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CASE STUDY

A Practical Approach to Incorporating Quantitative Neuroimaging Findings into Pediatric Neuropsychological Test Interpretation

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Abstract

To date, neuropsychological assessments have not capitalized on the enormous strides made in brain imaging during the twenty-first century. Fully incorporating advanced neuroimaging methods with clinical neuropsychological assessment data has great potential to enhance the understanding of neuropsychiatric and neurological sequalae in children with brain injury and disease. Using commonly available MRI sequences, readily available in any clinical setting, this article demonstrates a practical approach for deriving and incorporating quantitative image analyses of brain pathology with neuropsychological outcome.

Keywords Neuropsychological testing · Neuroimaging · Quantitative image analysis · Traumatic brain injury · Integration of neuropsychological/neuroimaging findings

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The individualized assessment process in clinical neuropsychology, combined with how interpretive conclusions are made, reflects a single case study approach in the evaluation of brain-behavior relations (Harvey, 2012). Indeed, the origins of clinical neuropsychological assessment are steeped in case studies that shaped our understanding of brain-behavior relations (Cipolotti & Warrington, 1995; Lezak et al., 2012). These origins pre-dated modern neuroimaging; therefore, contemporary methods of brain imaging had no bearing on original views about how neuropsychological tests could demonstrate underlying brain dysfunction. They also had no influence on neuropsychological test creation, development of normative data, or test interpretation (see Casaletto & Heaton, 2017; Eling, 2019). As characterized by Randolph (2002), neuropsychological measures and test batteries currently in use "…evolved as an amalgam of intelligence tests, various individual measures of "biological" cognition, and sensory and motor testing" (p. 307). In addition, prior to the introduction of modern neuroimaging, the basis for a variety of neurological categorizations used by neuropsychology for test development and interpretation was founded in available methodologies. These included neurosurgical interventions, post-mortem studies, penetrating skull fractures, electroencephalographic findings, and/or contrasting groups with obvious lateralized defects of motor (e.g., hemiplegia), sensory (e.g., visual field defect) or language (e.g., aphasia) function. For example, the left versus right hemisphere effects and the anterior versus posterior dichotomous approaches to neurological and neuropsychological categorizations were all originally established without brain imaging. This is also the case with the classic "organic brain syndrome" (OBS) classifications (see reviews by Black & Strub, 1981; Kertesz, 1983). From this background, neuropsychological test interpretation emerged as a "stand alone" process to infer brain-behavior relations, whether healthy or impaired. Through the use of established psychometric methods, norms, cut-scores, and clinical correlation, neuropsychological test interpretation examines test score patterns of strengths and weaknesses across tasks. These tasks reflect operationally defined cognitive and behavioral domains (e.g., memory, executive function), as well as, symptom reporting measures. Using traditional neuropsychological assessment and interpretation techniques as standalone methods, such analyses form

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the basis for differential diagnostic statements, conclusions and recommendations about the individual being assessed, and the health of their brain. However, they do so *without* reliance on neuroimaging findings. Neuropsychological test interpretation, even now, is used to *infer* where brain pathology may reside independent of neuroimaging findings.

As computed tomography (CT) and magnetic resonance (MR) imaging (MRI) came into common use in the 1980s and 1990s, updated standardization of neuropsychological assessment methods for normative comparison only used CT and/or MRI in the most cursory fashion, if used at all (Bigler, 2017). When used, neuroimaging findings from CT and/or MRI typically constituted a designation of whether brain pathology was evident as part of a "neurologically impaired" group, or to some extent, where coarse, localized, or lateralized damage may have been located. Even now in the twenty-first century, other than what information may be in a clinical radiological report, no commonly available neuropsychological assessment measure used in a clinical setting directly incorporates the abundant information currently available in contemporary neuroimaging (Bigler, 2016; Bigler & Allder, 2021a).

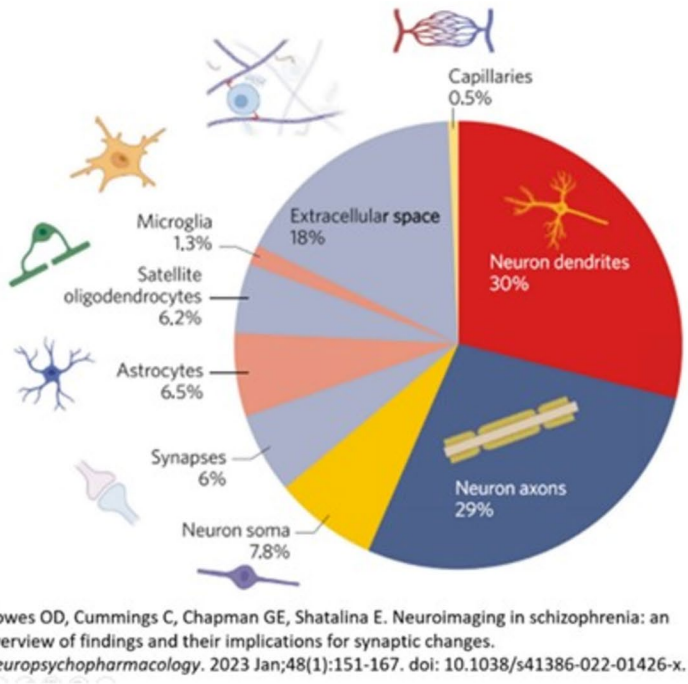
Contemporary neuroimaging interpretation has moved beyond just clinical statements about what may be visually identifiable in a scan image. When applied to structural neuroimaging, it now involves detailed quantification of the volume, size, shape or thickness of brain parenchyma.[1] Brain parenchymal volumes represent a proxy for structural brain integrity, and massive normative quantitative studies have been achieved and reported in the literature depicting normative values for every region of interest (ROI) or named brain structure (Bethlehem et al., 2022). All of these normative studies of neurotypical individuals, plotted by age and sex, show that healthy brains typically have a well-defined range of normative values specific to the named structure or ROI. The reason why quantitative comparisons of an individual's named brain structure or ROI reflects a clinically important metric is captured in Fig. 1. This figure, adapted from Howes et al. (2023) and Insel and Landis (2013), depicts what is represented within a mm^3 of MRI-defined brain parenchyma. Accordingly, when a named brain structure or ROI begins to display quantitative differences from the norm, even though an abnormality may not be visible, the increase or loss of parenchyma volume becomes a proxy indicator for aberration in brain tissue integrity. Furthermore, as volumetric changes occur within a named structure or ROI, this also means that brain networks connected with such regions will certainly be affected and likely degraded.

[1] Although there are other quantification techniques that tap diffusion and spectroscopic characteristics of brain parenchyma, those will not be addressed in the current case study, which will focus on volumetric analyses.

CT imaging is typically the triage method for rapid TBI assessment in emergency departments; however, since CT uses ionizing radiation, there are explicit guidelines for its use, in order to minimize radiation exposure (see Canadian CT Head Rules — Stiell et al., 2001; National Emergency X-Ray Utilization Study — Mower et al., 2005; New Orleans Criteria — Haydel et al., 2000). Therefore, especially on the mild end of the TBI spectrum, many individuals will receive no neuroimaging studies during the acute phase. While quantitative image analysis methods can be applied to CT imaging of TBI patients (see Majercik et al., 2017), due to better image resolution and anatomic identification capabilities, the emphasis with quantitative neuroimaging has clearly been on MRI (Bigler & Allder, 2021b). Despite most quantitative neuroimaging analysis methods being MRI-based, when CT imaging is performed at the time of the initial injury, it provides an acute, neuroanatomical, and neuropathological baseline reference for tracking pathological changes over time. The usefulness of viewing day-of-injury (DOI) CT will be shown below.

White matter, gray matter, and cerebrospinal fluid (CSF) all have unique MR signal intensity characteristics, which can be exploited via quantitative image analysis methods. As a result, MRI quantification has the greatest potential for clinical correlation with neuropsychological test findings (Bigler, 2015; Bigler & Allder, 2021a, b; Wilde et al., 2021). For example, T1-weighted images are excellent for showing anatomical (structural) detail and therefore frequently used in automated image quantification; however, this acquisition procedure also has limitations as it is less sensitive to CSF and parenchymal signal abnormalities (Bigler, 2015). That said, T1-weighted image quantification represents the more commonly performed image quantification method because it is excellent for region of interest (ROI) volumetrics and similar quantitative metrics (e.g., shape or cortical thickness). Standard T2-weighted MR sequences provide better distinction and delineation between CSF and brain parenchyma, which in turn creates improved detection of a variety of neuropathologies. For more subtle white matter pathology detection, the T2-fluid attenuated inversion recovery sequence (T2-FLAIR) is particularly sensitive to specific white matter pathologies that show up as a hyperintense signal, often referred to as a white matter hyperintensity (WMH), which can be quantified. In terms of detecting certain vascular pathologies, especially the hemorrhagic byproduct referred to as hemosiderin, because of its high iron content, the standard gradient recall echo (GRE), and the more current, susceptibility weighted imaging (SWI) sequence is sensitive to identifying microbleeds, with SWI being superior to GRE. The importance of detecting hemosiderin deposition in the TBI patient is its relation to traumatic axonal injury/diffuse axonal injury (Bigler, 2016; Bigler & Maxwell, 2011, 2012). There are also various diffusion and

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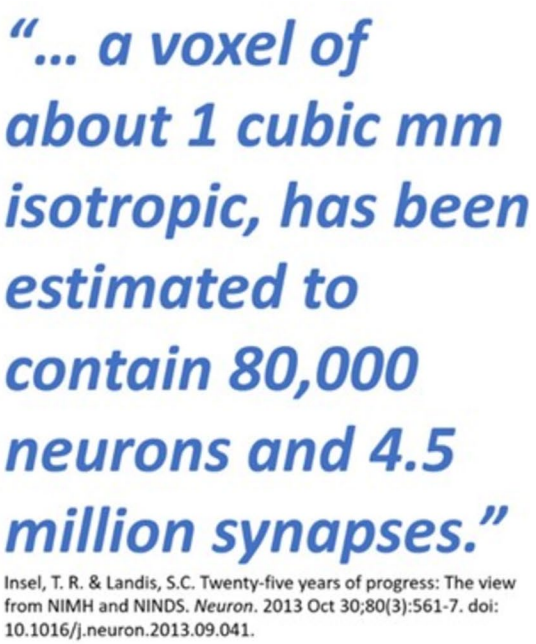


Fig. 1 Adapted figure from Howes et al. (2023) and Insel and Landis (2013), depicting what is represented within a mm^3 of MRI-defined brain parenchyma. On the left are the estimates of what constitutes human cortical gray matter. As depicted, there are complex, elemental cellular, neural, vascular, and cerebrospinal fluid filled components that form gray matter volume. The quote on the right from Insel and Landis (2013) provides an even better perspective for what functional components are within a single mm^3 of cortical gray matter. What this illustration implies is that deviations in quantitative neuroimaging provide the neuropsychologist with additional information, wherein the brain morphological changes may be occurring. Adapted from Howes et al. (2023), Creative Commons CC BY

spectroscopic MR procedures and sequences, but those will not be covered below because they are not currently readily available in most clinical settings. The importance of what has just been reviewed in this paragraph is that each MR sequence has the potential to provides a unique contribution to understanding the neuroanatomical and neuropathological effects of TBI that may underlie or be associated with neuropsychological test findings. Additionally, there are open source and commercially available quantitative neuroimaging analysis programs for T1, T2, T2-FLAIR, and GRE/SWI quantification (described below). With MRI quantitative neuroimaging analysis methods now readily available, the current analysis approach below outlines how these methods can enrich the understanding of neuropsychological impairments in a child with TBI. Notably, Wilde et al. (2021) provide a comprehensive review of both CT and MRI in assessing the TBI patient (see also Jantz & Bigler, 2014; Jantz, 2014).

There was a time when all of these analyses required operator-controlled methods for segmentation, tracing and classification of the MR image (Bigler et al., 2010a, b). Such tedious methods were completely impractical for assisting in the neuropsychological evaluation of the individual case with TBI. Those days are behind us. There are now fully automated image analysis programs that provide fast, reliable, and efficient image quantification of brain structures and potential underlying neuropathology within timeframes relevant for using such information in clinical assessment. As will be shown in the assessment approach below, clinical neuropsychological assessment can now begin to incorporate this wealth of anatomical and ROI data that is now readily obtained from contemporary MRI methods.

As Howieson (2019) has discussed, despite some modifications in test administration and improved normative data, the format of neuropsychological assessment has changed very little from the twentieth to the twenty-first century. In contrast, significant and rapid advancements in neuroimaging, especially in the area of quantitative neuroimaging analyses, have occurred in this same timeframe. As the twenty-first century emerged, many different types of sophisticated image analysis methods applicable to analyzing brain scan data of the individual, especially MRI, became accessible via open source or commercial means (Bash & Tanenbaum, 2021; Bigler, 2017; Cope et al., 2021; Tanpitukpongse et al., 2017).

Provided appropriate image acquisition protocols have been used, contemporary image analyses applied to an MRI scan permit detailed ROI quantifications of essentially all

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major areas of the brain (Bigler, 2015). Like neuropsychological assessment of the individual, quantitative MR image analyses reflect a case-study approach assessing the structural integrity of that individual's brain compared to a normative sample comprised of age-typical, healthy control participants. The most common quantitative MR-based metrics assess size, typically measured in volume or thickness if cerebral cortex gray matter is the target ROI. It also assesses gyrification metrics of the cortical surface, as well as shape and contour, to mention some of the most common metrics. If diffusion tensor imaging (DTI) is part of the acquisition protocol, detailed assessment of regional and specific white matter tracts and whole brain white matter integrity is possible. When a lesion or some type of identifiable pathology is present, size, volume, and location can also be quantified. As already stated, all of these quantitative MR analyses overviewed above can be achieved with open-source and/or commercially available programs (see below).

As outlined by Bilder and Reise (2019; see also Japardi et al., 2018) despite late twentieth and twenty-first century technological advances, neuropsychological assessment has not yet fully capitalized on technological progress in allied fields, especially neuroimaging. Miller and Barr (2017) refer to this as part of a "technology crisis" in the field of neuropsychological assessment. As part of their training in clinical neuropsychology, per the Houston Guidelines, pediatric neuropsychologists have had graduate course work and postdoctoral training in "functional neuroanatomy," "neuroimaging and other neurodiagnostic techniques," and a working understanding of "etiology" and underlying "pathology" of major "neurological and related disorders" (Hannay et al., 1998, p.162). Accordingly, pediatric neuropsychologists routinely include neuroimaging report findings in their clinical history write up of the patient being evaluated, but typically do not go beyond standard descriptive, qualitative statements about what may be in the neuroradiological report. Additionally, pediatric neuroradiological report findings tend to be directed toward lesion specific areas of pathology and/or global types of changes. While acknowledgement of visible pathological changes may be informative, considerable additional potential clinical information may reside in quantitative analyses of named anatomical areas and ROIs. For example, in cognitive and experimental neuropsychology, there is now an extensive body of research on correlative relationships between named anatomical structures/ROIs and neuropsychological domains like memory or executive function. In cases like a TBI pediatric patient with qualitatively defined temporal lobe pathology, understanding these relationships likely provides added information for the pediatric neuropsychologist by providing more specific quantitative size informatics about the hippocampus, amygdala, parahippocampal gyrus, etc. Furthermore, the standard clinical reading of a neuroimaging study does not provide quantitative information about focal lesion burden or how any of this affects neural networks associated with the temporal lobe damage. This type of quantitative neuroimaging and neural networks informatics has begun to be clinically applied in memory clinics assessing patients for dementia (Anstey & Maller, 2003; Koenig et al., 2020; Petersen et al., 2023; Tufail et al., 2021; Umfleet et al., 2020), as well as some epilepsy centers attempting to relate neurocognitive variables to seizure focus and MRI findings, especially in epilepsy surgery candidates (Addis et al., 2007; Tai et al., 2018). The point of this paper is to show how quantitative neuroimaging can be more broadly incorporated into clinical neuropsychological practice.

Cognitive neuroscience traces its origins to experimental neuropsychology and the pre-1970 era of cognitive psychology as well (see Posner & DiGirolamo, 2000), but cognitive neuroscience and experimental neuropsychology have fully embraced advances in neuroimaging methods and neural network informatics to explore unique brain-behavior relations, as shown by Streese and Tranel (2021). Such approaches typically provide in-depth, multimodal quantitative neuroimaging analyses to examine the association between neuroanatomical and neuropathological findings with a particular neurobehavioral and/or neurocognitive feature of a disorder or some specific neurologic condition. This type of approach that has been used in cognitive neuroscience and experimental neuropsychology has great relevance for pediatric neuropsychology as will be demonstrated below.

The enormous advances in quantitative neuroimaging have yielded numerous open-source publications. These now provide the clinician with explanatory tools to more fully understand the importance of focal and nonspecific pathology and its potential disruption of the brain networks that underly cognition and behavior. Indeed, as will be demonstrated below, advances in functional neuroimaging and DTI pathway analysis methods have revealed novel understandings of neural networks and these have direct implications for pediatric neuropsychology. Our objective is to illustrate how clinical and quantitative neuroimaging can better inform neuropsychological findings and interpretation, and we will demonstrate how practical applications utilizing quantitative neuroimaging results can be combined with improved understandings of neural networks to better understand neuropsychological test findings. We believe merging neuropsychological assessment results with quantitative neuroimaging and network informatics provides added value to both neuropsychological and neuroimaging findings of the child being examined. This reciprocal, consolidative integration of the two fields yields conclusions which would not be possible if examined as only solitary findings. We begin with the neuropsychological results from a child who sustained a severe TBI. This child was a participant in a study that focused on emotional and social changes that accompany

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significant TBI. A unique aspect of the study was its focus on children who ostensibly had good outcome from TBI, even severe TBI, as reflected in their return to school, including some regular classroom placements, although accommodations may have been implemented. Participant children underwent MRI studies and standard/conventional neuropsychological measures were administered along with behavioral rating scales, including those obtained from parents. All phases of assessment were done with institutional review board approval. Information regarding age at injury, age at testing, and educational history is not presented to protect the identity of the child.

Traditional neuropsychological tests and their interpretation, typically examine test scores by general domains, starting with the following four major domains: cognitive including language, emotional, behavioral, and motor/sensory-perceptual. Each of these domains possess several subdomains and a neuropsychological impairment may be manifested in just one domain or across multiple domains. Statistically, for a test score to indicate an impairment, the score needs to be substantially below the normative base for that measure and/or below an assumed baseline prior to injury, disease onset or disorder. Usually, for scores to be deemed clinically significant, they need to deviate beyond one standard deviation from presumed normative baseline (Lezak et al., 2012).

Neuropsychological Findings in a Case of Pediatric Severe TBI

Traditional Interpretation Approach

As part of the broader study, a prescribed battery of paper and pencil tests was obtained on the child in this example across two visits. These individually administered assessments were designed to obtain overall estimates of the four domains mentioned above. As a gauge concerning behavioral and emotional changes, parental rating scales were obtained as global indicators of what symptoms/problems may be subsequent to the acquired injury. Results of parental ratings and a summary of some of the neuropsychological test results are presented in Table 1.

From a traditional explanatory perspective of neuropsychological interpretation, review of these results indicates a disparity between cognitive and executive functioning, which fell within the average range of ability and acceptable normative standards, in contrast to quite variable emotional, behavioral, and social functioning, where rating scales raised questions about behavioral and emotional regulation in this child. The cognitive abilities measured by the subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) and Wechsler Intelligence Scale for Children, Fourth

Table 1 Results of neuropsychological assessment

Cognitive	
WASI	Score/%ile
Vocabulary	$T=45/46$
Matrix reasoning	$T=58/79$
FSIQ	SS = 102/55
WISC-IV	
Symbol search	SS = 10/50
Cancellation	SS = 13/84
Processing speed index	SS = 109/73
Executive functioning	
TEA-Ch	
Attentional control/switching	
Creature counting timing	SS = 9/37
Creature counting total correct	SS = 10/50
Sustained attention	
Walk don't walk	SS = 12/75
Code transmission	SS = 11/63
Emotional and behavioral adjustment	
BASC-2	
Externalizing problems	$T=78/98$
Hyperactivity	$T=84/99$
Aggression	$T=71/95$
Conduct problems	$T=73/97$
Internalizing problems	$T=74/98$
Anxiety	$T=53/63$
Depression	$T=95/99$
Somatization	$T=61/86$
Adaptive skills composite	$T=24/1$
Adaptability	$T=22/1$
Social skills	$T=29/1$
Leadership	$T=26/1$
Activities of daily living	$T=27/1$
Functional communication	$T=31/3$
Behavioral symptoms index	$T=85/>99$
Hyperactivity	$T=84/99$
Aggression	$T=71/95$
Depression	$T=95/99$
Attention problems	$T=71/99$
Atypicality	$T=81/98$
Withdrawal	$T=83/99$
Content scales	
Anger control	$T=67/93$
Developmental social disorders	$T=58/79$
Bullying	$T=70/95$
Emotional self-control	$T=81/99$
Executive functioning	$T=75/98$
Negative emotionality	$T=64/90$
Resiliency	$T=37/12$
Social competence	
ABAS II	Scaled score/%ile

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Table 1 (continued)

Adaptive skill area	
Communication	SS = 5/5
Community use	SS = 3/1
Functional academics	SS = 6/9
Home living	SS = 1/ < 1
Health and safety	SS = 3/1
Leisure	SS = 5/5
Self-care	SS = 3/1
Self-direction	SS = 7/16
Social	SS = 1/ < 1
General adaptive composite	SS = 63/ < 1
Broad adaptive domains	
Conceptual	SS = 81/10
Social	SS = 66/1
Practical	SS = 52/ < 1

WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). The two-subtest form (vocabulary and matrix reasoning) was administered to provide an FSIQ. *T*-score $M = 50$, SD = 10, FSIQ $M = 100$, SD = 15; WISC-IV, Wechsler Intelligence Scale for Children 4th edition (Wechsler, 2003). Scaled score $M = 10$, SD = 3, processing speed index standard score $M = 100$, SD = 15; TEA-Ch, The Test of Everyday Attention Q23 for Children (Manly et al., 1999). Scaled score $M = 10$; SD = 3; BASC 2, Behavior Assessment System for Children – 2nd edition (Reynolds & Kamphaus, 2004). *T*-score $M = 50$, SD = 10; ABAS-II, Adaptive Behavior Assessment System—Second Edition (Harrison & Oakland, 2003). Adaptive skill area $M = 10$; SD = 3, general adaptive composite and broad adaptive domains $M = 100$; SD = 15

Edition (Wechsler, 2003) noted in Table 1, measure expressive vocabulary, verbal knowledge, fund of information (vocabulary); nonverbal fluid reasoning (matrix reasoning); short-term visual memory, visual-motor coordination, cognitive flexibility, visual discrimination, and concentration (symbol search); visual selective attention, vigilance, and visual neglect (cancellation); and processing speed (symbol search, cancellation). The executive functions measured by the Test of Everyday Attention for Children (Manly et al., 1999) are attentional control/switching (creature counting) and sustained attention (walk don't walk, code transmission). The results from these various cognitive measures demonstrated average ability with no truly discrepant test scores in the above-mentioned neuropsychological measures. In contrast, the emotional and behavioral changes reflected in the Behavior Assessment System for Children, Second Edition (Reynolds & Kamphaus, 2004) and Adaptive Behavior Assessment System, Second Edition (Harrison & Oakland, 2003), where distinctly discrepant from the norm, suggesting that the post-TBI changes in this child were predominantly within the realm of behavioral dysregulation and faulty emotional control. Major changes with emotionally based impulse control and mood regulation are known outcomes from TBI (Hoskinson et al., 2019), especially thought to arise from the known vulnerability of frontal and temporal lobe regions to injury (Bigler, 2007, 2023), specific to disrupted temporolimbic integrity (Max et al., 2022). However, from the available neuropsychological test findings alone, this is merely conjecture.

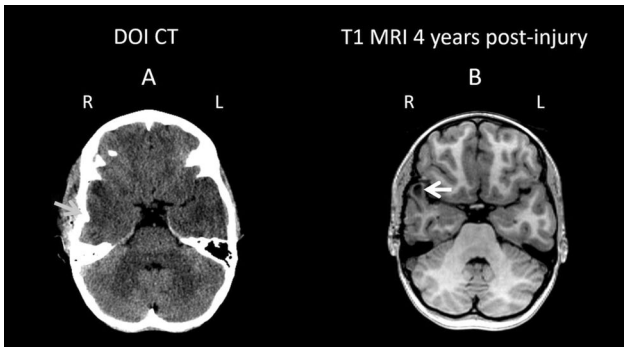


Fig. 2 Day of injury CT showing skull fracture (gold arrow) and 4-year follow-up T1-weighted MRI showing temporal lobe encephalomalacia in the right superior temporal gyrus (white arrow) and accompanying white matter degradation (compare the appearance of central white matter of the damaged right temporal lobe with the left)

Since the tradition within neuropsychological testing is a customary "stand alone" test interpretation approach, without the benefit of neuroimaging and/or postmortem confirmation, *all* inferences about frontotemporolimbic pathology being the basis for the neuropsychological test findings, secondary to the effects of having sustained a severe TBI, are but speculation. Fortunately, neuroimaging findings have the potential to address and objectively document inferences from neuropsychological testing about what underlying neuropathology and disrupted neural systems may be present. The first step in this process is the examination of whatever clinical neuroimaging may have indicated, as discussed in the next section.

Quantitative Neuroimaging Finding Integration Approach

Utility of Clinical Neuroimaging Findings in TBI

In TBI, especially at the moderate to severe level of injury, neuroimaging studies are standard of care procedures, emergently performed as part of initial triage, evaluation and treatment (Bigler, 2016). Such was the case in this child, where a day-of-injury (DOI) CT was performed as shown in Fig. 2. CT imaging demonstrated a right temporal bone skull fracture (yellow arrow, Fig. 2 on the left) along with areas of temporal lobe contusion underlying the depressed skull fracture and an epidural hematoma. DOI neurosurgery was performed to elevate the depressed right temporal skull

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fracture, contusion management and hematoma removal. Follow-up MRI was performed as part of the broader study in which this child participated. The clinical DOI CT findings support the presence of right temporal lobe pathology, with the 4-year post-injury follow-up MRI (see Fig. 2) demonstrating distinct, regional encephalomalacia of the anterior aspect of the right temporal lobe, corresponding with the region of where the original contusion was observed. While this type of clinical and qualitative information alone supports the neuropsychological inferences about potential temporolimbic pathology as a consequence of TBI, it does not fully address the extent of pathology and neural networks damaged by this type of temporal lobe injury. Quantitative neuroimaging methods have the potential to provide this additional information about neuropathological changes relevant to more fully understanding the neuropsychological findings, as will be outlined in the next section.

Added Value and Importance of Quantitative Neuroimaging Analyses That Informs Neuropsychological Interpretation

For the purpose of this paper, it is important to restrict the analyses to what can be derived from standard clinical imaging. If the approach described below is to be useful and extend to more routine clinical implementation in pediatric neuropsychological case interpretation, the analyses provided herein needed to be limited to commonly and universally available MRI methods used and accessible in clinical settings, as well as readily available neuroimaging quantitative analyses methods.

Most children with a history of significant neurological disorders will have had some type of neuroimaging prior to any referral for neuropsychological testing. Clinical scans are performed and interpreted at an imaging center, clinic or hospital radiology department. If a clinical MR scan was performed with the appropriate acquisition parameters, there will be a menu of additional options beyond the clinical report that can be explored in terms of image quantification and actual viewing of the images. As of this writing, these analyses require working with radiologists and/or neuroimaging experts to achieve the kinds of analyses and image viewing described below, although the future of neuroimaging will likely involve these types of analyses to be routinely available (see Bigler, 2017; Cope et al., 2021; Bash & Tanenbaum, 2021).

If the appropriate acquisition parameters have been obtained, there are now a variety of commercially and/or open-source methods used for image quantification, including the following, provided as merely an example, and not to be construed as an exhaustive list, nor as an endorsement of any type: FreeSurfer (https://surfer.nmr.mgh.harvard.edu/), NeuroQuant (https://www.cortechs.ai/products/neuroquant/), VolBrain (https://volbrain.net/), BrainReader (https://brainreader.net/), MDBrain (https://mediaire.ai/en/mdbrain/), and QMENTA (https://www.qmenta.com/).[2] Much of MR-based quantitative image analysis methods begin with the T1-weighted sequence, where the first step involves normalization of the scan image into 3-D standardized space along with image segmentation to differentiate white matter, gray matter, and cerebrospinal fluid (CSF), followed by ROI classification. ROI classification reflects a labelling method that identifies and outlines major neuroanatomical structures, typically using conventional nomenclature.

For example, Fig. 3 depicts the typical appearance of a classified coronal image from the NeuroQuant analyses in this case, showing the hippocampi (white arrows), along with all other cortical and subcortical ROIs. Table 2 summarizes some of the quantitative MRI analyses obtained in this case study.

What all quantitative MR analysis programs have in common, once the ROI classification has been established, is a broad spectrum of analyses that usually begins with ROI volume compared to a normative sample, or a within subject analysis of right versus left, to examine for significant asymmetries, as well as potentially other metrics. Since numerous quantitative analyses may be performed, the clinical imaging findings, like those from the DOI CT above (Fig. 2), assist in guiding the clinician as to which ROI analyses may be most important to examine. In this case, with clinically identifiable temporal lobe damage, the guiding questions are: what is the overall structural integrity of the right temporal lobe? and what quantitative neuroimaging findings provide context for defining neural network damage?

As a starting point, the hippocampal formation is very susceptible to damage in TBI (Bigler, 2023; Wilde et al., 2007), where the structural integrity of the hippocampus in the individual with a history of TBI relates to not only memory function but executive control and emotional regulation (Barch et al., 2019; Zhu et al., 2019). As shown from the NeuroQuant hippocampal volumetrics presented in Fig. 3, while hippocampal volume is within the average range,

[2] Bash and Tanenbaum (2021) provide the following additional synopsis on available quantitative neuroimaging methods: "CorTechs.ai (NeuroQuant™) and icometrix (icobrain™) dominate the commercial quantitative volumetric space in neuroradiology with numerous FDA-approved products for MRI and CT. Other companies with FDA-cleared products include Quantib (qQuant™), Corticometrics (THINQ™), and Siemens Brain Morphometry (AI-Rad Companion Brain MR for Morphometry Analysis™). SmartSoft's CoLumbo™ has a 510Kpending spine product that is currently cleared for marketing overseas. In addition to commercial offerings, many academic institutions have developed their own volumetric software or use free research-oriented platforms (e.g., FreeSurfer™, Voxel Based Morphometery™, Volbrain™, Brain MRI Cloud™, FastSurfer™, and FSL™) p. 41.".

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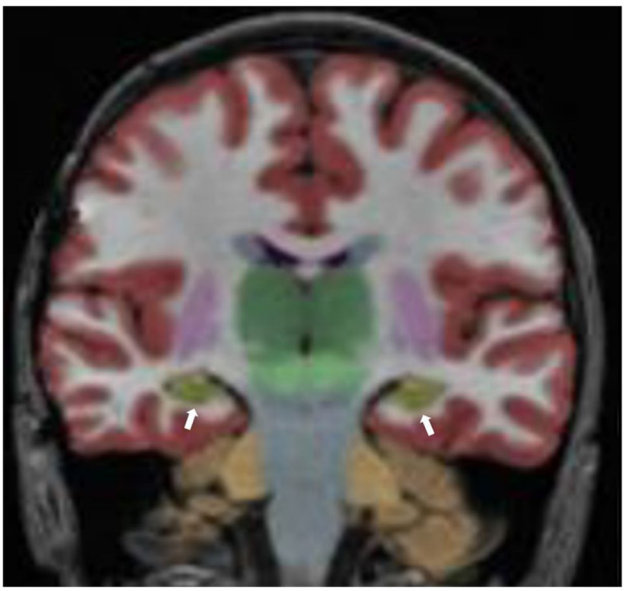


Fig. 3 Classified coronal image from a NeuroQuant analysis showing cortical gray matter (red), cerebral white matter (white), brainstem (blue-gray), ventral diencephalon (light green), thalami (dark green), caudate (light blue), hippocampi (dirty yellow; white arrows), nucleus accumbens (light orange), and cerebellar white and gray matter (dark orange). What is depicted in this figure is the segmented and classified image output extract from NeuroQuant analysis, where the white arrows point to the left and right hippocampi. NeuroQuant assessed hippocampal volume was 7.79 cm^3 (33rd percentile)

33rd percentile, it is nonetheless, low average, to be further discussed later in this report. The MDBrain analyses also performed confirmed the lower-than-average hippocampal volume (25.9th percentile) for the right hippocampus (see Table 2), as contrasted with a left hippocampal volume at the 46.2nd percentile. Such an asymmetric reduction in right hippocampal volume in a TBI case with known structural damage to the right temporal lobe, implicates volume reduction, secondary to the brain injury, predominantly affecting the right hippocampal complex. There were other right temporal lobe ROI reductions, along with right versus left asymmetries (see Table 2). For example, quantitative analyses demonstrated significant asymmetry in the amygdala, with right amygdala volume reduced in comparison to the left, and a very significant asymmetry in the size of the right temporal horn of the lateral ventricle, when compared to the left (see Table 2). Furthermore, the right temporal pole volume is reduced in comparison to the left. With volume reductions in multiple right temporal lobe ROIs, asymmetric dilation of the temporal horn indicates a more generalized pathological change within the temporal lobe, since in TBI of this type of ventricular enlargement is considered a reflection of passive expansion of localized ventricular CSF in response to parenchymal degradation involving the temporal lobe (Bigler et al., 2002). In particular, temporal horn increases related to reduced size of the hippocampus, amygdala, and the white matter temporal stem region, because these areas surround the temporal horn (Bigler et al., 2010a, b). Accordingly, asymmetric increase in right temporal horn size in this child with TBI implicates overall diminished right temporal lobe integrity compared to the left.

As further confirmation, Fig. 4, utilizing the fluid attenuated inversion recovery (FLAIR) Lesion Report from NeuroQuant, a more direct method for assessing white matter integrity of the right temporal lobe can be achieved. As depicted in Fig. 4, white matter hyperintense signal abnormalities are evident within the right temporal lobe, with a lesion burden assessed to been 1.43 cm^3 (see Fig. 4). Under normal, non-pathological circumstances, because medial temporal lobe structures participate in a multiplicity of cognitive and behavioral control functions, extensive white matter mediated, input–output connectivity occurs within the temporal lobe as temporal lobe structures interface with other regions throughout the brain (Kerr et al., 2007; Yeterian et al., 2012). From the FLAIR Lesion Report, extensive white matter damage is present, which would alter white matter connectivity of the right temporal lobe with the rest of the brain (see Hayes et al., 2016).

Returning to the other volumetric analyses as shown in Table 2, they all support more extensive pathological changes to the right temporal lobe than cannot be appreciated by just viewing the images. Healthy, age-typical brains tend to be generally symmetric at the cortical and subcortical level, which also relates to their functional connectivity (Mancuso et al., 2019). Accordingly, every patient can serve as their own control, and several of the quantitative image analysis programs incorporate an "asymmetry index" in their analyses. There are numerous factors that underly symmetry, but one "rule-of-thumb" is that homotopic ROIs typically vary within ~ 15%. If the right-left asymmetry of a given ROI or multiple ROIs substantially deviate beyond that expected variation, such findings may indicate pathological changes (Szabó et al., 2003; Ross et al., 2013, 2015; Barcelona et al., 2022). The reduced volume and highly asymmetric findings of the right temporal pole compared to the left (see Table 2), in conjunction with right hippocampus, amygdala, and temporal pole, as previously discussed, along with parahippocampal gyrus and entorhinal cortex being smaller on the right than the left, indicate generalized damage involving the right temporal lobe.

If the imaging center maintains a neuroimaging data set of age-typical, healthy controls, that MR-data set can be used to derive different types of voxel-based analyses to compare the individual with normative group data. This approach provides a method for whole-brain surface visualization of cortical changes, in this case from TBI, as presented in Fig. 5. This method of analysis is referred to

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Table 2 Volumetric analysis of right temporal lobe[a]

vol2Brain volumetry report						
Cortical	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)		Asymmetry (%)	
Temporal lobe	122.32 (8.715) [7.088, 8.774]	57.80 (4.118) [3.541, 4.413]	**64.52 (4.597) [3.514, 4.395]**		**−10.9914 [−6.256, 7.568]**	
Superior temporal gyrus	**13.56 (0.966) [1.012, 1.453]**	**6.36 (0.453) [0.535, 0.798]**	7.20 (0.513) [0.431, 0.701]		−12.3580	
Temporal pole	21.19 (1.510) [1.126, 1.711]	9.05 (0.645) [0.589, 0.882]	**12.14 (0.865) [0.516, 0.850]**		**−29.1984 [−9.385, 26.245]**	
MDBrain volumetery report						
Region	Right			Left		
	*%	Volume (ml)	Normal range (ml)	%	Volume (ml)	Normal range (ml)
Frontal lobe	93.8	104.8	85.6–107.4	92.4	101.6	83.6–04.6
Parietal lobe	58.6	52.7	44.8–59.0	69.7	54.5	45.4–59.8
Precuneus	55.8	12.4	10.2–14.2	66.4	12.5	9.9–14.1
Occipital lobe	81.2	36.6	28.9–39.6	91.0	41.0	31.2–43.0
Temporal lobe	23.2	68.3	63.2–79.3	90.7%	73.4	60.3–76.0
Hippocampus	25.9	3.6	3.2–4.5	46.2	3.5	2.9–4.0
Parahippocampal gryus	30.4	3.0	2.6–3.6	73.4	3.4	2.7–3.7
Entorhinal cortex	4.9	1.9	1.9–2.8	32.8	2.3	1.9–2.9
NeuroQuant general morphometry report						
Brain structure	LH volume (cm^3)	LH volume (% of ICV)	RH volume (cm^3)	RH volume (% of ICV)	Asymmetry index (%)*	
Lateral ventricle	3.76	0.25	5.65	0.38	−40.11	
Inferior lateral ventricle	0.30	0.02	0.44	0.03	−38.04	
Amygdala	2.30	0.16	1.85	0.13	21.71	
NeuroQuant multistructure atrophy report						
Brain structure	Volume (cm^3)		% of ICV (5–95% normative percentile)		Normative percentile	
Hippocampi	7.79		0.53 (0.47–0.63)		33	

All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the intracranial volume or ICV). The asymmetry index is calculated as the difference between right and left volumes divided by their mean (in percent). Values between brackets show expected limits (95%) of normalized volume in function of sex and age for each measure for reference purposes. Values outside the limits are bolded. The percentile in the MDBrain volumetry report gives the expected proportion of the normal population with the same covariates having a lower volume than the one measured (based on the measurements of a normal collective). *The asymmetry index is defined as the percentage difference between left and right volumes divided by their mean. [a]Each Quantitative Neuroimaging Program has its own unique method for data presentation

as deformation-based morphometry (DBM; Ashburner & Friston, 2000; Gaser et al., 2001; Shiohama & Tsujimura, 2022). The generated "heat map" is statistically derived by comparing, in this case, the TBI child's brain to the normative sample of age-matched individuals in the study. The statistical computation in these types of deformation analyses uses a color scheme where greater shades of blue reflect voxel-by-voxel reductions with the opposite shown in warm coloration, orange to red. Intermediate colors reflect voxels within the normal range of the comparison sample.

As visualized in the bottom left panel, reductions (blue colorization) are observed in the right anterior temporal lobe (red arrows) where the focal encephalomalacia was clinically noted (see Fig. 2), and quantitatively outlined in Table 2. The temporal pole reductions reflected in blue are quite distinct when compared to the left, in the anterior perspective (bottom left panel). Note some of the reduction in cortical volume extends to other right hemisphere regions, beyond just the temporal lobe. Referring back to Table 2, the deformation mapping permits visualization of the reductions quantitatively reported, where the parietal, including the precuneus and occipital regions were less in volume than the left. Column B shows in the top panel greater prominence of the right Sylvian fissure, which is an indication of temporal

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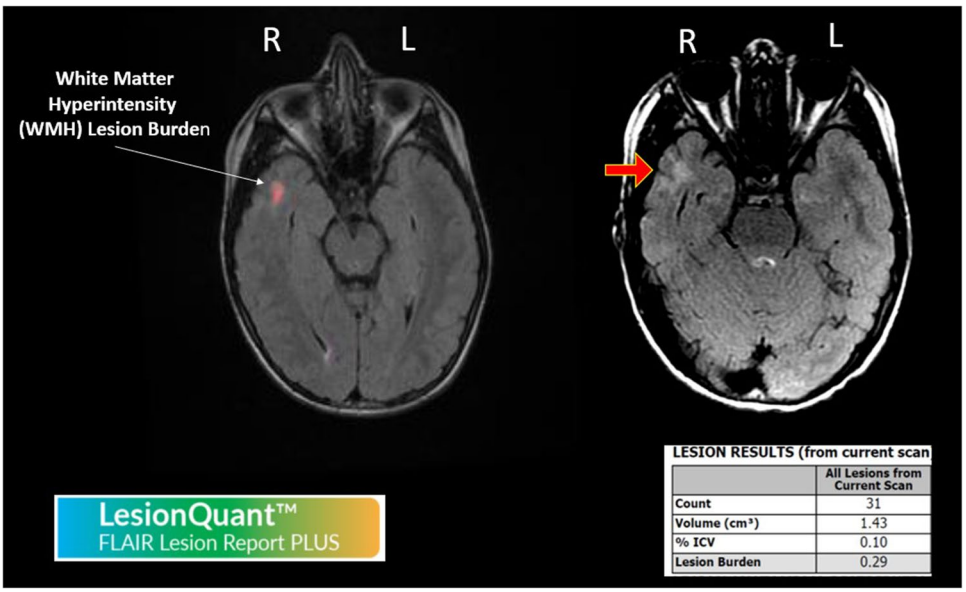


Fig. 4 LesionQuant FLAIR analysis as part of the NeuroQuant quantitative neuroimaging method demonstrating a 1.43-cm^3 white matter lesion burden

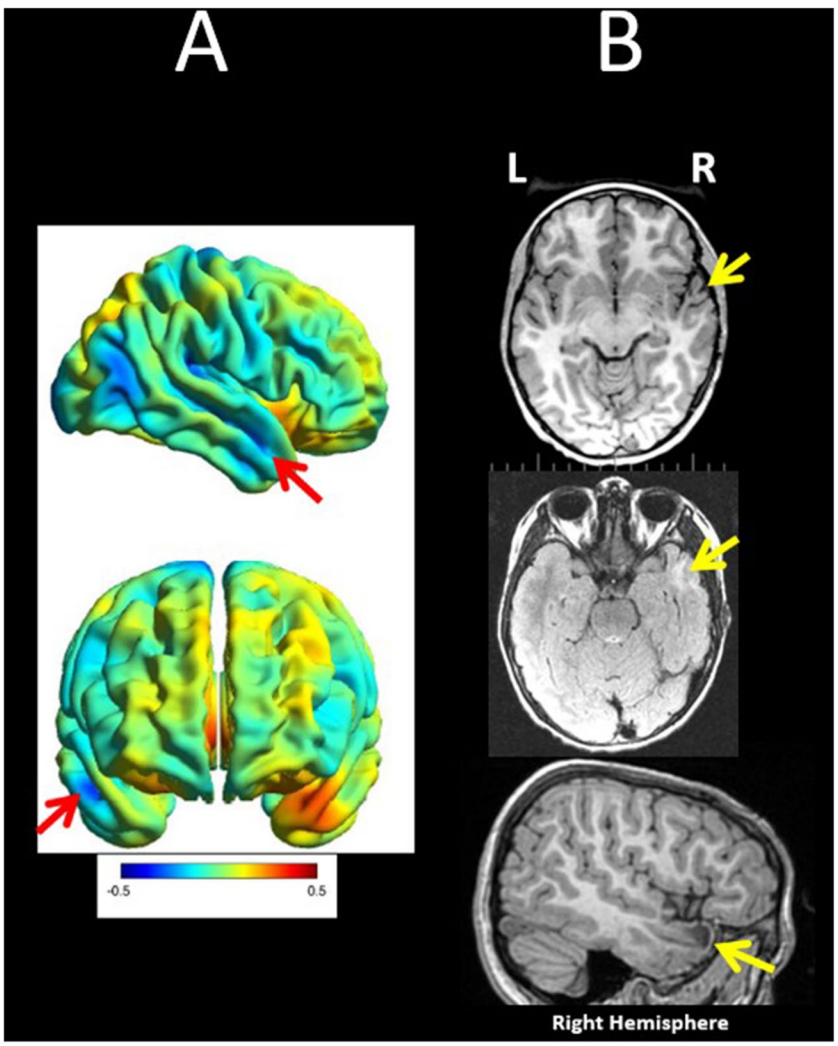


Fig. 5 **A** shows a deformation-based morphometry heat-map analysis. Cooler blue colors reflect voxel-by-voxel volume reductions compared to a normative sample. These changes align with the clinical visualization but with this type of deformation analysis, instead of a flat 2-D image or a table with a volumetric value, this method provides viewing of the entire brain in one 3-D image. As visualized in the bottom left panel, reductions are observed in the right anterior temporal lobe (red arrows) where the focal encephalomalacia was clinically noted (see Fig. 2), are quite distinct when compared to the left, in the anterior view (bottom panel). Note some of the reduction extends to other right hemisphere regions, beyond just the temporal lobe. **B** shows the MRI scans of this case study child where the top panel shows greater prominence of the right Sylvian fissure, another indication of temporal lobe atrophy. The middle panel presents another level depicting white matter hyperintensity abnormality, with the bottom panel showing a sagittal view depicting encephalomalacia and widening of the right Sylvian fissure, additional indicators of right temporal lobe atrophy

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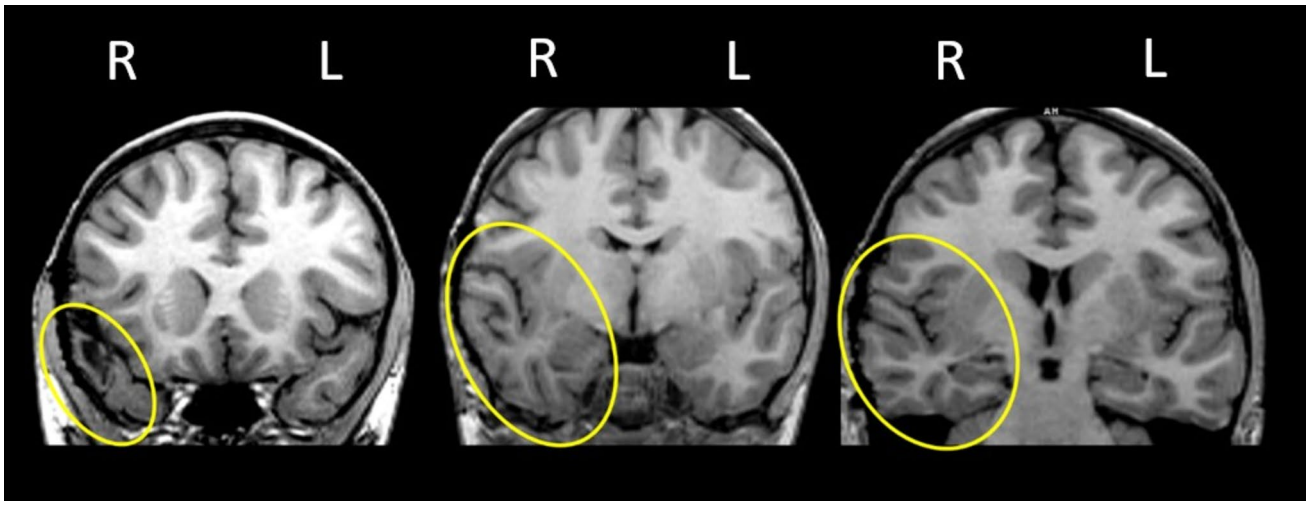


Fig. 6 The right temporal lobe is outlined with the yellow oval in coronal images at the anterior temporal pole (left), level of the amygdala (middle), and at the level of the hippocampus (right). When compared to the left temporal lobe, the right temporal areas of encephalomalacia (far left image) show a reduced appearance of healthy white matter in all three images, along with greater prominence of the Sylvian fissure on the right

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lobe atrophy, as well as potential frontotemporal atrophy. However, quantitative analyses reported in Table 2 show normal values for right and left frontal lobe, so the widening of the Sylvian fissure is most likely an indication of temporal lobe atrophy. The middle panel of Fig. 5 presents another level depicting white matter hyperintensity abnormality, with the bottom panel showing a sagittal view of the superior temporal gyral encephalomalacia and widening of the right Sylvian fissure, another indicator of right temporal lobe atrophy.

The clinical and quantitative analyses have unequivocally come together to demonstrate extensive pathology to the right temporal lobe, involving multiple temporal lobe ROIs including the temporal pole, medial and lateral temporal lobe structures as shown in Table 2 and Figs. 4 and 5. DTI was not performed, but that does not limit the understanding of potential pathways affected, as that can be inferred from structural neuroimaging findings. By knowing where either lesion pathology is present (i.e., areas of focal encephalomalacia and lesion burden FLAIR indices) and/or quantitative changes (i.e., volume reductions and asymmetric findings), by using existing DTI atlases, inferred pathway damage can be presented, as presented in the next section.

How to Infer Potentially Affected Specific White Matter Pathways When Only Structural MR and Quantitative Neuroimaging Are Available?

Fortunately, once pathology can be established through a combination of clinical and quantitative neuroimaging, there are extensive cognitive neuroscience studies and MR-based atlases that can be used to identify likely affected pathways. For example, the *Atlas of Human Brain Connections* by Catani and Thiebaut de Schotten (2012) and other similar publications that summarize neuroimaging connectomics to clinical disorders (see Cohen et al., 2021; Perovnik et al., 2022; Schirmer et al., 2021) provide the kind of background needed. Using existing pathway and network analyses combined with the known quantitative analyses and visualization of pathology guided by quantitative neuroimaging findings from the individual (Figs. 2, 3, 4, 5; Table 2) permits a recreation of networks damaged that likely underlie the neuropsychological changes, as will be explained next.

Figure 6 provides coronal images showing superior temporal gyral encephalomalacia and temporal lobe atrophy, confirmed by quantitative analyses (Table 2) and visual inspection as shown within the yellow oval outlines. Within the yellow oval of the middle image, at the level of the amygdala shows degraded white matter signal and reduction in comparison to the left temporal lobe. The far-right coronal image at the level of the hippocampus, within the yellow oval, shows continued degradation and reduced extent of white matter within the temporal lobe at this level compared to the left. While subtle, the size of the right hippocampus is visually reduced in comparison to the left (also, see Table 2), and note the temporal horn of the right lateral ventricle is more evident. Note in all three images, the greater prominence of the right Sylvian fissure when compared to the left.

Figure 7, from Catani (2022), depicts established white matter pathways superimposed on coronal images that correspond to the hippocampal and amygdala coronal image sections shown in Fig. 6. From the superimposed pathway comparison with quantitative and visible pathology, the following long associative tracts would likely be compromised: different components of

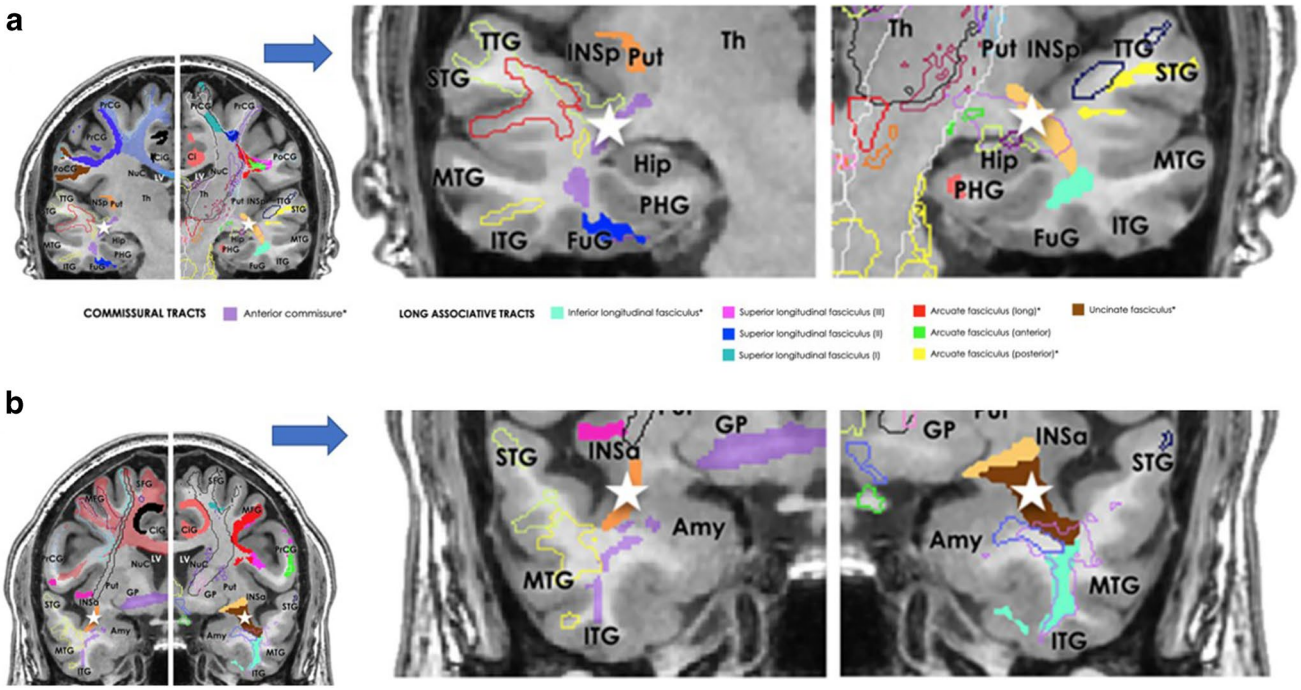


Fig. 7 MRI coronal slices through the temporal lobe at the level of the hippocampus (**a**) and the amygdala (**b**) from a of a healthy brain. These images are color coded to show short white matter associative and commissural tracts (displayed in the right hemisphere) and major white matter projection and long association tracts (left hemisphere). The white star is the temporal stem. Returning to Fig. 6, regions/areas of encephalomalacia, atrophy, and white matter burden, in conjunction with the volumetric changes of temporal lobe ROIs in Table 2, inferences can be made as to which white matter pathways and tracts would be affected, by also incorporating established DTI tractography from Fig. 8. Adapted from Catani (2022) Adapted from Catani (2022) and used with permission from Elsevier

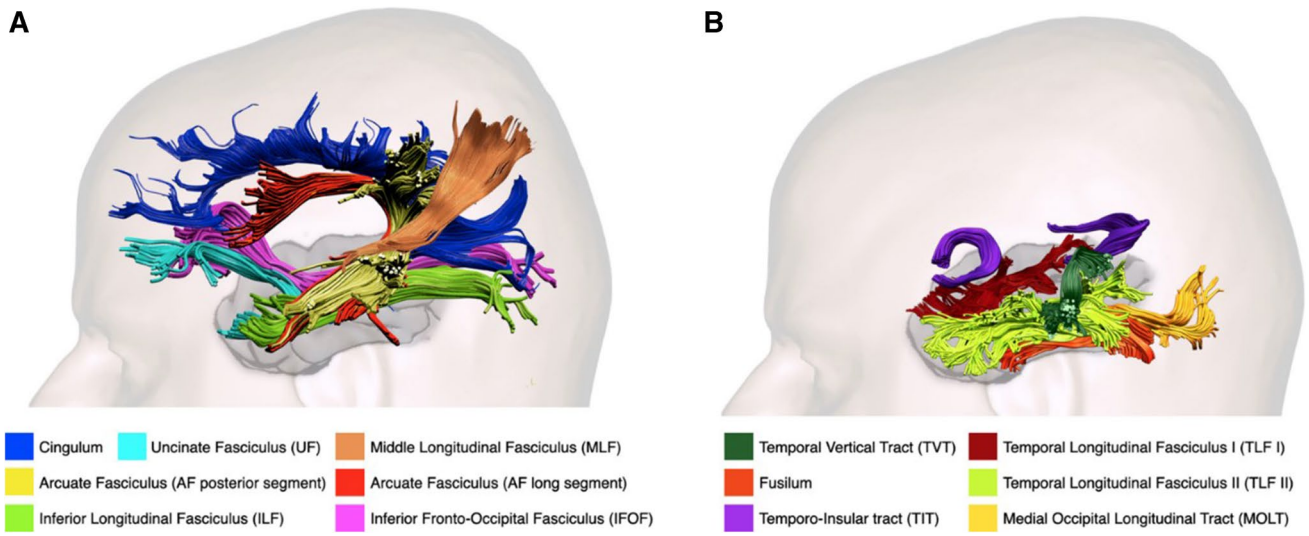


Fig. 8 DTI tractography reconstructions of the temporal association pathways showing the general location of white matter pathways and tracts. This permits a visualization of the likely affected tracts as discussed in Figs. 6 and 7 as well as the discussion within the text. **A** Major interlobar association pathways and **B** shorter interlobar and intralobar temporal tracts. Adapted from Catani (2022) and used with permission from Elsevier

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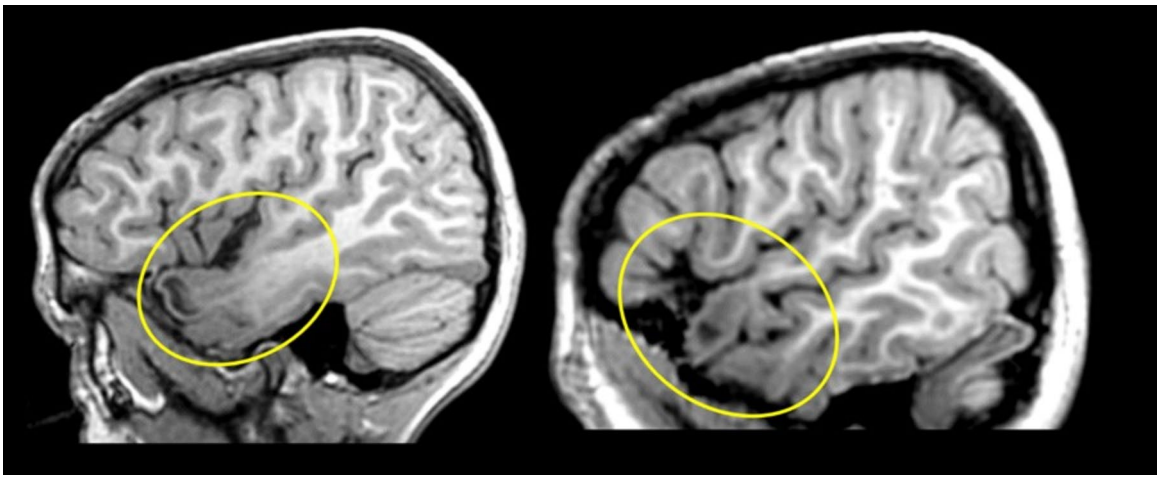


Fig. 9 Sagittal T1-weighted images depicting regions of encephalomalacia, white matter degradation and Sylvian fissure prominence of the right temporal lobe damage of this case study. Note on the right it appears that some of the encephalomalacia extends into the inferior frontal area as well. This type of lateral, surface imaging can be used to deduce pathway/tract damage as well, inferred from established anatomical atlases as presented in Fig. 10

the superior longitudinal fasciculus, arcuate fasciculus, inferior longitudinal fasciculus, temporal stem in general, anterior commissure, and uncinate fasciculus. Figure 8 shows the DTI-based tractography of these pathways, where the structural coronal image with the identified areas of damage and pathway compromise, the DTI-derived tracts can be visualized.

There is another approach that can be undertaken, by examining cortical surface pathology, again from direct visualization and/or quantitative analyses. Figure 9 is a lateral T1-weighted image in the sagittal plane showing the anterior temporal lobe pathology describe above, where compared with the deformation mapping of the cortical surface as shown in Fig. 5, it can be inferred that the anterior temporal pole, superior and middle temporal lobe gyri are especially affected, and based on quantitative analyses, medial temporal lobe regions also are damaged.

Also, from Catani (2022), a lateral surface atlas (Fig. 10) can be examined in association with the neuroimaging findings that also demonstrates the likely affected fasciculi, as depicted in Figs. 6, 7, 8. Again using this approach, confirmation for likely compromise of the affected pathways as described in the previous paragraph, is established. With pathway damaged now established, how to infer what networks are affected? This will be presented in the next section.

Network Neuroscience, Application/Integration of Clinical and Quantitative Neuroimaging Findings to Enhance Understanding of Neuropsychological Test Results and Neurobehavioral Outcome

From Table 2 and the deformation analyses, some extensive volumetric differences in the right temporal lobe are present, which also appear to extend beyond the temporal lobe as well, including the right precuneus. Similar to the above method of mapping out likely pathway damage by knowing the underlying structural and likely pathway damage, based on the quantitative analyses (Figs. 6, 7, 8, 9, 10), this can now be mapped onto known neural networks.

Much is known about the cortical organization of major neural networks associated with cognitive domains of function, based on functional neuroimaging (Lee et al., 2013). However, at the time of this writing, while network image analyses are a major part cognitive neuroscience with clinical application, such analyses are time-consuming and require a combination of functional and diffusion MR sequences not routinely obtained. A work around solution is to use currently available, well-established, empirically derived network and pathway analyses that are published and readily available for comparison. If one of the quantitative methods involves 3-D rendering or surface deformation mapping, as was done in this case (see Fig. 5), areas of pathological change can be superimposed upon existing network maps. This can also be achieved by understanding the structural pathology from the quantitative analyses, as presented in Table 2 and what was shown in Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10. This will be presented in the next section on "Network Analyses."

Network Analyses

One of the established network analyses with direct application to assist with interpretation of pediatric neuropsychological test results began with Yeo et al. (2011) and fMRI-based extractions of brain networks representing

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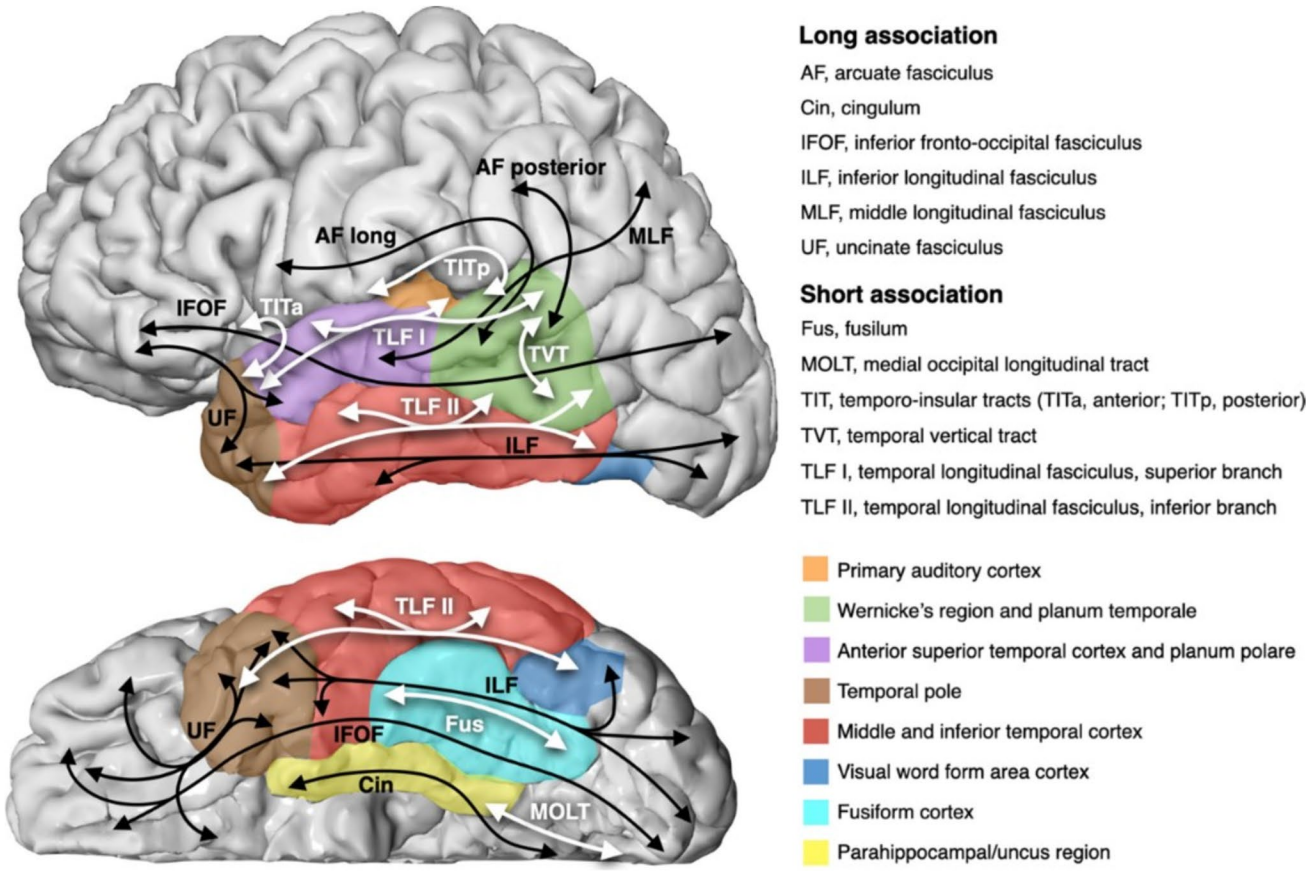


Fig. 10 Cortical gyral surface atlas with anatomical landmarks depicting associated tracts and white matter pathways from Catani (2022). By comparing pathology from quantitative assessments (Table 2), deformation analysis (Fig. 5) and visual inspection (Figs. 2, 4, 6, and 9) solid inferences about where tract damage within the temporal lobe would affect white matter integrity and connectivity. Adapted from Catani (2022) and used with permission from Elsevier

major neurocognitive domains. As noted in Fig. 11, Yeo et al. (2011) mapped out seven commonly researched, large-scale neurocognitive networks (visual network, somatomotor network, dorsal attention network, ventral attention network, limbic network, frontoparietal network, default mode network), which have been well documented by other independent investigators (Gordon et al., 2018; Gratton et al., 2016). There are more (see Uddin et al., 2019), but for ease of presentation in this case study, the original 7-network findings of Yeo et al. (2011) will be used. These networks are color coded for ease in identification, as depicted in Fig. 11. One of the major advances in network neuroscience is how widely separated many brain regions are, which when interconnected form a functional network. Because of the critical nature of white matter connectivity in these networks, for normal functioning, all networks are highly dependent on healthy, intact white matter (Bigler, 2013). For example, functioning within the default mode network (DMN -colorized as red) requires the integration and reciprocity of frontal, parietal and temporal lobe connectivity, as depicted in Fig. 11.

By using established neural network publications, quantitative and clinical findings that depict regions of greatest pathology can be applied to and mapped onto the established maps like those provided by Yeo et al. (2011). For example, comparing the heat-mapped right hemisphere findings from the deformation analyses as shown in Fig. 5, to the Yeo et al. surface network maps (the bottom two images) in Fig. 11, along with the known quantitative temporal lobe findings (see Table 2), the most distinct temporal pathology would be within the limbic (cream) and default mode (red areas) networks with likely some involvement of the frontoparietal (yellow) executive control network. Recall that what is shown in the deformation heat map was backed by quantitative ROI volume analyses showing distinct volume loss in the temporal pole, reduced overall temporal lobe volume as well as parahippocampal gyrus volume reduction. Note in the network analysis by Yeo et al., the dark (black) area that contains the medial temporal lobe memory network and insular cortical interoceptive processing networks, for technical reasons, is not shown on this cortical surface network illustration. Nonetheless, by the quantitative

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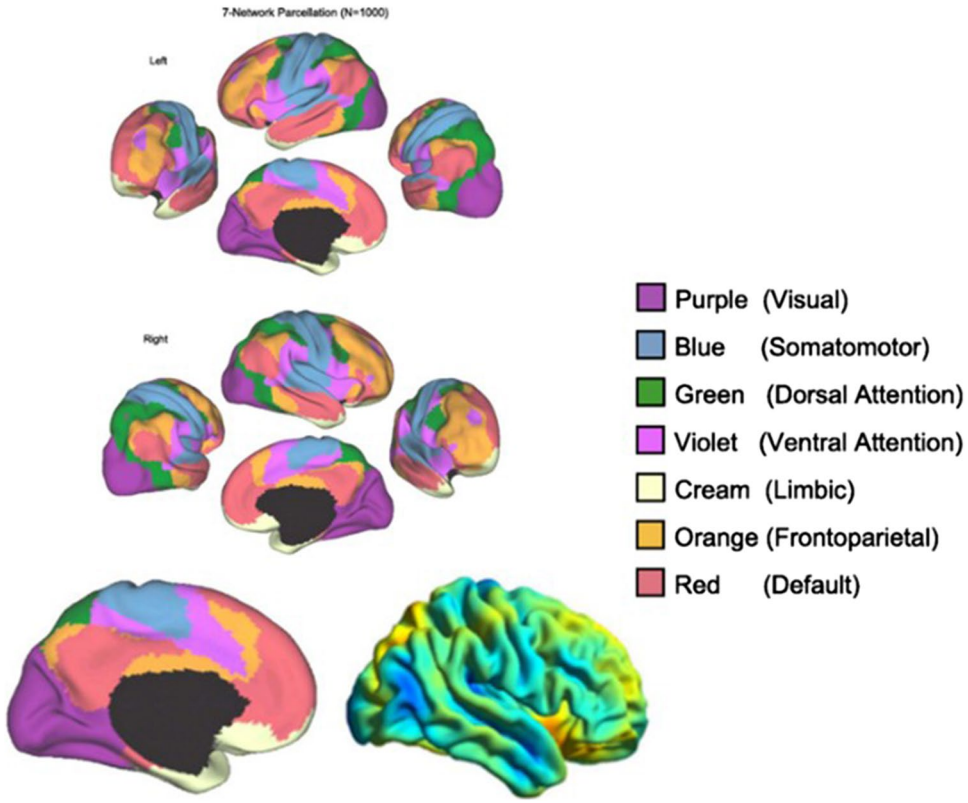


Fig. 11 Functional MRI connectivity mapping of cortical brain regions involved in seven neurocognitive networks (visual network, somatomotor network, dorsal attention network, ventral attention network, limbic network, frontoparietal network, default mode network). Adapted from Yeo et al. (2011). The deformation mapping from the participant in this case study is depicted in the lower right image where the blue reflects size reductions in the temporal lobe area and other regions. By viewing these changes and those in Table 2 and the quantitative FLAIR lesion burden (Fig. 5; Table 2), various inferences can be made as to what networks are affected

analyses performed, it is evident that these medial temporal lobe regions were also damaged, and this would include the memory network.

Discussion

Using an approach with both pediatric neuropsychological results and neuroimaging findings, we have shown how that information can be better integrated in understanding outcome from TBI. That is, with generally intact neurocognitive testing, the post-injury changes appear to be mostly causing behavioral dysregulation and impaired emotional control. While the index event was a severe TBI and children with severe TBI are more likely to exhibit changes in social and emotional functioning (Petranovich et al., 2020), confirmation of this can only come with the neuroimaging findings. Since changes in emotional/behavioral regulation may have a variety of etiologies, neuropsychological tests alone cannot directly address the location and extent of underlying brain pathology. In contrast, being able to explicitly show damage within the right temporal lobe, including likely temporolimbic and DMN network disruption involving the temporal lobe damage, such findings support the neurogenic basis to the reported emotional/behavioral deficits from this TBI (see Bickart et al., 2023). While neuropsychological findings may offer speculation about underlying brain pathology, confirmation of such pathology comes from neuroimaging. The methods we have outlined above provide a way to further analyze potential brain pathology and disrupted neural pathways as well as networks of likely significant importance in understanding pediatric neuropsychological test results.

All types of changes and updates are occurring in the arena of neuropsychological assessment in order to develop improved methods that tap technology, both in terms of test administration and scoring and interpretation (Bilder et al., 2022; Gottlieb et al., 2022; Merkley et al., 2022). For example, efforts to improve norms more sensitive to a host of demographic variables are underway, along with more universally used methods for a world-wide implementation of testing protocol (Loring et al., 2022; Olson et al., 2022; Smerbeck et al., 2023). Likewise, changes are occurring with digital and telehealth assessments in neuropsychology (Carlew et al., 2020; Carotenuto et al., 2021; Wong et al., 2021). As improvements occur with digital assessment methods, this in turn, may lead to digital formats aided by machine-learning that provide methods for even better integration of neuroimaging findings with neuropsychological assessment techniques.

As demonstrated in the integrative volumetric neuroimaging assessment process laid out above, quantitative neuroimaging that has become automated is now information potentially available in any pediatric neuropsychological

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case where neuroimaging has been performed. It is likely in the future that there will be comprehensive databases of healthy, age-related, neurotypical controls that will become routine normative neuroimaging sample comparisons for ever-increasing quantitative neuroimaging analyses techniques. With the proper imaging protocols, all types of structural and network analyses will be available to probe in a correlative way with neuropsychological testing (Griffanti et al., 2022). With the proper standardization in combination with machine and deep-learning methods, future neuropsychometric-neuroimaging algorithms could be developed with a high degree of clinical relevance for improved neuropsychological interpretation.

The purpose of this paper has been to provide practical approaches for deriving and incorporating added information derived from quantitative image analyses of an injured brain. We outline a general approach that could be applied in any pediatric neuropsychological assessment setting where clinical neuroimaging has been done and quantitative analyses undertaken. For the purposes of this paper, only the MR-sequences that would be common in any clinical setting have been used. Hopefully, as has been shown, rich, clinically relevant information can be extracted from contemporary neuroimaging methods that enhances the interpretation of pediatric neuropsychological assessment results, by providing additional information about regional changes in brain integrity and the likely association of affected neural tracts and networks.

There are numerous large-scale neuroimaging studies underway throughout the world. Initiatives like the Enhancing Neuroimaging in Genetics through Meta Analysis, or ENIGMA, (https://enigma.ini.usc.edu) have focused on bringing together and harmonizing large normative, TBI, and other neurological and/or neuropsychiatric datasets such that statistical power can be achieved to examine numerous neuroimaging factors associated with brain injury, neurological, and neuropsychiatric outcome (see Olsen et al., 2021). There are large-scale prospective studies like the Adolescent Brain Cognitive Development (ABCD: https://abcdstudy.org) study that tracks quantitative neuroimaging findings, medical variables, and neurocognitive and emotional functioning in adolescent participants over time (Casey et al., 2018), where some have experienced a TBI (Degeilh et al., 2023; Lopez et al., 2022). In such cases, pre-injury neuroimaging and a within subjects design will provide powerful findings of what may be specific to TBI effects versus what may have pre-existed the TBI. These types of investigations ultimately will provide the clinician and research with extensive correlative data that has not heretofore been available.

Given the potential utility and clinical implications for a variety of DTI methods, along with task-based fMRI (tb-fMRI) and resting-state fMRI (rs-fMRI) advances in the understanding of brain network integrity and network connectivity critical to neuropsychological functioning, in the future when this technology becomes more automated and standardized, DTI, tb-fMRI, and rs-fMRI, likewise, will become even more useful instruments to also integrate with neuropsychological findings in assessing pediatric TBI clients during the acute, subacute, and chronic phases post-injury. This may especially add insight into any compensatory network rerouting that occurs and add value to quantitative analyses during the chronic stage of recovery as described in our quantitative neuroimaging findings integration approach to pediatric neuropsychological assessment of TBI.

As for improved implementation, in order for the integrated approach of neuroimaging findings with neuropsychological test results proposed in this case report to be more routinely implemented by pediatric neuropsychologists, it begins with basic training. As is well established for neuropsychological subspecialty Ph.D. training programs that follow the Houston guidelines (https://uh.edu/hns/hc.html), neuroanatomy and neuroimaging training are already an integral part of the educational and training process, so that aspect is already in place. Additionally, ongoing educational and continuing educational programs are currently available for the established practitioner provided by different professional societies and their CE programs. Regarding the automated and quantitative neuroimaging analyses used in this case study, these are becoming routinely available at the time neuroimaging is performed, as most radiology and neuroimaging centers have the capability of running them. Therefore, this information will become even more readily available to pediatric neuropsychologists in the future. Relatedly, there are ever-increasing applications of machine learning and artificial intelligence approaches to neuroimaging analysis (Chio & Sunwoo, 2022; Monsour et al., 2022), that in the future likely will also become routine and need to be integrated into training opportunities and pediatric neuropsychological assessment result interpretations.. Furthermore, undoubtably, more publications such as this one, will likewise find their way into the hands of trainers, students, and practitioners and help keep them up to date as neuroimaging technology assessment software continues to evolve.

An integrated approach of incorporating neuroimaging findings into the neuropsychological interpretative process has implications for forensic neuropsychological consultation. Although neuropsychological assessment procedures are certainly standalone in the sense that they do not require neuroimaging findings to make diagnostic conclusions (Lezak et al., 2012), the objectivity that neuroimaging provides, as demonstrated in this paper, can certainly provide considerable external support for neuropsychological diagnostic decision-making based on neuroimaging findings. While there are numerous quantitative neuroimaging analytics that are now commercially

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available, major ones like NeuroQuant (used in this report) are approved by the Food and Drug Administration (FDA) (https://www.cortechs.ai/company/news/fda-510k-clearance-2017/). Likewise, as demonstrated in this case report, various specific abnormalities (e.g., encephalomalacia, white matter hyperintense signal abnormalities) are clinically visible and identifiable in neuroimaging scans. What quantitative neuroimaging analyses provide is a basis for comparing these clinically identifiable abnormalities in an individual with acquired brain injury to demographically matched healthy, neurotypical samples, thereby providing additional indices as to the level of objectively identifiable brain pathology, with relevance to neuropsychological correlates. Everything presented in this case report was based on structural CT and MRI and not on any aspect of functional neuroimaging or diffusion tensor imaging, where legal issues of admissibility have been raised (Brindley & Giordano, 2014; Langleben & Moriarty, 2013; Shenton et al., 2018). Quantitative findings have excellent reproducibility which supports their utilization in clinical application and research (Bigler et al., 2020; Dennis et al., 2023; Fong et al., 2021; Wilde et al., 2016). What we have presented in terms of neural network theory, as applied to neuropsychological outcome, also comes from an empirical application of neuropsychological tests with advanced neuroimaging methods (Reber et al., 2021). Accordingly, what we have presented in this case review represents a state-of-the-art application of neuroimaging analyses to better inform the pediatric neuropsychologist about the clinical inferences that can be made about documentable brain pathology and neuropsychological outcome.

Finally, the injured pediatric brain presented herein, had distinct focal brain pathology, but less severe pediatric TBI, as well many other neurological and neuropsychiatric conditions, may only have subtle, nonspecific changes. This is where a large research effort needs to be directed to provide clinical correlation data between neuropsychological test and quantitative brain metrics.

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Authors Contribution All authors contributed to the study conception and design. All authors read and approved the final manuscript.

Declarations

Disclaimer This case study was research based, and the individual or family was not in any litigation.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors have no relevant financial or non-financial interests to disclose. EDB is a retired, professor emeritus of Psychology and Neuroscience, Brigham Young University, who does some forensic consultative work.

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