Designing the reader's journal

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Neurology® 2016;87:962–963

In this issue, we present one vision of what *Neurology*® may look like in the future, side by side with our usual format.

The editorial and publishing teams hold a retreat on a yearly basis to discuss matters of common interest on actionable themes. Late last year we met to discuss "the journal of the future." Some have predicted the death of print by now; however, many of our readers, along with advertisers, still value the power of print. To rephrase, then: What should the print journal of the future look like?

Before describing the trial issue, it is worth taking a moment to consider context. The current design of the green journal is 10 years old. We have tweaked some aspects—the Table of Contents cover no longer exists, having given way to a graphic that is more easily translatable to apps or screen. The entire portfolio of American Academy of Neurology publications will soon be redesigned to provide a fresher look for our readers. At the time you read this editorial, the design companies will have been chosen, and the 1- to 2-year redesign process will have begun. But before a new look can be developed, it is important to know what the content will be. Determining the content and its format was the main focus of our retreat.

We heard from our publishers, and from representatives of other journals, who shared their thinking about redesign. What do readers want? It will likely come as no surprise that surveyed readers pay closest attention to titles (short, declarative statements, please, no questions) and to abstracts. Few read entire articles, though researchers may do so. *The BMJ* (in UK print editions) and *Science* now publish 1-page versions of articles for print, while publishing the entire article online. (As with many other journals, *Neurology*'s canonical version is online rather than in print.) The American Academy of Pediatrics has changed its process of content delivery across all its publications; *Pediatrics* now publishes only abstracts in print.

There are limitations to our current print format and design. *Neurology* currently publishes in print full-length articles, of differing length depending on content: from 100-word Neuro*Images* to 3,500-word special articles, such as Views & Reviews. We allow flexibility in length if the methods demand it. But we rarely publish longer articles, and while our editors are convinced that most studies can be adequately communicated within the limits we have set, some studies require greater length for full treatment. It is possible we are missing valuable content as a result. To compensate, we use online material to supplement the main article content. Many readers find it inconvenient, however, to read an article in print, but then to open their phone, tablet, or computer to see the supplement.

Our working hypothesis, then, is that most readers will prefer a shorter article that they can read in its entirety, while those seeking the full content (and possibly longer articles) can go online. Our aim for this issue is to test this hypothesis. Herein is a current version of *Neurology* with a batch of articles that are exemplars of the 1-page treatment. We have added context: what is known, how this work fills a gap, next steps. There is enough discussion to identify the limitations, but also the strength of the findings, and to highlight the actionable results. The advantages are several. More readers (from patients to reporters) may be enticed by our content, and may find it more accessible. Neurologists may be encouraged to read more outside their areas of interest. And there is no loss of content, as the full version is online. *The BMJ* was one of the leaders in this ELPS—electronic long, paper short—approach, and we were fortunate to have Dr. Jose Merino, an editor at *The BMJ*, present this approach at our retreat.

Take a look, read both versions of an article or two (in print and online as appendices to this editorial and as supplemental data to their full articles), and let us know what you think on the linked Feedback Survey available at: http://tinyurl.com/Neurology2016. The survey will be open until September 27. Like most hypotheses and aims, the new format may be spot-on, or not; it may raise more questions than it answers; but whatever the outcome, it will inform the future content of *Neurology* and its future design.

STUDY FUNDING

No targeted funding reported.

Supplemental data at Neurology.org

From the Strong Epilepsy Center and University of Rochester Medical Center, Rochester, NY.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the author, if any, are provided at the end of the editorial.

DISCLOSURE

Robert A. Gross, MD, PhD, FAAN, is supported for educational endeavors from the University of Rochester Medical Center's Clinical and Translational Science Award from the NIH. Since his appointment as Editor-in-Chief in 2009, Dr. Gross has ceased participation in industry-sponsored clinical trials and speakers' bureaus. He receives an honorarium from AAN as Editor-in-Chief of *Neurology*. Go to Neurology.org for full disclosures.

The 11-year long-term follow-up study from the randomized BENEFIT CIS trial

OPEN

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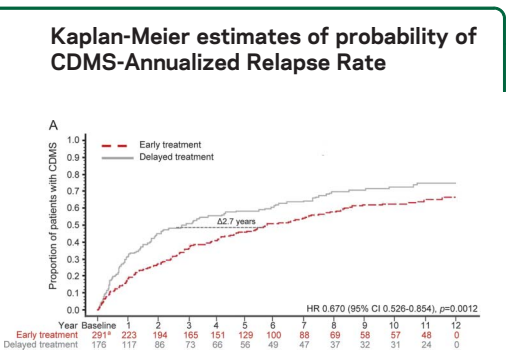
Neurology® 2016;87:964

This article appears in full in this issue on page 978 and online at Neurology.org, doi: 10.1212/WNL.0000000000003078



Study question: In patients diagnosed with clinically isolated syndrome (CIS), does immediate treatment with interferon beta-1b reduce the long-term risk of conversion to clinically definite multiple sclerosis (CDMS) compared to delayed treatment?

Summary answer: After 11 years, risk of conversion to CDMS remained lower in those receiving immediate treatment.

What is known and what this paper adds: The results of the study support initiating treatment of CIS before conversion to CDMS, and provide Class IV evidence that such treatment may provide benefits over the long term compared to a delay in starting treatment.

Design: As part of the phase 3, international, multicenter BENEFIT trial, patients with a CIS and 2 or more clinically silent MRI lesions were randomized (5:3) to 250 μg interferon beta-1b (early treatment group) or placebo (delayed treatment group) every other day for 2 years or until conversion to CDMS, after which patients receiving placebo could switch to interferon beta-1b. Results from a prospective, comprehensive follow-up at 11 years (BENEFIT-11) are reported here.

Participants and setting: Of the 468 patients in BENEFIT, 278 enrolled in BENEFIT-11, including 167 originally assigned to active treatment and 111 to placebo. Baseline characteristics between the 2 groups were similar. Sixty-two percent of patients were on a disease-modifying therapy, including 31% on interferon beta-1b.

Primary outcome(s): The primary outcome measure was the proportion of patients in each group converting to CDMS, assessed by modified Poser criteria, by the time of BENEFIT-11.

Main results and the role of chance: Early treatment was associated with a reduced risk of conversion to CDMS, with a hazard ratio of 0.670 (95% CI 0.526–0.854), $p = 0.0012$. Sixty-seven percent of all patients receiving early treatment had converted to CDMS by the time of BENEFIT-11, compared to 75% of those receiving delayed treatment. Early treatment was associated with a longer time to first relapse (median [Q1, Q3] days: 1,888 [540, not reached] vs 931 [253, 3296]; $p = 0.0005$), and lower overall annualized relapse rate (0.21 vs 0.26; $p = 0.0018$). The Kaplan-Meier estimate of 50% probability of CDMS indicated an average delay of conversion of 2.7 years for early vs delayed treatment (figure).

Kaplan-Meier estimates of probability of CDMS-Annualized Relapse Rate

Harms: The reported adverse events were consistent with the known profile of interferon beta-1b, with no serious adverse effect during BENEFIT 11. No new safety signals were detected at year 11.

Bias, confounding, and other reasons for caution: Some patients from the original trial were unavailable for follow-up. However, the follow-up study included a large proportion of patients from the original trial, and the follow-up patient population was similar to the original trial. Treatment allocation was unblinded for all patients by 5 years after randomization.

Generalizability to other populations: Because of the international, multi-center design of the trial, the results are likely to be generalizable to other populations.

Study funding/potential competing interests: This study was funded by Bayer HealthCare Pharmaceuticals, the manufacturer of the study drug, and the analysis was performed by an employee of Bayer. Go to Neurology.org for full disclosures.

Trial registration number: NCT01795872.

Stroke outcomes with use of antithrombotics within 24 hours after recanalization treatment

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Neurology® 2016;87:965

This article appears in full in this issue on page 996 and online at Neurology.org, doi: 10.1212/WNL.0000000000003083

Study question: Are current guidelines for witholding antithrombotic treatment until 24 hours post-recanalization justified?

Summary answer: Early treatment was associated with a reduced risk for any hemorrhagic transformation (HT), but not for symptomatic HT, and was not associated with improved functional outcomes at 3 months.

What is known and what this paper adds: Current recommendations are for antithrombotic treatment after 24 hours post-recanalization. This study provides data indicating that earlier treatment may be safe, and may reduce the risk of HT.

Participants and setting: The study examined 712 patients at a single center with lesion-documented ischemic stroke treated with recanalization.

Design, size and duration: The study was a retrospective analysis of a prospective registry, with patients enrolled between 2007 and 2015. Timing of antithrombotic administration was at the discretion of the treating physician.

Primary outcome(s), risks, exposures: The primary outcome measures were the occurrence of any HT as shown on MR or CT, and a modified Rankin Score of 0–1 at 3 months.

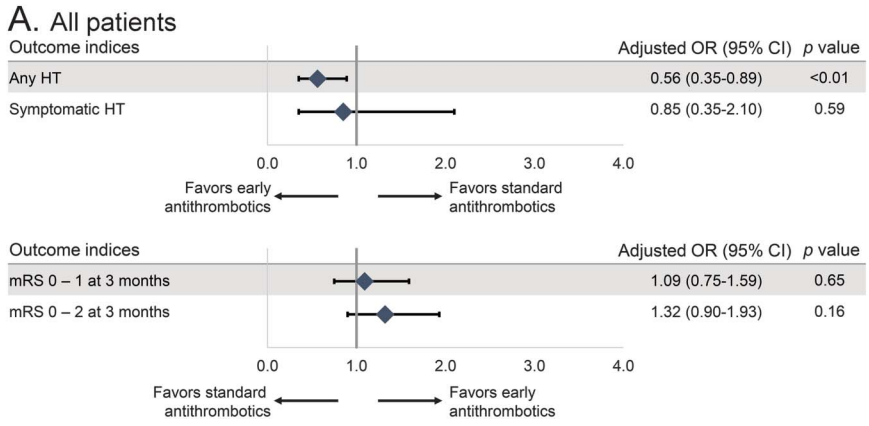
Main results and the role of chance: Early initiation of antithrombotics was associated with decreased odds of having any HT (adjusted OR, 0.56; 95% CI, 0.35–0.89), but was not associated with reduced odds of symptomatic HT (0.85; 0.35–2.10). Early initiation was not associated with a more favorable functional recovery at 3 months after stroke.

Bias, confounding, and other reasons for caution: The study was a retrospective analysis of patients at a single center. Antithrombotics were used earlier more often in younger and less severe patients. The low numbers of patients with symptomatic HT (23, or 3.2%) may reduce the robustness of the statistical analysis.

Generalizability to other populations: The results are not necessarily generalizable to patients with other demographic or clinical characteristics.

Study funding/potential competing interests: The study was funded by the Seoul National University Bundang Hospital Research Fund. Go to Neurology.org for full disclosures.

Stroke outcomes associated with use of early antithrombotics



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Retinal microvasculature and white matter microstructure

The Rotterdam Study

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Neurology® 2016;87:966

This article appears in full in this issue on page 1003 and online at Neurology.org, doi: 10.1212/WNL.0000000000003080

Study question: Can retinal vascular measurements be used as a marker for damage to brain white matter not visible on standard structural MRI scans?

Summary answer: Narrower arterioles and wider venules in the retina are associated with poorer cerebral white matter microstructure, especially in women.

What is known and what this paper adds: Microvascular damage in the retina may reflect similar changes in the cerebral microvasculature. This study shows that easily obtained evidence of retinal microvascular damage correlates with subtle but potentially important white matter damage.

Participants and setting: The study population was drawn from the Rotterdam Study, a prospective cohort study of the elderly in The Netherlands. This imaging study included 2,436 individuals for whom retinal imaging and diffusion tensor (DT) MRI data were available.

Design: Retinal arteriolar and venular calibers were analyzed semi-automatically from fundus photographs. White matter microstructure was assessed using DT MRI.

Primary outcome(s): The primary outcome was the association of retinal vascular calibers with markers of normal-appearing white matter microstructure.

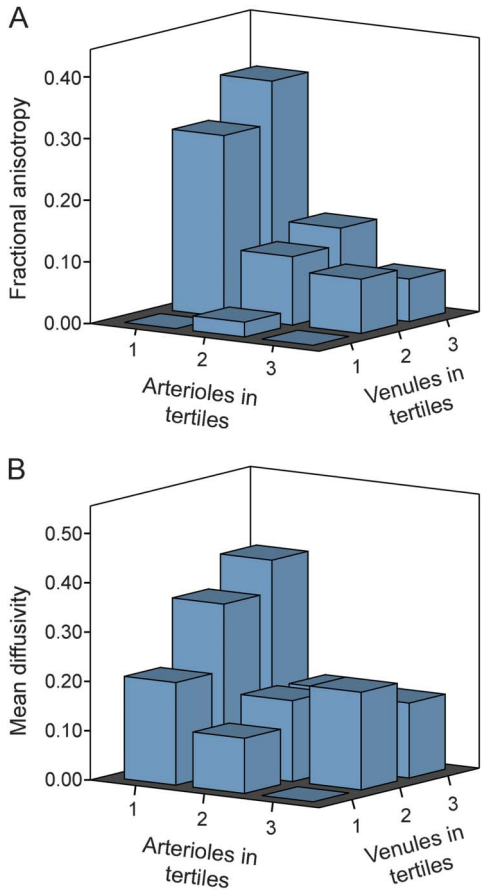
Main results and the role of chance: Narrower retinal arterioles and wider retinal venules were both associated with poor white matter microstructure, as shown by a decrease in fractional anisotropy and an increase in mean diffusivity, as well as other measures. The associations were stronger in women.

Bias, confounding, and other reasons for caution: The study was cross-sectional rather than longitudinal, so that the temporal connection between retinal pathology and cerebral pathology is unclear. In addition, potential confounders such as previous blood pressure or cholesterol levels were not fully taken into account.

Generalizability to other populations: Those in the study were mainly middle-class Caucasians from European countries, which may limit the generalizability of the findings to other economic and ethnic groups.

Study funding/potential competing interests: The study was funded by a group of university, government, and foundation grants. Go to Neurology.org for full disclosures.

Stratified analyses on the association of (A) arteriolar and (B)venular calibers with white matter microstructure measures



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Sirolimus for epilepsy in children with tuberous sclerosis complex

A randomized controlled trial

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Neurology® 2016;87:967

This article appears in full in this issue on page 1011 and online at Neurology.org, doi: 10.1212/WNL.0000000000003077

Study question: Can the MTOR1C inhibitor sirolimus reduce seizure frequency in children with tuberous sclerosis complex (TSC)?

Summary answer: Sirolimus did not reduce seizure frequency compared to standard care.

What is known and what this paper adds: Preclinical work has shown the potential of mTOR1C inhibition for control of seizures due to TSC-causing mutations, and in an uncontrolled study, the mTOR1C inhibitor everolimus reduced seizure frequency in 12 of 20 TSC patients. The current study explores the potential benefit of sirolimus in a randomized, controlled trial.

Design: This 1-year study used a randomized, controlled, cross-over design to assess the efficacy of 6 months of sirolimus titrated to a specified blood trough level. Assignment to standard care alone or standard care plus sirolimus was generated by computer, and all patients switched treatment arms at 6 months.

Participants and setting: The study enrolled 23 of a planned 30 children with TSC and intractable epilepsy (ages 1.8–10.9 years).

Primary outcome(s): The primary outcome was seizure frequency as assessed by daily seizure diary, kept by parents, beginning 1 month before randomization.

Main results and the role of chance: Sirolimus reduced seizure frequency by 41% in the intent-to-treat group, and 61% in the 14 children who achieved target trough drug level, but neither result was different from seizure reduction during standard care.

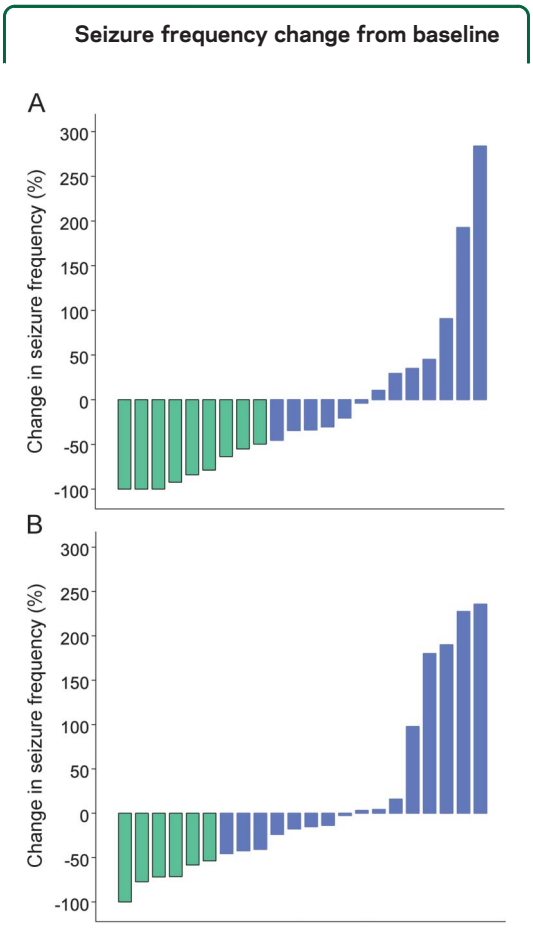
Harms: Aphthous ulcers occurred in 7 patients, and only during treatment with sirolimus. Other adverse events more common on sirolimus included acne-like skin lesions and respiratory and other infections.

Bias, confounding, and other reasons for caution: The low number of patients enrolled, and the tendency of TSC patients to fluctuate in seizure number and severity over time, are possible factors contributing to the failure to support the hypothesis.

Generalizability to other populations: The results are applicable to other populations with TSC.

Study funding/potential competing interests: The study was funded by the Dutch Epilepsy Foundation. Go to Neurology.org for full disclosures.

Trial registration number: NTR3178.



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Evolution of clinical features in possible DLB depending on FP-CIT SPECT result

OPEN

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Neurology® 2016;87:968

This article appears in full in this issue on page 1045 and online at Neurology.org, doi: 10.1212/WNL.0000000000003076

Study question: In patients with possible dementia with Lewy bodies (DLB), which core and suggestive features best predict an abnormal dopamine transporter scan?

Summary answer: Parkinsonism was the best predictor of an abnormal dopamine transporter scan.

What is known and what this paper adds: Distinguishing DLB from non-DLB dementia is important, since the management of symptoms in DLB is different compared to non-DLB dementia. This study provides evidence that baseline parkinsonism in possible DLB may increase the likelihood that a DLB diagnosis will be confirmed with a scan.

Participants and setting: As part of a multicenter, randomized, open-label Phase 4 trial of the dopamine transporter SPECT agent ^{123}I-FP-CIT, patients with possible DLB were enrolled.

Design, size, and duration: After a baseline visit, 170 patients were randomized 2:1 to receive a scan or no scan, with both patient and treating physician aware of the assignment. Patients were followed up at 8 and 24 weeks post-baseline.

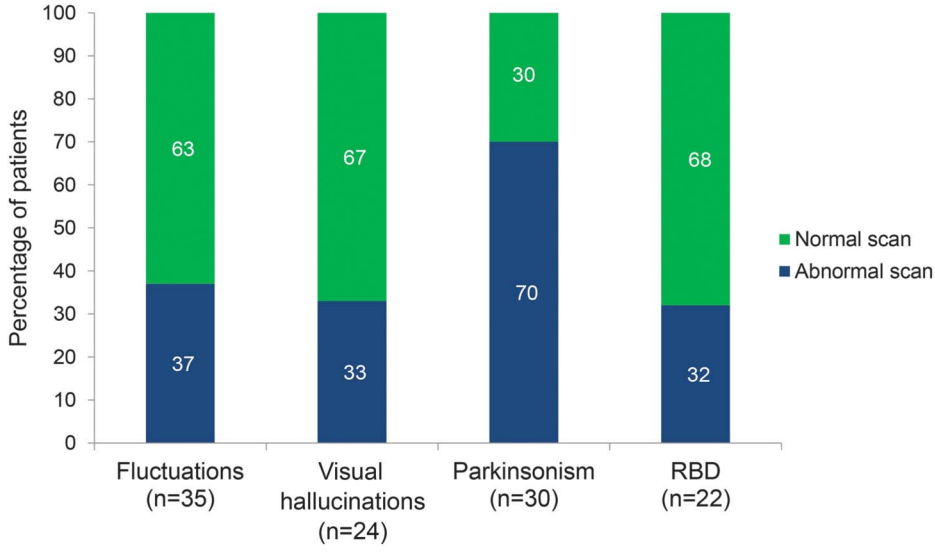
Main results and the role of chance: Among patients receiving scans, only parkinsonism was highly predictive of an abnormal scan, with 70% of patients with parkinsonism having reduced dopamine transporter uptake. In contrast, abnormal scans were seen in only 32%–37% of patients with fluctuations, hallucinations, or REM sleep behavior disorder ($p = 0.001$).

Bias, confounding, and other reasons for caution: The absence of autopsy data prevented confirmation of the diagnosis.

Generalizability to other populations: The results of this largest DLB imaging study to date, drawn from multiple centers in different countries, are likely to be generalizable to other DLB populations.

Study funding/potential competing interests: The study was funded by GE Healthcare, patent holder for DaTscan. Employees of the company also contributed to the design, data collection, and analysis. Go to Neurology.org for full disclosures.

Percentage of abnormal and normal scans for each characteristic feature of DLB at baseline



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Twelve-month recovery of medical decision-making capacity following traumatic brain injury

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Neurology® 2016;87:969

This article appears in full in this issue on page 1052 and online at Neurology.org, doi: 10.1212/WNL.0000000000003079

Study question: How does the time course of recovery of medical decision-making capacity after traumatic brain injury (TBI) depend on the severity of injury?

Summary answer: Most individuals with any form of TBI will have some impairment in their medical decision-making ability shortly after injury. In mild injuries this capacity is regained within 1 year.

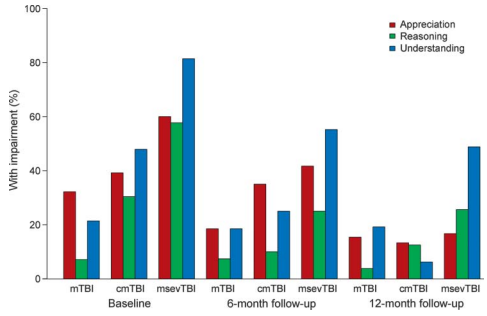
What is known and what this paper adds: This study expands the understanding of the pace of recovery of complex medical decision-making abilities after TBI, demonstrating significant recovery differences over time between milder and more severe forms of injury. The results indicate a need for longitudinal monitoring of recovery of this decisional ability after TBI.

Participants and setting: The study enrolled 177 individuals from multiple sites at a single center, including 111 who had sustained a TBI and 66 healthy controls. Within the TBI group, injuries were classified as mild (mTBI; n = 28), complicated mild (cmTBI; n = 23), or moderate/severe (msevTBI; n = 60), based on TBI Model Systems criteria.

Design, size, and duration: Participants were assessed at baseline and at 6 and 12 months post-injury, using the Capacity to Consent to Treatment Instrument (CCTI). The CCTI presents the patient with hypothetical medical decision-making situations, and evaluates the patient's ability to express a treatment choice, to make a reasonable treatment choice (when the alternative is unreasonable), to appreciate the consequences of the choice, to provide reasons for the choice, and to express understanding of the medical context and risks and benefits of the choice.

Primary outcome(s), risks, exposures: The primary outcome was performance on the 5 CCTI consent abilities at each time point.

Level of impaired decisional abilities across TBI group and time



Main results: TBI patients as a group performed as well as controls at all time points in their abilities to express a choice and to make a reasonable choice. In mTBI, consent abilities for appreciation and understanding were impaired at baseline, but had returned to normal by 6 months. In cmTBI, appreciation, reasoning, and understanding consent abilities were all impaired at baseline; appreciation and reasoning had returned to normal by 6 months, and understanding by 12 months. In msev TBI, all 3 consent abilities remained impaired at 6 months, and reasoning and understanding remained impaired at 12 months.

Bias, confounding, and other reasons for caution: The small number of moderate TBI patients prevented comparison between moderate and severe TBI, and one-quarter of patients did not complete all 3 study visits.

Generalizability to other populations: The small sample size and single site may limit generalizability to other populations.

Study funding/potential competing interests: Funded by the National Institute on Child Health and Human Development (1R01HD053074–Marson, PI). The CCTI is owned by the UAB Research Foundation (UABRF). Both UABRF and Dr. Marson have received royalties for the CCTI. Go to Neurology.org for full disclosures.

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Neurology 2016;87;962-969
DOI 10.1212/WNL.0000000000003075