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White matter integrity correlates with depressive symptomatology in temporal lobe epilepsy

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ABSTRACT

Rationale: White matter abnormalities occur in both temporal lobe epilepsy (TLE) and depression, but there is limited research examining the depression–white matter association in depressed individuals with TLE. This study examined the relationship between white matter integrity (WMI) and depression including the influence of age at seizure onset, in adults with TLE, TLE and depression, and depression only.
Methods: Thirty-one adults were in one of three groups: TLE without depression (TLE; n = 11), TLE with depression (TLE + DEP; n = 9), and depression without TLE (DEP; n = 11). Participants completed structured interviews for depression diagnosis and severity. White matter integrity was estimated based on fractional anisotropy (FA) calculated in frontotemporolimbic (FTL) and non-FTL regions in the JHU DTI atlas.
Results: In adults with TLE (n = 20), depressive symptomology was significantly correlated with FA in non-FTL regions and trended toward significance in FTL regions. These associations were found in FTL (statistically significant) and non-FTL (trended toward significance) regions in participants with childhood seizure onset but not in those with adolescent/adult seizure onset.
Conclusions: Current results suggest that WMI, within FTL and non-FTL regions, are associated with depressive symptomology in adults with TLE. This association may be most notable in those with childhood-onset epilepsy. These findings could have important implications for the conceptualization and clinical care of neuropsychiatric comorbidities in TLE.

1. Introduction

Depression is the most frequently occurring neuropsychiatric comorbidity in epilepsy with up to 55% of individuals with epilepsy experiencing a depressive disorder in their lifetime [1–3]. Although this epilepsy–depression link was previously conceptualized as a reaction to psychosocial stressors (e.g., life obstacles, stigma), it is now hypothesized that a shared neurobiologic pathogenic mechanism contributes to depression in epilepsy [2,4]. One possible mechanism is white matter (WM) abnormalities, as both Major Depressive Disorder (MDD) and Temporal Lobe Epilepsy (TLE) are independently associated with WM abnormalities as assessed by diffusion tensor imaging (DTI) [5–8].

Three recent meta-analyses of DTI markers of WM integrity (WMI) in MDD have identified decreased fractional anisotropy (FA; higher values generally interpreted as indicating greater white matter coherence) in the superior longitudinal fasciculus (SLF) [5], frontooccipital fasciculus (FOF) [5,6], genu/body of corpus callosum (CC) [6,8], left anterior limb of the internal capsule [8], right inferior longitudinal fasciculus (ILF) [6], and right posterior thalamic radiation [6]. Severity of MDD has been specifically associated with decreased FA in the genu of CC [8]. Further, decreased FA in the solitary tract [9] and increased FA in the corticospinal tract [10] have been reported in MDD compared to controls.

Similarly, a meta-analysis examining WM changes in TLE identified FA reductions and mean diffusivity (MD) increases in the multiple of WM regions (primarily bilateral), including anterior CC, cingulum, external capsule, uncinate fasciculus (UF), and ILF [7]. MD indicates the average magnitude of water diffusion in an image voxel. Higher MD values indicate greater average magnitude of diffusion and are generally associated with lower white matter coherence. One recent study examining the depression–epilepsy link utilized DTI and found increased depressive symptoms in the 21 adults with TLE were associated with lower FA in UF and higher MD in the hippocampus [11].

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Epilepsy is highly prevalent across the lifespan and can involve child-specific (e.g., slowing or halting of development) and adult-specific (e.g., accelerated aging) consequences [4]. Prior studies have identified neural differences between early-onset (EO) and late-onset (LO) TLE, with patient with EO TLE showing lowered hippocampus connectivity [12], elevated diffusion coefficient in ipsilateral hemispheric and temporal lobe white matter [13], gray matter excess (primarily frontal) [14], and hippocampal abnormalities [15]. WM differences have also been identified in EO/LO MDD, with EO showing increased FA, yet LO showing decreased FA in various frontotemporolimbic (FTL) regions [16].

These findings of altered white matter integrity (WMI) in mainly, but not exclusively, FTL regions in both TLE and in depression provided the motivation for the current study. To better understand functional neuroanatomy for the bidirectional relationship between TLE and MDD, we sought to identify the potential role of white matter in comorbid TLE and depression. A secondary objective was to examine the influence of age at seizure onset on the association between depression and WMI. We examined WMI using the DTI-derived metric of FA in FTL regions previously shown or hypothesized to be involved in TLE and depression. Participants were adults with TLE, both TLE and depression, or depression only. To assess the specificity of our FTL hypothesis, we examined group differences in FA and DTI in select a priori non-FTL regions including supratentorial projection fibers and one subtentorial fiber bundle.

Our overarching hypothesis was that decreased WMI in FTL regions would be associated with greater severity of depressive symptoms in adults with epilepsy. Specifically, we hypothesized the following: 1) that depression severity would be associated with FA in FTL regions; 2) that depression severity would be unassociated with FA in non-FTL regions; and 3) that depression–white matter associations will show inconsistencies by age of epilepsy onset (i.e., child vs. adolescent/adult). Our analysis is limited to fractional anisotropy. This DTI scalar metric provides information about white matter structural integrity [17] and is the most widely reported measure of WMI. The decision to focus on FA is consistent with our goal of examining WMI in relation to depression in TLE and non-TLE, and our relatively small sample. FA is influenced mainly by axonal membranes; myelin and axon numbers, size, and packing density playing secondary roles [17].

2. Methods

2.1. Participants

Thirty-one adults underwent brain imaging, including MPRAGE and DTI, as part of participation in a study examining the relationship between TLE and depression. Participants were divided into three groups: TLE without depression (TLE; n = 9), TLE with depression (TLE + DEP; n = 11), and depression only without TLE (DEP; n = 11). Individuals in the two groups with depression (TLE + DEP and DEP) were required to meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria [18] for Major Depressive Disorder (MDD) or Dysthymic Disorder based on the *MINI International Neuropsychiatric Interview* (M.I.N.I.) [19]. All patients spoke English as their primary language. Patients with TLE (groups with TLE and TLE + DEP) were recruited from an outpatient neurology practice and were required to have complex partial (focal) epileptic seizures of definite or probable temporal origin, as defined by continuous video-EEG monitoring of spontaneous seizures demonstrating temporal lobe seizure onset. All participants with TLE had nonlesional causes for their epilepsy. The group with depression alone (DEP) was recruited from hospital-based outpatient psychiatry clinics and community advertisements. Exclusion criteria for all groups included presence of other neurologic conditions unrelated to the etiology of the seizure disorder (e.g., multiple sclerosis, Parkinson's disease, stroke, dementia), presence of intellectual disability, history of or current substance abuse (*DSM-IV* criteria), and a history of bipolar disorder or psychosis (*DSM-IV* criteria).

2.2. Procedure

Patients meeting criteria for inclusion were scheduled for an in office appointment and provided informed consent at the onset of their visit. Trained research staff administered cognitive measures. A neuropsychologist, blind to participants' cognitive performance, administered mood assessments. Chart review was conducted to obtain demographic variables and epilepsy characteristics. Participants were scheduled for MRI on the day of or within 1 month of the office appointment. The Rhode Island Hospital Institutional Review Board approved this study and its procedures.

2.3. Measures

The Hamilton Depression Rating Scale-21 (HAM-D) [20] is a 21-item, clinician-rated interview, that measures depression on a rating scale of 0–4, 0–3, or 0–2, depending on the specific item. The HAM-D was used as a measure of depression symptom severity. This study utilized the total score, with higher scores indicating greater depressive symptomatology.

The two-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI) [21] was administered to obtain a brief measure of intelligence to characterize the sample and to ensure that groups were matched on global cognitive skills.

2.4. Diffusion tensor imaging

DTI data were collected on a Siemens 1.5 T scanner with 6 diffusion-encoding directions (b = 0, 1000 s^2/mm) FoV = 128 × 128, 40 slices, voxel dimensions 1.8 × 1.8 × 4.0 mm. The protocol was run three times resulting in three b0 volumes and 18 diffusion-weighted imaging (DWI) volumes (6 directions × 3 acquisitions). Diffusion tensor imaging data processing was performed in FSL 5.0. For each participant, a mean b0 volume (b0-mean) was constructed by first registering DTI acquisitions 1 and 3 to acquisition 2 using FSL FLIRT and then summing and averaging the registered volumes. To improve signal-to-noise, the three DWIs for each of the six diffusion-encoding directions were separately registered using FLIRT to the mean b0 volume (e.g., for acquisition 1 to b0-mean, acquisition 2 to b0-mean, acquisition 3 to b0-mean) and then averaged to obtain a mean DWI for each of the six directions. Eddy current correction was performed on the averaged data. To obtain mean fractional anisotropy (FA) for each person, DTIFIT was run. FA maps were then registered to standard MNI space.

White matter tracts were selected as regions of interest (WM-ROIs) a priori from the Johns Hopkins University White Matter Tractography Atlas provided in FSL [22]. Based on literature review [5–8], we selected WM-ROI to emphasize FTL connections with demonstrated or hypothesized involvement in TLE or in depression. Frontotemporolimbic regions were corpus callosum (genu, body, and splenium), cingulum (hippocampal & cingulate gyrus portions), fornix (column and body & crus component/stria terminalis), superior longitudinal fasciculus, and uncinate fasciculus. Superior longitudinal fasciculus is characterized as FTL, although we recognize this pathway links frontal, parietal, and temporal regions, which we selected based on prior association with depression. Based on literature review, we selected 3 non-FTL control regions based on hypothesized lesser involvement in either depression or in TLE. These included three supratentorial regions: corticospinal tract, and cerebral peduncles, and one infratentorial region, the pontine crossing fibers. We included the sagittal stratum (inferior longitudinal fasciculus and inferior frontooccipital fasciculus), but did not include it in a composite score as it is a non-FTL region that has previously been shown to be associated with depression [23]. Individual WM-ROI masks were applied to each participant's FA volumes to obtain mean FA for each region. Two composite scores (means) were computed for FA in FTL and non-FTL regions (e.g., FA summed across all FTL regions

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