronal loss and sclerosis.[108] Subsequent studies demonstrated a link between hippocampal volumes and memory performance before epilepsy surgery, and preoperative left hippocampal volumes were also predictive of the risk of preoperative to postoperative memory change.[58,109,110] Abnormalities in left hippocampal volume have also been shown to be associated with some language-based abilities including confrontation naming[111] and fluency.[112]

Thalamus

The degree to which the thalamus is affected in chronic mTLE is increasingly recognized and there is now a demonstrated link between atrophy of the thalamus and performance on measures of memory and intelligence in TLE.[113,114] In addition, prior fluorodeoxyglucose positron emission tomography research demonstrated that verbal memory was affected in the context of ipsilateral thalamic hypometabolism in patients with left TLE.[115]

Basal Ganglia

Negative symptoms including affective flattening, alogia and avolition, anergia, apathy, anhedonia, and loss of social drive have been reported in patients with TLE.[116,117] These patients also exhibit cognitive and psychosocial correlates that are not seen in patients with TLE without negative symptoms, but neuroimaging correlations with cortical regions were nonspecific and limited only to increased total CSF.[116,117] Geary and coworkers[118] hypothesized that basal ganglia and anterior cingulate regions of interest play a role in the expression of negative symptoms in epilepsy and compared a matched group of TLE patients with and without negative symptoms with healthy controls (N = 22 per group). They found that TLE patients with negative symptoms exhibited significantly reduced volumes in the putamen and globus pallidus, that these volumetric abnormalities were independent of self-reported depression, and that there were specific significant relationships between alogia with

volumes of the putamen and globus pallidus, and affective flattening with volume of the putamen.[118]

Frontal Lobe

There has been considerable interest in the neural basis of reported impairments in executive function among patients with TLE and their relevance to "secondary" frontal lobe or frontostriatal pathology. Keller and colleagues[119] examined prefrontal and hippocampal volume using sterology and VBM in 30 controls and 26 left and 17 right TLE patients. Assessment of executive functions included evaluation of response inhibition, working memory, and lexical fluency. They found volume reduction of the ipsilateral hippocampus as expected, but also volume reduction in regions of the prefrontal cortex. In addition, there were significant associations between prefrontal cortex and executive function including working memory with all prefrontal regions examined except right dorsal prefrontal cortex; lexical fluency with left dorsal prefrontal cortex, whole left prefrontal cortex, and left hippocampus; and response inhibition with left ventral prefrontal cortex). Along related lines, an earlier positron emission tomography investigation of patients with TLE showed that extension of hypometabolism into the ipsilateral frontal lobe was associated with cognitive consequences. [120]

Examining 36 patients with unilateral mTLE using VBM, Bonilha and colleagues[121] addressed the extrahippocampal correlates of memory performance. In addition to the contributions of hippocampus, entorhinal, and perirhinal cortices to general and verbal memory, they found that atrophy of the cingulate and orbitofrontal cortex was also associated with disrupted memory performance.

Temporal Lobe

In addition to the investigations of memory and the integrity of the hippocampus reviewed previously, there have been several investigations of temporal lobe structure and memory for unfamiliar and familiar faces.[122,123] These studies include bilateral investigation of T2 relaxation time in hippocampus, amygdala, and fusiform gyrus, showing that worse immediate but not delayed memory was correlated with greater differences in T2 values between left and right fusiform gyrus and hippocampus. Griffith and colleagues[124] examined the relationship between [18F] fluorodeoxyglucose positron emission tomography and performance on a task of famous face recognition, naming, and generation of semantic information in 12 patients with TLE. Strong relationships between all aspects of the Famous Faces Task and the left temporal pole were revealed, whereas Famous Faces Task correlations with the right temporal pole were not significant. These findings indicated that the left temporal pole was associated with lexical and semantic retrieval of knowledge of famous persons in patients with TLE.

Cerebellum

The traditional view of cerebellar function is that it contributes primarily to movement and motor control; however, converging animal and human studies indicate that the cerebellum contributes to a variety of higher cognitive abilities, including specific types of memory.[125,126] Human memory is composed of multiple systems, each mediating specific forms of learning and each dependent on different neuronal networks for efficient operation.[127,128] A clear behavioral and anatomic distinction exists between the conscious recollection of facts and events (explicit or declarative memory) versus memories that are inaccessible to conscious recollection but that are expressed through changes in skills, habits, and other forms of simple associative learning (implicit or procedural memory).[127,128] Classical conditioning, a fundamental form of implicit associative learning, is one type of procedural memory, and conditioning of the eyeblink response is the most commonly investigated conditioning paradigm. The neural circuitry underlying this associative learning has been well characterized

and shown to be dependent on the cerebellum.[129] There is now evidence that cerebellar atrophy in TLE is associated with compromised classical eyeblink conditioning.[130]

Cortical Surface Features

Several studies have demonstrated distributed abnormalities in the cortical mantle of patients with unilateral TLE. Only one investigation has examined the association of cognition with cortical surface features (gyral and sulcal curvature, cortical area, and thickness).[56] Among TLE patients, measures of cortical curvature (gyral and sulcal) were significantly associated with performance IQ, verbal and visual memory, simple and complex psychomotor processing, and speeded fine motor dexterity. Total surface area was associated only with verbal IQ.

Amygdala

Abnormalities of the amygdala have been shown to have a relationship with psychopathology both in children[131] and adults with epilepsy.[132] In addition, early onset right mTLE has been shown to be associated with poor facial recognition[133] or for facial emotional processing to be affected following right anterior temporal lobectomy.[134]

CSF

Links between measures of CSF and cognition are uncommon but robust. Indices of total CSF have been associated with measures of cognition including total impairment index.[135,136] Total CSF has also been found to be related to measures of negative symptoms (eg, apathy, anhedonia) but not positive symptoms (eg, hallucinations) or depression in TLE.[117]

Cerebrum Volume

Investigating 28 adult patients with lateralized TLE, Baxendale and coworkers[137] found 15 to exhibit extrahippocampal abnormalities on quantitative MRI analysis. Thirteen of the patient group overall had global or bilateral memory impairment. Bilateral memory deficits were significantly associated with both the presence of cerebral abnormalities and poor postoperative seizure control ($P<.05$). They concluded that disproportions in the regional distribution of gray and white matter in patients with hippocampal sclerosis may form the structural basis of global memory disturbance in patients with TLE.

White Matter Volumes: Cerebrum

Traditional volumetric measures of cerebral white matter volume have been found to have significant associations with multiple cognitive domains including nonverbal intelligence, memory, executive function, and psychomotor processing speed.[138] In addition, total cerebral white matter volumes have been shown to be associated with reaction time and mental scanning efficiency.[139]

White Matter Volume: Corpus Callosum

Volume of the corpus callosum has been found to be reduced in TLE, particularly those with childhood onset.[77,140] Volume of the corpus callosum was found to be significantly related to measures of nonverbal problem solving, immediate memory, complex psychomotor processing, and speeded fine motor dexterity.[140]

White Matter Microstructure: DTI

Recent studies have examined relationships between specific white matter regions or tracts and aspects of cognition and behavior. Flugel and colleagues[141] evaluated diffusion characteristics of TLE patients with (N = 18) and without (N = 20) interictal psychosis and correlated diffusion measures with neuropsychological test scores. The investigators sampled frontal and temporal

white matter regions and found that TLE patients with interictal psychosis had greater white matter compromise, as measured by FA, in these brain regions. Further, FA reductions were correlated with cognitive dysfunction and increased negative symptoms. Diehl and colleagues[142] compared the integrity of the uncinate fasciculus, an important frontotemporal white matter tract, between healthy controls (N = 10) and patients with lateralized TLE (N = 28). They demonstrated that TLE patients have bilateral uncinate fasciculus diffusion abnormalities. In patients with left TLE, the integrity of the left uncinate fasciculus was related to verbal memory performances, whereas the integrity of the right uncinate fasciculus was associated with visual memory scores. McDonald and colleagues[143] examined the relationship between cognitive performances and the integrity of several white matter tracts including the uncinate fasciculus, arcuate fasciculus, fornix, parahippocampal cingulum, inferior frontooccipital fasciculus, and corticospinal tract in 17 patients with TLE and 17 healthy controls. Verbal memory and language performances were correlated with MD and FA values of multiple cortical-to-cortical association tracts and limbic projection tracts, particularly in the left hemisphere. Further, cognitive performance was related to anatomic derangements in connections that were germane to the specific cognitive task, such as the relationship between arcuate fasciculus and language scores. These studies demonstrated a clear association between abnormal white matter connections and adverse cognitive outcomes and supported the disconnection model of cognitive dysfunction in patients with TLE.

Multimodality Imaging

Several studies have used fMRI to examine language reorganization in TLE and found that patients with left TLE have a greater propensity for bilateral language representation.[144,145] It was unclear, however, whether such functional reorganization was associated with structural asymmetry in the language network. Recent investigations have combined fMRI and DTI tractography to answer this question.[146] In these studies, patients underwent fMRI tasks, such as reading comprehension and verb generation, to activate language areas in the inferior frontal and superior temporal lobes. DTI tractography was then used to delineate the structural connections between fMRI-defined language areas. Using this combined imaging technique, Powell and colleagues[147] found that left TLE patients had reduced left hemisphere and increased right hemisphere white matter connections, when compared with controls and right TLE patients. Further, a greater degree of lateralization to the left hemisphere was correlated with greater decline in naming function after a dominant hemisphere temporal lobe surgery.[148] The abnormal structural lateralization found in DTI was congruent with fMRI activation patterns and established the important relationship between structure and function in brain regions salient for language processing.

There is no question that anatomic abnormalities in TLE are distributed in nature throughout the brain and have clinical relevance through their association with cognition or behavior. The unique and nonoverlapping associations between specific cognitive abilities and anatomic areas remain to be further determined.

THE LIMITATIONS OF MODAL COGNITIVE PROFILES

Modal or average cognitive profiles clearly help to convey a sense of the overall cognitive burden associated with TLE, an average burden that seems surprisingly onerous. Similarly, modal or average neuroimaging profiles convey a similar impression regarding the neuroanatomic burden. The symmetry between these modal cognitive and neuroimaging profiles helps to make the cognitive pathology understandable. Although helpful, these average profiles are just that, averages, and may not be particularly representative of individual patients. There is considerable variability across patients in their patterns of both cognitive and structural abnormalities and the authors have argued that one way to understand this variability is through the study of so-called "cognitive phenotypes."[149–151]

Using cluster analysis and analyzing age- and education-adjusted cognitive domain scores, the authors identified three neuropsychological profile types in adult TLE (Fig. 5). One group was characterized by relatively preserved mentation (47% of sample); a second group demonstrated more generally affected mentation but with particular memory impairment (24% of sample); and a third group exhibited diffuse cognitive impairment with especially impaired memory, executive function, and motor-psychomotor processing speed (29% of sample).[149]

Within the context of an average profile of generally affected mentation (see Fig. 1), discrete underlying cognitive profile types could be identified. In addition, these groups exhibited varying cognitive prognoses over a subsequent 4-year interval. Most interestingly, these groups also had distinct patterns of associated underlying neuroanatomic abnormality.

Specifically, depicted in the accompanying figures and bar graphs are patterns of anatomic abnormality associated with these cognitive phenotypes. Abnormalities in cortical thickness are evident across the cognitive phenotypes detected bilaterally in several areas (Fig. 6), unilaterally in others (Fig. 7), along with volumetric abnormalities in subcortical structures and cerebellum (Fig. 8), and targeted white matter tracts (corpus callosum) (Fig. 9). The link between cognitive profile and corresponding neuroanatomic abnormality is telling and speaks to the anatomic reality of identified neuropsychological profiles in TLE.[150] Buried within modal profiles of both cognition and anatomic abnormality are groups that vary substantially in their cognitive and associated anatomic status.

IS TLE UNIQUE?

The evidence presented indicates that patients with chronic TLE often exhibit cognitive and quantitative neuroimaging abnormalities that extend beyond the primary zone of seizure onset with significant associations between specific "extratemporal" structural abnormalities and cognitive impairments. These patterns may have their origin in considerable part from the effects of epilepsy and its causes on neurodevelopment as well as progressive abnormalities in a subset of patients. There is suggestive evidence that similar patterns may be evident in other epilepsy syndromes (eg, juvenile myoclonic epilepsy). Early neuropsychological investigations reported impairments in higher level executive functions consistent with the primary thalamofrontal pathophysiology of juvenile myoclonic epilepsy.[152–154] Some recent reports suggest more distributed neuropsychologic impairment,[155] findings that become understandable in the context of recently reported widely distributed cortical thinning in juvenile myoclonic epilepsy (Fig. 10).[156] The degree to which extrathalamofrontal abnormalities are linked to distributed neuropsychologic impairments and the presence and characteristics of phenotypes of structure-function abnormalities remain to be investigated in this and other epilepsy syndromes.

It is hypothesized that within most if not all epilepsy syndromes there exists a distribution of cognitive phenotypes that are linked to structural, metabolic, and other neuroimaging features. These structural abnormalities will lend shape to the patients' neuropsychologic profile. In addition to these structural abnormalities with associated neurobehavioral consequences will be the added the perhaps more variable influence of factors such as antiseizure medications and their particular adverse cognitive profiles,[21] variations in epileptiform and other waveform abnormalities,[157–160] complications of the disorder,[25] and postictal effects. In addition, familial susceptibilities and other factors will influence cognitive status.[161,162]

EPILEPSYAND COGNITION: BRIDGING THE OLD AND NEW LITERATURES

This article describes a developing architecture of cognitive impairment in the epilepsies, moving from the long established traditional focus on the relationship between neuropsychological status and clinical epilepsy characteristics (eg, seizure frequency, seizure

severity, duration of epilepsy, age of onset, etiology, medications), to one focusing on interrelationships between underlying anatomic, metabolic, and other neurobiologic correlates of the epilepsies with critical cognitive and behavioral functions. This is a paradigm shift that has a strong influence on the understanding of the neuropsychology of epilepsy. The older literature, however, is reliable, well understood, and clinically meaningful. Is there some way to understand the intersection of the cognition and clinical seizure feature and the cognition and neuroanatomy literatures (Fig. 11), and are there methods that might help inform the understanding of the neuroanatomic pathways through which clinical seizure features exert their impact on cognition in epilepsy?

In a first step to address this issue, the authors tested a mediator-moderator model to determine how overall cognitive impairment, total CSF, and duration of epilepsy were associated and whether duration of epilepsy affected cognition directly or through a structural neuroimaging marker (brain atrophy reflected in total CSF) (Fig. 12). It was found that total CSF mediated the relationship between duration of epilepsy and cognitive impairment.[136] That is, the longer the duration of epilepsy, the more abnormal the total CSF, with resulting greater cognitive impairment. The impact of duration of epilepsy on cognition was mediated by the degree of overall brain atrophy reflected in total CSF. This represents a crude initial approach to a complex problem, but this statistical approach may have some use in understanding these complex relationships and the move toward a more unified understanding of the neuropsychologic consequences of the epilepsies.

CONCLUSION

The landscape of cognitive impairment is clearly in transition from a long-standing focus on the relationship between cognitive function and clinical epilepsy features to one linking cognitive impairment to a multitude of neuroimaging parameters. Whether it will be possible to derive a broad understanding of cognition, clinical epilepsy features and neuroimaging markers remains to be determined. This represents an interesting research challenge for the future.

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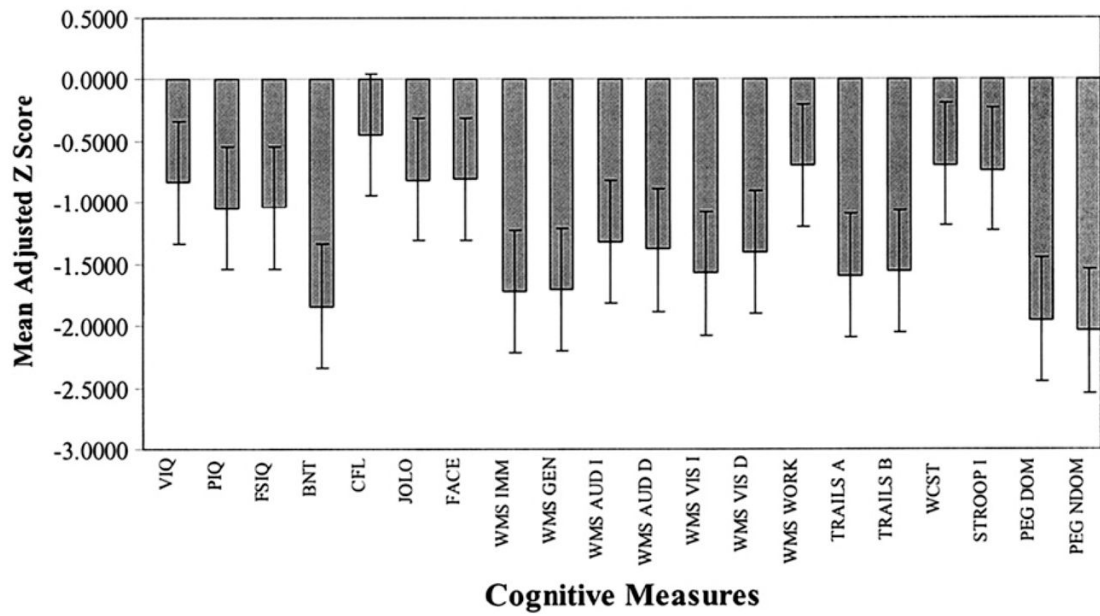
Fig. 1.
Mean adjusted (age, gender, education) z scores for patients with TLE compared with healthy control subjects. (*From* Oyegbile TO, Dow C, Jones J, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004;62:1736–42.)
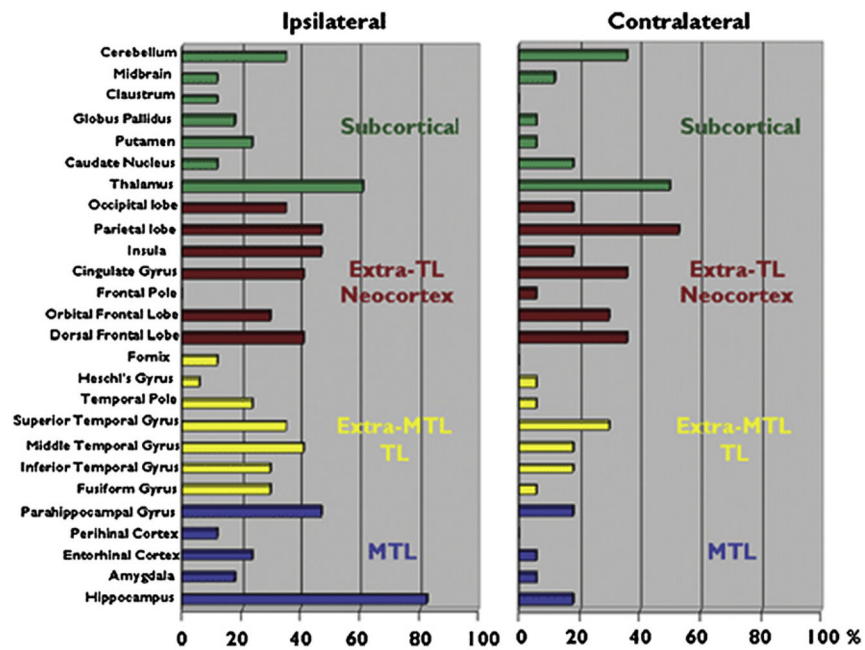
Fig. 2.
Twenty-six brain regions found to be significantly reduced in volume in patients with TLE
relative to healthy controls. The results are presented ipsilateral and contralateral to the
epileptogenic focus. MTL, medial temporal lobe; TL, temporal lobe. (*From* Keller SS, Roberts
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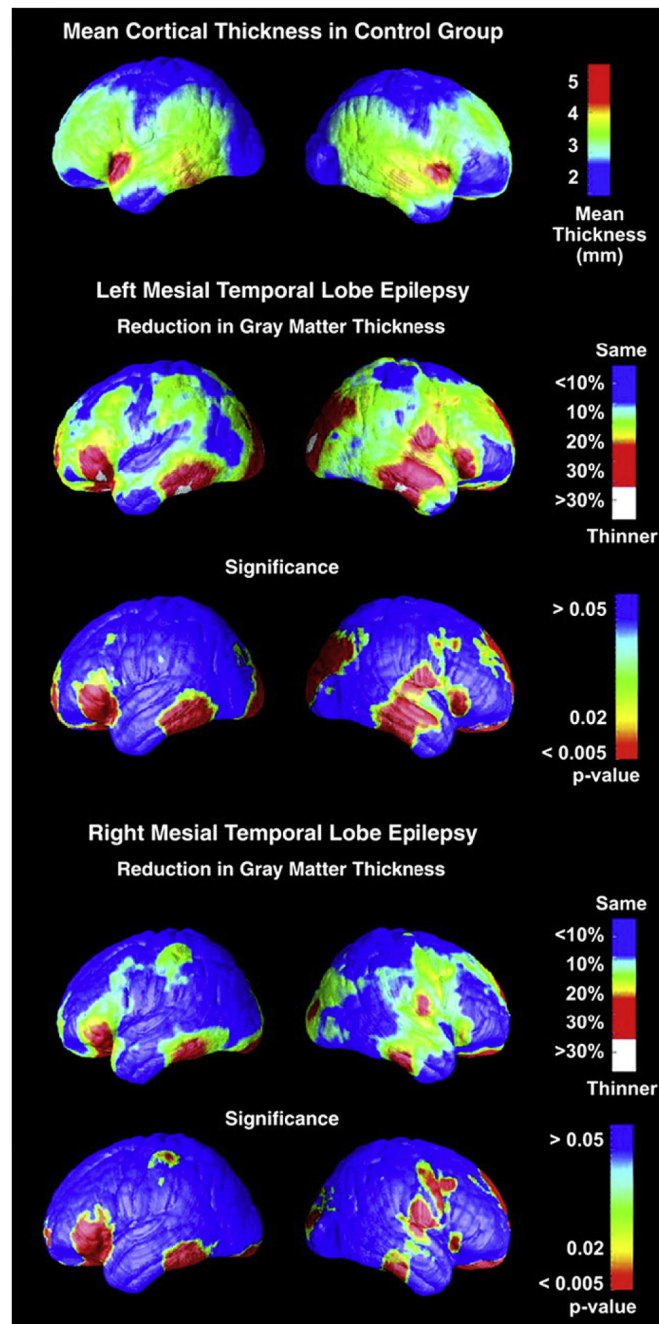
Fig. 3.
Cortical thickness maps: regional reduction in mTLE groups. (*From* Lin JJ, Salamon N, Lee AD, et al. Reduced neocortical thickness and complexity mapped in mesial temporal lobe epilepsy with hippocampal sclerosis. Cereb Cortex 2007;17:2007–18.)
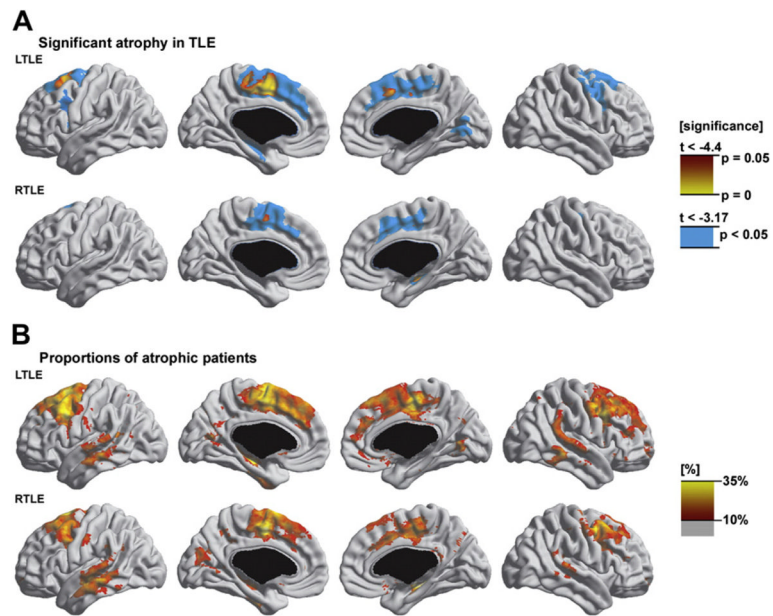
Fig. 4.
Atrophy in TLE. Significant atrophy in TLE (*A*). Proportions of atrophic patients (*B*). (*From* Bernhardt BC, Worsley KJ, Besson P, et al. Mapping limbic network organization in temporal lobe epilepsy using morphometric correlations: insights on the relation between mesiotemporal connectivity and cortical atrophy. Neuroimage 2008;42:515–24.)
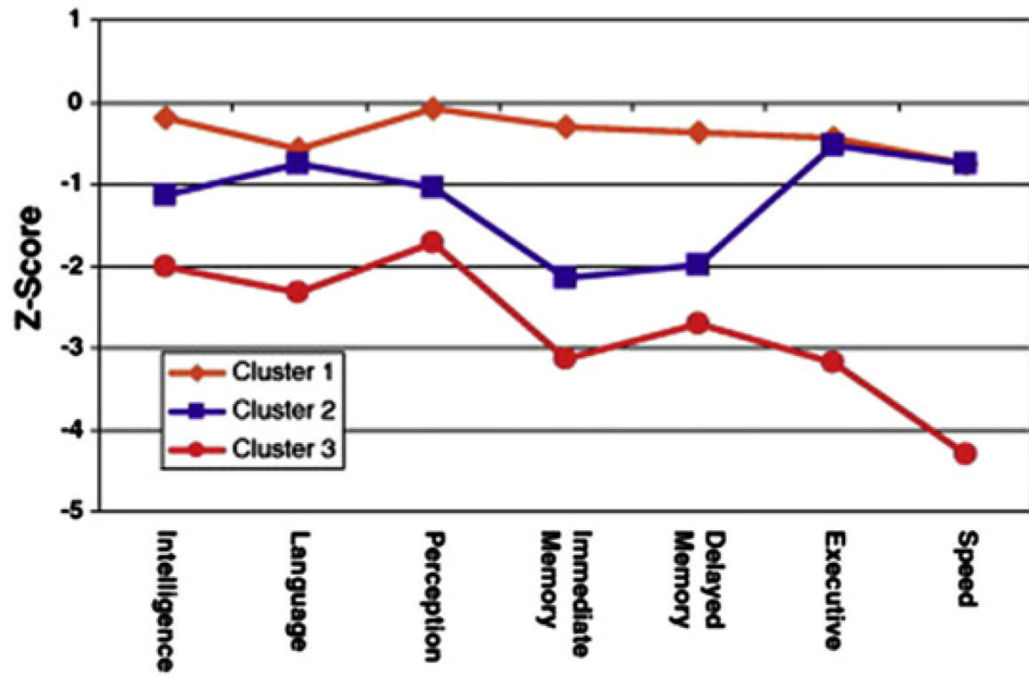
Fig. 5.
Cognitive Phenotypes in TLE. (*From* Hermann B, Seidenberg M, Lee EJ, et al. Cognitive phenotypes in temporal lobe epilepsy. J Int Neuropsychol Soc 2007;13:12–20.)
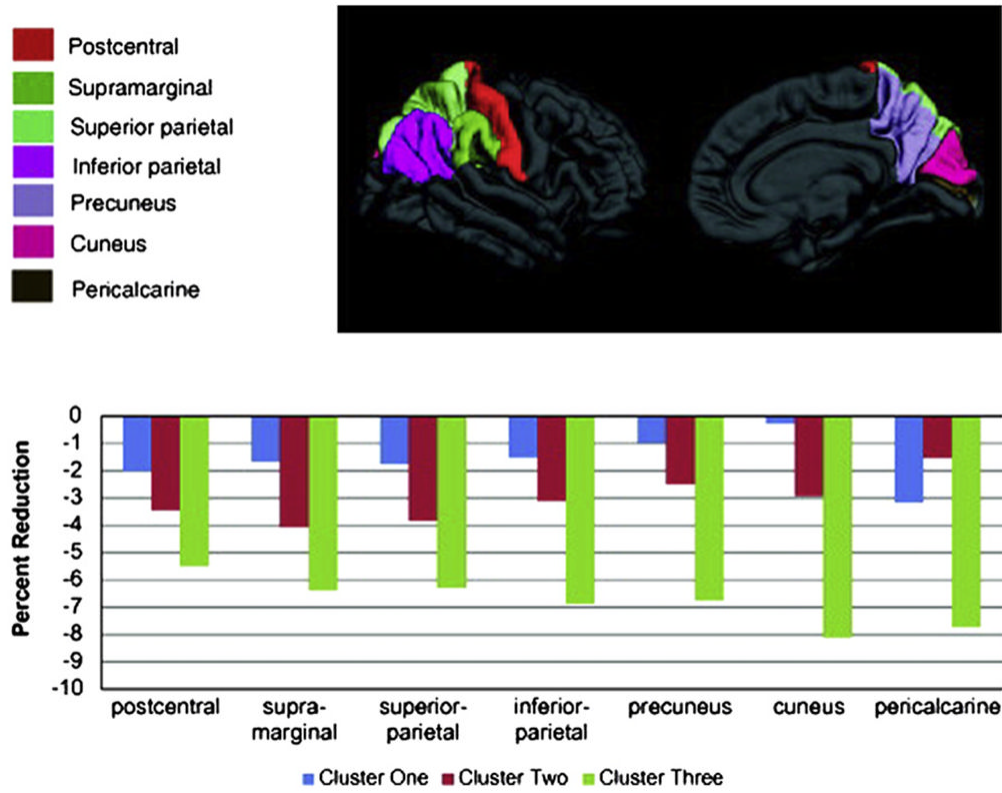
Fig. 6.
Bilateral reductions in cortical thickness across cognitive phenotypes. (*From* Dabbs K, Jones J, Seidenberg M, et al. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15(4):445–51.)
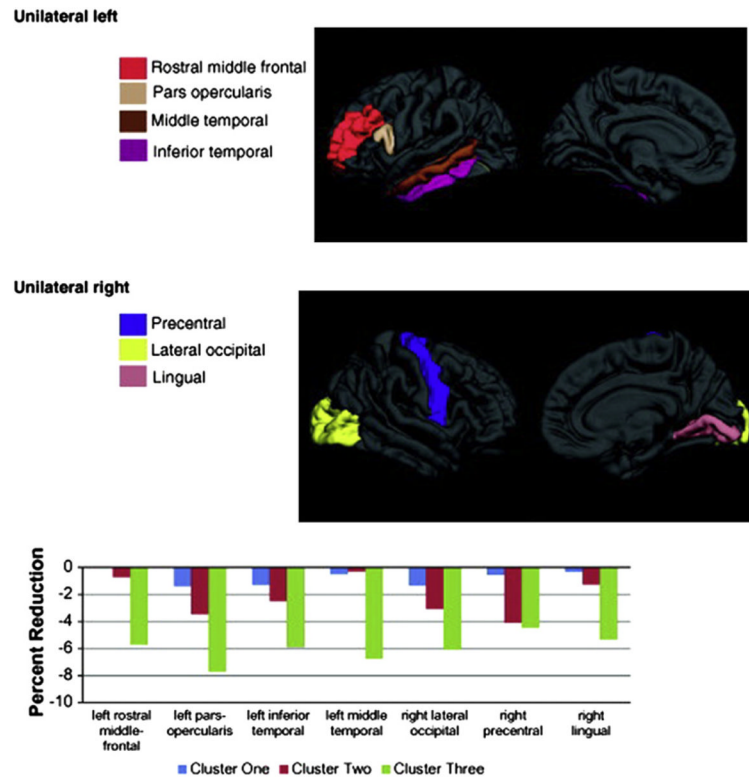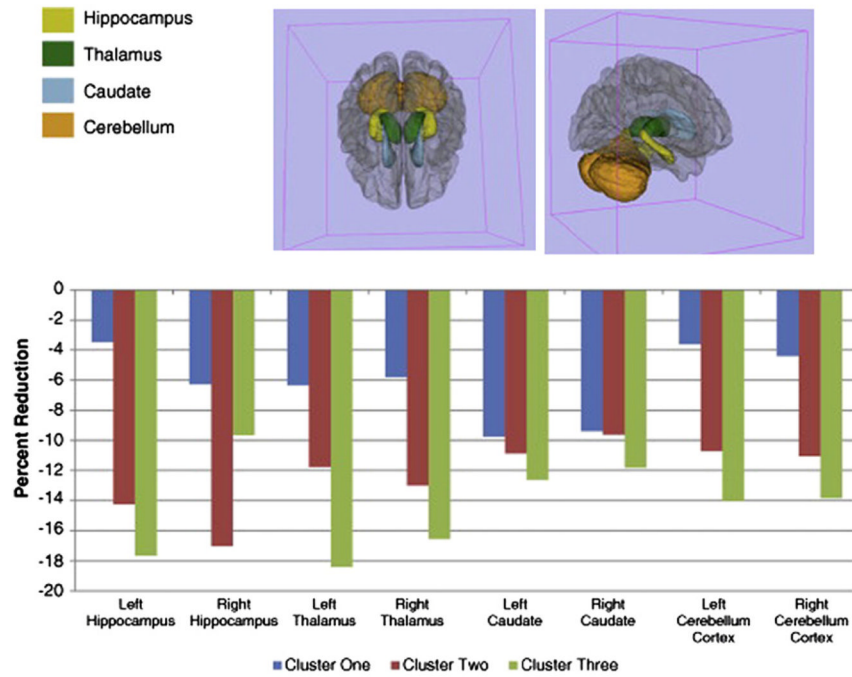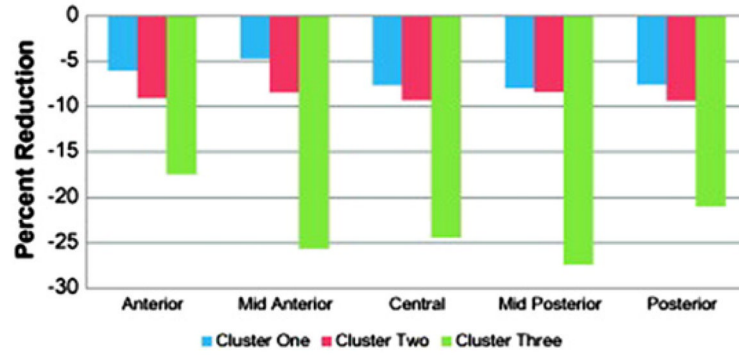
Fig. 7.
Unilateral reductions in cortical thickness across cognitive phenotypes. (*From* Dabbs K, Jones J, Seidenberg M, et al. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15(4):445–51.)

Fig. 8.
Volumetric reductions in subcortical and cerebellar regions across cognitive phenotypes.
(*From* Dabbs K, Jones J, Seidenberg M, et al. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15(4):445–51.)

Fig. 9.
Volumetric reductions of the corpus callosum across cognitive phenotypes. (*From* Dabbs K, Jones J, Seidenberg M, et al. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15(4):445–51.)
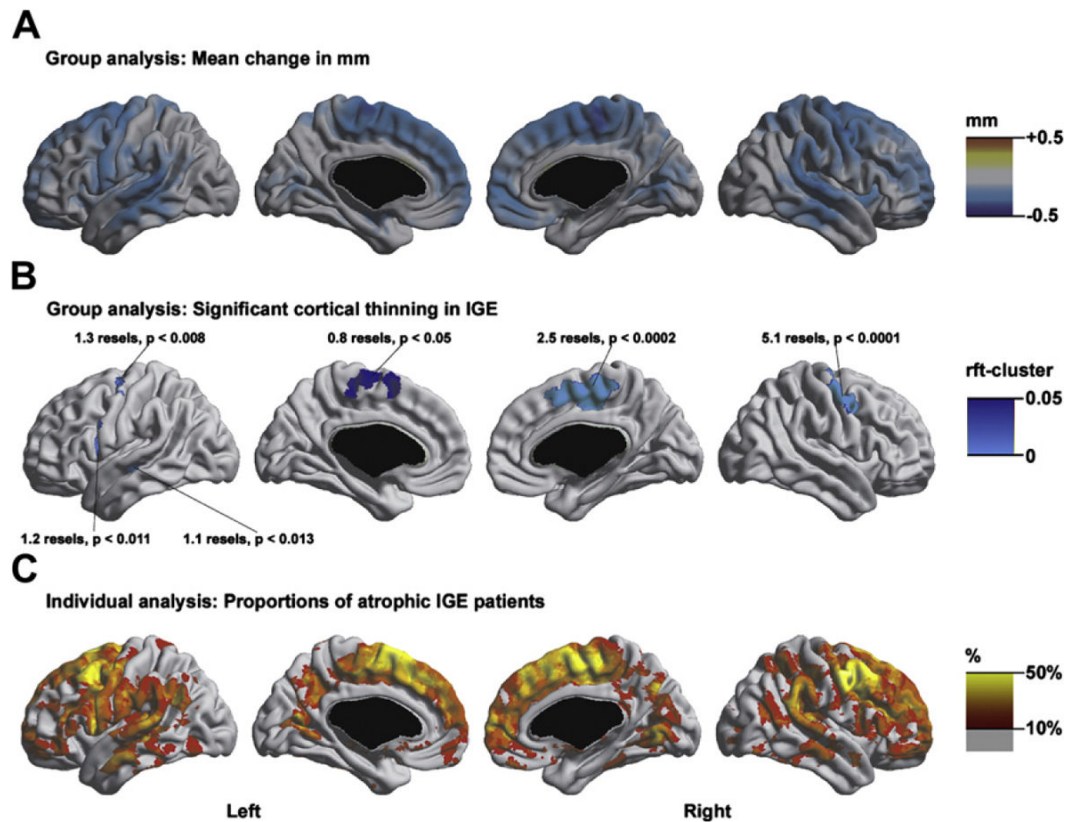
Fig. 10.
Group and individual analyses of cortical thickness. (*A*) Absolute differences in cortical thickness (in millimeters) between idiopathic generalized epilepsy (IGE) patients and controls. (*B*) Areas of significant cortical thinning in IGE compared with controls. Peak positions and resolution elements (ie, resels) of significant clusters after random field theory (rft) correction are shown (cluster threshold $t \leq -3.2$, cluster extent threshold 0.8 resels). (*C*) Individual analysis. At each vertex, the corresponding proportion of atrophic patients with a thickness z-score of ≤ -2 SD with respect to healthy controls is shown. Only fractions above 10% are displayed. In controls, no vertex displayed a prevalence of atrophy above 10%. Individual analysis showed widespread atrophy in more than 10% of patients; up to 40% of them had atrophy localized in the same areas detected by the group analysis. (*From* Bernhardt BC, Rozen DA, Worsley KJ, et al. Thalamo-cortical network pathology in idiopathic generalized epilepsy: insights from MRI-based morphometric correlation analysis. Neuroimage 2009;46:373–81.)
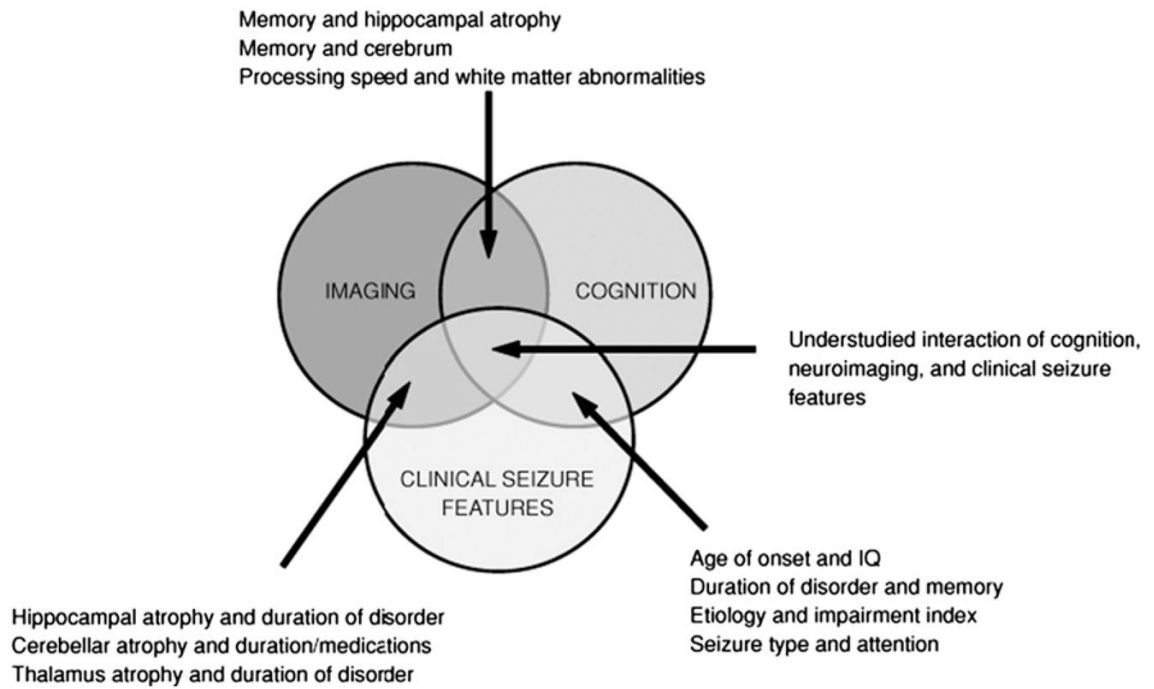
Fig. 11.
The intersection of imaging, cognition, and clinical epilepsy characteristics. (*From* Oyegbile TO, Bhattacharya A, Seidenberg M, et al. Quantitative MRI biomarkers of cognitive morbidity in temporal lobe epilepsy. Epilepsia 2006;47:143–52.)
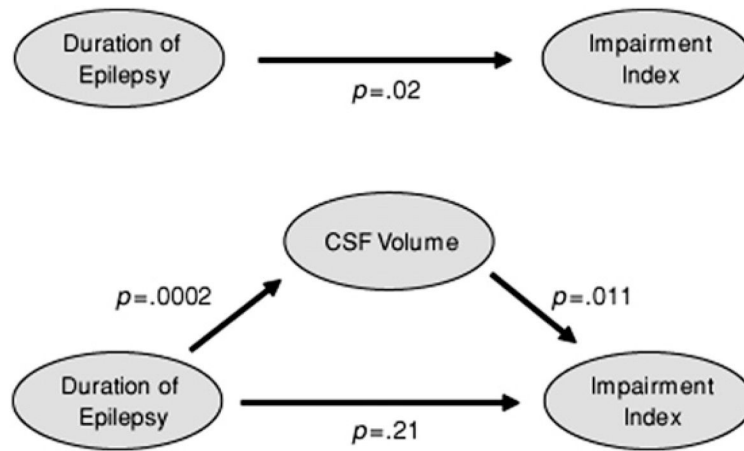
Fig. 12.
Quantitative MRI biomarkers of cognitive morbidity in temporal lobe epilepsy. (From Oyegbile TO, Bhattacharya A, Seidenberg M, et al. Epilepsia 2006;47(1):143–52.)