Alleviation of symptom burden following deep brain stimulation in moderate-to-severe brain injury

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ABSTRACT

Many patients experience high symptom burden for many years following moderate-to-severe traumatic brain injury (TBI). Here, we use the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), a self-report questionnaire that tracks the severity of chronic symptoms that impact quality of life, to evaluate longitudinal changes following deep brain stimulation (DBS) in participants with chronic, moderate-to-severe TBI (msTBI), and to compare findings to the natural recovery observed in the TRACK-TBI Longitudinal cohort. The DBS cohort consisted of the five participants with msTBI in the CENTURY-S trial (CENtral Thalamic Deep Brain Stimulation for the Treatment of Traumatic Brain InjURY, NCT02881151) who received DBS. The total mean RPQ score decreased from 35.0 (SD 8.7) to 18.4 (SD 18.5). 3 participants reporting 10, 8, and 4 symptoms (of a possible 16) as moderate or severe at baseline reported 0 symptoms at this level at treatment end. A fourth participant showed a 50% decrease in the number of moderate to severe symptoms, from 10 to 5. A sample of 107 patients with msTBI from the TRACK-TBI Longitudinal study served as a comparison group. The TRACK-TBI Longitudinal RPQ total score remained stable from one-year post-injury (mean 13.84. SD 12.61) to the first follow-up at either 2, 3, 4, or > 5 years post-injury (mean 14.47. SD 12.98). More TRACK-TBI Longitudinal participants experienced worsening moderate to severe symptoms than improvement (Increased: N=44; Decreased: N=28; No change: N= 28). Participants in the CENTURY-S trial with chronic msTBI (3 to 18 years post injury) achieved marked improvements after DBS in total symptom burden and in the number of symptoms reported as moderate to severe in contrast to participants in the TRACK-Longitudinal sample whose RPQ scores remained stable. These observations suggest that DBS of the central lateral thalamus

alleviates chronic TBI-related symptoms, surpassing the natural recovery documented in the TRACK-TBI Longitudinal cohort.

Introduction

Chronic cognitive impairment after moderate to severe traumatic brain injuries (msTBI) is a common and devasting problem for more than half of those incurring such injuries.[1-4] In the recent CENTURY-S trial (**CEN**tral **T**halamic Deep Brain Stimulation for the Treatment of Traumatic Brain Inj**URY),**[5] we demonstrated that central thalamic deep brain stimulation (CL/DTTm-DBS) improved longstanding deficits in executive regulation of processing speed and mental control in a small cohort of msTBI participants using performative tests of cognitive function (Trail Making Test [TMT]). CENTURY-S was undertaken to assess the safety and efficacy of deep brain stimulation (DBS) in msTBI. Efficacy analyses demonstrated improvement in executive function evidenced by increases in processing speed of 15-52% on Part B of the TMT, the pre-selected outcome measure, in all five participants who completed the study.[5] Performance on this well-validated quantitative measure was compared to natural history controls from Dikmen et al.[2] and shown to have significant relative improvement.[5] These observations support the predicted effect of driving improved executive attention performance through modulation of frontal striatal networks.[6] However, assessing the impact of CL/DTTm-DBS on quality of life is more difficult. Among secondary measures obtained during the trial, the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is an established self-report questionnaire used to track the burden of chronic symptoms that impact quality of life.[7] The RPQ is an NINDS TBI common data element recommended for monitoring symptom burden in adults with TBI (NIH CDE Repository).[8] Serial reassessment showed improvement (reduction) in the RPQ total score in 4 of the 5 CENTURY-S participants, with 3 participants improving more than 60% between presurgical baseline and treatment end.[5] The RPQ captures a broad range of TBI-induced symptoms in the msTBI population. Within the items on the RPQ, a specific set

overlapped with questions used in the general screening procedures for CENTURY-S (the RPQ itself was not used for this purpose in the original study). Recruiting materials stated that the intervention targeted "trouble with focus, attention, and memory", and verified the persistent impact of these difficulties on vocational and educational activities.[5]

To compare the severity of symptom burden and changes induced by CL/DTTm-DBS in the CENTURY-S msTBI group with a larger population of msTBI patients, we examined RPQ data acquired by the TRACK-TBI network, comprised of 18 Level 1 trauma centers in the U.S., which enrolled 2,697 participants with clinically-suspected TBI within 24 hours of injury between February 26, 2014 to July 27, 2018. TRACK-TBI participants were eligible for inclusion if they had a head computed tomography [CT] scan ordered by a treating clinician, confirmation of TBI based on objective evidence of brain injury [e.g., positive head CT] and/or evidence of altered consciousness consistent with the American Congress of Rehabilitation Medicine definition of TBI.[9] Participants were followed in-person at 2 weeks, 6 months, and 12 months post-injury, and by telephone at 3 months post-injury using a comprehensive assessment battery consisting of measures of level of consciousness, cognition, psychological health, physical and sensory symptoms, participation, quality of life, and global level of function. The original cohort of TRACK-TBI participants subsequently became eligible for the TRACK-TBI Longitudinal study if they were alive at one-year post-injury, were at least 17-years old, had a known admission GCS total score between 3-15 and completed either the 6-month or 12-month TRACK-TBI follow-up. These participants then completed up to three additional annual follow-ups between 2- and 9-years post-injury (+/- 3 months). All TRACK-TBI Longitudinal follow-ups were conducted by phone beginning in January 2019 using the TRACK-TBI measures that could be administered remotely.

Machamer and colleagues reported on changes in TBI-related symptoms using the RPQ .[10] Participants with mild TBI (mTBI) were compared to those with msTBI at 2 weeks, 3 months, 6 months, and 12 months post injury. Mean RPQ scores were similar for the mTBI and msTBI groups up to 6 months but were higher for the msTBI group at 12 months. Cognitive symptoms showed little change after 6 months for the TBI group as a whole. Symptoms that were reported most frequently up to 12 months included poor memory, concentration difficulty, fatigue, headache, sleep disturbance and irritability with cognitive symptoms the most consistent and prevalent.[10] A second TRACK-TBI Longitudinal study found elevated TBI-related symptom burden, defined as RPQ >15, in 43% of msTBI patients at 1 year post injury, remaining stable though 5 years post-injury.[11]

Here we sought to compare RPQ data from CENTURY-S (pre- and post-DBS) to natural history data acquired from msTBI patients in the TRACK-TBI Longitudinal cohort to assess its utility as an outcome measure in DBS patients with msTBI. We hypothesized that self-reported persistent symptoms as captured by the RPQ would improve after DBS, particularly executive functions specifically targeted by the intervention. We also hypothesized that the improvement in self-reported symptoms related to DBS would be greater than expected from the natural history cohort undergoing standard of care treatments. To test these hypotheses, we compared longitudinal changes in RPQ-reported symptoms in the CENTURY-S sample against changes observed in participants followed in the TRACK-Longitudinal study.

Methods

Participants

All participants were enrolled in the CENTURY-S study (NCT02881151) and consented under the Stanford University IRB for this study. Participants were required to have a history of msTBI (Glasgow Coma Scale score: 3-12) with persistent functional disability lasting at least 24 months post-injury (Glasgow Outcome Scale – Extended score: 5-7).[5] Of 419 individuals screened, 15 were enrolled, and nine were excluded (on the basis of varying inclusion criteria, see Schiff et al. 2023). The six candidates who met all eligibility criteria continued to surgery (see Schiff, et al. Nat Med, 2023 for a full listing of inclusion/exclusion criteria). One participant was subsequently exited from the study due to a severe postoperative infection and study procedure non-compliance. Five participants completed all follow-up assessments, including the RPQ at pre-surgical baseline and at the end of the 90-day treatment phase. Participants ranged in age from 22 to 60 years and from 3 to 18 years post-injury at enrollment. CENTURY-S was an open-label pilot study with no internal control group.

Participants in the TRACK-TBI Longitudinal study included those in the original TRACK-TBI study who were at least 2 years post injury.[11] Of 387 msTBI patients 21 to 65 years of age, 231 did not have an RPQ score at 1 year; 49 of the remaining 156 participants did not have any follow-up RPQ score, resulting in an analysis sample of 107. We considered their RPQ score at 1 year as their baseline measure. The earliest follow-up RPQ data occurred 2-4 years post injury for 82 individuals and 5 or more years for 25 individuals. Participants all had GCS scores of 3-12 on admission to TRACK-TBI, similar to participants in the CENTURY-S trial. Demographic and injury characteristics for both cohorts are provided in Table 1.

Rivermead Post-Concussion Symptoms Questionnaire

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) measures the presence and severity of 16 symptoms associated with concussion. Participants were asked to rate the following question: Compared with before the accident, do you now (i.e., over the past 7 days) suffer from: headaches, feelings of dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed or tearful, feeling frustrated or impatient, forgetfulness/ poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision and restlessness.[7] Symptoms are rated on a 5-point scale from (0) not experienced (1) no more of problem (2), a mild problem, (3) moderate problem, and (4) severe problem. Items rated as 1 are recoded to 0 by test reporting convention which reflects the meaning of "1" as 'no more of a problem' compared with before the accident. The total symptom score, ranging from 0 to 64, is the sum of all symptom scores. Study personnel administered the RPQ to participants at pre-surgical baseline, and after completion of the postsurgical washout, treatment and post-treatment withdrawal phases. For purposes of this study, the primary endpoint was the change in RPQ total score from the pre-surgical baseline to the end of the treatment phase. We followed previously established precedent and defined better (i.e., lower) symptom burden as a total score less than or equal to 15.[11-13] Individual item scores were also categorized as burdensome symptoms if they were reported as a moderate or severe problem (score of 3 or 4, recoded as "yes", respectively vs 0,1 or 2, reported as "no").

Statistical analysis

Descriptive statistics (e.g., mean, median, percentage of change in scores between timepoints) were calculated to summarize RPQ total score, total number of symptoms, total number of moderate and severe symptoms, and number of symptoms by symptom

type. Scatterplots showing the relationship of baseline RPQ total scores to follow-up RPQ total scores, as well as number of moderate and severe symptoms from baseline to follow-up are presented. Group differences were tested using the Wilcoxon ranked-sum test. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using SAS, version 9.4 (SAS Institute, Inc.).

Results

RPQ total score and number of symptoms reported

Figure 1a shows the RPQ total scores for CENTURY-S participants at pre-surgical baseline and treatment end. The total mean score decreased from 35.0 (SD 8.7) to 18.4 (SD 18.5). The median score was 37 at baseline, with all participants well above the cut-off of 15 for low symptom burden. Three of the five participants demonstrated marked improvements in total score (declines of 95%, 82%, and 62%), with all three participants' scores well below the cut-off of 15 (nominally RPQ total scores of 2, 6, and 8). The number of symptoms endorsed decreased for three participants, (in P1 from 11 to 1; in P5, from 10 to 3; and in P6 from 8 to 4) (Figure 1b) the same participants showing the greatest decrease in RPQ total score.

Number of moderate to severe symptoms reported

Participants showed substantial improvements in the number of moderate to severe symptoms reported at the pre-surgical baseline and at the end of the treatment phase. Notably, 3 participants reporting 10, 8, and 4 symptoms (of a possible 16) as moderate to severe at baseline reported 0 symptoms at this level at treatment end. A fourth participant showed a 50% decrease in the number of moderate to severe symptoms, from 10 to 5 (Figure 2).

Symptoms most frequently reported (i.e., ≥ 3 participants) as moderate to severe at the pre-surgical baseline were (1) being irritable, easily angered, (2) feeling frustrated, (3) poor concentration, and (4) taking longer to think (5 of 5) and (5) forgetfulness/poor memory (4 of 5) (Figure 3a). Only 1 participant continued to report 4 of 5 of these symptoms as moderate to severe at treatment end, while 2 of 5 participants who initially reported taking longer to think as a moderate to severe symptom maintained this rating at treatment end. Three symptoms reported as moderate or severe at baseline (headache, feelings of dizziness, and light sensitivity) were no longer considered burdensome at treatment end.

Comparison of RPQ results with TRACK-TBI Longitudinal

Item-by-item responses for both TRACK-TBI Longitudinal and CENTURY-S participants are presented in Figure 3. Symptoms endorsed by at least 4 of the 5 CENTURY-S participants included irritability, frustration/impatience, poor memory, poor concentration, and taking longer to think (3a). All five of these symptoms were rated much lower after DBS. Three of the 5 participants indicated that all five of these symptoms had fully resolved while 4 of 5 indicated that all but "taking longer to think" had resolved by treatment end. In contrast, the TRACK-TBI Longitudinal cohort showed stable or increased symptom severity from baseline to first follow-up (Figure 3b).

While the CENTURY-S RPQ total mean score decreased from 35.0 (SD 8.7) to 18.4 (SD 18.5), the TRACK-TBI Longitudinal RPQ total score remained stable from one-year post-injury (mean 13.84, SD 12.61) to the first follow-up at either 2, 3, 4, or ≥ 5 years post-injury (mean 14.4, SD 12.98).

Figure 4 shows a scatterplot of the total number of symptoms reported by TRACK-TBI Longitudinal and CENTURY-S participants at baseline relative to the earliest follow-up. Three of the 4 CENTURY-S participants had follow-up values significantly lower than their corresponding baseline measures. The TRACK-TBI Longitudinal participants show the same number of participants having improved RPQ total scores (N=47) as those who worsened (N=47), while 13 participants saw no change. The median change was -13.0 and 0 for CENTURY-S and TRACK-TBI Longitudinal participants, respectively (p=0.019).

Figure 5 shows a scatterplot of the total number of symptoms rated as moderate to severe by TRACK-TBI Longitudinal and CENTURY-S participants at baseline relative to the earliest follow-up. Three of the CENTURY-S participants decreased their number of moderate or severe symptoms to 0 from 10, 8, and 4 at baseline, and one decreased the number by half, from 10 to 5. At follow-up, more TRACK-TBI Longitudinal participants experienced worsening moderate to severe symptoms than improvement. (Increased: N=44; Decreased: N=28; No change: N= 28). The median change was -5.0 and 0 for CENTURY-S and TRACK-TBI Longitudinal participants, respectively (p=0.004).

Discussion

We found that participants with chronic msTBI who underwent treatment with CL/DTTm-DBS demonstrated greater and more consistent improvement in total symptom burden on the RPQ than those enrolled in a natural history cohort. Mean RPQ total scores decreased 47% from 35 (SD 8.7) to 18.4 (SD 18.5). The changes observed in the CENTURY-S sample sharply diverged from the natural history observations in the TRACK-TBI Longitudinal cohort which remained stable (one-year post-injury, mean 13.84, SD 12.61; follow-up, mean

14.47, SD 12.98). While all 5 CENTURY-S participants were well above the cutoff for low symptom burden (> 15) at baseline (Range= 21-43), 3 of 5 (60%) achieved total symptom scores well below cutoff (Total score= 8, 6, and 2, respectively) after DBS. All three of these participants reported no moderate to severe symptoms at treatment end and also ended the three-month treatment period with an overall low symptom burden (RPQ total scores ≤15). While these results should be considered in the context of a small sample size, the magnitude and consistency of the changes observed considered against the extended chronicity (mean 8.8 years), heterogeneity of structural injuries (see Supplemental material, Schiff et al. 2023), and wide age range of the participants, suggest a robust effect of DBS.

Characterizing the number and severity of scores capturing 'neuropsychological deficits' on neuropsychological test batteries have been proposed to capture symptoms which may have an important weight in assessment of overall disease burden.[14] Thus, assessing the number of symptoms reported as either moderate or severe demonstrated that 4 of 5 CENTURY-S participants showed a marked reduction, and 3 no longer reported any burdensome symptoms at follow-up. The extent of change in symptom burden noted in the CENTURY-S participants is in sharp contrast to the comparison sample drawn from the TRACK-TBI Longitudinal study. In the TRACK-TBI Longitudinal cohort, 74% of participants reported either no change or a worsening of both total and moderate to severe symptoms. The change in symptom burden between the two cohorts reached statistical significance in non-parametric tests, recognizing the small sample size in the CENTURY-S trial. A larger study is needed to confirm the current findings.

The RPQ results obtained in the CENTURY-S cohort correspond very closely to findings from narratives we obtained through semi-structured interviews conducted with both participants and paired surrogates.[15-17] Narratives revealed that memory and cognitive symptoms as well as

difficulties with self-regulation, frustration, and irritability were frequently experienced by participants pre-DBS. Following DBS, four of five participants described improvements in memory and attentional focus, while three participants reported improvements in self-regulation. These findings are also consistent with the RPQ domains that improved the most after DBS (i.e. executive function and emotional control). Narrative reports obtained from family members provided further and independent confirmation of these improvements in some individuals identifying improvement not noticed by the participants themselves.[15-17]

In the aggregate, these observations emphasize that long-term symptoms in msTBI survivors can be influenced by partially restoring activation to frontal-striatal neurons even years after injury (Schiff et al 2023); chronic down-regulation of these systems has been shown to associate with cognitive outcomes in msTBI measuring GABAergic tone using flumazenil PET in both longitudinal evaluation of the early subacute to ~18 month post-injury time periods[18] and a cross-sectional study including patients years after injury[19]. CL/DTTm-DBS is proposed to restore the dynamic range of the chronically down-regulated frontal and striatal neurons, allowing them to recover a sustained, higher bandwidth of information processing. The observed alleviation of symptom burden is proposed to originate in this return of more flexible and reliable corticothalamic functioning[5,20]. These results support the use of the RPQ to assess the effects of DBS on TBI symptom burden, including subjective complaints related to executive dysfunction. TBI sequelae that may not be captured with standardized, performative tests but continue to impact daily function and quality of life can be detected by the RPQ to inform treatment needs. Thus, the RPQ appears to be a useful patient-reported outcome (PRO) measure to assess the effectiveness of interventions aimed at reducing symptom burden in patients with msTBI. This is important as PRO based measurements have been prioritized by the US FDA to

evaluate new therapeutics and to date no effective therapy for msTBI has been identified requiring innovation of relevant PRO metrics.

Limitations

An important limitation at present is the lack of an anchored minimal clinically important difference (MCID) for the RPQ. Mercier et al.[21] proposed an MCID for the RPQ of 4.6 based on a case-control study of 146 mild TBI patients by Silverberg and Otamendi[22]. In their study, they reported an empirical estimate of an RPQ difference that appeared to accompany a clinically meaningful difference in how onset symptoms guided clinical management. Specifically, the two groups differed in their initial symptom reporting, their receipt of prolonged rest advice, and in a meaningful real-world outcome in terms of their return to productivity. return to productivity. While the RPQ itself has been used in formal assessment of the MCID of the WHODAS[23], an anchor-based assessment of the MCID for RPQ has not yet been determined. Using this as a guide, our findings of a mean reduction of 16.6 points would reflect a greater than a three-and-half-fold increase over that estimated MCID. Here we note also that the five symptoms most frequently reported as moderate to severe, specifically those used to determine eligibility for the CT-DBS trial, showed a large decrease and may further inform an "RPQ-5 MCID" for executive function in future CL/DTTm DBS studies. Another limitation is the lack of a concomitantly collected functional outcome measure directly comparable to the RPQ in this cohort. A suitable candidate is the WHODAS 2.0 measure[19] for which an MCID has been estimated using the RPQ as an anchor.[20] Importantly, the WHODAS 2.0 can be administered both to participants and family members and could parallel extracted accounts of reported outcomes obtained in narrative studies.[15-17]

Conclusion

Deep brain stimulation of the central lateral thalamus reduced TBI-related symptoms (particularly moderate to severe symptoms) in a cohort of chronically impaired participants

(mean time after injury 8.8 years). Comparing the overall improvements observed in the CENTURY-S cohort to the TRACK-TBI Longitudinal cohort, 43% of the TRACK-TBI population (all studied between 1 year and 2 to 9 years after injury) continued to exhibit an elevated TBI-related symptom burden (>15 points on the RPQ total score). Notably, while all the CENTURY-S cohort demonstrated a comparatively elevated TBI-related symptom burden on enrollment (mean RPQ total =35 versus TRACK-TBI Longitudinal mean RPQ total score=13.84), three of the participants reduced total burden below 15 points on the RPQ. These findings strengthen the relationship of the improvement observed with CL/DTTm-DBS on performative measures of executive function[5] to the real-world burden of post-TBI disabilities. Importantly, a subset of RPQ items showed the broadest improvement in the CENTURY-S cohort and reflect impaired executive attention and function. These observations suggest the further use of the RPQ total score and potentially a defined subset of items to measure and evaluate this intervention.

Transparency, Rigor, and Reproducibility

Transparency, Rigor, and Reproducibility

The CENTURY-S study was preregistered at clinicaltrials.gov (clinicaltrials.gov NCT02881151). The analysis plan for the primary endpoint, processing speed on part B of the trail-making test, was registered prior to beginning data collection. Six participants with msTBI, between 3- and 18-years post-injury underwent deep brain stimulation within the central lateral (CL) and the associated medial dorsal tegmental (CL/DTTm) tract. Six participants were safely implanted, and five participants completed the study. One participant was withdrawn for protocol non-compliance. The CENTURY-S clinical protocol and results overview are available at https://clinicaltrials.gov/study/NCT02881151. The primary measure of this analysis is the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), which is a standard in the field. Statistical analyses were performed using SAS statistical software version 9.4.

The TRACK-TBI study was preregistered at clinicaltrials.gov (clinicaltrials.gov NCT2119182). The TRACK TBI Longitudinal study was not preregistered. The comparison group sample size of 107 participants was based on the number of participants in the TRACK-TBI Longitudinal sample with moderate or severe TBI who were age 21-65 at the time of their injury. Of 387 msTBI patients 21 to 65 years of age, 231 did not have an RPQ score at 1 year; 49 of the remaining 156 participants did not have any follow-up RPQ score, resulting in an analysis sample of 107. The TRACK-TBI Longitudinal data were collected by trained examiners over the telephone without knowledge of the question addressed in this paper. The TRACK-TBI clinical protocol and outcome procedures are available at https://tracktbi.ucsf.edu/. The earliest follow-up data obtained after 2 years post-injury was used. The analysis plan was not formally

preregistered. Data analysts were aware of the groups and hypotheses. Statistical tests were non-parametric and assumed that the change in RPQ scores was monotone regardless of baseline score. No replication or external validation studies have been performed or are planned/ongoing at this time to our knowledge. Investigators interested in the long-term outcome data from the TRACK-TBI Longitudinal study can submit a Data Collaboration Request to the TRACK-TBI Executive Committee through the following website (tracktbi.ucsf.edu/collaboration-opportunities

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Authors' Contributions

Conception and design of the study: L.M.G., N.R.T., J.M.H., J.T.G., and N.D.S. Acquisition and analysis of data: L.M.G., J.C., J.B., J.D.V., N.R.T., J.M.H., J.T.G., and N.D.S. Drafting a significant portion of the article or figures: L.M.G., N.R.T., J.C., J.B., J.T.G., and N.D.S.

Author Disclosure Statement

JMH and NDS are co-founders and shareholders of ReEmerge, a start-up company formed by Cornell University, Stanford University, and the University of Utah to develop central thalamic DBS to treat moderate to severe TBI (msTBI). JMH, and NDS are coinventors on a patent held jointly by Stanford University, Cornell University, and the University of Utah for the use of CL/DTTm DBS to treat msTBI. NDS is an inventor on additional patents held by Cornell University for the use of CL/DTTm DBS to treat msTBI. LMG, NRT, JDV, and JTG are scientific advisors to ReEmerge.

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References

1. Corrigan JD, Cuthbert JP, Harrison-Felix C, et al. US population estimates of health and social outcomes 5 years after rehabilitation for traumatic brain injury. *J Head Trauma Rehabil*. 2014;29(6):E1-E9. doi:10.1097/HTR.0000000000000020

2. Dikmen SS, Machamer JE, Powell JM, Temkin NR. Outcome 3 to 5 years after moderate to severe traumatic brain injury. *Arch Phys Med Rehabil*. 2003;84(10):1449-1457. doi:10.1016/s0003-9993(03)00287-9

3. Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):430-438. doi:10.1097/HTR.0b013e3181c133e9

4. Hauger SL, Borgen IMH, Forslund MV, et al. Participation in the Chronic Phase after Traumatic Brain Injury: Variations and Key Predictors. *J Clin Med*. 2023;12(17):5584. Published 2023 Aug 27. doi:10.3390/jcm12175584

5. Schiff ND, Giacino JT, Butson CR, et al. Thalamic deep brain stimulation in traumatic brain injury: a phase 1, randomized feasibility study. *Nat Med*. 2023;29(12):3162-3174. doi:10.1038/s41591-023-02638-4

6. Baker JL, Ryou JW, Wei XF, Butson CR, Schiff ND, Purpura KP. Robust modulation of arousal regulation, performance, and frontostriatal activity through central thalamic deep brain stimulation in healthy nonhuman primates. *J Neurophysiol*. 2016;116(5):2383-2404. doi:10.1152/jn.01129.2015

7. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol*. 1995;242(9):587-592. doi:10.1007/BF00868811

8. U.S. Department of Health and Human Services, National Institutes of Health. (n.d.). *Rivermead Post-Concussion Symptoms Questionnaire (RPQ)*. NIH Common Data Elements (CDE) Repository. Retrieved December 29, 2025, from https://cde.nlm.nih.gov/formView?tinyId=XJyVBFEmP

9. Hicks, R., Giacino, J., Harrison-Felix, C., Manley, G., Valadka, A., & Wilde, E. A. (2013). Progress in developing common data elements for traumatic brain injury research: Version two– the end of the beginning. *Journal of Neurotrauma*, *30*(22), 1852–1861. https://doi.org/10.1089/neu.2013.2938

10. Machamer J, Temkin N, Dikmen S, et al. Symptom Frequency and Persistence in the First Year after Traumatic Brain Injury: A TRACK-TBI Study. *J Neurotrauma*. 2022;39(5-6):358-370. doi:10.1089/neu.2021.0348

11. Nelson LD, Temkin NR, Barber J, et al. Functional Recovery, Symptoms, and Quality of Life 1 to 5 Years After Traumatic Brain Injury. *JAMA Netw Open*. 2023;6(3):e233660. Published 2023 Mar 1. doi:10.1001/jamanetworkopen.2023.3660

12. Thompson, J. M., Potter, S., Sanderson, M., & Fleminger, S. (2016). Approaches to establishing validated cut-off scores on the Rivermead Post Concussion Symptoms Questionnaire (RPQ). *Brain Injury*, 30(5-6), 770.

13. Wilson L, Boase K, Nelson LD, et al. A Manual for the Glasgow Outcome Scale-Extended Interview. *J Neurotrauma*. 2021;38(17):2435-2446. doi:10.1089/neu.2020.7527

14. Silverberg, N. D., Crane, P. K., Dams-O'Connor, K., Holdnack, J., Ivins, B. J., Lange, R. T., Manley, G. T., McCrea, M., & Iverson, G. L. (2017). Developing a cognition endpoint for traumatic brain injury clinical trials. *Journal of Neurotrauma*, *34*(2), 363–371. doi.org

15. Fins, J. J., Wright, M. S., Henderson, J. M., & Schiff, N. D. (2022). Subject and family perspectives from the central thalamic deep brain stimulation for traumatic brain injury

study: Part I. Cambridge Quarterly of Healthcare Ethics, 31(4), 419–443. https://doi.org/10.1017/s0963180122000226

16. Fins, J. J., Wright, M. S., Shulman, K. S., Henderson, J. M., & Schiff, N. D. (2023). Subject and family perspectives from the central thalamic deep brain stimulation trial for traumatic brain injury: Part II. Cambridge Quarterly of Healthcare Ethics,1–24. https://doi.org/10.1017/s0963180123000518

17. Gerber LM, Shulman KS, Wright MS, Schiff ND, Fins JJ. Qualitative Analysis of Symptoms from the Central Thalamic Deep Brain Stimulation Trial for Traumatic Brain Injury. *NeuroRehabilitation*. 2025;56(2):143-151. doi:10.1177/10538135241296732
18. Kang Y, Jamison K, Jaywant A, et al. Longitudinal alterations in gamma-aminobutyric acid ($GABA_A$) receptor availability over ~ 1 year following traumatic brain injury. Brain Commun. 2022 Jun 15;4(4):fcac159. doi: 10.1093/braincomms/fcac159. PMID: 35794871; PMCID: PMC9253887.
19. Woodrow RE, Grossac J, Hong YT, et al. Outcomes and Mechanisms Associated With Selective Thalamic Neuronal Loss in Chronic Traumatic Brain Injury. JAMA Netw Open. 2024 Aug 1;7(8):e2426141. doi: 10.1001/jamanetworkopen.2024.26141. PMID: 39106064; PMCID: PMC11304117.
20. Schiff ND. Mesocircuit mechanisms in the diagnosis and treatment of disorders of consciousness. Presse Med. 2023 Jun;52(2):104161. doi: 10.1016/j.lpm.2022.104161. Epub 2022 Dec 20. PMID: 36563999.

21. Mercier LJ, Fung TS, Harris AD, Dukelow SP, Debert CT. Improving symptom burden in adults with persistent post-concussive symptoms: a randomized aerobic exercise trial protocol. *BMC Neurol*. 2020;20(1):46. Published 2020 Feb 5. doi:10.1186/s12883-020-1622-x

22. Silverberg ND, Otamendi T. Advice to Rest for More Than 2 Days After Mild Traumatic Brain Injury Is Associated With Delayed Return to Productivity: A Case-Control Study. Front Neurol. 2019 Apr 12;10:362. doi: 10.3389/fneur.2019.00362. PMID: 31037065; PMCID: PMC6476280.

23. World Health Organization. Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0). World Health Organization; 2010.

24. Snell DL, Silverberg ND. Derivation of a minimal clinically important difference score for the WHODAS 2.0 in mild traumatic brain injury. *NeuroRehabilitation*. 2023;52(2):249-257. doi:10.3233/NRE-220004

Figure Titles and Legends

Figure 1 title:

CENTURY-S trial: (a) RPQ total scores by participant, pre-surgery and at treatment end, (b) number of symptoms reported by participant, pre-surgery and at treatment end.

Figure 2 title:

CENTURY-S trial: Number of moderate to severe symptoms reported pre-surgery and at treatment end by each participant

Figure 3 title:

Number of participants reporting moderate to severe symptoms by individual symptom at baseline and at next follow-up (a) in CENTURY-S participants (n=5), (b) in TRACK-TBI Longitudinal cohort (n=107),

Figure 4 title:

Scatterplot of RPQ total scores for TRACK-TBI Longitudinal and CENTURY-S participants.

Footnote 1: red dots represent participants in CENTURY-S trial; black dots represent patients in TRACK-TBI Longitudinal.

Footnote 2: median change = -13.0 for CENTURY-S participants compared with 0.0 median change for TRACK-TBI Longitudinal patients; p=0.0185 by Wilcoxon rank-sum test.

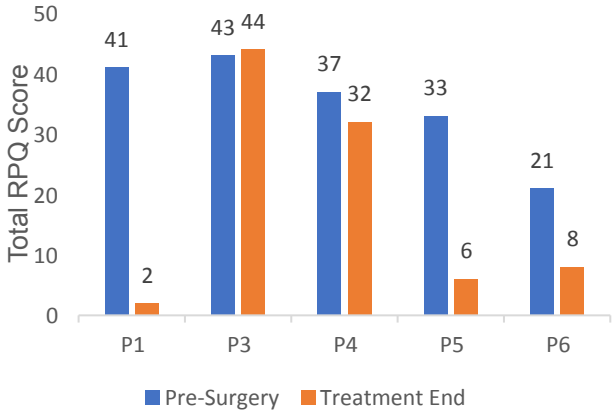
Number of TRACK-TBI Longitudinal patients above line (worsened) = 47; number of TRACK-TBI Longitudinal patients below line (improved) = 47; number of TRACK-TBI patients with no change = 13.

Figure 5 title:

Scatterplot of total number of moderate to severe symptoms reported for TRACK-TBI Longitudinal and CENTURY-S participants

Footnote 1: red dots represent participants in CENTURY-S trial; black dots represent patients in TRACK-TBI Longitudinal. Jittered dots represent where more than one participant has the same baseline and follow-up number of moderate to severe symptoms.

a



b

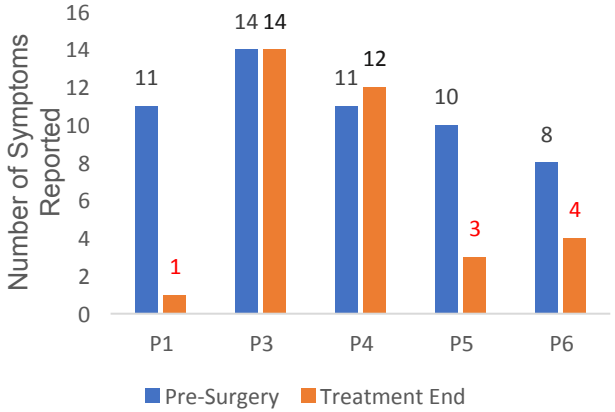


Figure 1. CENTURY-S trial: (a) RPQ total scores by participant pre-surgery and at treatment end, (b) number of symptoms reported by participant.

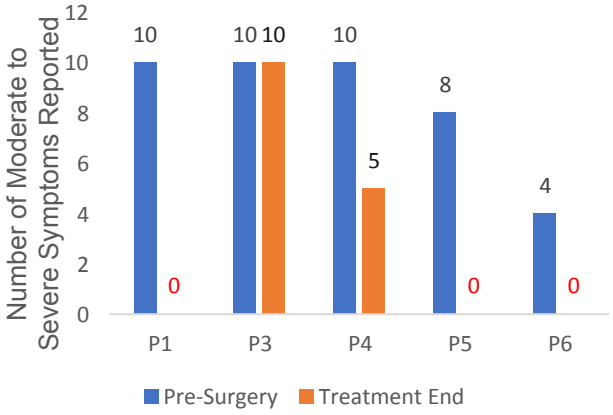


Figure 2. CENTURY-S trial: Number of moderate to severe symptoms reported pre-surgery and at treatment end by each participant

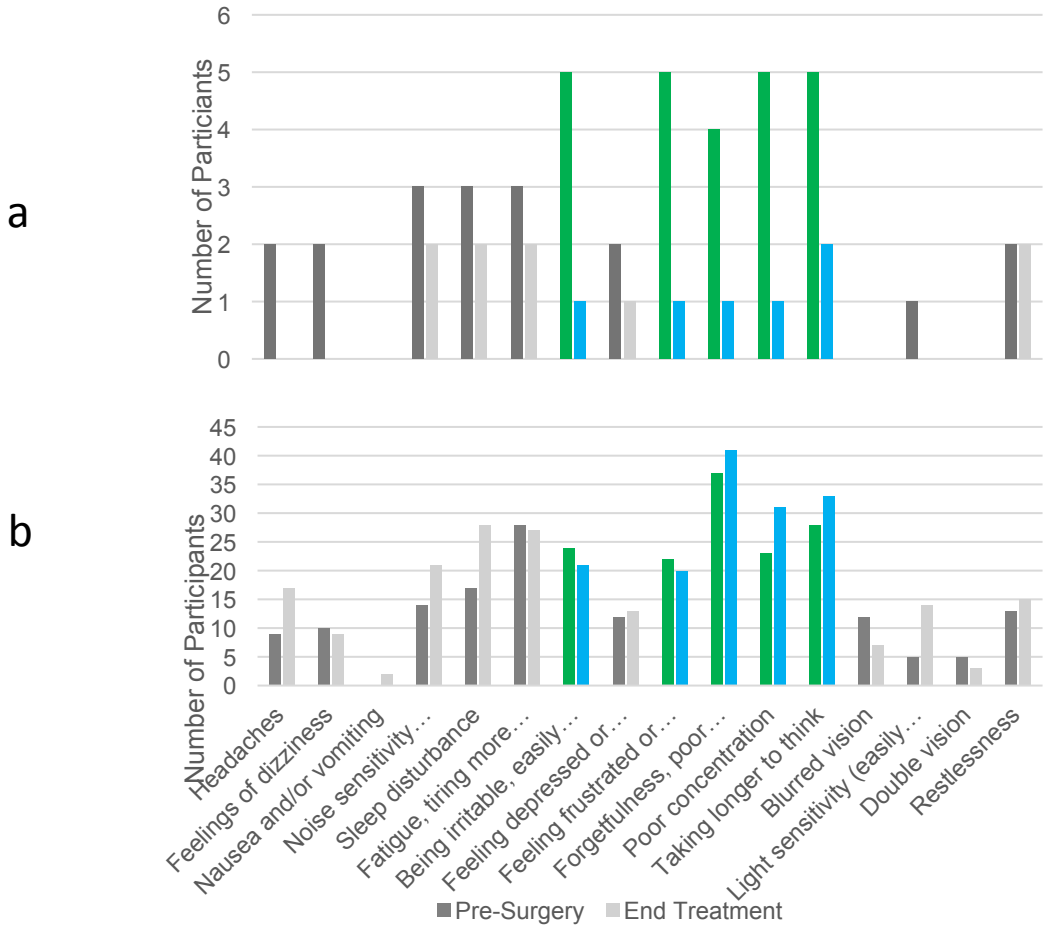


Fig. 3. Number of participants reporting moderate to severe symptoms by individual symptom at baseline and at next follow-up (a) in CENTURY-S participants (n=5), (b) in TRACK-TBI Longitudinal cohort (n=107)

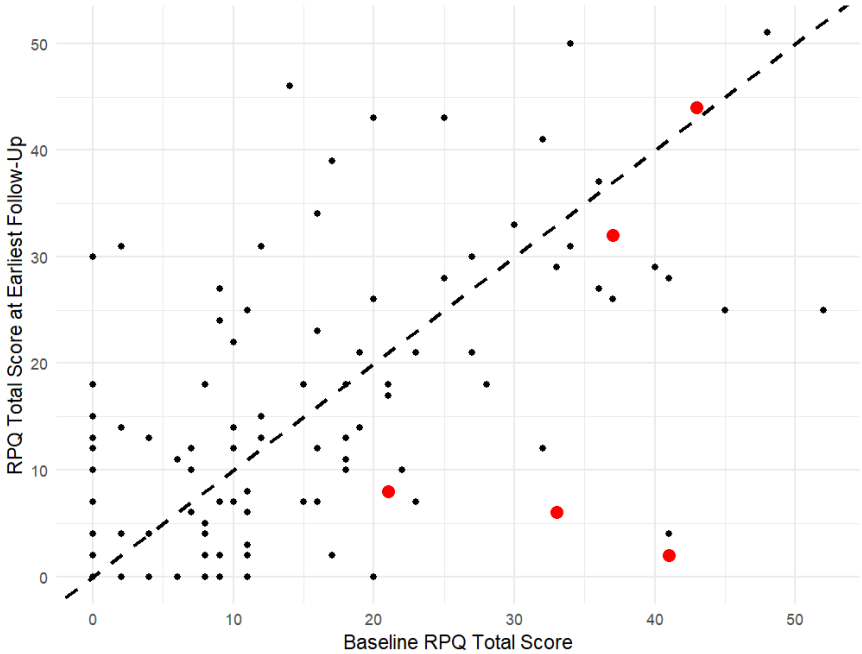


Figure 4. Scatterplot of RPQ total scores for TRACK-TBI Longitudinal and CENTURY-S participants.

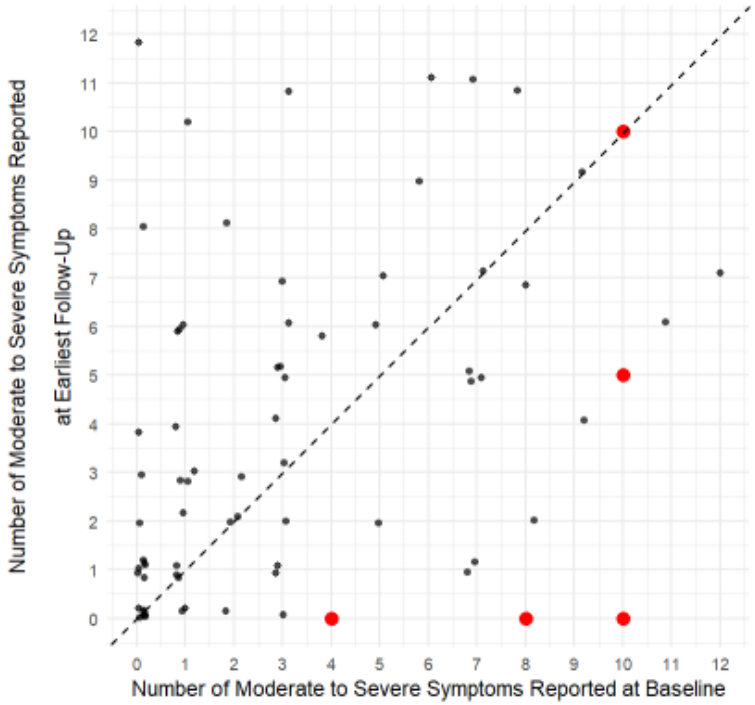


Figure 5 Scatterplot of total number of moderate to severe symptoms reported for TRACK-TBI Longitudinal and CENTURY-S participants