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Functional brain network modularity predicts response to cognitive training after brain injury

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ABSTRACT

Objective: We tested the value of measuring modularity, a graph theory metric indexing the relative extent of integration and segregation of distributed functional brain networks, for predicting individual differences in response to cognitive training in patients with brain injury.

Methods: Patients with acquired brain injury (n = 11) participated in 5 weeks of cognitive training and a comparison condition (brief education) in a crossover intervention study design. We quantified the measure of functional brain network organization, modularity, from functional connectivity networks during a state of tonic attention regulation measured during fMRI scanning before the intervention conditions. We examined the relationship of baseline modularity with pre- to posttraining changes in neuropsychological measures of attention and executive control.

Results: The modularity of brain network organization at baseline predicted improvement in attention and executive function after cognitive training, but not after the comparison intervention. Individuals with higher baseline modularity exhibited greater improvements with cognitive training, suggesting that a more modular baseline network state may contribute to greater adaptation in response to cognitive training.

Conclusions: Brain network properties such as modularity provide valuable information for understanding mechanisms that influence rehabilitation of cognitive function after brain injury, and may contribute to the discovery of clinically relevant biomarkers that could guide rehabilitation efforts.

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Brain injuries impair components of goal-directed cognition, such as attention and working memory, disrupting the ability to accomplish life goals. Although improvements after training of higher cognitive functions in patients with brain injury are documented,[1] there is a deficiency of research on neural factors that explain significant variation in recovery of function and response to rehabilitation across individuals. Measurable brain network properties that likely influence the capacity of individuals to benefit from rehabilitation could provide valuable clinical biomarkers that could guide the treatment of cognitive dysfunction after brain injury.

The state of functional brain networks may influence how the brain manages information and changes with experience.[2–5] Rehabilitation of complex cognitive functions may be influenced by the relative extent of integration and segregation of functional networks (i.e., "modules") distributed across distant brain regions.[6] Cortical lesions and subcortical axonal damage can disrupt this "modular" network organization[7,8] normally exhibited by the brain.[9,10] Thus, we hypothesized that differences in brain modularity among individuals might predict the potential for patients to learn during cognitive training after brain injury. In the present study, we examined the graph theory metric of modularity, an index of the balance between functional integration and segregation of networks, during a state of tonic attention regulation as patients underwent fMRI scanning. We investigated baseline modularity as a putative basis for variation in the response of patients with acquired brain injury to a previously implemented cognitive training protocol for attention and executive functions.[11]

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

METHODS **Patients.** Sixteen patients (age range: 24–62 years; sex: 9 women) with chronic acquired brain injury (≥6 months) participated in the intervention study. Physicians and treatment providers from several San Francisco Bay Area hospitals referred participants to our study. Entry criteria including clear reports of plausible mechanism of injury, with evidence of neurophysiologic disruption (loss of consciousness, posttraumatic confusion/amnesia), and clear onset of impaired executive function, with reports of current function corroborated by patients and significant others. All participants were on stable medication regimens and had no active illicit drug use, severe depression, aphasia, or other criteria that would impede participation in the intervention or measurements. Three participants completed partial baseline assessments, but withdrew because of changes in health, family situation, and job demands. Of the remaining participants, 11 participated in the MRI and neuropsychological measures necessary for inclusion in the present study (others declined because of claustrophobia, concerns regarding discomfort from positioning, fatigue, or illness); therefore, results are constrained to these individuals. The source of brain injury varied among the patients, resulting from trauma (n = 8), stroke (n = 1), tumor resection (n = 1), and chemotherapy (n = 1). Eight of the patients had lesions affecting cortical and white matter regions that were visible with MRI using fluid-attenuated inversion recovery and magnetization-prepared rapid acquisition with gradient echo images. The location of the lesions varied among participants. A more thorough description of the demographic and injury characteristics of this subset of patients is provided in our previous report.[12]

Standard protocol approvals, registrations, and patient consents. Participants provided informed consent according to procedures approved by the institutional review boards of the California Pacific Medical Center, University of California, San Francisco, and San Francisco VA Medical Center.

Intervention design. The cognitive training in goal-oriented attention self-regulation involved 20 hours of group-based training, 3 hours of individual training, and approximately 20 hours of home practice over 5 weeks. Training incorporated 2 key components: (1) regulation of distractibility via mindfulness-based attention regulation training; and (2) active application and practice of goal-oriented attention self-regulation skills in daily life and with self-generated complex goals.[11,13] Trainers monitored the engagement of participants in all aspects of cognitive training, either directly during training sessions or by referring to the participants' logbooks. The comparison intervention consisted of a 2-hour educational session about brain health and wellness. This experimental condition did not involve cognitive skills training and was primarily used to examine the effects of repeated testing.

In a crossover design, we randomized eligible patients to receive either the cognitive training (8/16 patients) or education intervention (8/16 patients) during the first 5-week study period. The patients then switched over to the alternative intervention for the second 5-week study period. Of the 11 patients completing the measures necessary for the present study, 4 started with cognitive training and 7 started with education intervention. All patients completed neuropsychological testing at 3 time points: assessment 1 before any participation in interventions, assessment 2 at the end of the first study period (5 weeks), and assessment 3 at the end of the second study period (10 weeks). Although most patients (6 of 11 patients) in the present study completed MRI scans at all 3 assessment periods, 5 patients could not be included in the education analysis because of technical issues with MRI scans, leaving 6 data points for the education analysis.

Neuropsychological testing. Attention and executive function were measured using a composite score composed of the average *z* score of the following neuropsychological measures: Letter Number Sequencing, Wechsler Adult Intelligence Scale III[14]; Auditory Consonant Trigrams at 9, 18, 36[15]; Digit Vigilance Test time and errors[16]; Design and Verbal Fluency Switching[17]; Trails B[16]; Stroop Inhibition/Switching time and errors; and Stroop Inhibition time and errors.[17] To minimize practice effects, whenever feasible, alternative test forms (Verbal Fluency Switching, Digit Vigilance) were used for repeated administrations, and/or norms for repeated testing were used (Auditory Consonant Trigrams).

We quantified changes in attention/executive functions after each intervention condition by subtracting the composite attention and executive function domain score after the intervention condition from before intervention.

Brain imaging methods: MRI acquisition and preprocessing. We acquired a 5-minute fMRI scan after subjects underwent T1-weighted magnetization-prepared rapid-acquisition gradient echo and T2-weighted fluid-attenuated inversion recovery structural scans. Before the fMRI scan, patients received the following instructions: "For the next 5 minutes, relax and focus on the cycle of your breathing. It is ok to let your mind wander, but try to refocus on your breathing. Keep your eyes open and do not fall asleep." We restricted the analysis of fMRI data to baseline scans, defined as the first available MRI scan before participation in the intervention conditions.

We acquired images using a 3-tesla Siemens Magnetom Trio whole-body magnetic resonance scanner (Siemens AG, Erlangen, Germany) with a transmit-receive 12-channel quadrature birdcage head coil at the University of California, San Francisco Neuroscience Imaging Center. Eligible subjects underwent a sequence consisting of 300 T2*-weighted echoplanar images, with slice thickness, 5 mm; 0.5 mm slice gap; 18 slices; repetition time, 1,000 milliseconds; echo time, 27 milliseconds; flip angle, 62°; and matrix, 64 × 64 axial field of view, discarding the first 3 volumes to allow for scanner equilibration.

We conducted image preprocessing using Analysis of Functional Neuroimaging Software (AFNI: v2008-07-18-1710).[18] We slice-time–corrected and realigned the echoplanar image data using a 6-parameter affine registration to correct for head motion. We regressed out the mean nuisance signal from estimated head motion, ventricles, and white matter. Using SPM8, we segmented CSF and white matter and eroded and merged the identified clusters to produce a mask of the ventricles and of the white matter for each subject. In the case of segmentation failures, we hand-corrected and/or hand-drew the masks. We generated the nuisance covariates by finding the mean time series of voxels within the nuisance masks.

The results from scans in which participants exceeded our a priori motion threshold of 2-mm rotation or translation were handled by removing the frame in which the event occurred and the 2 preceding frames before preprocessing. This procedure was necessary for only one of the 28 reported scans. Any significant relationships between movement parameters and modularity were ruled out by examining data for Pearson correlations between movement parameters and modularity scores.

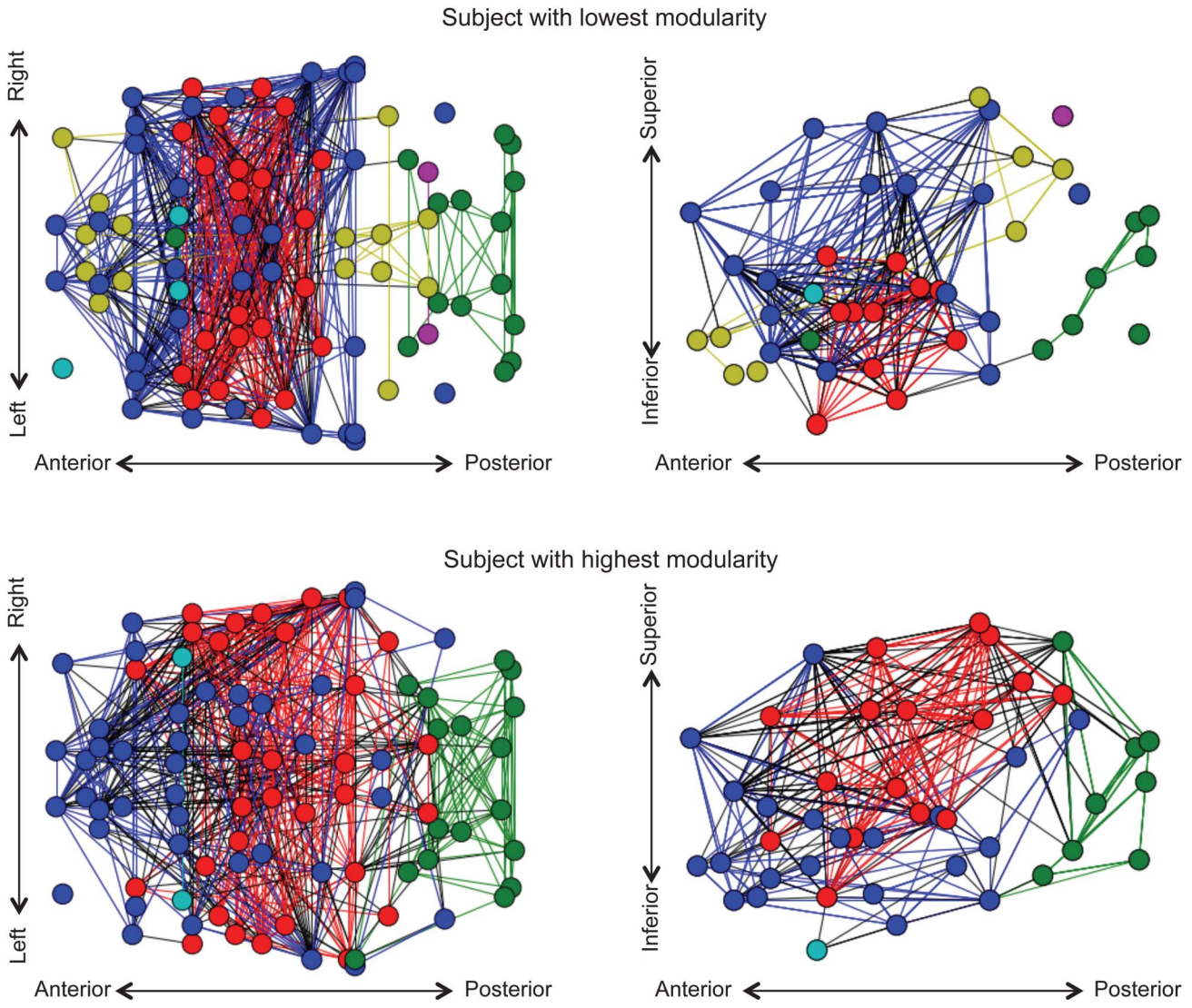
fMRI data analysis: Modularity analysis. Blood oxygen level–dependent fMRI signal was used to identify large-scale brain functional networks on a subject-by-subject basis. Whole-brain parcellation was conducted in native space using the anatomical automatic labeling atlas, which parcellates the brain into 90 cortical and subcortical (45 per hemisphere) regions of

interest.[19] With each region of interest serving as a network node, use of the standard anatomical atlas allowed us to define anatomically standardized brain networks for each subject. Adjacency matrices were constructed by computing Pearson correlations between the mean time series (i.e., average across voxels) of each pair of nodes.[20] Adjacency matrices were binarized by applying a threshold fixing the total number of edges to a particular connection density, allowing direct comparison of network properties across participants.[21,22] Network analysis was conducted across a range of connection densities (0.05, 0.075, 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, and 0.25), ranging from 0.05 to 0.25 in increments of 0.025, to reduce the impact of threshold selection on results. The Python package NetworkX was used to create and analyze the graphs.[23]

Graphs were partitioned into subnetworks (i.e., modules) using a simulated annealing technique that maximizes modularity across the brain.[24,25] This data-driven approach results in a network partition that maximizes modularity without taking into account a priori knowledge of brain network organization or specifying the number of networks that must be present. It achieves this by searching for the partition that maximizes the number of connections within modules and minimizes the number of connections between modules. The modularity metric reflects the strength of modular network organization by summing the difference between the fraction of within-module connections to the total fraction of connections across modules, thus ranging from 0 (random) to 1 (completely modular). The extent of modular organization was characterized for each individual, with the integrated modularity—the sum of modularity values across all computed connection densities—used as the primary metric of interest. Although the report focuses on the integrated modularity metric, all results were consistent across individual cost values.

RESULTS **Baseline measurements of modularity.** We computed integrated modularity values, the sum of modularity values across all connection densities, for each subject (range: 2.35–4.39; median: 3.44; mean: 3.5 ± 0.6). Figure 1 illustrates networks for subjects

Figure 1 **Examples of modular brain graphs**



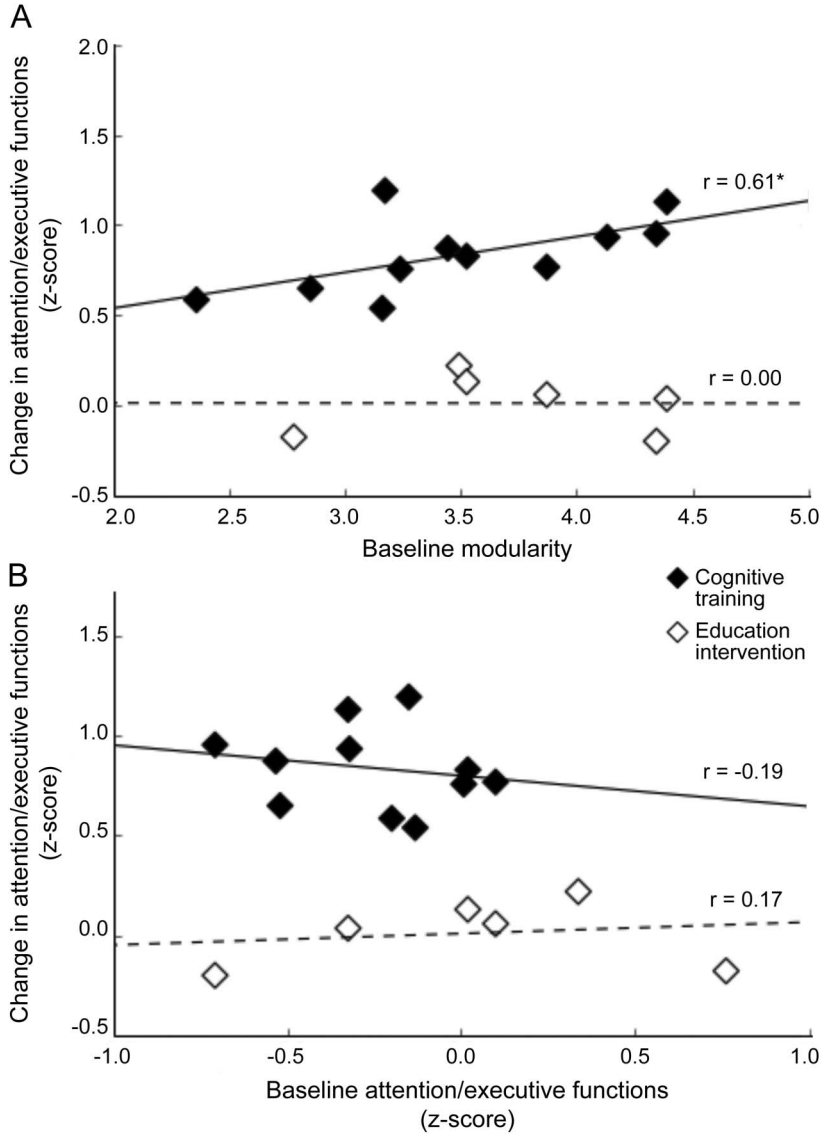
Brain graphs illustrating identified modules, with the nodes and edges in each module represented by a different color. Representative graphs are shown for the individuals with the lowest and highest baseline modularity (respectively, 0.25 and 0.48) at a cost of 0.15.

with the lowest and highest modularity values at cost 0.15 (range: 0.25–0.48; median: 0.36; mean: 0.37 ± 0.07), for which all brain graphs were composed of 3 to 6 modules. To assess whether a relationship between the presence or absence of visible lesions and baseline modularity existed, we compared modularity scores for the individuals with brain lesions against those without lesions. We found no significant difference in modularity scores in patients with and without lesions (data not shown).

Relationship between baseline modularity and the effects of cognitive training. As previously reported, performance on tests of attention/executive functions improved after the cognitive training intervention, but not after the education intervention.[11] Here, we determined the extent to which improvement in attention/executive functions after cognitive training could be predicted by differences in baseline modularity (measured before training). We found that baseline modularity values correlated positively with improvement in attention/executive functions after cognitive training (Pearson correlation $r = 0.61$, $p < 0.05$; see figure 2A). Specifically, patients with higher baseline modularity exhibited greater improvement in attention/executive functions with cognitive training relative to those with lower baseline modularity. There was no relationship for the education intervention.

Relationship between baseline neuropsychological function and the effects of cognitive training. We determined the extent to which changes in attention/executive functions after cognitive training could be predicted by differences in baseline executive function (measured before training). We found no significant correlation between these 2 variables (Pearson correlation $r = -0.19$, $p > 0.57$; see figure 2B). As expected, baseline neuropsychological function did not relate to changes with the education intervention.

Figure 2 Relationship between baseline measures of integrated modularity and behavior with response to training



Relationship of baseline integrated modularity (A) or baseline attention/executive functions (B) with change in attention/executive functions after cognitive training (black symbols) and education interventions (white symbols). *$p < 0.05$.

DISCUSSION We have proposed that the integration of distributed brain networks has a critical role in the recovery and rehabilitation of goal-directed cognitive control functions.[6,26] We investigated the relationship between a property of brain network organization and the response of patients with acquired brain injury to cognitive training and education intervention. Before participation in cognitive training, we assessed brain network organization using the network parameter modularity, which indexes the balance between integration and segregation of brain networks. Patients engaged in a constrained "rest task" during 5-minute fMRI scans, which allowed for a brief assay of functional network organization during a period of tonic attention regulation. Baseline modularity measured during a regulated "resting" brain state predicted the magnitude of improvement in attention/executive functions observed following cognitive training. As expected, we did not observe improvement in attention/executive functions or a predictive relationship of modularity following the education intervention (which assessed for practice effects via repeated testing). The sample size for the education intervention was small, but our previous study with a larger group did not observe a systematic change in attention/executive functions following the education intervention.[11] Of note, baseline attention/executive functions did not predict response to training, supporting the notion that brain measures may provide markers of function not captured by traditional behavioral measures.

Measurements of large-scale brain network organization have been useful for explaining injury-related cognitive deficits,[27,28] symptom severity,[29] and recovery.[30] Modular network organization may be of particular importance for patients with acquired brain injuries. Theoretical work suggests that modularity constrains the flow of information across the brain[2] and enhances the ability of networks to rapidly reconfigure in response to environmental influences and tasks.[3,4,31] Lower modularity (but not other overall network measures) was shown to be associated with more severe symptoms in patients with mild postconcussive syndrome 6 months postinjury,[32] suggesting that disruptions of modular network organization may interfere with processes of recovery from brain injuries more generally. We extend this work by identifying a relationship between modularity and learning in the context of rehabilitation training.

Our findings further the study of neural factors that influence learning, suggesting that modularity during a regulated brain network state may mediate an individual's readiness to learn and engage in training. Fluctuations in brain state influence brain activity and behavior.[33] Modularity influences learning and behavioral plasticity, reflecting an important aspect of a dynamically regulated brain state.[5,34] Regulation of brain state between periods of engagement in goal-directed cognitive tasks likely influences performance during later episodes of goal-directed action.[35] So-called "resting" states are associated with higher modularity than "working" states,[36] suggesting that more modular network configurations may serve as an ideal launching platform for engagement in goal-directed cognition. The brief assay of functional brain organization developed for the purpose of the present study uses a tonic self-regulation task. We chose this method to provide some constraint on the intended mental activity during scanning. It is not clear whether similar results would be found with a more standard, unconstrained "rest" scan; future work could explore differences between the constrained tonic self-regulation task used in the present study (relax and focus on breathing) vs the more common unconstrained "rest" task (mind wandering). It is possible that the tonic attention regulation task may be a more sensitive predictor of learning and focus than a standard, unconstrained rest task.

Variability in brain structure, especially from heterogeneous brain lesions, has been a challenge for the study of brain–behavior relationships in recovery and rehabilitation. Network theory provides a potential unifying framework for addressing questions in the context of structural variability across individuals. Quantitative measures that characterize large-scale brain network organization may be useful for understanding brain function in patients, providing information beyond structural, behavioral, and other functional measurements. For example, the effects of heterogeneous lesions have been difficult to characterize, but we previously demonstrated that the effect of focal lesions on brain network organization among patients with focal lesions depends on the role that the lesion site has in large-scale brain networks.[8] Specifically, lesions to regions important for communication between functional networks lead to more profound disturbances to modular network organization than lesions to regions important for communication within functional networks. Even when other techniques reveal no apparent structural damage, disrupted brain function may be apparent in properties reflecting characteristics of functional brain networks.[37,38] In the present study, the magnitudes of modularity measured could not be explained by whether or not patients had visible lesions on structural MRI scans.

The link between functional brain network organization and behavioral consequences of training/learning have not been well explored. Studies that investigate neural factors that may underlie variability in response to training are particularly scarce. This study provides a preliminary foundation to build on, which suggests that biomarkers of brain network organization such as modularity may have utility in guiding rehabilitation approaches after brain injury. A recent investigation of the relationship between brain network parameters and response to a behavioral intervention (placebo analgesia induced by verbal suggestion) also documented an association between baseline functional network organization and efficient translation of behavioral information into a therapeutic response.[39] This line of work supports the possibility that further characterization of individual brain network properties may contribute to advances in the personalization of medical treatment, where measurements reflecting brain network properties may inform treatment approaches by adding to information from structural brain characterization and measurements of behavior.

The present study has some notable limitations, while providing hypotheses for future investigation. The study design involved a preset duration of training for the purposes of standardizing the study protocol, and thus the study did not address questions regarding possible differences with other durations of therapy. Also, the education intervention had a small sample size. This arm was included in the study design primarily to control for effects not specific to the cognitive training intervention, such as changes from random fluctuation or from repeated testing. Although the main findings for the cognitive training intervention are not affected by the smaller comparison sample, the data may not be sufficient to confidently confirm the specificity of the main findings.

Moreover, a larger overall sample size for both types of interventions may allow for examination of other brain–behavior relationships.

This line of research will benefit from further investigations of the importance of brain network parameters for the timing, duration, and approach to rehabilitation training after brain injury. It is possible that some individuals are more or less "ready to learn" than others, and that different approaches could be valuable for different patients based on parameters of brain-state regulation. Investigation of the time course of changes in network properties and behavior over the course of training may reveal important insights into the biological mechanisms that support the learning process. Furthermore, the predictive value of modularity incites questions regarding to what extent brain network parameters may be modified by training, medications, or other intervention approaches. For example, is it possible that the regulation of functional brain network organization might be a target of intervention, in preparation for other rehabilitation treatments? Changes in network parameters with cognitive training will be a subject for future work using longitudinal MRI. These lines of investigation have much to reveal about the role of brain network function in the learning process and the parameters that underlie individual differences in disruption and recovery after brain injuries.

AUTHOR CONTRIBUTIONS

K.L.A., A.J.-W.C., T.N.-A., C.G., E.M.N., and M.D. designed and conceptualized the study. K.L.A., A.J.-W.C., and M.D. were involved in analysis or interpretation of the data as well as drafting and revising the manuscript for intellectual content.

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DISCLOSURE

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