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Examining network dynamics after traumatic brain injury using the extended unified SEM approach

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Abstract The current study uses effective connectivity modeling to examine how individuals with traumatic brain injury (TBI) learn a new task. We make use of recent advancements in connectivity modeling (extended unified structural equation modeling, euSEM) and a novel iterative grouping procedure (Group Iterative Multiple Model Estimation, GIMME) in order to examine network flexibility after injury. The study enrolled 12 individuals sustaining moderate and severe TBI to examine the influence of task practice on connections between 8 network nodes (bilateral prefrontal cortex, anterior cingulate, inferior parietal lobule, and Crus I in the cerebellum). The data demonstrate alterations in networks from pre to post practice and differences in the models based upon distinct learning trajectories observed within the TBI sample. For example, better learning in the TBI sample was associated with diminished connectivity within frontal systems and increased frontal to parietal connectivity. These findings reveal the potential for using connectivity modeling and the euSEM to examine dynamic networks during task engagement and may ultimately be informative regarding when networks are moving in and out of periods of neural efficiency.

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Introduction

Traumatic brain injury (TBI) is the most common neurological disorder in young adults, with an annual incidence of 1.7 million and societal costs including lost productivity estimated at $60 billion (Centers for Disease Control and Prevention, N.C.f.I.P.a.C.; Available from: http://www.cdc.gov/traumaticbraininjury/). Unfortunately, there remains much unknown about how neural systems adjust to TBI and the factors associated with recovery. Over the past decade there has been a dramatic increase in the use of functional neuroimaging techniques such as blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) to examine cognitive, sensory, and motor dysfunction in neurologically impaired samples. To date, fMRI has provided new avenues to study brain functioning and unparalleled opportunities to examine brain disorders.

In the clinical neurosciences, fMRI methods have traditionally been used to document between-group differences with focus on mean BOLD signal change between healthy and clinical samples. While informative, these between-group comparisons are often insensitive to individual differences in response to injury. This problem is particularly important in neurological disorders that are notoriously heterogeneous, such as TBI; findings observable at the group level likely reflect only gross brain responses and are unlikely to be sensitive to injury-specific adjustments in neural systems, making any inferences about the individual unfeasible. The goal of the current study is to demonstrate the use of a novel connectivity method for documenting changes in neural networks over time in the individual after TBI. We aim to elicit short-term plasticity via repeated exposure to a

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demanding cognitive task. We focus our analyses on within-subject change in neural network responsivity by examining network changes before and after task practice to observe how a disrupted neural network accommodates a novel task. By focusing on individual change using advanced brain connectivity modeling, the objective is to move beyond the common practice of documenting task-specific, regional brain responses that differentiate clinical and healthy samples. Instead we directly address the fundamental heterogeneity in TBI by analyzing the subtle network shifts occurring in the individual associated with performance change during task acquisition.

Functional imaging and network change after TBI

One rapidly growing literature using functional imaging methods to examine deficits after neurological compromise has focused on information processing and working memory (WM). Working memory is the ability to maintain a small amount of information "in mind" for online manipulation and use (Baddeley and Della Sala 1996) and one of the most widely studied areas of cognitive dysfunction in the clinical fMRI literature. Deficits in WM and processing speed have received extensive attention because they are at the foundation of numerous other cognitive processes and deficit here is nearly universal following neurological compromise (Albantakis and Deco 2011; Army Individual Test Battery: Manual of directions and scoring 1944; Cohen et al. 2000; Collette et al. 1999; Deluca et al. 2000; Demaree et al. 1999; Friston 2009; Gates and Molenaar 2012; McDowell et al. 1997; Morris and Baddeley 1988; Smith et al. 2011). (Albantakis and Deco 2011; *Army Individual Test Battery: Manual of directions and scoring* 1944; Cohen et al. 2000; Collette et al. 1999; DeLuca et al. 2000; Demaree et al. 1999; Friston 2009; Gates and Molenaar 2012; McDowell et al. 1997; Morris and Baddeley 1988; Smith et al. 2011).

With few exceptions (see Sanchez-Carrion et al. 2008b), there have been relatively consistent results in the WM literature, with studies of moderate-severe TBI most commonly demonstrating increased involvement of parietal and prefrontal cortex (PFC), and in particular right PFC (for review see Hillary et al. 2006). However the meaning of this neural recruitment remains uncertain (see Hillary 2008; Turner and Levine 2008; Sanchez-Carrion et al. 2008a,b; Hillary et al. 2006; Maruishi et al. 2007; Scheibel et al. 2007) because it is unclear that this increased resource use has anything specifically to do with TBI given that similar PFC recruitment is commonly observed in healthy adults during high task loads and appears to be a non-specific consequence of neurological disruption more generally (Hillary et al. 2006; Hillary 2008). For example, the common finding of right PFC recruitment may not be directly linked to pathophysiology in TBI given the purported role of the right hemisphere in handling task novelty and cognitive challenges (Pardo et al. 1991; Gazzaniga 2000; Honma et al. 2010). At least part of the difficulty in determining the nature of PFC recruitment is that functional imaging studies comparing healthy and TBI samples have a host of persistent methodological problems making data interpretation complex. Investigators focusing on group differences must guarantee identical task performance between the samples; only when comparable performance is achieved can one hope to reliably interpret the meaning of BOLD signal change between groups (Hillary 2008; Price and Friston 1999; Price et al. 2006; Price and Friston 2002; Friston et al. 1996). This requirement for performance control is inherently limiting for investigators who are primarily interested in studying *deficit* after injury. Moreover, there is variability in task-induced brain activation for even very well defined cognitive tasks (e.g., the "n-back", the most commonly used working memory task); neural involvement is greatly influenced by factors such as age, education, and, most importantly, task performance (Bergerbest et al. 2004; Braver et al. 1997; Rypma et al. 2006). Given the natural variation in task-induced networks representing normal cognitive functioning, isolating the meaning of "abnormal activation" profiles is a daunting task, even before considering the influence of a brain disorder with heterogeneous outcomes such as TBI. Given these considerations, the tradition of documenting the mean fMRI signal change alone is not ideally suited to inform us how flexible neural systems adapt to injury and disease. Such an approach successfully isolates regional mean differences in the fMRI signal during a task, but simply leaves unknown what the rest of the brain is doing to adjust to injury. A primary point of emphasis in the current study is to focus on *network change in the individual* and we will make use of a "task-practice" paradigm in order to examine shifts in dynamic networks occurring over the course of task engagement.

Developments in effective connectivity Beginning with seminal work by McIntosh and Gonzalez-Lima in the 1990s (McIntosh and Gonzalez-Lima 1991; 1992) there has been significant interest in adapting effective connectivity methods to model brain data. The past 15 years has seen a proliferation of available statistical techniques and there has been some application to the understanding of brain disorders (Rosanova et al. 2012; Leavitt et al. 2012; Hillary et al. 2011; Turner et al. 2011), but successful application of these modeling approaches has been slow. There remain significant problems for nearly every method to date; recent work by Smith et al. (2011) highlights the difficulties that arise when attempting to identify directed relations among neural network nodes. One consistent approach in effective connectivity is to determine the chronology of neural events by integrating information about "lagged" (or time dependent as in Granger Causality/ Vector Autoregression) and contemporaneous (or co-occurring as in structural equation modeling) influences on the model. The critical evaluation of effective connectivity models by Smith and colleagues calls into question the likelihood that "lagged" effects hold any physiological meaning given the common failure to model the BOLD signal and the temporal difference in the BOLD response between brain regions (Friston 2009). Overall, the findings by Smith and colleagues are sobering and reveal that, while correlational analyses are largely reliable and consistent, when comparing 28 approaches for effective connectivity in data simulations, none were capable of adequately modeling the direction of influence between-nodes.

Beginning with work by Kim et al. (2007), recent developments in structural equation modeling, including the extended unified structural equation modeling, (euSEM) (Gates et al. 2010; Gates et al. 2011) and group iterative procedures (Gates and Molenaar 2012) have worked to permit valid and reliable measurement of effective networks that surpass previous methods examined by Smith and colleagues. The euSEM is capable of reliable estimates of both contemporaneous (i.e., concurrent) and lagged (i.e., time dependent) directed relationships among regions of interest (ROIs). We recently used the euSEM to examine "early" vs. "late" task acquisition effects after TBI (Medaglia et al. 2011). Because the euSEM can model the effect of task input on specific connections; using this procedure we observed an important hemisphere effect with individuals with TBI showing greater task input in the right hemisphere whereas the influence of task input was observed primarily in the left hemisphere in healthy adults.

For the current study it is a goal to examine within-subject change after TBI in a formal task practice paradigm. We will make use of a recently developed procedure for valid group modeling (Group Iterative Multiple Model Estimation, GIMME) (Gates and Molenaar 2012) in order to directly examine the influence of task practice on an extended 8-node network. There are several advantages to the use of the euSEM with GIMME. GIMME detects signal from noise by looking across individuals to arrive at a group model that ideally describes individuals comprising the group. Recently GIMME was shown to produce valid group models even in the presence of heterogeneity across participants (invaluable for the current study), which is unique to this approach (Gates and Molenaar 2012). To do so, GIMME first arrives at a group model (i.e., a set of paths that explain the majority of individual's models) then, using the group model as a foundation, opens up paths on the individual-level that will improve model fit indices for each individual. This procedure affords a feature-based approach to grouping data that retains individual model structures as opposed to concatenating data across individuals which is the current standard but can yield misleading results (Kim et al. 2007). GIMME can be applied in a purely data driven manner (when no a priori information about the connectivity maps are available), in a partly data-driven and partly-confirmatory manner (in which particular connections are a priori included in the solution and/or particular connections are forbidden to be included in the solution), and in a purely confirmatory manner. GIMME is publicly available at http://www.personal.psu.edu/kmg311/Programs/GIMME%20Program/.

While we focus here on modeling BOLD fMRI data to determine inter-node influence, it should be emphasized that the underlying characteristics of neuronal action (e.g., timing and synchrony of dendritic and axonal activity) cannot be isolated based upon the BOLD response alone. The low temporal resolution inherent in fMRI (the hemodynamic response essentially operates as low resolution temporal filter for the neural response) and biological nature of the vascular response (which may differ across regions) makes it impossible to assess activity on the temporal order at which neuronal activity occurs (i.e., milliseconds). What effective connectivity maps using fMRI data can show is if the BOLD signal in a region statistically predicts the BOLD signal in itself or other regions after considering other predictors of regional activity. This includes modeling the autoregressive influence of an ROI on itself at a previous time point. For our purposes, this will be the basis for determining "direction of influence" and arrows between nodes are used to identify these statistical relationships.

Goals of this paper: We aim to examine how a disrupted neural network acquires a novel task with repeat exposure (i.e., task practice). Here we advance our previous work in a group of individuals with chronic TBI (see McIntosh and Gonzalez-Lima 1992; Gates et al. 2010) with the goal of: 1) examining connectivity changes after task practice, 2) using the GIMME, a novel grouping procedure within the euSEM, in order to directly examine within-group heterogeneity and permit a data-driven approach to TBI sub-groups. Previous work examined the influence of practice on mean signal change in prefrontal cortex (Hillary et al. 2011) and connectivity during task acquisition without formal task practice (Medaglia et al. 2011), and the current study will combine these analyses using a refined approach (GIMME, see Gates and Molenaar 2012) to examine the influence of practice on brain connectivity. We anticipate that focusing on system-level brain changes over time in the individual matches the scale that treatments are actually delivered (i.e., patient-specific response).

Study hypotheses

Through the use of task practice designs we anticipate network changes associated with improving performance.

Hypothesis 1: Over the course of new learning, the euSEM will reveal a diminished role of the right prefrontal cortex relative to the left prefrontal cortex and this effect will be larger for individuals who show better learning. This hypothesis is based upon the cross-sectional work examining mean BOLD signal changes revealing significant recruitment of right PFC during periods of slowed processing (see Hillary et al. 2006) which may be attributable to increased requirements on attentional control resources (Pardo et al. 1991; Honma et al. 2010).

Hypothesis 2: The euSEM will reveal diminished influence of frontal areas over posterior areas during task practice and this effect will be larger for individuals who show better learning. This hypothesis is based upon the presumption that as task procedures are formalized, there will be greater task representation in posterior regions and diminished demand on anterior cognitive control systems.

Methods

Subjects Twelve individuals with TBI (ages 19-55) were recruited at least 1-year post injury (see Hillary et al. 2011; Medaglia et al. 2011). TBI severity was defined using the Glasgow Coma Scale (GCS) in the first 24 h after injury (Teasdale and Jennett 1974). GCS scores from 3 to 8 were considered “severe” and scores from 9 to 12 were considered “moderate”. Candidates for the study were excluded if they had a history of previous neurologic disorder such as TBI, seizure disorder, or significant neurodevelopmental disorder such as schizophrenia or bipolar disorder. Finally, participants were excluded if they remained in treatment for concomitant spinal cord injury, orthopedic injury, or other injury making it difficult to remain still in the MRI scanner. Patients with focal contusions and hemorrhagic injuries were included unless injuries required neurosurgical intervention and removal of tissue resulting in gross derangement of neuroanatomy. Of note, the focus here is on within-subject change in the TBI sample as it relates to performance change and recovery. While an age and education matched healthy control sample was recruited and can be referred to for context, these data are de-emphasized given the primary goal to examine network change during task practice in TBI.

Neuropsychological assessment

Cognitive testing emphasized WM, processing speed, and response inhibition. Tests include the Digit Span test from the WAIS-III (Wechsler 1997), the Stroop task (Jensen and Rohwer 1966; Stroop 1935), and the Trail Making Test, trials A & B (Army Individual Test Battery: Manual of directions and scoring 1944).

Methods for MRI data acquisition

All imaging data were acquired using a Philips 3 T and 6-channel SENSE head coil (Philips Medical Systems, Best, The Netherlands) or a Siemens 3 T Magnetom scanner. While the goal of this study focuses largely on within-subject comparisons, efforts were made to guarantee comparability between scanner datasets including using comparable acquisition parameters. Detailed analysis of the BOLD signal characteristics within this dataset revealed no differences in the data between MRI machines in signal-to-noise ratio for detecting mean signal changes during task perturbations. First, high resolution T_1-weighted MPRAGE images (9.9 ms/4.6 ms/8° repetition time/echo time/flip angle (TR/TE/FA), $240\times204\times150$ mm^3 field of view (FOV), $256\times205\times150$ acquisition matrix, 2 averages) were acquired. Echo planar imaging (EPI) parameters consisted of: 2000 ms/30 ms/89°, TR/TE/FA, 230×230 mm^2 FOV, 80×80 acquisition matrix, 34 4-mm-thick axial slices with no gap between slices. Data preprocessing of the fMRI data was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm8). Data preprocessing steps included realignment of EPI data, coregistration of the EPI and T1 MPRAGE, normalization to a standardized T1 template, and spatial smoothing with a Gaussian kernel of 8 x 8 x 10 mm^3 (for other data preprocessing details see 33,40).

Cognitive paradigms for examining processing speed and WM To examine connectivity we use the n-back, a well-established task to examine WM functioning (Kirchner 1958; Speck et al. 2000) and all methods are consistent with Medaglia et al., (Medaglia et al. 2011). This block-design paradigm begins with a 30-s baseline followed by 8 individual 20 s experimental blocks alternating with 14-s baseline measurements (i.e., fixation stimulus). The task included a 1-back and a 2-back, with 72-point font size letters presented in the center of the screen every two seconds (ten letter presentations per block) in pseudo-random order for twenty-second “on” blocks. The subjects were instructed to press a response button as quickly as possible to the target stimuli, where target stimuli were defined as whenever the current letter was the same as the letter immediately preceding it (1-back task) or two letters prior (2-back task). During each 10-letter block, three or four target stimuli were presented at random time points to which subjects should respond. During each rest period, subjects were instructed to fixate on a small asterisk presented at the center of the display screen. Subjects performed one run each of the 1-

back and 2-back in the scanner. Subjects then engaged in task practice outside of the scanner, during which they completed one novel run of 1-back and one novel run of 2-back that followed the same design described above. Subjects were then permitted to take a ten-minute break. Finally, subjects re-entered the scanner and performed one more run of 1-back followed by a run of 2-back using identical parameters and stimuli as in the first session to facilitate new learning. For our purposes, we focus on the 2-back to document change in network connectivity before and after task practice.

Determining activation for WM tasks For both WM tasks, activation was determined by comparing change in the hemodynamic response during the 20-s experimental blocks against baseline (i.e., fixation) using a *t*-test, a minimum cluster level of 10, and a statistical threshold set at $p<.001$ (Note: a liberal alpha level was maintained in order to guarantee inclusion of the full WM network). There were two reasons for not including a control task as a baseline here. First, it is not a primary goal in this study to isolate specific cognitive mechanisms (e.g., separate WM encoding from rehearsal); the goal is to examine changes in neural networks as they relate to task performance. Second, as noted above, there are a number of methodological pitfalls associated with using complex control tasks in clinical samples, including differential subtraction between subjects (Hillary 2008; Price and Friston 2002).

Procedure for euSEM and GIMME The procedure for using the euSEM is consistent with Hillary et al. (2011), but with the addition of the recently developed Group Iterative Multiple Model Estimation (GIMME; Gates and Molenaar 2012). The covariance matrices used for the euSEM analysis (or uSEM when there is no influence of cognitive task modeled) include the ROI time series at time t (where each "t" is a single brain volume or TR) and the same ROI time series at the next time t-1 (lagged series). For the euSEM analysis, the covariance matrices also include two time series of the effects of task input (for both t and t-1) convolved with a canonical hemodynamic response function. The bilinear series examines the influence of task input on the relationship between ROIs by examining each ROI time series at each time t multiplied by the convolved task input series at time t.

For group data, the euSEM and uSEM are fit using GIMME which is initiated by comparing a null model to each subject's data. This results in a matrix of Lagrange Multiplier equivalents, called "modification indices" (Jöreskog & Sörbom 1992) and indicates the degree to which each individual's model would improve if a given parameter was freed (i.e., a connection was created). Parameters for both lagged and contemporaneous effects are modeled for the uSEM (no task). When considering the influence of task "input", the euSEM is used to model the lagged and contemporaneous as well as task and bilinear effects. The GIMME program makes use of the aforementioned modification indices to identify which parameter, if freed, would improve the greatest number of subjects' models to the greatest extent. The goal at this stage is to identify the ideal model from which group inferences may be made, so it is required that the majority of individuals' models improve if a given parameter is freed. The criterion for how many subjects' models must improve if the parameter is freed, or the "similarity criterion", was set to be 75 % based upon the recommendations made by Smith et al. (2011) based upon session length [(e.g., 60 min.: 100 %; 10 min.: 95 %; 5 min.: 77 %; 2.5 min.: 59 % (p.887)]. The program repeats these steps iteratively until the criterion is not met and those connections not meeting the 75 % criteria are pruned. Next, GIMME identifies connections to free on the individual level in a semi-confirmatory manner. Instead of starting with an empty model, the first iteration applies the group structure to the individual and estimates the connection weights. Then, the automatic search procedure within Lisrel identifies iteratively which parameter according to the modification indices would optimally improve the model. Finally, nonsignificant betas are removed (providing they do not exist for the group structure) and a confirmatory model is used for the fit. For greater detail regarding this procedure please see (Gates et al. 2010; Gates et al. 2011; Gates and Molenaar 2012).

Rationale for analytic approach

To examine the hypotheses, we use the GIMME procedure to compare subgroups of subjects based upon changes from pre to post practice during the n-back. For our purposes we model 2-back data where we anticipate the greatest load demand and potentially greater network shifting after task practice. The goal of this analysis is to illustrate the use of this connectivity approach in examining heterogeneous responses. In doing so, we aim to determine if natural subgroups emerge that separate subjects based upon task acquisition.

Results

Behavioral performance during the task

Demographic and neuropsychological data are available in Table 1. When examining behavioral data in the scanner, accuracy did not improve in the TBI sample from pre to post practice (pre-practice: 85 %, $SD=16.5$; post-practice $=81$ %, $SD=17.1$). There was variable improvement in reaction time (RT) and given the demonstrated relationship between

Table 1 Demographic, clinical and cognitive variables describing the TBI sample

	Demographic/Clinical Information mean (sd) where applicable
Age	33.4 (11.8), range: 18–53
Education (years)	14.3 (2.8), range: 12–20
Gender	6 m, 6 f
GCS score	4.7 (3), range: 3–12
LOC (days)	9.5 (5.9), range: 1–21
Acute Care Stay (days)	21.4 (16.3), range: 6–60
Acute CT/MRI injury sites (number of subjects)	DAI (4); Right frontal (4); Left frontal (2); parietal (6); PVA (4); Temporal (2)
Time since injury (years)	8.4 (6.6)
Injury Mechanism	MVA =9, MVA-P =1, Fall =1, Sports =1
Trail making test A	34.0 (8.9), *z*-score: −1.28; Ranges: 22–48 (secs)
Trail making test B	83.4 (35.1), *z*-score: −1.05; Ranges: 32–144 (secs)
Stroop	88 (20.3), *z*-score: −0.61; Ranges: 51–112 (raw score)
Digit Span	17.5 (11.3), *z*-score: 0.11; Ranges: 10–22 (raw score)

GCS Glasgow coma scale; *DAI* diffuse axonal injury; *PVA* periventricular area; *MVA* motor vehicle accident; *MVA-P* motor vehicle accident against pedestrian; *SD* standard deviation; Normative data for determining *z*-scores for Digit span were based upon [42], for the Stroop test [55] and for the Trail Making tests [56]

RT and neural recruitment during goal directed behavior (see Hillary et al. 2010; Rypma et al. 2006), we focus here on RT changes. To examine the variability over the course of task practice, we divided each session in half and analyzed them as "early" and "late" effects for both pre- and post-practice. Examining RT early and late both before and after practice revealed nonlinear effects; RT consistently declined from early to late during the first session before practice (pre-practice "early": RT: 822 msecs, SD=181, pre-practice "late": 725 msecs, SD=191). Post-practice, however the sample showed inconsistent learning; roughly half the sample maintained the learning effects or even improved and half showed slower RTs from early to later in the second session and the net effect was no difference from early to late post-practice (Post-practice "early": RT=737, SD=185; Post-practice "late": RT=737, SD=232). We therefore separated the TBI sample into a group of individuals who exhibited reduced processing efficiency or learning loss (LL) during the second session (mean RT=718.9, SD=232.2 early after practice and mean RT=836.7, SD=255.9 late after practice) and a group of individuals who sustained learning (SL) after practice (mean RT=801.5, SD=230.5 early after practice and mean RT=677.4, SD=248.4 late after practice) (see Fig. 1). Based upon these results, we conducted additional euSEM analyses to examine the connectivity in these two distinct subgroups (see Results below). Of note, the LL and SL groups could not be dissociated based upon age, education or other clinical factors such as GCS score or medication use.

Results: pre-practice

The euSEM analysis revealed a common model for the 12 subjects (12-euSEM). Figure 2a shows the results for the most common connections for the TBI group during the pre-practice runs. The common model here reveals PFC connectivity and anterior to posterior connectivity consistent with the frontoparietal attention circuit. There is also consistent between hemisphere communication between the anterior cingulate regions, parietal regions, and the superior cerebellum.

Results: post-practice (Hypotheses 1 and 2)

A model was estimated using GIMME for the 12 subjects for post-practice data sets (see Fig. 2b) where this model represents those connections most consistently observed in 12 subjects during the post-practice period. Similar to the pre-practice findings, the subjects demonstrated PFC interconnectivity (with possible change in the direction of influence) and anterior to posterior connectivity. One significant difference is the highly significant relationships between right ACC and right parietal regions and increasing left to right connectivity in ACC regions. Post-practice results are consistent with pre-practice effects observed in parietal to parietal connections, parietal to cerebellar connections, and between hemisphere connections in the cerebellum.

Post-practice "learners" (Hypotheses 1 and 2)

To permit behavioral change to guide the analysis, we also examined the RTs for all subjects during the post-practice period and separated the subjects based upon the RT findings shown in Fig. 1. We then conducted an additional GIMME analysis using this RT grouping for the LL and SL groups. The results of this analysis are depicted in Fig. 3a,b. Primary findings include overlapping findings between the "sustained learners" and the original post-practice model for many connections including left to right frontal, anterior cingulate, and cerebellar connectivity. These two models also exhibited nearly identical right parietal to left cerebellar and left parietal to left frontal connectivity. The most significant differences were observed in the influence of right PFC on left parietal region and highly

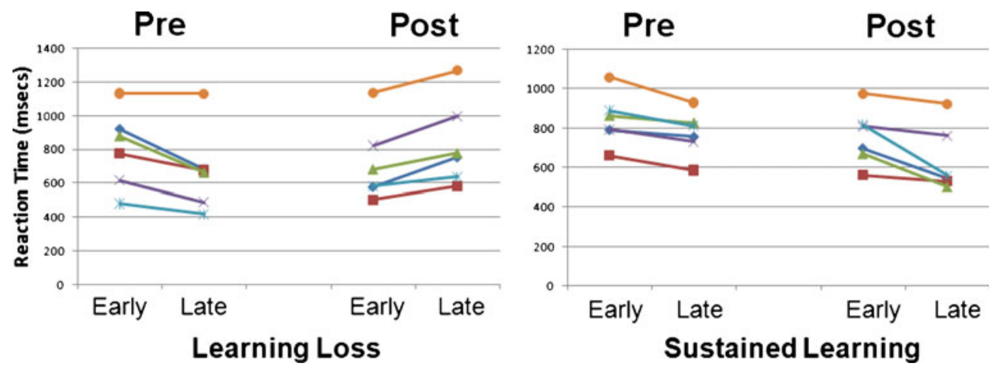

Fig. 1 Reaction times for two TBI subgroups for Pre and Post practice periods during the 2-back. While most subjects show decreasing RTs from early to late pre-practice ("Pre" for both groups), the Learning Loss group shows generally increasing RTs from early to late post-practice. The Sustained Learning group shows either sustained or improved performance (i.e., diminished RTs) from early to late post-practice. The plotted data represents individual subjects

significant connections between left and right parietal regions reciprocally. When examining the 6 subjects with "learning-loss", there were fewer connections with moderately high or higher beta weights (e.g., >.4) and several connections that do not appear in other models. For example, the left PFC to right parietal connection, right ACC to left PFC connection, and influence of ACC on bifrontal regions are not observed in any other model (see Fig. 3a, b). These models are heretofore referred to as the LL-euSEM and SL-euSEM for the 6-subject euSEM results for the LL and SL groups. Of note, while these two groups differ for RT by design, there did not appear to be consistent trends in accuracy that could account for the slowing in the LL group (i.e., speed vs. accuracy tradeoff) (LL accuracy pre =79 %, post =78 %; SL accuracy pre =86 %, post =82 %). Comparison of neuropsychological test results revealed comparable numbers between subgroups but the mean education for the SL group was greater by more than 3 years (SL mean =15.8, sd=3.4; LL mean =12.6, sd=1.2). Also the mean "time since injury" was greater in the SL group (SL mean =10.4 years, sd=7.6; LL mean =6.5 years, sd=5.6), although time since injury held only very weak correlation to neuropsychological performance (Trails B r=0.24; Stroop r=−0.16; Digit Span r=0.07).

Discussion

The goal of this paper was to demonstrate the use of a recently developed statistical procedure for examining heterogeneous network responses after TBI. The modeling approach used here, euSEM with GIMME, permits unbiased modeling of network connections and one of the most reliable grouping procedures available for effective connectivity (Gates and Molenaar 2012). Here we make use of these analytic tools to examine short-term network changes associated with practicing a WM task after TBI.

The convention of examining mean BOLD signal change provides a snapshot of the most salient topographical regions associated with experimental stimulation. This approach leaves much unknown about how the involved regions interact, their relationship to behavior, and network dynamics over time. Ideal rehabilitative efforts after TBI target symptoms at the individual level and we anticipate that functional imaging studies may provide greater information for intervention in TBI if the approach focuses on: 1) within-subject change, 2) dynamic neural networks.

The analyses conducted here were meant to be illustrative of how a novel effective connectivity approach can be used to examine plasticity in TBI and they reveal several findings worth commentary. Based upon the study hypotheses, we anticipated that ideal task acquisition (learning exhibited as faster RTs) would be reflected as 1) diminished role of right PFC on the left hemisphere, and 2) greater representation in posterior attentional systems, or parietal connectivity, and diminished DLPFC and ACC connectivity. Partial support for these hypotheses was observed, in particular when comparing the LL and SL models (see below).

When considering all four models (pre-, post-, LL, and SL-euSEMs), several "universal" connections were observed: 1) left to right anterior cingulate connectivity, 2) inter-cerebellar connectivity with greater left influence over right Crus I, and 3) between-hemisphere parietal communication with greater influence of the right hemisphere on the left. These connections may represent basic network communication, or network "attractor states" that permit fluid, efficient functioning (see Albantakis and Deco 2011; Katori et al. 2011). If so, further examination into the consistency and robustness of these connections will determine if these components of the network serve as an anchor around which

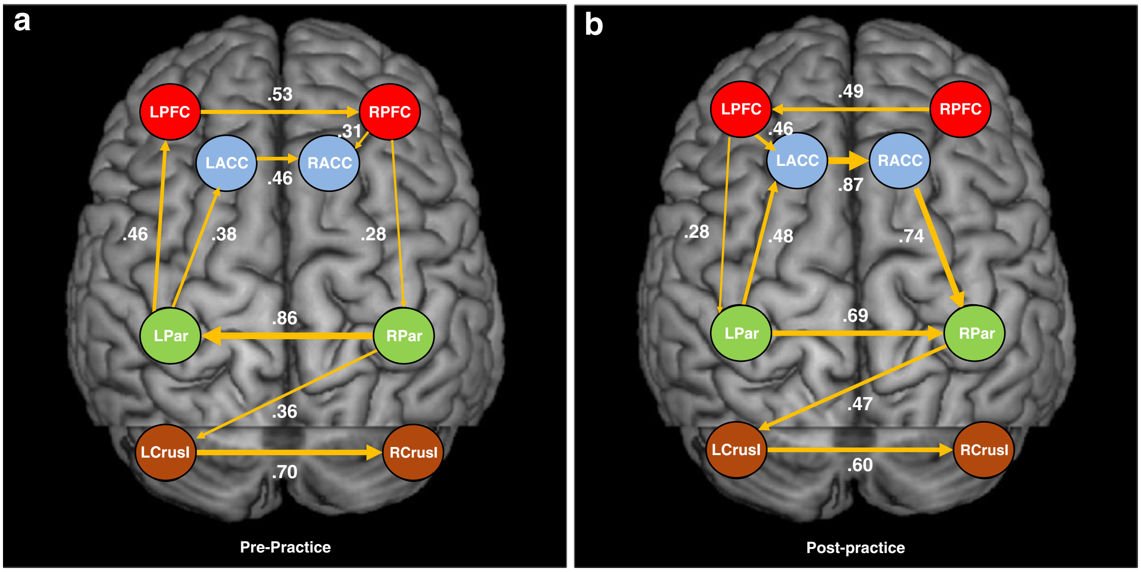

Figure 2a,b: Network models for pre-practice (2a) and post practice (2b)

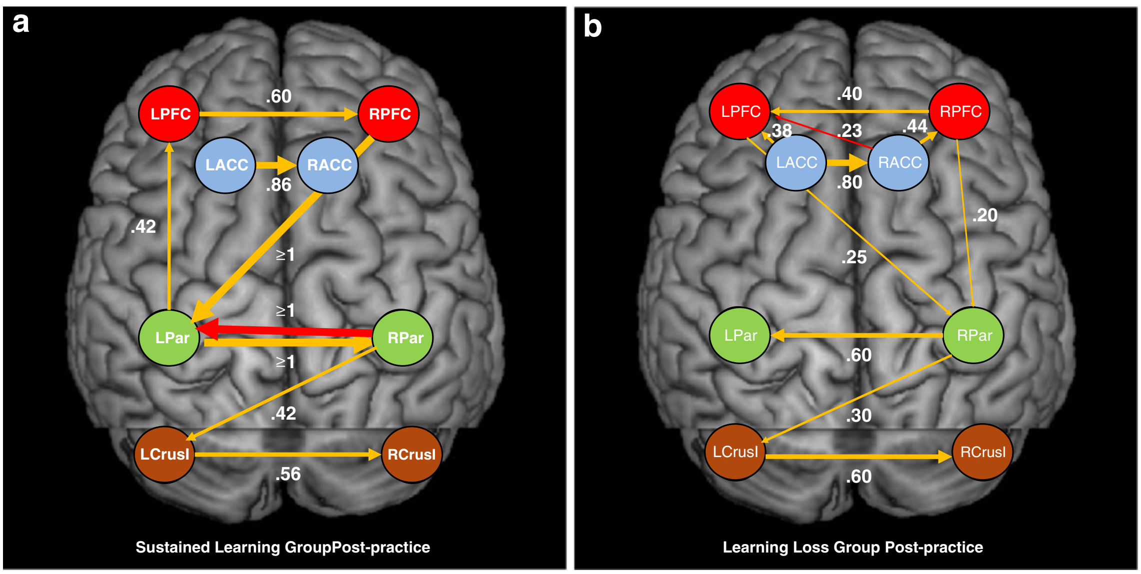

Figure 3a,b: Sustained learning group post-practice (3a) and learning loss group post practice (3b)

Fig. 2 **a**,**b**–3 **a**,**b** Connectivity results for separate euSEM with GIMME models with arrows indicating the influential relationship between nodes. Each arrow indicates a reliable connection observe within the sample. The "thickness" of each connection is the average beta weight in the group for that connection (beta value labeled for each connection). For all figures: Gold = positive relationship, Red = negative relationship, *L* left, *R* Right, *PFC* prefrontal cortex, *Crus1* Cerebellar Crus 1, *Par* parietal lobe

network plasticity can be expressed. If these fundamental network connections can be reliably identified across studies, samples, and even tasks, investigators may provide nuanced dependent variables for examining the influence of clinical intervention.

With respect to the pre-practice trials, subjects consistently showed the anticipated learning observed as diminished RTs from early to late during the task. Mirroring the consistency observed in these behavioral profiles, euSEM analysis (Fig. 2a) reveals inter-hemispheric connectivity between all homologous regions and greater influence of left on right hemisphere.

Post-practice, not all subjects continued to learn and some even showed slowed performance as the task progressed. In the post-practice analysis, the connections were largely consistent with the model generated prior to task practice, with several notable exceptions. First, the post-practice model demonstrated significant influence of right ACC on right parietal systems not observed in the pre-practice model. Also, the right PFC influence on right ACC is not evident here as it is in the primary model, but left PFC has previously unobserved influence on the left ACC. There is also left parietal to left ACC influence not observed pre-practice. The reason for these discrepancies is not clear, although the mean behavioral performances between the two groups was different; the pre-practice performance was initially 150 ms slower than post-practice (852 ms vs. 702 ms during the "early" period) and the pre-practice group showed significant improvement (127 ms) compared to the post-practice group (0 msecs). Thus, these subtle differences in connectivity may be attributed to a more dynamic network during task acquisition in the pre-practice model compared to the more stable period behaviorally for the post-practice model. That is, the pre-practice model may permit greater malleability as the system moves to an optimal learning state and the post-practice model represents an increasingly stable, less flexible network as learning asymptotes. These data demonstrate some consistency in network dynamics after injury and future work might start with these connection profiles to determine the reliability of these findings and the timeline and predictive validity of these network connections.

To further examine heterogeneous performance responses after task practice, we conducted two additional euSEM analyses based upon subject performance: LL-euSEM and SL-euSEM. When examining the LL-euSEM and SL-euSEM models, there were a number of connection differences between groups. First, the SL-euSEM model was more consistent with the post-practice model, including left to right influence in frontal, anterior cingulate, and cerebellar regions. The post-practice and SL-euSEM models also exhibited nearly identical right parietal to left cerebellar and left parietal to left frontal connectivity. The post-practice and SL-euSEM models are visually distinct and quantitatively different from the LL-euSEM model, with the LL model showing hyperconnectivity between PFC and ACC regions. There is some support for hypothesis one in this finding; diminished learning and/or performance was associated with greater right PFC and ACC influence in the model. Consistent with hypothesis two, where we anticipated greater connectivity in anterior networks in cases of diminished learning and this is also observed. Thus, after task practice, we observe here that greater right hemisphere representation and greater bilateral PFC and ACC cross-talk may have association with diminished sustaining learning. Given the heavy reliance upon PFC and ACC in the LS group, we might interpret this as increased need for attentional control as the task is more slowly processed over time (see Cohen et al. 2000; Miller and Cohen 2001). These observations are consistent with our previous work focusing on the "early" vs. "late" effects in cortical connections in healthy controls; task exposure resulted in diminished connectivity anteriorly and greater anterior to posterior connections (Hillary et al. 2011).

The findings here provide a preliminary look at how a novel connectivity approach can be used to examine task practice and heterogeneous responses after TBI. This approach allows us to separate the notoriously heterogeneous brain responses following TBI by focusing our analyses on within-subject change in neural network responsivity. By focusing on individual change using the most advanced brain connectivity modeling available, the goal is to move beyond the common practice of documenting task-specific, regional brain responses that differentiate clinical and healthy samples. Instead we directly address the fundamental heterogeneity in TBI by examining the subtle network shifts occurring in the individual that predict performance and recovery. There is very little work using connectivity to examine how disrupted neural systems adapt to injury, but we anticipate that such approaches offer unparalleled opportunity to document plasticity after injury from a systems neuroscience perspective (Sporns 2011).

Connectivity modeling offers important advantages for understanding the plasticity that governs new learning and may offer insights into the network shifts that permit task acquisition years after TBI onset. Rehabilitation efforts are geared toward maximizing this potential and connectivity methods may move this field closer to understanding how a disrupted neural system adapts to injury and continues to acquire new information. While there is heterogeneity in the response during this WM task, there are also common connection features that emerge consistently between subjects. These data are encouraging for the use of effective connectivity in heterogeneous clinical samples.

Study limitations and future directions

The current study illustrates the use of effective connectivity to examine hypotheses regarding within-subject change following TBI. However it is not without limitations including a modest sample size of individuals with reasonably heterogeneous background with respect to age and the number of years post injury. Also, this study required the use of separate MRI scanners which may add additional variance during data collection and dampen sensitivity to effects. We anticipate that the focus on within-subject change helps to ameliorate some of these concerns.

As noted above, BOLD fMRI maintains inherent limitations with respect to high temporal resolution measurement. The current data should not be interpreted here as one node "causing" another node to become active. Moreover, ROI-driven work implicitly simplifies an extended network in order to examine those regions purported to play a critical role in functioning. For our purposes, we focused on regions most likely to have been “recruited in traditional WM studies in TBI. Even given the limitations to this method, we do anticipate that the euSEM modeling employed here gives us a sense for a potential hierarchy of the most robust network effects.

For connectivity modeling to advance our understanding of neuroplasticity and inform the next generation of rehabilitation efforts, there are several critical future directions to be pursued. First, the reasons for the differences that we observe between models remains speculative, so continued examination using effective connectivity approaches is needed to document the reliability of these findings, including examination in other groups, tasks, and situations including important demographic (e.g., age) and clinical factors (e.g., diffuse vs. focal injury). The mean values for education and time since injury were different for the LL and SL groups and while neuropsychological performance was comparable, factors such as premorbid education and recovery time may interact after TBI to influence neural connectivity and future work should consider these possible nonlinear effects. Second, with regard to task practice, the current design permitted examination of gross BOLD signal changes using a block design which holds inherent limitations in time scale, offering only a gross overview of the network components involved in the task. Continued network analysis requires use of event-related designs to improve temporal resolution, but also so that connections can be defined as a function of performance change. Effective connectivity approaches such as the euSEM with GIMME now provide the opportunity to include RT or accuracy as a vector of interest, thus allowing for documentation of those connections most highly influenced by performance change (Gates and Molenaar 2012). Finally, advancements by connectivity modeling require verification using additional imaging modalities (e.g., high density EEG, magnetoencephalography), thus providing complimentary data and crucial support that the observed changes are neural as opposed to vascular in nature.

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