The Scale of Neurodegeneration in Moderate-to-Severe Traumatic Brain Injury: A Systematic Review of Longitudinal Studies

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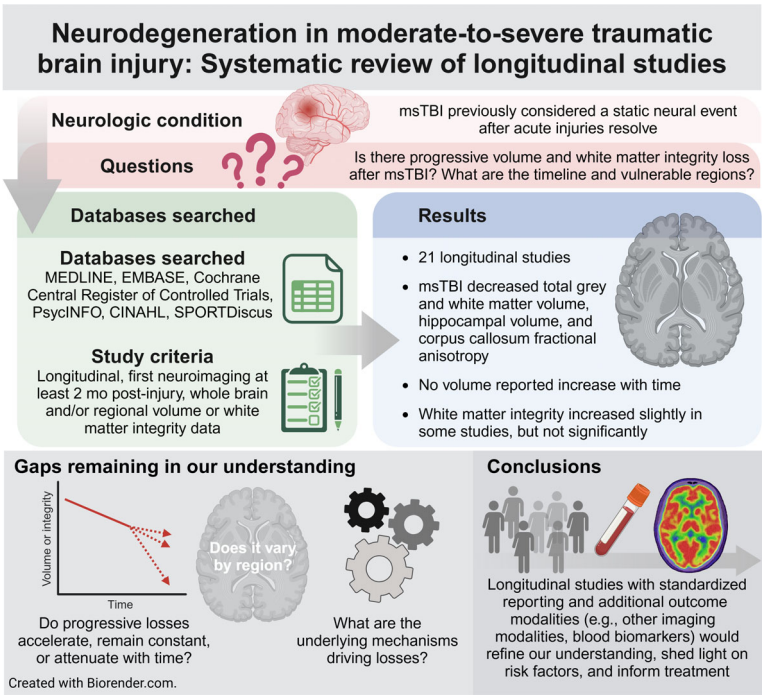

Synthesis of Literature: Neurodegeneration in Moderate-Severe TBI.

Objective: Although moderate-to-severe traumatic brain injury (msTBI) was once considered a static neural event following resolution of acute injuries, numerous studies now demonstrate progressive losses to volume and white matter integrity in the months and years postinjury, leading to a paradigm shift in our understanding. These findings have yet to be synthesized. Therefore, our objective was to assimilate longitudinal studies of chronic msTBI to better elucidate the scale and timelines of neurodegeneration, regions of vulnerability, and ongoing gaps in the literature.

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Additional supporting information can be found in the online version of this article.

Methods: As per our published systematic review protocol (see PROSPERO CRD42019117548), 6 electronic databases were searched from inception to June 2024. Included studies examined adults (> 17) with msTBI, were longitudinal with first acquisition at least 2 months postinjury, and reported whole brain and/or regional volumetrics or fractional anisotropy (FA).
Results: We identified 21 studies, with and without controls, and computed annualized percent change for the limited studies with overlapping regions and timelines with sufficient data. Overall, widespread progressive volumetric and FA losses were observed, with no evidence of accelerated progression across time. No volumetric but some FA increases (predominantly nonsignificant) were observed. Annualized percent changes in ascending order were: total grey matter volume (−0.28%), total white matter volume (−0.65%), hippocampal volume (−1.98%, bilaterally), and corpus callosum FA (−3.15%).
Interpretation: Gaps in our understanding include mechanisms of degeneration, whether progressive losses remain constant or attenuate with time, and how patterns vary by region. Longitudinal research with 3 timepoints, standardized reporting, and additional outcome modalities (eg, functional magnetic resonance imaging [fMRI], and blood biomarkers) would refine our understanding and inform treatment research.

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Moderate-to-severe traumatic brain injury (msTBI) is prevalent, disabling, and ubiquitous,[1–3] with an estimated 1% of the global population living with long-term TBI-related consequences.[4] As such, msTBI is now understood as a chronic disease, and it is associated with low life satisfaction,[5] elevated depression and anxiety,[6–8] as well as social isolation,[9] suicidality,[10] and homelessness.[11] Research into the enduring effects of TBI has been increasing as public awareness of its long-term impacts has grown. Accordingly, working groups have been created to better understand, prevent, and manage this injury to reduce its burden.[12–15] Despite this, our capacity to improve recovery has been modest.[16]

A likely contribution to these poor long-term outcomes is neurodegeneration.[17] The relatively recent reconceptualization of msTBI as a neurodegenerative disorder challenges[18] the traditional assumption that msTBI follows a stable neurological course after the resolution of acute brain damage. However, there is now extensive evidence that msTBI is a progressive disorder, with degeneration of grey and white matter in the months and years postinjury,[5,6,19,20] alongside evidence of post-recovery behavioral decline in the chronic stages.[21,22] Moreover, focal neurodegeneration within a region of interest (ROI) putatively disrupts network connectivity of the parent network, leading to even broader neurological and behavioral sequalae.[23–25] Arguably, this view that msTBI is a progressive disorder is not yet widely accepted in clinical contexts – where it is assumed that any early gains in recovery are maintained into the later chronic stages.[26]

Importantly, this reconceptualization opens new avenues for treatment research and development. However, developing interventions to offset declines and improve outcomes requires answering key questions about neurodegeneration, such as what regions experience neurodegeneration, to what extent, and when. The large number of studies that have revealed evidence of neurodegeneration following msTBI vary considerably with respect to design, time of imaging, and regions studied, among other factors. This creates disparities between study findings. For example, some studies report that neurodegeneration occurs in up to 95% of patients with msTBI,[27] whereas others report deteriorative brain changes in approximately half of their sample.[28] Therefore, a consolidation of evidence is needed to begin to answer these key questions.

Accordingly, we performed a systematic review that aimed to improve our understanding of the scale and patterns of neurodegeneration in msTBI. Our specific aims were to better understand: (1) the scale or magnitude of structural neurodegeneration following msTBI, (2) the timelines of degeneration, and (3) the patterns of these findings with respect to (i) volumetric changes, operationalized as annualized percent change where possible, and (ii) white matter integrity changes (as measured per fractional anisotropy [FA]). We also aimed to understand and characterize gaps and limitations in the current literature, to help inform future research in the field. Finally, we offer methodological recommendations for future research to allow for better comparisons between studies.

Methods

Our systematic review methods have been described in detail in a previously published protocol paper[29]; a PROSPERO submission (CRD42019117548) associated with this review was also published prior to beginning our search. This study is reported as per the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (Supplementary Data S1). The methods are described below in brief.

Our search strategy (using medical subject heading [MeSH] and text keywords) was developed under the guidance of a health sciences librarian, and included 2 search sets, namely, one related to traumatic brain injury and

the other pertaining to neurodegeneration. The search was run in 6 health sciences databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PsycINFO, CINAHL, and SPORTDiscus), from inception to May 2024, adapting the syntax of the search as appropriate for each database. All search results were collated (with duplicates removed), and imported into *abstrackr*,[30] an online tool for article screening. Screening was performed in 2 rounds: first, the titles and abstracts were screened by 2 reviewers (authors L.M. and A.C.) independently for relevance, and, second, articles that passed the initial screen were evaluated in full for final inclusion by the same 2 reviewers. Throughout the screening process, conflict resolution was performed with another author (author B.S.) serving as arbiter; any screening discrepancies were resolved with the arbiter re-examining the article against the a priori inclusion/exclusion criteria. Briefly, studies were included if they studied adults (aged 18–65 years) with msTBI in the post-acute stages of injury. No limitations were placed on design, and both cross-sectional and longitudinal studies were included. However, given the heterogeneity of the data, a post hoc decision was made to include only longitudinal studies given the sufficient volume of these studies and their ability to better capture changes over time. Nonetheless, data on the cross-sectional studies (which do not permit an understanding of neurodegenerative change across time) are provided in the online supplement (Supplementary Data S2). Studies that exclusively studied milder brain injuries were excluded, as were those that used animal models (Fig 1). We included English language studies only, although no studies were excluded on the basis of language.

The 2 independent reviewers then extracted data from the final sample of articles using an extraction sheet developed by the senior authors. Data presented descriptively, as meta-analysis was not possible given that the studies used different units of measurement, and the time period of the studies varied considerably. Study quality was appraised by 2 authors (B.S. and L.M.) in accordance with the NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[31] (Supplementary Table S3).

Results

Based on our search, we identified 12,754 studies. Of these articles, 10,198 remained after the duplicates were removed. Overall, 155 articles passed the title and abstract screening. Subsequently, at the full-text level, 134 articles were excluded leaving 21 longitudinal studies in our final sample, with a median publication year of 2014 (2008–2023). As detailed below, the samples were predominantly male subjects, which is consistent with the demographics of this population, and focused on adults with an average age of 34 years.

Our results are reported in 2 sections, based on study design: longitudinal without controls, and longitudinal with controls. (Please see Supplementary Data S2 for the results for the cross-sectional study findings, which were retrieved incidentally through our search given it did not filter based on study design.) Dividing the results in this manner permits a more direct comparison between similar studies and makes findings more interpretable.

In some cases, original findings were reported without absolute values and/or in images (eg, imaging "heatmaps" demonstrating regions of change or graphically as scatter or bar plots, without a supporting table providing specific values), which precluded extraction of between-group or percent change values; instances of this are noted in each results table. Further, given that the unit of measurement was not consistent across studies (eg, volumetric studies may have measured regional) and/or brain changes in cubic length units (ie, mm^3, cm^3) or units of volume (eg, mL), we report the original published values as well as a percent change or difference score, the latter of which was calculated by the review authors. Providing the percent change or difference values where possible, permits a more direct comparison across studies.

Importantly, variations in the temporal gaps between studies (eg, some studies conducted their baseline and follow-up assessments within months of one another, whereas other studies had gaps of several years) may inflate or minimize the actual differences in percent change between the studies. For a subset of studies and regions where there were sufficient data to collate, we were able to calculate annualized percent change, which helps to obviate this limitation. Specifically, this was calculated for data from longitudinal studies with controls, as this is the only design-type that permitted a between-group (ie, msTBI vs healthy) comparison over time. We also performed "min-max" scaling to findings, to handle heterogeneity in reporting units, as appropriate, and represented these data in figures. Studies in each table are ordered with respect to the time of the magnetic resonance imaging (MRI) assessment. Therefore, studies with assessments during the early stages of injury (minimum of 2 months postinjury) are presented first, followed by those where the first imaging was performed later postinjury. This permits easier interpretation of degenerative changes from a temporal perspective (that is, to understand whether there is increasing, decreasing, or consistent atrophy in the early vs later chronic stages of injury).

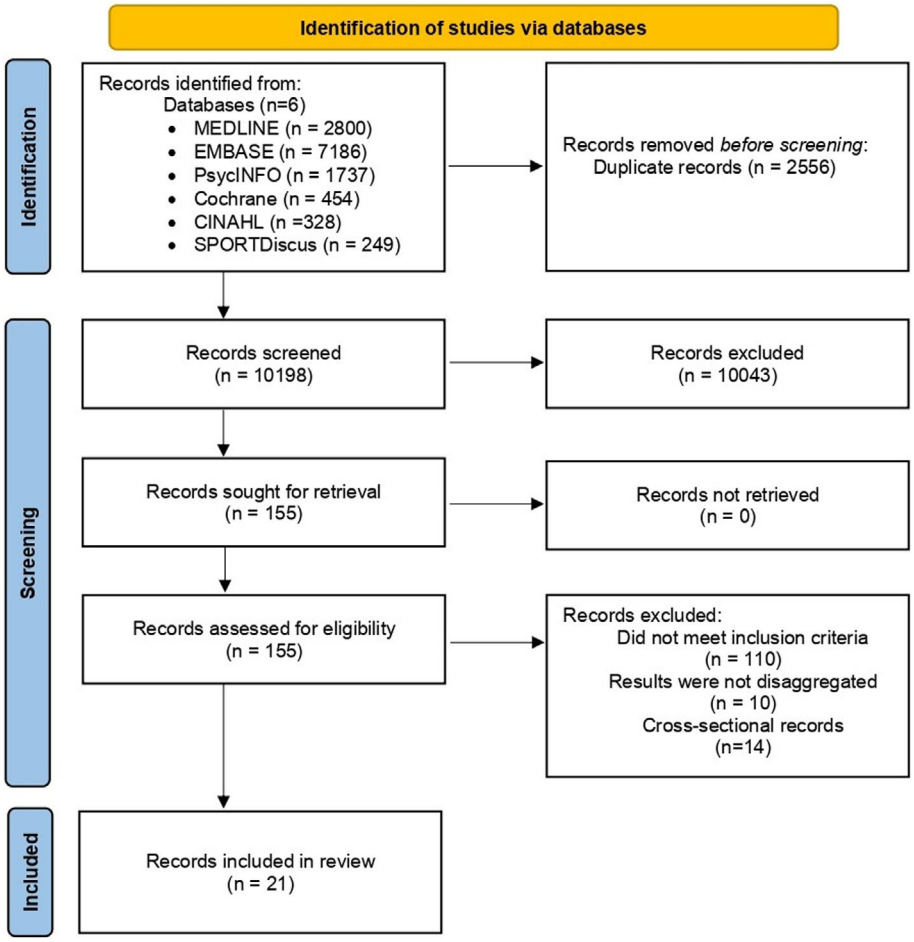

FIGURE 1: The PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened, and the full texts retrieved. Records that met the inclusion criteria but provided volume or FA data combined across mild, moderate, and severe TBI groups, without disaggregating the results for each group (or at least stratifying between mild TBI and msTBI), were categorized as "Results were not disaggregated" and excluded. FA = fractional anisotropy; msTBI = moderate-to-severe traumatic brain injury; PRISMA = preferred reporting items for systematic reviews and meta-analyses; TBI = traumatic brain injury.

Longitudinal Studies without Controls

Six studies without controls (published between 2008 and 2021; N = 153; 4 with overlapping samples[28,32–34]) longitudinally examined changes following msTBI (Figs 2A,B). On average, baseline imaging was performed at 3.52 months (SD = 1.99) postinjury, with a second measurement taken at a mean of 18.4 months (SD =12.7) postinjury; 33% of studies included a third timepoint, where imaging was performed, on average, at 12.1 months (SD = 0.27) postinjury. It should be noted that the 3 timepoint studies typically performed all assessments within the first year of injury (hence the third scan at 12.1 months), whereas the 2 timepoint studies sometimes performed the second scan beyond 1-year postinjury (yielding an average assessment time of 18.4 months). The mean age of study samples was 34.3 years (SD = 4.26), and samples were predominantly from male subjects. Average years of education was 12.9 years (SD = 1.56) per the 5 studies that reported on this information. Across all studies, motor vehicle collisions were the most common mechanism of injury, accounting for at least 50% of injuries. Details are summarized in Supplementary Table S1. All studies were deemed to be of "good" quality (ie, the highest quality rating) per our evaluation (see Supplementary Table S3).

Overall, these non-controlled longitudinal studies consistently demonstrated volumetric decrements across time in the chronic stages of msTBI and numerous declines in FA, and only 1 observation of improvement (insular gyrus) and 2 of stability (insular gyrus and postcentral sulcus).

With regard to how frequently specific structures were examined, the limbic system structures, including the hippocampus and fornix, were among the most commonly studied region. Hippocampal volumes were consistently found to decrease over time, although with the

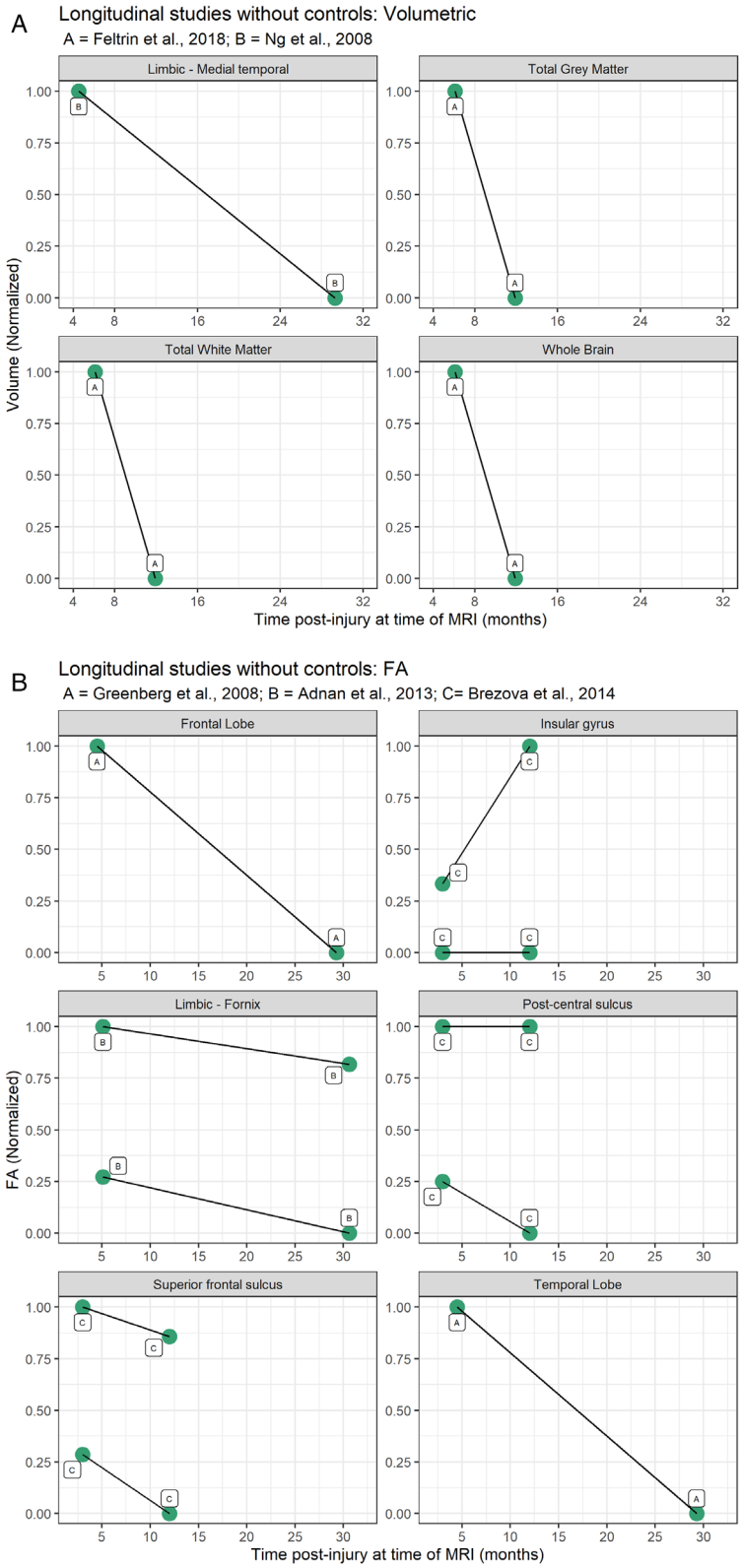

FIGURE 2: (A) Longitudinal within-subject data for studies that reported raw volumes at each timepoint, with figures plotting normalized volume (by means of minmax scaling) by time postinjury, categorized by region. See Supplementary Table S1 for more detail on the individual studies for which percent difference could be calculated.[28] A single study reported on raw CSF volumes, but these findings are not reported in the figure above, in order to focus on parenchymal brain volumes. (B) Longitudinal within-subject data for studies that reported raw volumes at each timepoint, with figures plotting normalized FA (by means of minmax scaling) by time postinjury, categorized by region. See Supplementary Table S1 for more detail on the individual studies for which percent difference could be calculated. FA = fractional anisotropy.

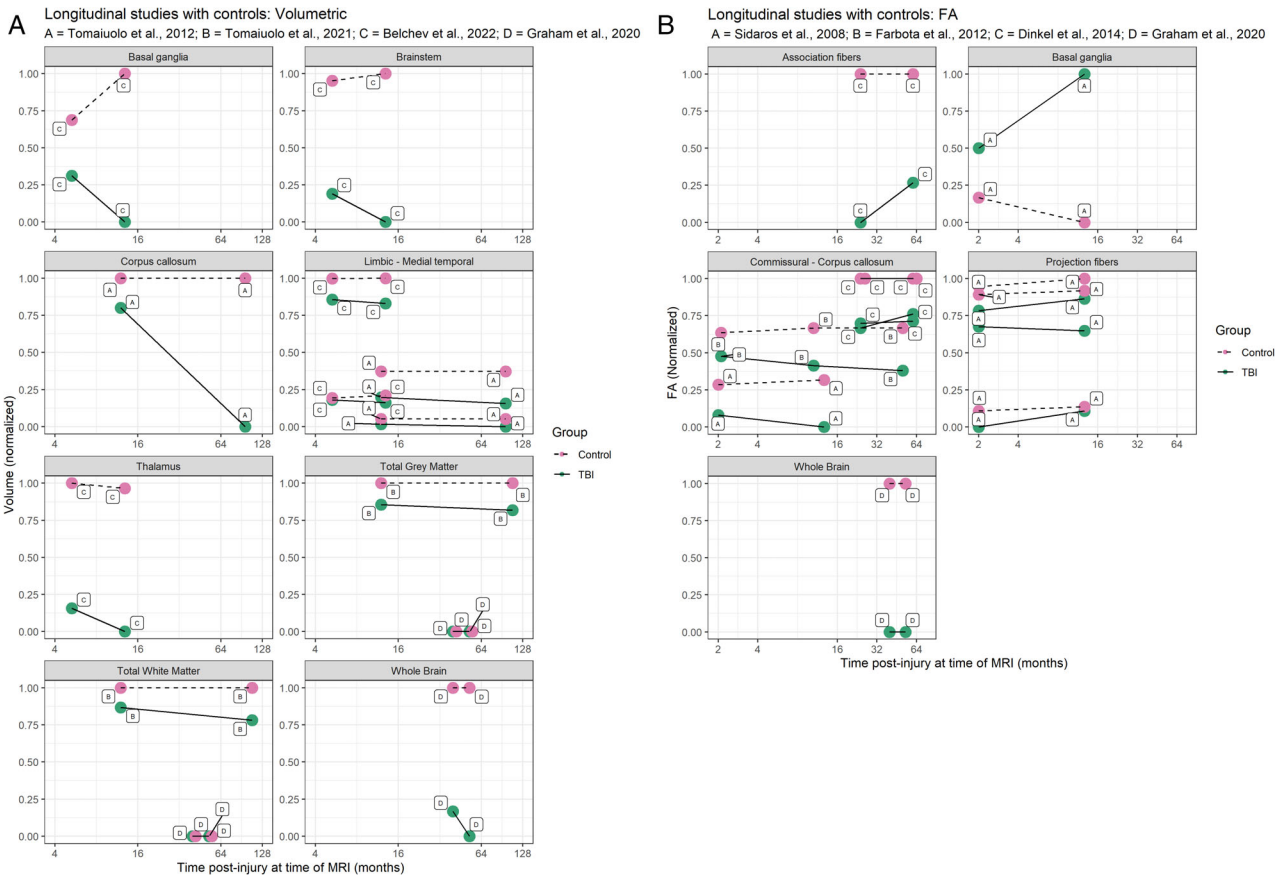

FIGURE 3: (A) Longitudinal data plotting normalized (per minmax scaling) volume for msTBI and healthy controls by time postinjury, categorized by region for studies that reported raw volumes at each timepoint. See Supplementary Table S2 for more detail on the individual studies for which percent difference could be calculated. The x-axis has been log-scaled to improve figure readability. (B) Longitudinal data plotting normalized (per minmax scaling) FA for msTBI and healthy controls by time postinjury, categorized by region for studies that reported raw volumes at each timepoint. See Supplementary Table S2 for more detail on the individual studies for which percent difference could be calculated. The x-axis has been log-scaled to improve figure readability. Where one paper has more than one structure represented within a figure above, we have included a superscript coding. FA = fractional anisotropy; msTBI = moderate to severe traumatic brain injury.

degree varying between study samples.[28,33,35] One paper found that white matter showed greater reductions in severe TBI compared to moderate TBI.[35] Another study reported that the monthly rate of total white matter volume reduction was greater during the 6 to 12-month interval rather than the 2 to 6-month interval (0.68% per month vs 0.25% per month, respectively).[36]

With regard to white matter integrity, one study measuring outcomes at 5 and 30 months postinjury, found that the right and left crux of the fornix decreased in FA by 5.70% and 5.40%, respectively, with the fornix body decreasing by 10.7%.[34] Another study by the same group using overlapping patients reported bilateral reductions in FA in both the frontal and temporal lobes[32] across the same timepoints.

Longitudinal Studies with Controls

There were 15 studies with control groups (published between 2008 and 2024) that longitudinally examined degenerative changes in msTBI; 8 of these had overlapping samples (Figs 3A,B).[27,37–43] On average, baseline imaging was performed at 8.3 months postinjury (n = 538, SD = 16.93), with a second measurement taken at 33.6 months postinjury (n = 482, SD = 14.4). Four studies included a third measurement, where imaging was performed, on average, at 35.95 months postinjury (n = 121, SD = 17.1). At baseline, the mean age of the individual samples was 39.7 years (SD = 5.5), and the samples were predominantly from male subjects. In 8 studies that reported on this information, the average years of education was 15.27 years (SD = 3.38). Across all studies, motor vehicle collisions were the most common mechanism of injury (44% or greater). Whereas all studies presented below included a healthy control group, only 8 studies matched the controls on age and sex. Within each study, we reported first on its cross-sectional findings and then on its longitudinal results (eg, if a study performed measurements at 5 and 12 months postinjury,

we reported between-group differences cross-sectionally for both the 5- and 12-month timepoints, and then the longitudinal change from 5 to 12 months, relative to change in the control group). Details are summarized in Supplementary Table S2. All longitudinal studies were of "fair" or "good" quality, with none evaluated as being of "poor" quality (see Supplementary Table S3).

Overall, these longitudinal controlled studies consistently found decrements in the volumetric studies in patients versus healthy controls. Notably, in diffusion tensor imaging (DTI) studies, there was comparable FA decline, increase, and stability across time in patients compared with controls.

With regard to the most commonly assessed volumetric structures, this was similar to studies reported on in the prior section. Namely, the primary global volumetrics assessed pertained to total brain volume (in mL or as a percent of intracranial volume) which were calculated to be 6.3% to 8.8% lower in patients with msTBI versus controls (see Supplementary Table S2 for details on study populations and timing of assessments). Total grey and white matter volume (again in units such as cm^3 or as a percentage of intracranial volume) were also assessed, with a broader range of groupwise change (for msTBI vs controls, the calculated percent change ranged from 1.7% to 9.2%). Of note, the percent change values calculated based on data from one study examining sTBI specifically[40] approached nearly 25% at long-term follow-up. The regions of study were also similar, with studies most frequently examining changes in the hippocampus, amygdala, corpus callosum, and brainstem structures.

With respect to the timelines of neurodegeneration, and whether there is greater degeneration in the earlier or later chronic stages of injury, there were 3 longitudinal, controlled studies measuring a common region (whole brain volume change). Each of these studies examined volume change at a different time window, and, helpfully, the time between assessments within each of the studies was of comparable duration. In one study, within-group analyses showed that from 2 to 12 months postinjury, the brain volume was reduced by 4.00% and 0.18% in the TBI group and the controls, respectively.[44] A second study, measuring from approximately 12 to 22 months postinjury, found that whole brain volume loss was 1.51% in the TBI group compared to 0.22% in controls,[37] reflecting less total brain volume loss in the later chronic stages of injury than the earlier chronic stages. The third study, examining even later postinjury, from approximately 40 to 53 months postinjury, found whole brain volumes of patients (measured as the percentage of intracranial volume) with respect to healthy controls was reduced by 6.3% at approximately 40 months postinjury and 7.6% at approximately 53 months postinjury.[38] Taken together, these 3 studies do not provide evidence that magnitude of degeneration is accelerating from the early to the later stages of injury.

There are 3 studies (examining different metrics) that included 3 neuroimaging timepoints, which again potentially permitted exploration of whether the extent of degeneration increases or decreases as we move further postinjury. One study by Brennan and colleagues[45] examined total white matter, total ventricular volume, and cerebellar volume from 3 to 6 to 12 months postinjury, each as a percentage of intracranial volume. Total white matter volumes were 22.33% (3 months postinjury), 22.01% (6 months postinjury) and 21.58% (12 months postinjury), with statistically significant decline between the first and third timepoints. Ventricles showed the same pattern across time (17.46% to 17.86% to 17.94%), with significant decline from the first to the third timepoint. Although absolute volumes declined across the 3 timepoints in the cerebellum (7.67% to 7.64% to 7.56%), no changes were significant. The absence of statistically significant change across the first 2 timepoints in these studies unfortunately precludes inferences about change across time. Farbota and colleagues[43] studied white matter of the genu over 3 assessments (at approximately 2, 12, and 52 months postinjury), reporting FA values of 0.67, 0.63, and 0.61 at each of these timepoints, respectively, with significant groupwise differences (in comparison to healthy controls) at each of these timepoints. Lastly, Belchev et al[41] examined volumetric changes in cortical and subcortical regions at approximately 5, 12, and 33 months postinjury. They reported that patients with sTBI had significantly greater monthly percent change decreases in the accumbens and marginally greater percent declines in the amygdala, brainstem, thalamus, and the left hippocampus as compared with healthy controls from 5 to 12 months postinjury. Further, the slopes from 5 to 12 and from 12 to 33 months postinjury did not differ significantly in the patients, indicating ongoing atrophy, without evidence of acceleration or deceleration. Together, these data suggest that neurodegeneration in patients with msTBI continues beyond the first year of injury, but there is no evidence that rate of degeneration increases across time (and as patients get older).

Similar to the longitudinal studies without controls, the limbic system structures showed notable volume reductions. For example, over a 7-year period from approximately 1 to 8 years postinjury, Tomaiuolo et al found (per a within-subjects analysis) that the volume of the left and right hippocampi of the TBI group decreased by 7.60% and 10.6%, respectively.[42] In this same study,

between-group comparisons to controls at approximately 1 year postinjury showed that hippocampal volume was approximately 33% less in the TBI group versus the healthy control group, a difference that increased to approximately 43% by 8 years postinjury.[42] However, it should be noted that we cannot ascertain when during this period this extensive volume loss occurred.

Global and regional losses to white matter integrity were observed in 3 longitudinal studies with controls. Across all studies, between-group analyses showed that the TBI group had reduced FA values compared with the healthy controls, at timepoints ranging from approximately 2 to approximately 60 months postinjury. A series of large, within-group analyses showed that white matter integrity deteriorated from earlier to later timepoints, with the exception being the posterior limb of the internal capsule and centrum semiovale, which showed increases in FA of 4.70% and 11.4% from 2 to 12 months postinjury, respectively.[46] As a percentage of intracranial volume, white matter was shown to decrease by approximately 3.5% in patients with msTBI from 3 to 12 months postinjury.[45]

In the Table, we present annualized percent change values for ROI for which we had data from at least 2 studies to permit collation, namely total grey, total white, and hippocampal volumes, and corpus callosum FA. We report an unweighted annualized percent change (computed as a simple average of values reported in multiple studies, unadjusted for sample size), as well as a weighted annualized percent change (which is weighted based on the sample size of each study).

It is also important to note some methodological considerations that were not captured in the table above. Namely, the paper by Farbota and colleagues had a full sample of 46, although only 35 had usable neuroimaging data at both timepoints. The Tomaiuolo et al[42] paper collected neuroimaging data on controls at baseline, but used this as a comparison for both timepoints, which therefore did not control for aging-related changes. They also had a larger sample of 16 at the first assessment, but only 11 for the second assessment. In the 2021 paper by Tomaiuolo et al,[40] the control values were taken as a mean across timepoints. Attrition in the Sidaros et al 2008 paper[46] resulted in 30 patients and controls being assessed at baseline, but 23 patients and 14 controls, respectively, at follow-up. The paper by Farbota et al[43] reported on other regions and white matter tracts in MRI figures, but those data were not extractable for Supplementary Table S2. Last, the Kumar et al[47] paper reported on "hemorrhagic diffuse axonal injury DAI" versus "non-hemorrhagic DAI," with only the latter included in this review.

Discussion

With robust atrophy observed across whole brain and regional measurements, both in the early and later chronic stages of injury, this review provides further support for the reconceptualization of msTBI as a progressive neurodegenerative disorder as we have previously contended,[17,18] challenging the prevailing clinical assumptions of stability throughout the chronic stages of injury. A number of groups have now independently reported on progressive volume and white matter integrity losses across time in patients with msTBI out to more than 10 years postinjury. This systematic review is the first to consolidate the evidence base of longitudinal studies of neurodegeneration in msTBI, and comparisons across studies raise empirically testable questions for future research, as discussed below.

Scale and Patterns of Neurodegeneration

Two types of longitudinal studies were examined in the review, those with and without controls. The six longitudinal studies without controls reported similar timelines of assessment, with the first imaging assessment performed between 3 and 6 months postinjury, and the follow up scan completed between 12 and 30 months postinjury. Significant progressive volume and FA declines across time were widely reported. These comparable timelines of assessment permit a coarse comparison of change across different regions. Volumetric declines ranged from < 1% (cortical grey) to 8% (cerebrospinal fluid [CSF]) across studies. Changes in white matter integrity, measured by FA, varied widely, from 0% change (in the post central and insular gyri) to declines of over 21% (in the right frontal and temporal lobes), raising the question of disproportionate progressive vulnerability of anterior and superior white matter. Given the vulnerability of this broad brain region in acute msTBI, the findings further speak to the question whether those regions with greater acute injury are more susceptible to ongoing demise. Our group, for example, found local expansion of lesions in the chronic stages of injury (see Ng et al[28]) suggesting that localized mechanisms, such as protracted immune activation, might propagate further compromise to tissue,[48] and, more recently (see Woodrow et al[49]), findings consistent with transneuronal degeneration from acute lesions within the thalamic nuclei were observed. As well, both Cole et al[37] and Brennan and colleagues[45] reported that neurodegeneration was more pronounced in cortical sulci than gyri, providing additional insight into the pattern of neurodegeneration. In addition to ROI-based analyses, future studies are encouraged to examine differences in sulci and gyri, to build on the insights offered by the aforementioned studies.

In addition to the longitudinal studies above, there were 15 longitudinal studies with controls. Here, annualized percent change values could be computed for a subset of studies, providing a more precise characterization of progressive brain changes (see the Table). Annualized percent change calculations were possible for 4 brain regions drawn from 7 studies.[38,40–43,46,50] The unweighted and weighted values illustrated the same pattern: the highest percent decline across time was in corpus callosum FA, followed by hippocampal volume, followed by total white matter volume, and then followed by total grey matter volume. Overall, these annualized values ranged from −3.15% and −5.69% (corpus callosum FA, weighted and unweighted, respectively) to −0.28% and −0.09% (total grey matter, weighted and unweighted, respectively).The relative vulnerability of the corpus callosum indicated by these calculations could represent disproportionate vulnerability of all white matter more broadly. However, this explanation is mitigated by volumetrically similar findings observed for the corpus callosum by Tomaiuolo et al,[42] whose data allowed us to compute a percent difference between the TBI group and the healthy control group of 10.5% at 12 months postinjury, increasing markedly to 66.6% at 96 months postinjury. As well, Green and colleagues,[27] examining the corpus callosum at the single case level, found differences in the proportion of patients with progressive volume loss within its substructures, with 45.4% showing losses in the genu and 75.0% showing losses in the body and the splenium. Such granular differences again do not support the idea of a general vulnerability of white matter as opposed to the corpus callosum, and perhaps even specific regions of the corpus callosum, more specifically. Nonetheless, further prospective research is needed given that Dinkel et al[50] found contrasting findings in the corpus callosum to those above. Based on their data, we calculated the percent differences in FA values between the TBI group and the healthy control group of 23.5% at 24 months postinjury, but only 16.2% at 60 months postinjury. Overall, these findings raise the hypothesis for future research that (i) the corpus callosum, the largest structure of the brain, and a wholly white matter structure, may be disproportionately vulnerable to progressive decline in the chronic stages of msTBI, which (ii) may be related to its disproportionate vulnerability in the acute stages of injury.[51]

The neurodegeneration findings in the current review are compatible with those of large scale, multicenter cohort studies of msTBI (part of the ENIGMA initiative) that have examined brain age. More specifically, a recently published 7-cohort trial involving 343 patients with TBI (ranging from complicated mTBI to severe TBI) and 197 healthy controls, showed that the predicted brain age difference between the injury group and the controls increased with time postinjury.[52] A mean deviation of 5 years between brain age (modeled using T1-weighted anatomic images) and chronological age was observed. In their cohort, these changes were observable decades following a single injury. Such large-scale cross-sectional data support the findings of this review of volumetric neurodegeneration in the chronic stages of msTBI.

Timelines of Degeneration: Acceleration, Stability, or Attenuation Across Time?

Longitudinal, controlled studies that examined a common brain region across early and later time windows of roughly the same width (which was the case for whole brain volume) offered an opportunity to preliminarily elucidate timelines of neurodegeneration within the current review.[38] In the study with the earliest window of assessment of whole brain volume (from 2 to 12 months postinjury), the volume declined by 4.00% in the msTBI

TABLE. Annualized Percent Change, Based on Longitudinal Studies With Controls

	Region	Unweighted Annualized Percent Change	Weighted Annualized Percent Change
Volumetric – whole brain	Total grey matter	−0.28%	−0.09%
	Total white matter	−0.65%	−0.22%
Volumetric – regional			
	Hippocampi	−1.98%	−2.4%
White matter FA	Corpus callosum	−3.15%	−5.69%

The reviewers calculated annualized percent change as $\left[\left(\frac{\text{Volume at Timepoint 2}}{\text{Volume at Timepoint 1}}\right)^{\frac{1}{7}} - 1\right] \times 100$.

FA = fractional anisotropy.

group as compared to 0.18% in the healthy control group.[44] When the whole brain volume was assessed in a later window, from 12 to 22 months postinjury, there was greater progressive volume loss in the msTBI group versus controls (1.51% vs 0.22%, respectively),[37] but taken together, the 2 studies suggested an attenuation in the rate of decline. Finally, whole brain volume loss examined from 40 to 53 months postinjury (operationalized as the percentage of the intracranial volume) was 6.3% and 7.6% in patients versus controls, respectively,[38] consistent with the hypothesis that rate of decline shows a possible tapering across time.

Another opportunity to study timelines was in studies with more than 2 outcome assessments of the same brain regions. There were 3 studies that included 3 neuroimaging assessments. These assessments included regional, volumetric monthly percent changes from approximately 5 to 13 to 33 months postinjury,[41] global volumetrics from 3 to 6 to 12 months postinjury,[45] and FA changes in the genu from 2 to 12 to 52 months postinjury.[43] Across these studies and the various metrics used, neurodegeneration was ubiquitously observed, and it continued across time, but again the data suggested attenuation across the timepoints, with a predominance of degenerative change within the first year of injury.

Clinical Implications

Given the observed suggestion of attenuation of degeneration across time, these findings suggest that the most vulnerable period postinjury, and one that may require more intensive intervention, is (approximately) the first year. As elevated anxiety[8] (see below) and reduced cognitive stimulation[53] within the first year of injury have been associated with progressive hippocampal volume loss, these offer candidate targets for prophylaxis research. Whether early intervention would mitigate degeneration in the years that follow requires study.

To date, there is limited research into the clinical and functional implications of the findings described in this review, but a recent study from our group showed that early progressive left hippocampal losses were predictive of greater cognitive (verbal retrieval) losses thereafter.[54] These findings, along with other evidence of progressive behavioral declines in the chronic stages,[21,53,54] and the increased risk of dementia that is associated with reduced brain volume, particularly of the hippocampi,[55] underscore the need for ongoing research and treatment in offsetting deterioration in the chronic stages of msTBI.

The clinical implications are particularly concerning in that the degeneration of a discrete ROI can have broader impact, if the ROI is part of a larger structural or functional network. For example, a recent longitudinal study of 35 patients with msTBI (assessed at a median of 16 and 194 days postinjury) and 35 healthy controls found greater structural network deviation in the injury group, and that acute structural network deviation was predictive of chronic functional outcome,[56] as measured with the Glasgow Outcome Scale Extended (GOSE). As well, studies have also shown that structural damage can lead to structural connectivity changes, resulting in compensatory changes in functional brain activity.[57]

Mechanisms

Understanding the cellular mechanisms of these deteriorative changes is needed to aid in the development of targeted clinical trials to improve msTBI outcomes. Candidate mechanisms of delayed grey and white matter losses in the chronic stages of injury include neuroinflammation[58–62] and oxidative stress, both of which can attenuate neurogenesis.[63] In line with this mechanism, our group found that after TBI, a higher level of anxiety—which has been associated with elevated neuroinflammation[64] —was unidirectionally predictive of subsequent progressive hippocampal volume loss.[8] Other candidate mechanisms include compromised microtubule transport[65,66] and compromised glymphatic system.[67] In addition, at the cellular level of analysis is the question whether cell death or transneuronal degeneration play a causal role in the volume losses observed or whether shrinkage of neuropil (eg, reduced spines, synapses, and arborization) and/or volume loss in cell bodies tied to reduced production of proteins and consequent reduction in cytoplasmic volume explain outcome variance.[68] A mechanistic understanding of these losses would aid in our understanding of the role of msTBI in the development of Alzheimer's disease and other dementias,[69] an area of active debate.

Gaps in our Understanding and Recommendations for Future Research

In completing this review, we were able to identify gaps in our knowledge with respect to the scale, patterns, and timelines of neurodegeneration. These are outlined below, along with recommendations for future research.

Scale. With respect to the scale of neurodegeneration, there is a large evidence-base which demonstrates that progressive volume reductions (globally and regionally) and decreases in FA are commonplace following msTBI. Absolute magnitudes of change could not be measured because of heterogeneity in reporting of volumes (ie, geometric units, cc^3 or mm^3 vs data reported as a percent of intracranial volume vs absence of raw values). We would encourage future researchers in this area to

report whole brain and regional volumetric data using geometric units (cc^3 or mm^3), as this would support meta-analysis and a better understanding of the scale of neurodegeneration.

Regional Patterns. Regarding the patterns of neurodegeneration across regions measured, studies focused disproportionately on some regions relative to others, which may introduce selection bias. Frequently studied regions included the corpus callosum, as well as limbic structures, which in some studies were the exclusive focus. Global measures of grey and white matter and CSF were also disproportionately studied.

As well, it is not clear as yet whether the spatial patterns observed in these predominantly group-level studies mask heterogeneity across patients, which is a cardinal feature of msTBI. Several studies have either examined at the single case level using longitudinal control data from within the study as normative indices (see Green et al[27]) or utilized mixed-effects modeling with random effects, which also offers a more granular understanding of the findings[35,37,45] and would allow for measurement of possible prognostic indicators of degeneration.[70] The studies above that used mixed-effects models generally reported that slopes (ie, rates of decline) were greater in the TBI group versus the healthy control group, and intercepts were also lower in the injury groups. Both of these approaches are recommended going forward, and our group is currently engaged in another systematic review[70] (in progress) that takes aim at understanding predictors of neurodegeneration. We also recommend the use of large-scale, longitudinal normative volumetric MRI data in healthy adults (eg, OASIS-3)[71] to facilitate measurement of change at the single case level. Another recommendation is the inclusion of multiple regions of measurement within all studies, and the development of a common set of regions. Logical selection principles would include those structures most commonly affected by msTBI and those structures commonly associated with functional/clinical consequences, for example, the corpus callosum, hippocampi, thalamic nuclei, temporal poles, and orbital and dorsolateral frontal regions. A benchmark typically unaffected region (eg, occipital) is also recommended.

Comparing and collapsing across studies is currently precluded by the inconsistency of metrics for reporting volumes. The reporting of volumetric data using geometric units (as above) would permit meta-analysis at a regional level and is thus recommended.

Last, given the gaps in comparisons across regions, a more detailed description of regions of interest would aid future research, specifically whether structures were manually segmented or segmented using atlas-based methods, given that regional volumes can differ by method of extraction.

Timelines. Currently, we do not have sufficient data to achieve more than a coarse understanding of timelines of neurodegeneration, as some timepoints are less well-studied than others, making temporality of change difficult to ascertain. Developing neurodegeneration trajectories will require additional longitudinal research that includes 3+ timepoints within the same study, all within the chronic stages of injury. These would ideally range from the early to late periods of injury, to elucidate aging-related changes.

Our review only analyzed neuroimaging data that were collected at >2 months postinjury, given that edema may not be resolved earlier postinjury. The resolution of edema can in turn influence (confound) measurement of volume loss that is caused by degeneration. We recommend that future studies consider the resolution of acute events prior to performing a baseline neuroimaging assessment.

Behavioral and Functional Imaging Neurological Correlates. We have demonstrated along with others that there are progressive cognitive declines in the chronic stages of injury when we examine samples at the single case level[21,22,72] and we have also demonstrated declines in executive functioning even at the group level.[73] However, very few studies have examined behavioral correlates of progressive neural declines (but see Green et al 2023[54]). We recommend concurrent measurement of cognitive function to compare to neuroimaging findings. The msTBI measures from the NIH Toolbox[74,75] Common Data Elements are recommended to facilitate comparison between studies.

There remains very limited understanding as to whether there are functional imaging declines concomitant with structural degeneration in msTBI, or whether there is functional compensation despite (or in response to) structural change. Future studies should use longitudinal functional imaging approaches such as functional MRI (fMRI) in parallel with structural measures to address these questions.

Sampling. In general, future research studies should aim to include more diverse samples, with (at minimum) a greater representation of female subjects. Recent systematic reviews have recognized that there are considerable sex effects in brain injury.[76–78] These sex differences may extend to differences in pathological features of brain injury, the biochemical response to injury, as well as recovery.

Limitations

The timepoints and regions studied as well as the imaging methods used varied considerably between studies, which precluded our ability to meta-analyze our findings. We were also unable to control for all salient demographic (eg, age, sex, and education) and clinical (eg, the lowest Glasgow Coma Scale [GCS] score and length of post-traumatic amnesia [PTA]) when reporting findings, as these variables were not reported for all studies; the values we reported are therefore not adjusted for these potential moderators. It is also important to note that some studies did not match for age and/or sex, whereas others did. We did not quantify this imbalance in matching and recognize it as a limitation of our work. In addition, we were unable to account for differences in MRI set up, which may have impacted the measurements reported in our review. In line with this, there are other imaging modalities (such as computed tomography [CT], positron emission tomography [PET], single photon emission computed tomography [SPECT], and spectroscopy) that can be used to measure and quantify changes in msTBI, but these data were not included in our review given its focus on MRI volumetrics and white matter changes. As well, the measures we included (namely FA) can be confounded by mechanical forces and associated neuroinflammation per animal studies,[79] and therefore FA changes may not reflect neurodegeneration per se, highlighting a potential limitation of this measure. Furthermore, given the heterogeneity in how data were reported, we were not always able to calculate the percent change (or difference), annualized or otherwise. However, given the number of studies reviewed, representing more than 1,000 patients (albeit with some overlapping cohorts), and that grey and white matter volume losses in addition to reduced FA were consistently reported, our review finds that even with heterogeneous methods there is considerable and consistent signal indicative of progressive deterioration in msTBI.

Conclusions

Our systematic review identified 21 longitudinal studies studying neurodegenerative changes in msTBI. We were able to begin to characterize the scale, patterns, and timelines of neurodegeneration in msTBI; we offered a series of specific recommendations to help to improve our understanding with respect to each of these areas, focusing in particular on the methods of reporting findings, and including a broad set of regions measured. Across the large majority of the studies, neurodegenerative changes were observed. These changes were observed when measuring whole brain metrics including total grey or white matter volume, or regionally (with an emphasis on the hippocampi and corpus callosum, 2 regions with the most reported data that allowed for collation). With respect to the timelines of neurodegeneration, we found evidence of change from the early (initial months postinjury) to late chronic (10+ years postinjury) periods of msTBI. Although the data we reviewed do not permit development of neurodegenerative trajectories in msTBI, we do have sufficient evidence to suggest that neurodegeneration in this population is not limited to a single (early) time window, although the findings indicate that the rate of atrophy does not accelerate over time, either stabilizing or decelerating from the early to later postinjury period. Our review consolidates the evidence base, which shows that neurodegeneration in msTBI is widely reported, whereas also identifying gaps in our understanding that still persist (primarily with respect to patterns and timelines of neurodegeneration). Future longitudinal research is required to address these gaps and better understand the mechanisms of neurodegeneration to thereby inform targets for intervention.

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Author Contributions

B.S., B.C., and R.G. contributed to the conception and design of the manuscript. L.M., A.C., and B.S. contributed to the interpretation of studies included in the manuscript. L.M., B.S., and R.G. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

The authors have no conflicts of interest to declare.

Data Availability

The data used to produce this review are available from the authors upon reasonable request.

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