Dynamic versus Static Functional Network Analysis after Experimental Rodent TBI

Rachel Fox[1,2], Afshin Paydar[1,2], Azad Azargushasb[1,2], Samuel Vander Dussen[1,2], Neil G. Harris[1,2]

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INTRODUCTION

- Dynamic Functional Connectivity (dFC) shows connectivity at individual timepoints to capture switching between clustered brain states.
- Static Functional Connectivity collapses brain patterns across session time
- dFC has been shown to be more sensitive to certain clinical outcomes and provides the advantage of capturing temporal FC changes surrounding connected brain states.
- **Aim 1:** To investigate the relationship between dynamic brain states and network-level differences as a result of traumatic injury.
- **Aim 2:** To compare the value of dynamic FC as compared to known injury-related differences in static FC and behavioral outcomes.

DYNAMIC FUNCTIONAL CONNECTIVITY

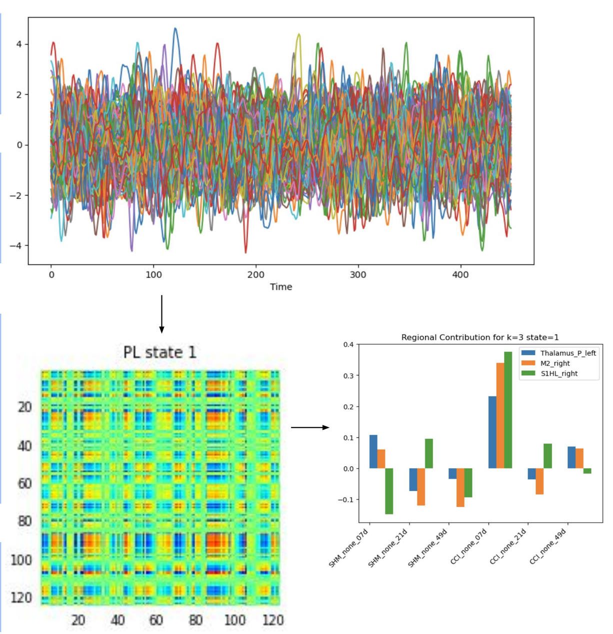
Leading Eigenvector Dynamic Analysis (LEiDA) computes the leading eigenvector for each region, clustering these into recurring brain states.
LEiDA reduces variation while decreasing overlap in the data compared to other dFC methods.

Resting-state or task-based time course

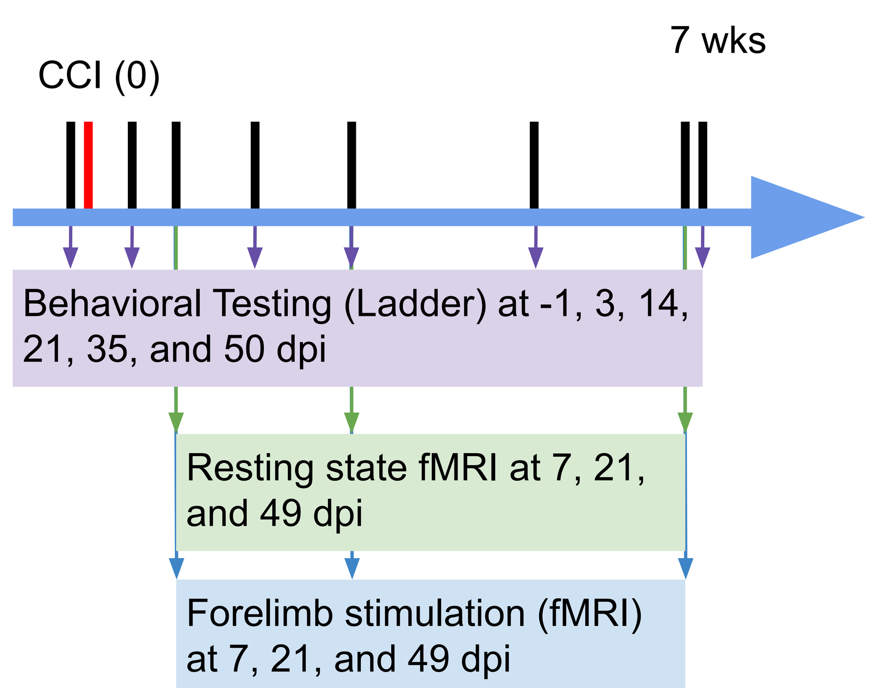
Calculate phase coherence to obtain eigenvectors

Use leading eigenvector to capture dominant connectivity patterns using k means clustering

Compute metrics and statistics on dFC states

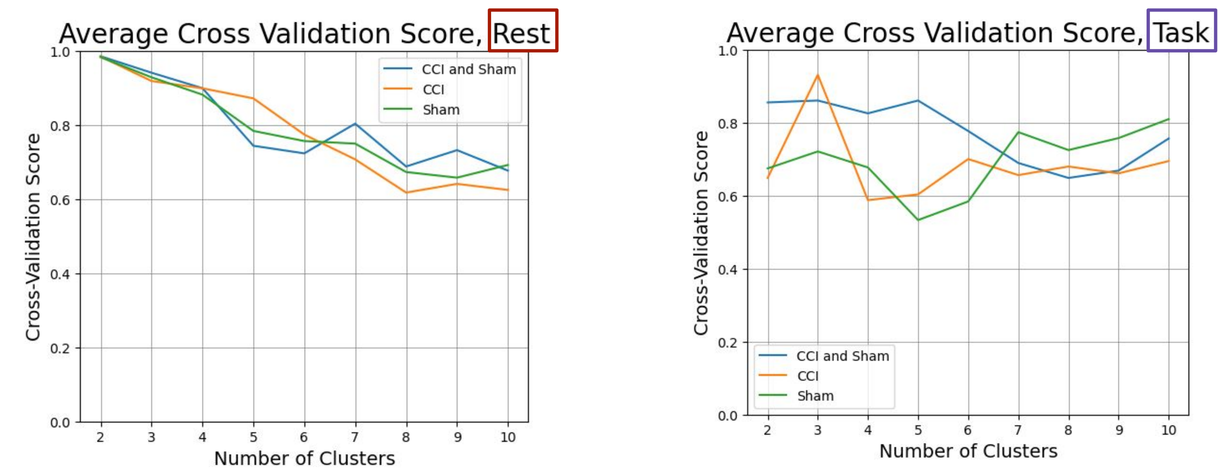


EXPERIMENTAL DESIGN

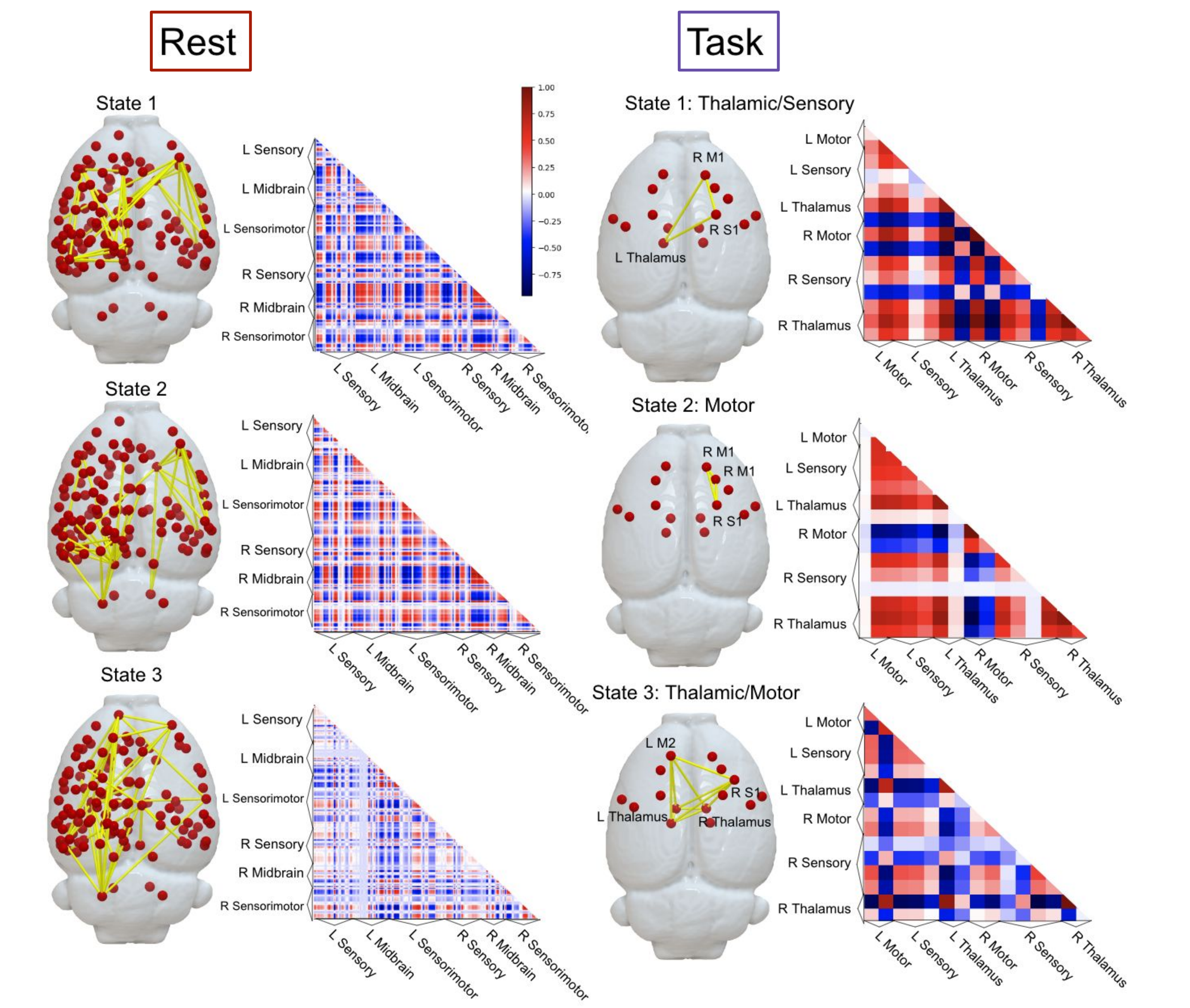


- 23 Adult Male Rats (15 CCI, 8 Sham)
- Controlled cortical impact (CCI) injury over the left frontal cortex
- MRI imaging at rest and during left forelimb stimulation at 7, 21, and 49dpi
- Behavioral Testing (Ladder Task), fMRI with left forelimb stimulation, rsfMRI baseline
- Dynamic functional connectivity was calculated for both resting state and task at each timepoint and compared across groups

CLUSTERING INTO DYNAMIC BRAIN STATES



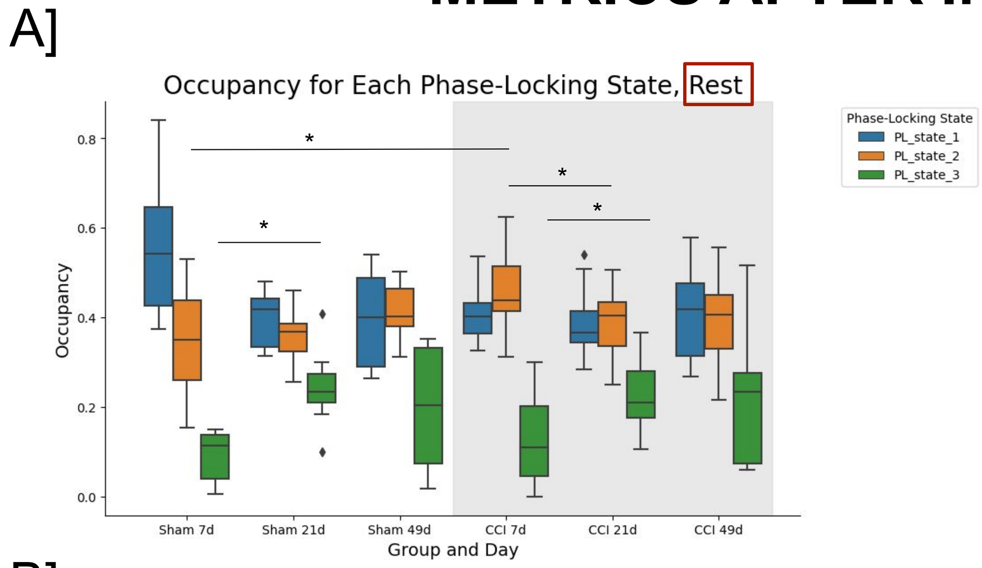
Dynamic Functional Connectivity Clustered into Patterned Brain States
Clustering was conducted using CCI only, Sham only, and CCI and Sham combined. Average cross-validation scores to determine the optimal number of clustering states revealed a difference in the optimal number of states depending on the groups included.



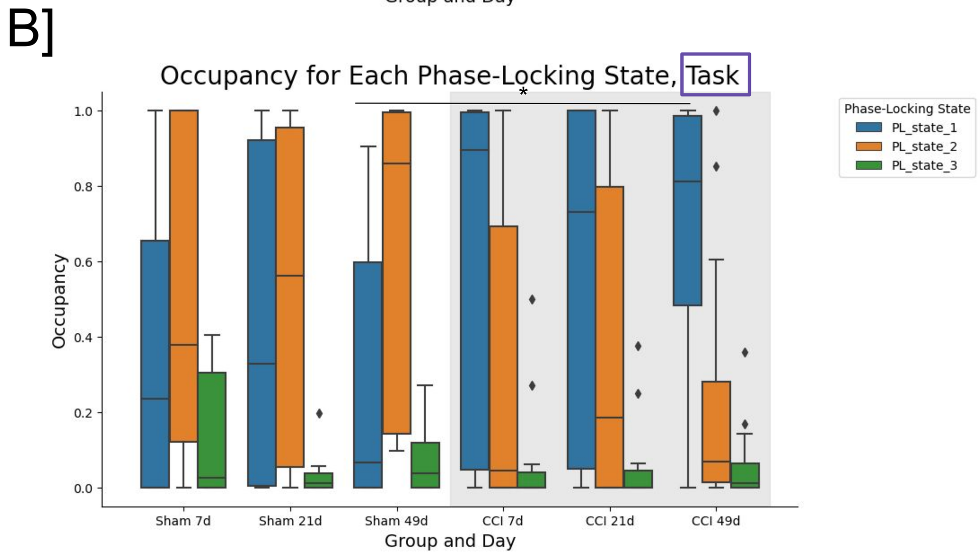
Mapping of Dynamic Brain States
Mapping of connected regions across the whole brain within TBI and sham groups in k=3 phase-locking states in A] resting state and B] task as computed using the Leida algorithm. States 1 and 2 are relatively similar at rest, while state 3 demonstrates differences.

DYNAMIC FUNCTIONAL CONNECTIVITY METRICS AFTER INJURY

A]

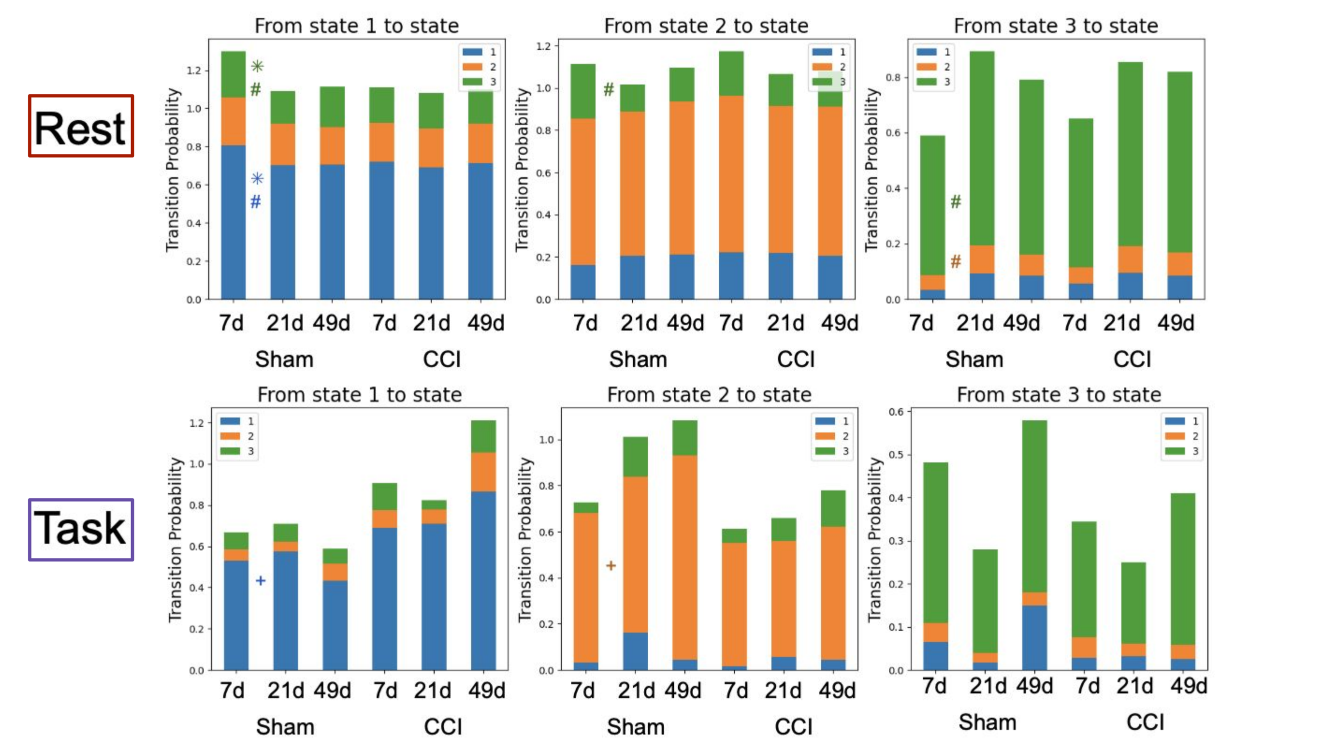


B]



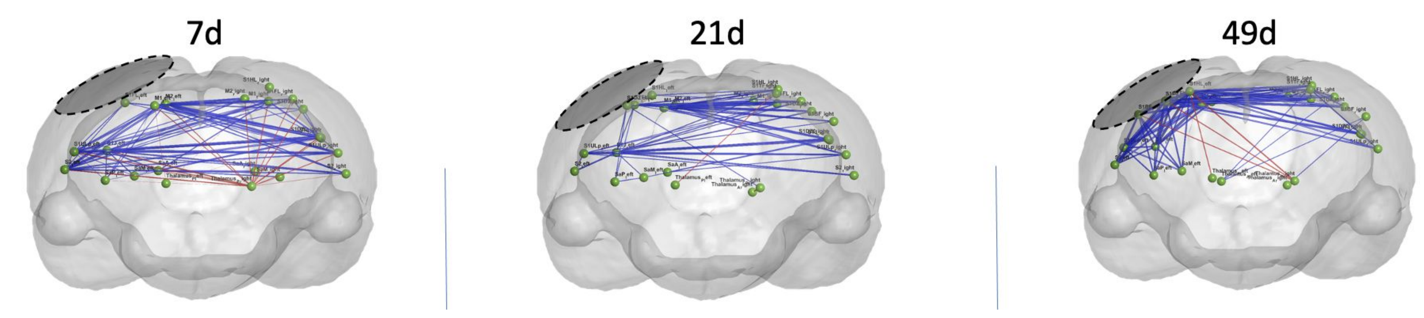
Dynamic State Metrics: Occupancy
Occupancy in each phase-locking state by group and day A] at rest and B] during task for k=3 states ($p<0.05$, bonferroni corrected). Occupancy represents percentage of occurrences in each state.

A] At rest, there is a significant difference in hippocampal state 2 occupancy at 7 dpi and in posterior neocortical and hippocampal states at 7 and 21dpi in CCI rodents.
B] In task, injured rodents spend significantly more time sensorimotor states than shams at 49 dpi.



Dynamic State Metrics: Transition Probabilities
Transition probabilities between PL states at k=3 states for both Rest and Task. Kruskal-Wallis test revealed a group x time difference in state transition probabilities at rest ($p<0.05$) between states 1 to 3 and 1 remaining in state 1. There were no group x time differences during task. +/#/✳ = significant effect of group / time / group x time, $p<0.05$

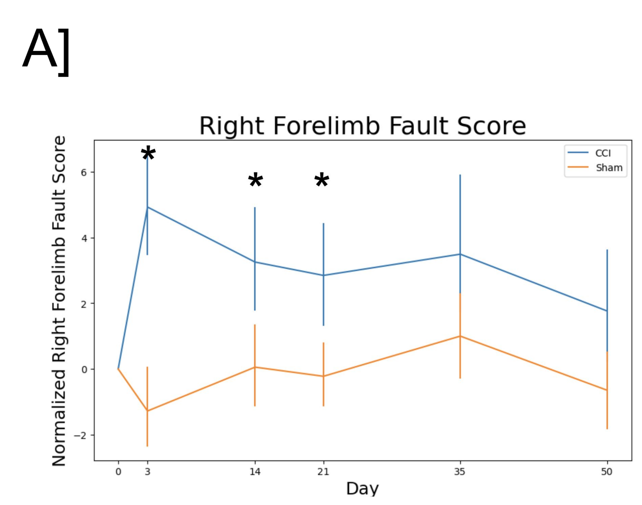
STATIC FUNCTIONAL CONNECTIVITY



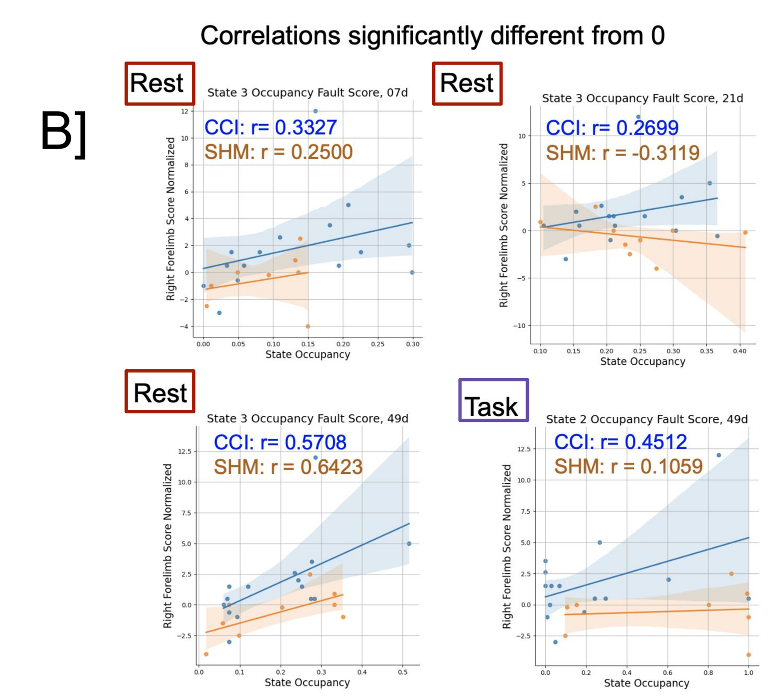
Static Functional Connectivity at Resting State
Static Functional connectivity (previously presented) demonstrated hyperconnectivity across the perilesional cortex that strengthened over time. Blue: CCI>Sham, Red: CCI<Sham

DYNAMIC FC AND BEHAVIORAL TESTING

A]



B]



Relationship between Behavioral Measure (Ladder Task) and dFC measures of State Occupancy in Resting State and Task
A] CCI had a significantly greater Normalized Right Forelimb Fault Score at 3, 14, 21 ($p<0.05$, Bonferroni corrected), and trending towards significant at 50 dpi ($p=0.06$).
B] Correlation between state occupancy and 50 day Right Forelimb Fault Score is significantly different from 0 in CCI rats ($p<0.05$, no significance after correction), with shams shown for comparison, in state 3 occupancy at all timepoints during rest and state 2 at 49d during task.

SUMMARY AND CONCLUSIONS

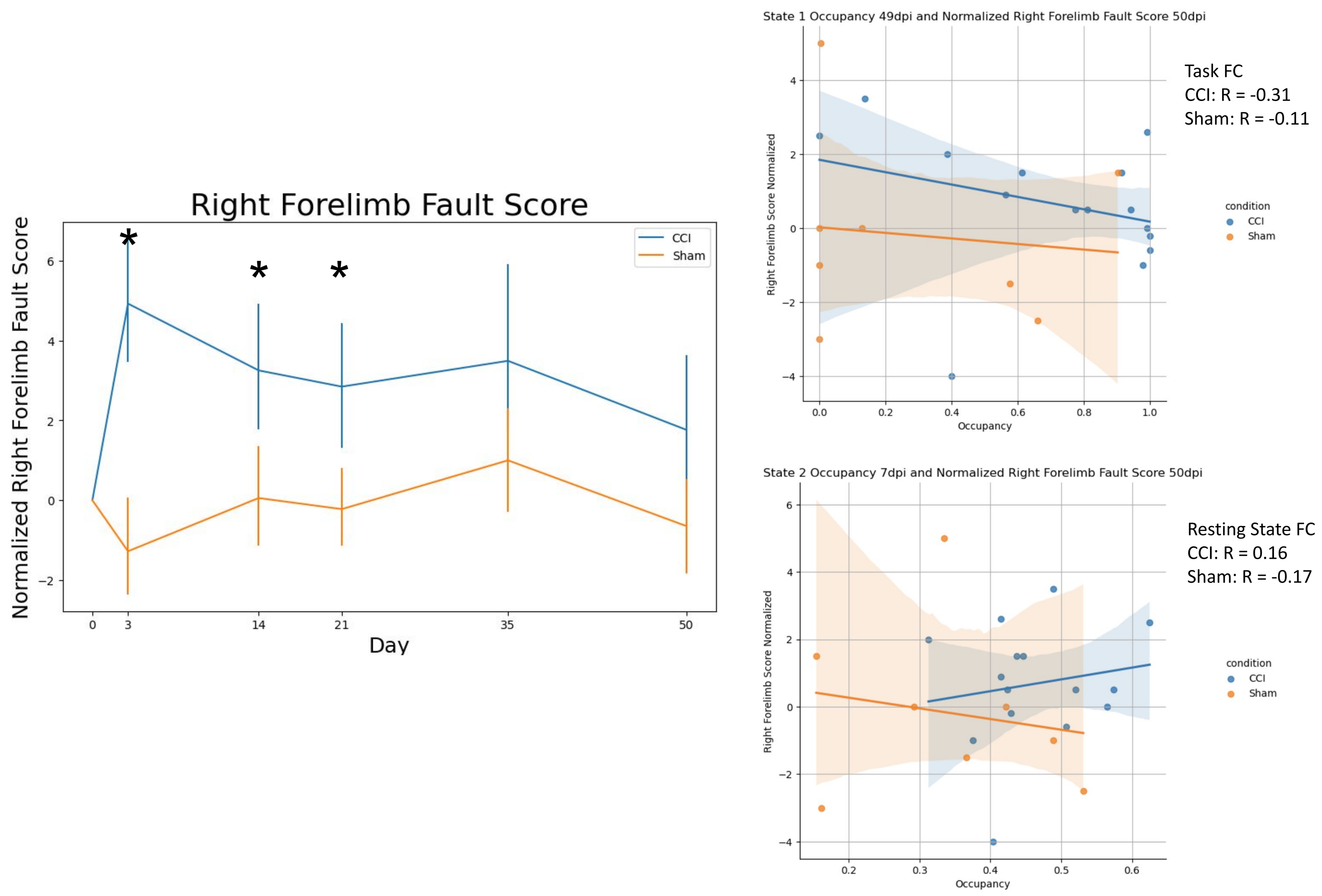
- dFC computed using LEiDA demonstrated increased state occupancy in sensorimotor states during task, and mild differences in transition probabilities between groups and across time after injury
- Unlike static FC, dynamic FC was less sensitive to differences related to injury
- There were some significant correlations between state occupancy and fault score
- Further investigation is necessary to determine the value of dynamic versus static FC and the possibility of intrinsic network differences between CCI and Sham that affect dynamic states.

References: Cabral et al; 2017 Sci Rep:7(1):5135

Funding: Funding: NIH NINDS NS091222 and UCLA Brain Injury Research Center

Figures

1. General graphic of dFC paradigm + study paradigm (methods figure)
2. Clustering quality of Leida and determination of optimal clustering for rest and task and for sham vs TBI (cross validation); Brain states projected across brain/connectivity matrices using optimal number of clusters
3. State transition probabilities/stats and occupancy for rest and task (Leida)
4. More stats (Leida)
5. Behavioral correlation with dFC data (simple correlation analysis, see if occurrence of state from resting state FC correlates with group difference in behavior)

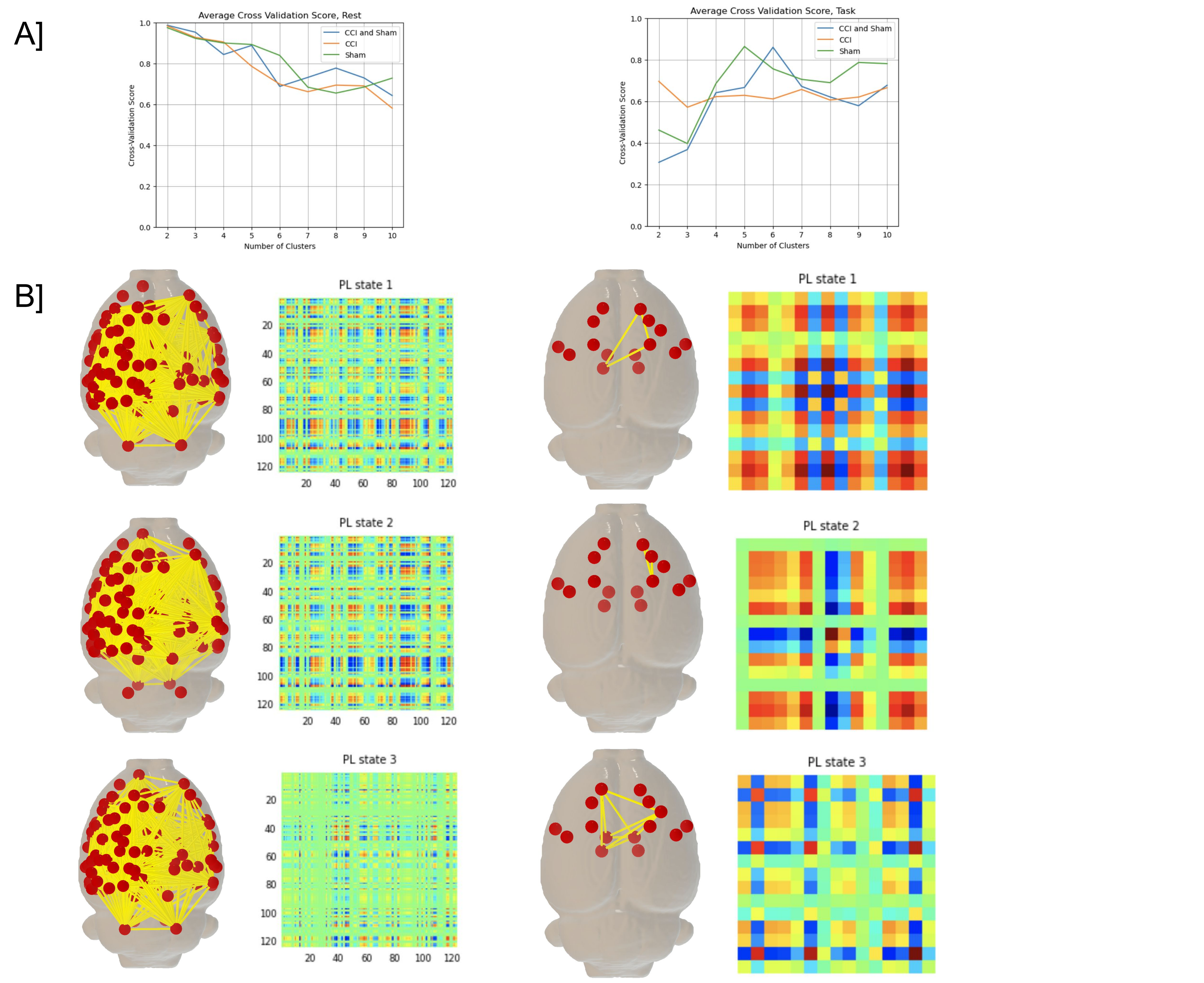


Relationship between Behavioral Measure (Ladder Task) and dFC measures of State Occupancy in Resting State and Task

[A] There was a significant difference in the Normalized Right Forelimb Fault Score at 3, 14, 21 ($p<0.05$, Bonferroni corrected), and 50 dpi ($p=0.06$).

[B] Correlation plot between State Occupancy (7dpi, state 2 in rest, 49dpi, state 1 in task) and Normalized Right Forelimb Fault Score at 50 dpi corresponding to timepoints with significant differences in state occupancy at k=3 states. There was no significant correlation between state occupancy and long-term behavioral outcomes.

In task-based analysis, state 1 contains left thalamus, right-M2, right-S1, hindlimb region, state 2 contains right motor cortex, state 3 contains bilateral thalamic and motor regions.

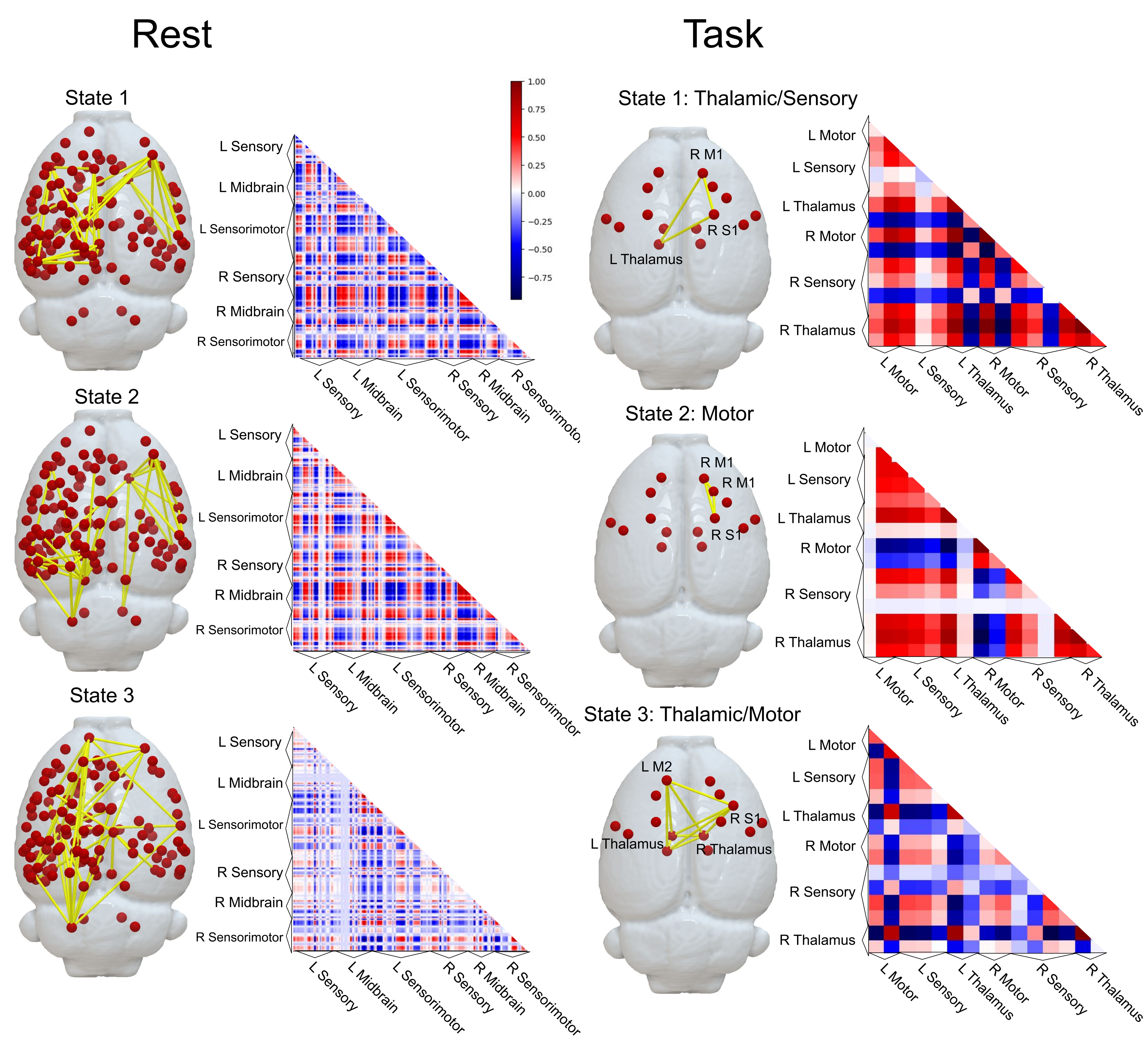


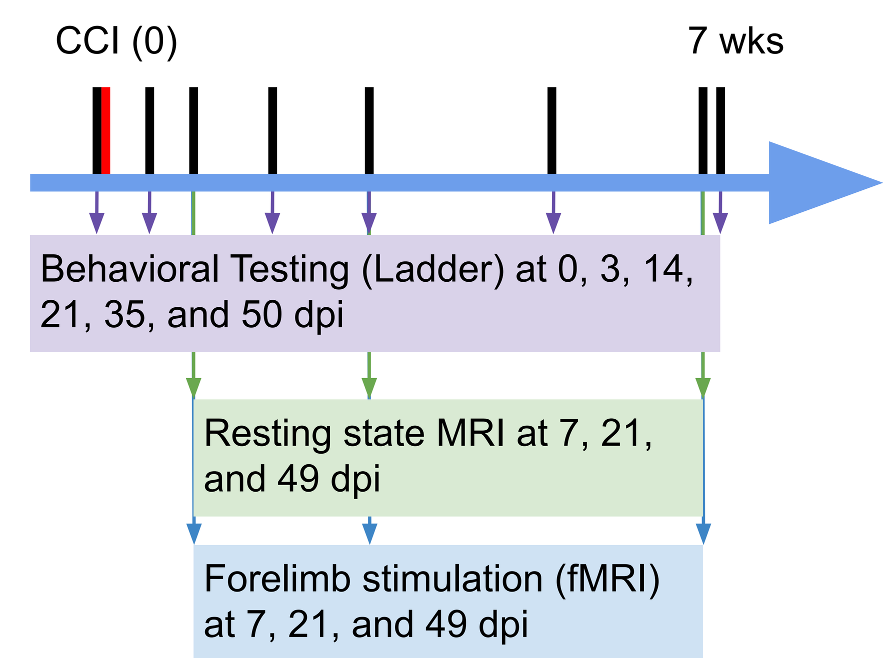
A] Average cross-validation scores to determine the optimal number of clustering states for rest and task, separated by CCI only, Sham only, and CCI and Sham combined in phase-locking computation. There is a difference in the state with the highest cross-validated score depending on whether groups were combined in state calculation. This could indicate an intrinsic different in dynamic network architecture after injury, making it difficult to compute comparable states.

B] Correlation matrices and mapping of connected regions across the whole brain for k=3 phase-locking states as computed using the Leida algorithm. Rodents spend the highest percentage of time in state 1, followed by the subsequent states.

In task-based analysis, state 1 contains left thalamus, right-M2, right-S1, hindlimb region, state 2 contains right motor cortex, State 3 contains bilateral thalamic and motor regions

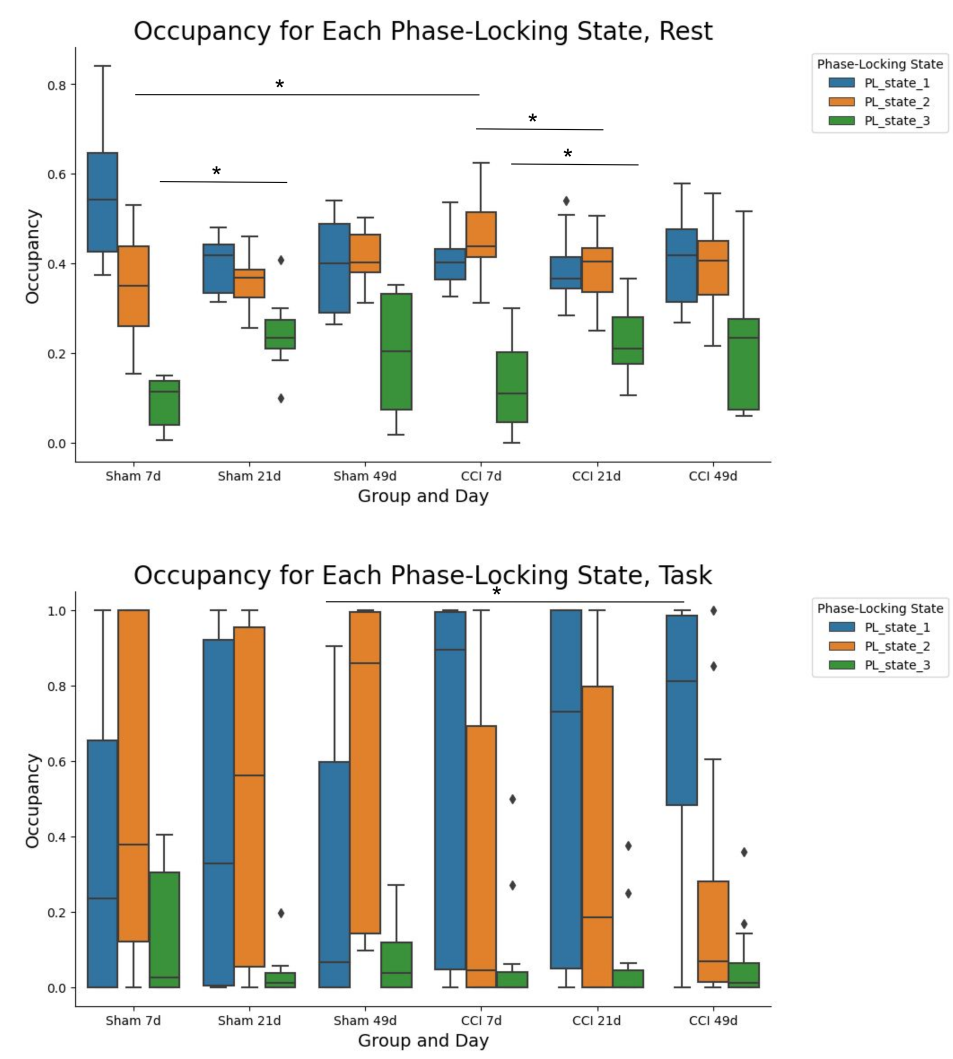
At rest, state 1 contains bilateral sensorimotor and frontal regions, state 2 contains bilateral midbrain/hippocampal regions, state 3 contains bilateral frontal regions.



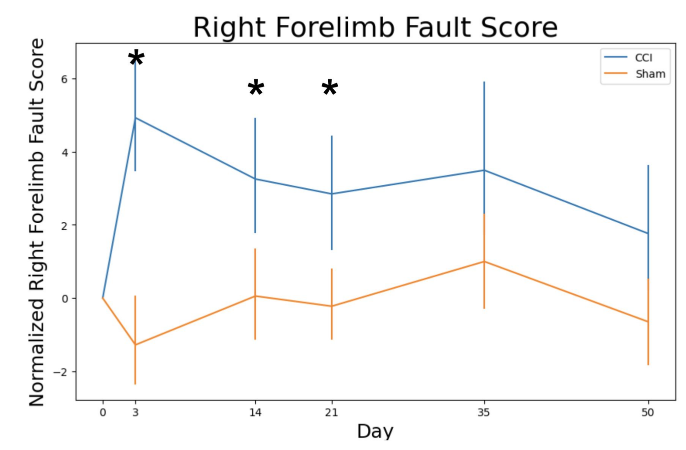


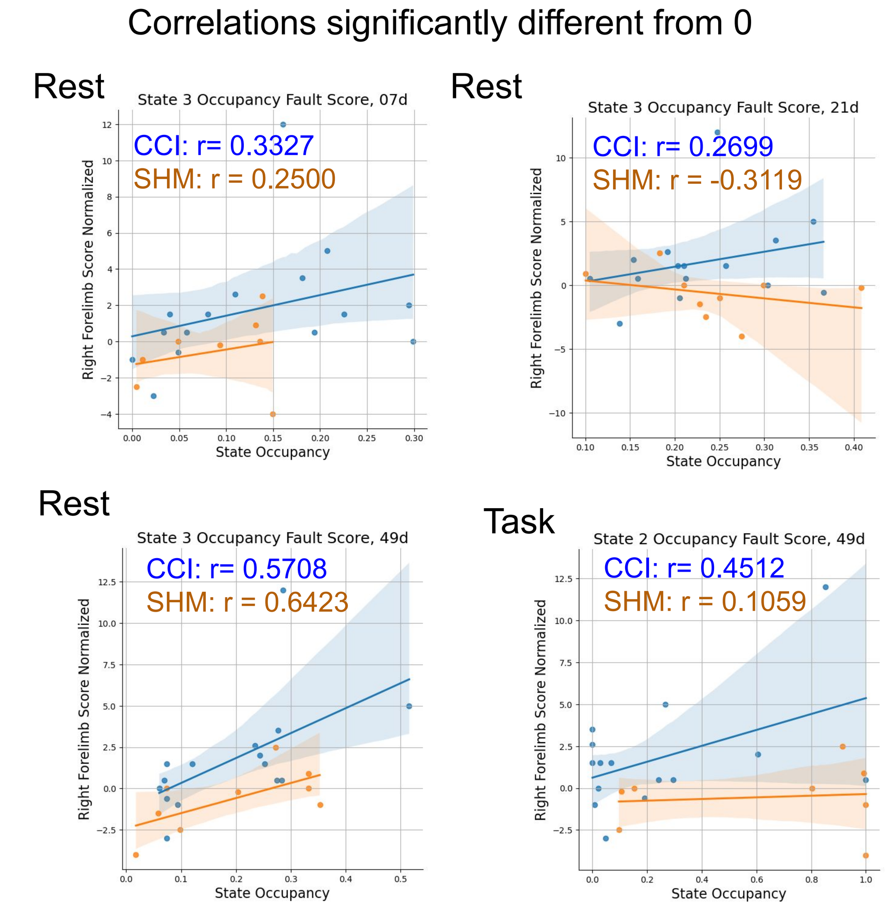
Experimental Design

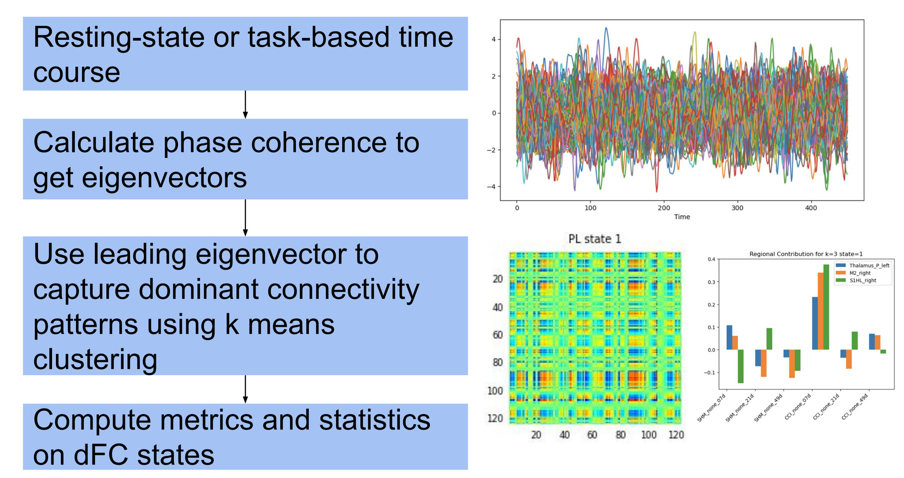
Rodents were subject to baseline behavioral testing using the ladder task, measured by forelimb fault scores. CCI or sham injury (n=8 shams, n=15 CCI) was inducted at day 0, and behavioral testing, resting state MRI, and fMRI with forelimb stimulation (task) were conducted. Dynamic functional connectivity was calculated for both resting state and task at each timepoint and compared across groups.

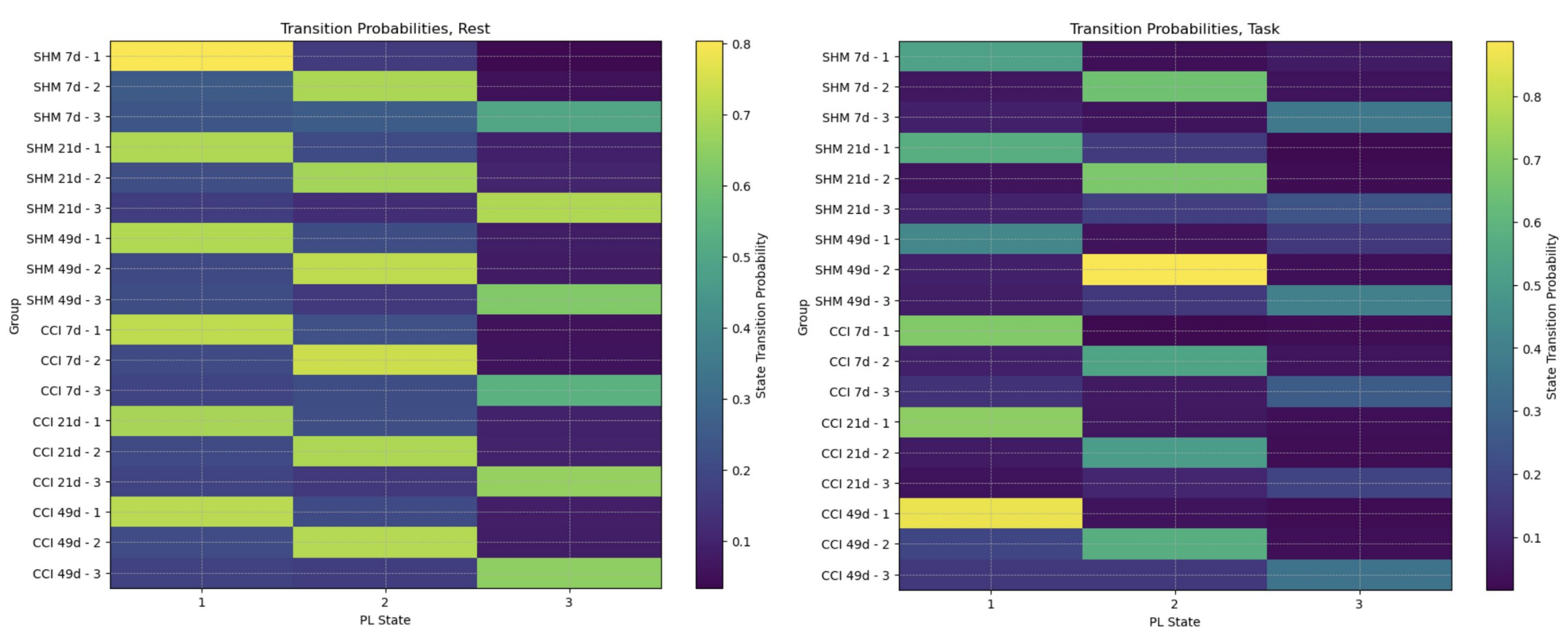


Occupancy in each phase-locking state by group and day A] at rest and B] during task for k=3 states. Occupancy is represented by the percentage of occurrences in a state during the duration of the imaging period.
A] There is a significant difference in occupancy in state 2 (midbrain/hippocampal) for injured versus shams at 7 dpi and in injured rodents in states 2 and 3 (bilateral frontal) between 7 and 21 days post injury ($p<0.05$, bonferroni corrected).
B] Injured rodents spend significantly more time in state 1 (sensorimotor) than shams at 49 dpi ($p<0.05$, bonferroni corrected).









Transition probabilities between PL states at k=3 states for both A] Rest and B] Task based analysis.
A] Kruskal-Wallis test revealed a group x time difference in state transition probabilities at rest ($p<0.05$) between states 1 to 3 and 1 remaining in state 1.
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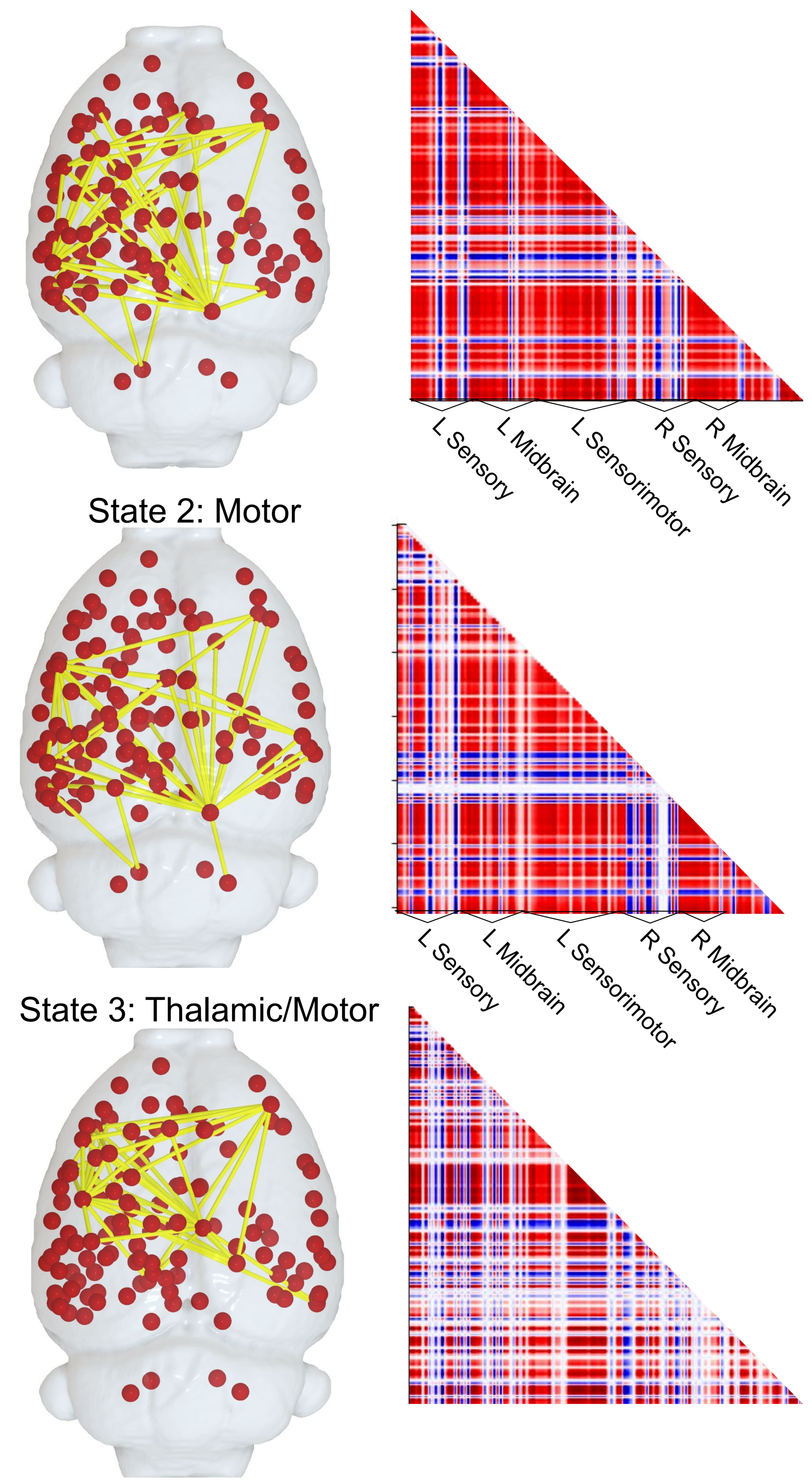

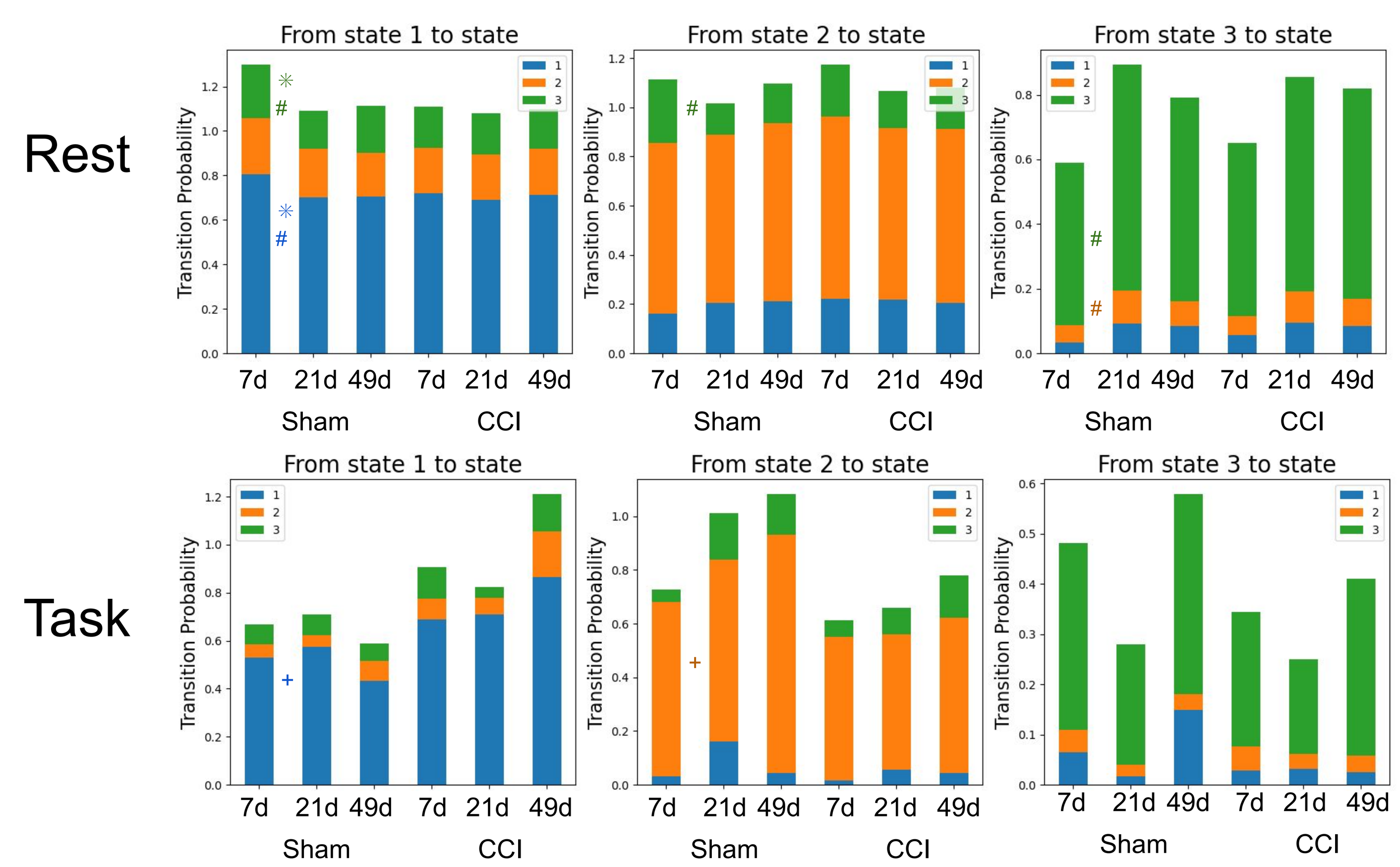

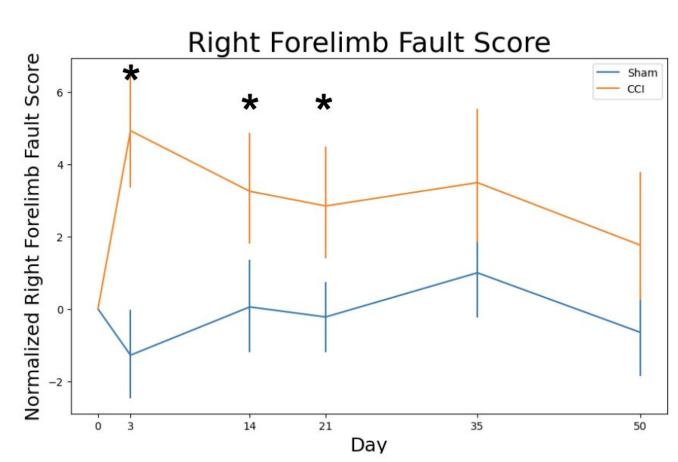

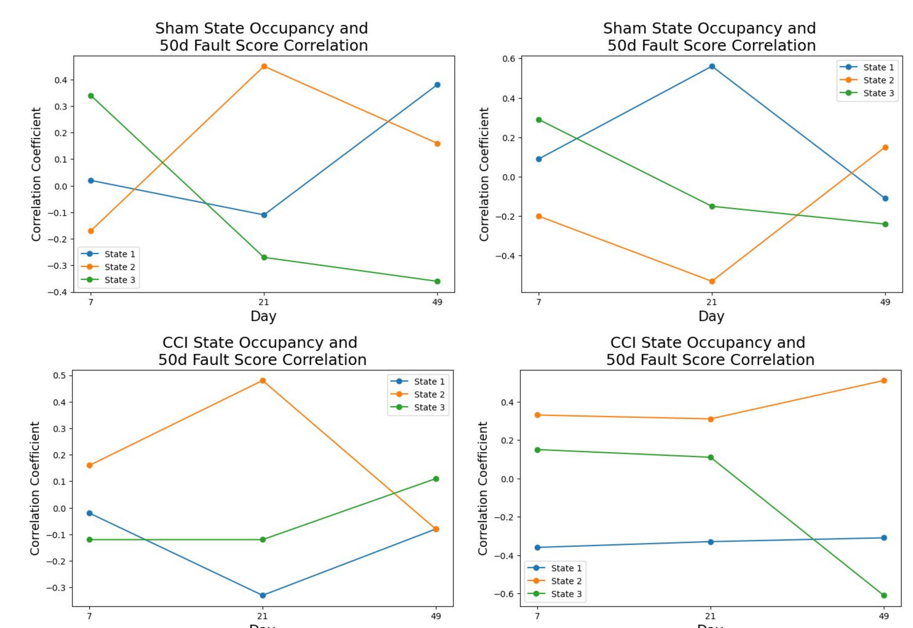

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- Static Functional Connectivity determines patterns in averaged signals across time
- dFC has been shown to be more sensitive to certain clinical outcomes and poses the advantage of capturing temporal FC changes surrounding connected brain states
- **Aim 1:** To investigate the relationship between calculated dynamic brain states and network-level differences as a result of traumatic injury
- **Aim 2:** To compare the value of dynamic FC as compared to known injury-related differences in static FC and behavioral outcomes

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LEiDA reduces variation while decreasing overlap in the data compared to other dFC methods

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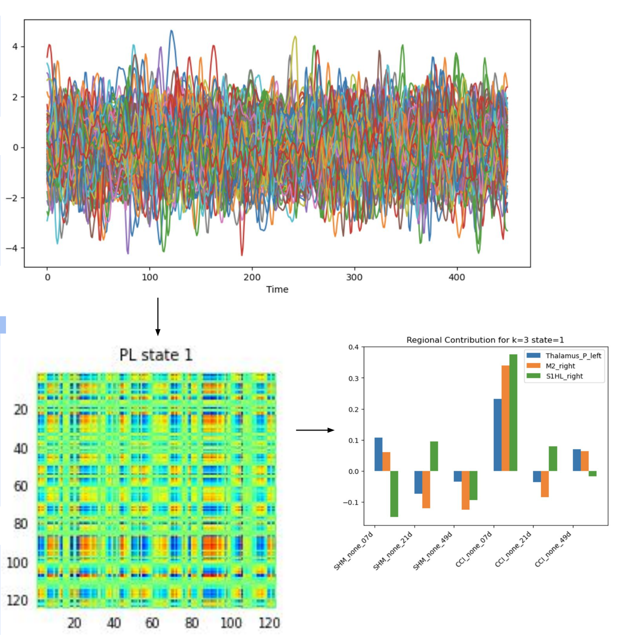
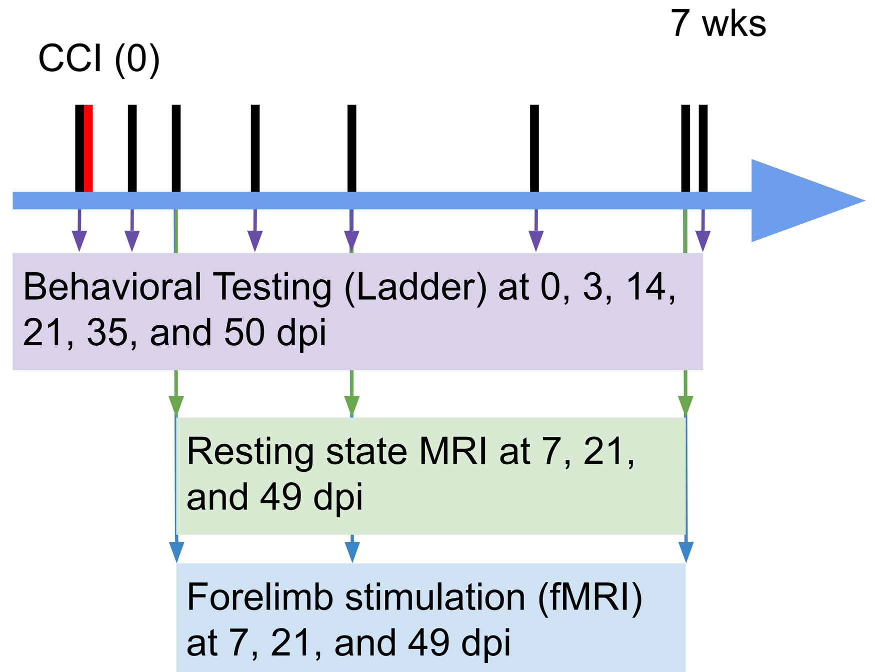


EXPERIMENTAL DESIGN



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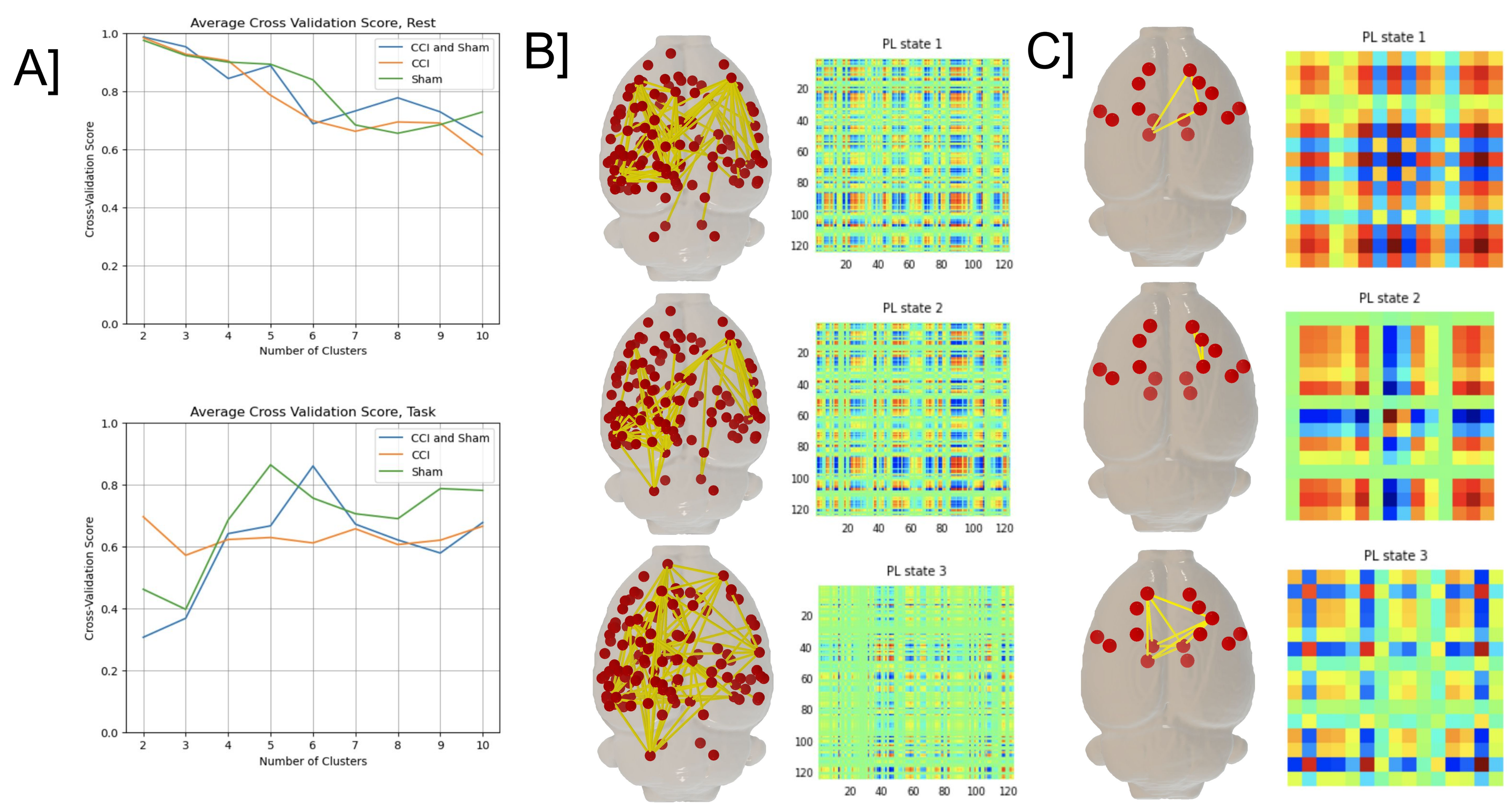
CLUSTERING INTO DYNAMIC BRAIN STATES



Dynamic Functional Connectivity Clustering into Patterned Brain States

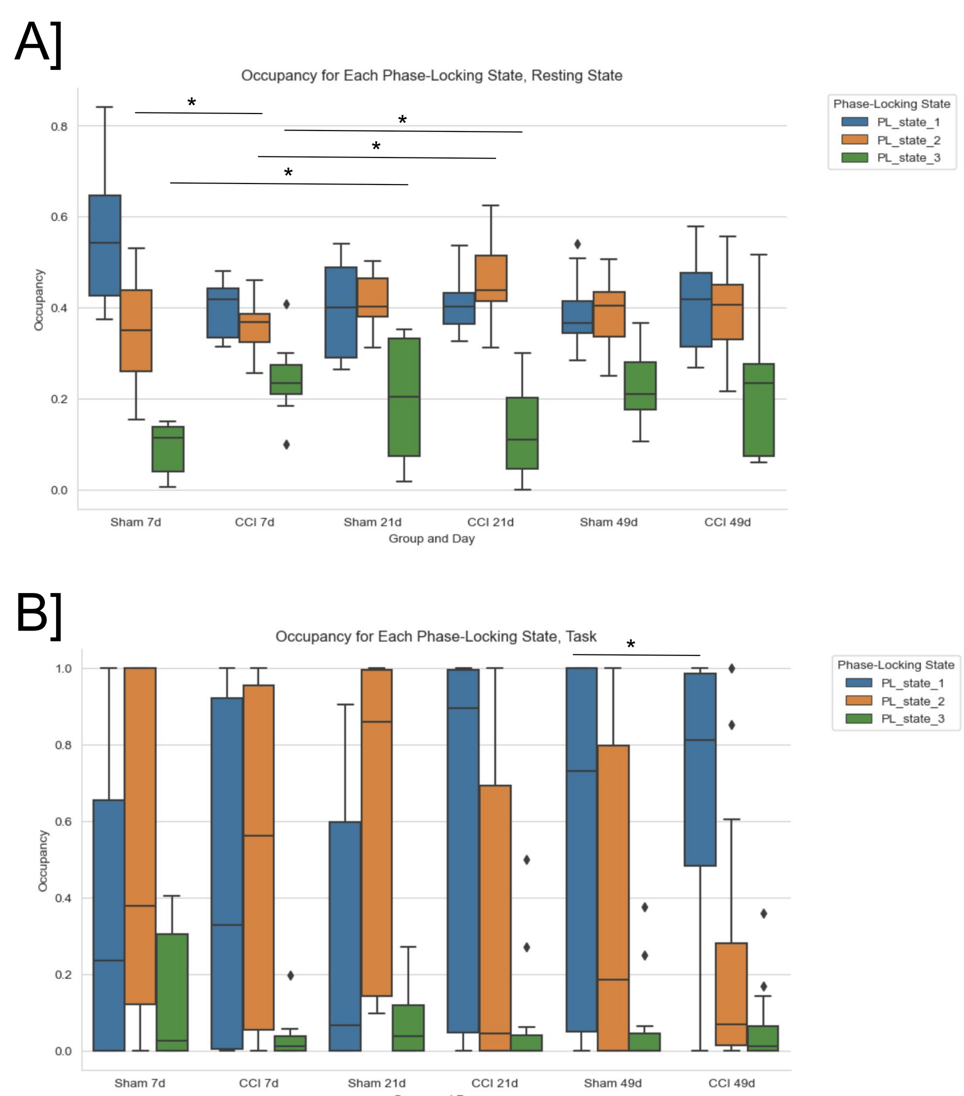
A] Average cross-validation scores to determine the optimal number of clustering states for rest and task, separated by CCI only, Sham only, and CCI and Sham combined in phase-locking computation. There is a difference in the state with the highest cross-validated score depending on whether groups were combined in state calculation. This could indicate an intrinsic different in dynamic network architecture after injury, making it difficult to compute comparable states.

B-C] Correlation matrices and mapping of connected regions across the whole brain within TBI and sham groups in k=3 phase-locking states in B] resting state and C] task as computed using the Leida algorithm. Rodents spend the highest percentage of time in state 1, followed by the subsequent states. For rest, edges with R/z values at the top 1% were plotted onto the brain surface.

Each state was phenotyped by major brain regions through thresholding. At rest, state 1 contains greatest centroid values (representing contribution to that state) in bilateral insular cortex and primary sensory cortex, state 2 in bilateral hippocampal regions, and state 3 in bilateral retrosplenial granular and dysgranular cortex.

In task-based analysis, state 1 contains left thalamus, right-M2, right-S1, hindlimb region, state 2 contains right motor cortex, state 3 contains bilateral thalamic and motor regions.

DYNAMIC FUNCTIONAL CONNECTIVITY METRICS AFTER INJURY



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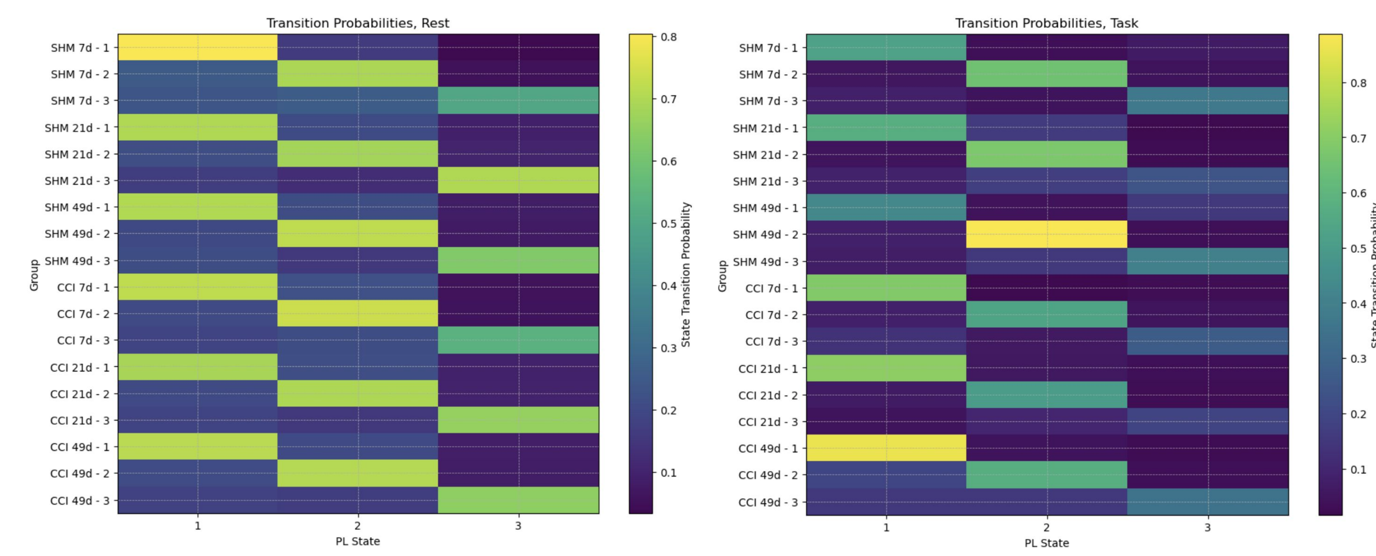

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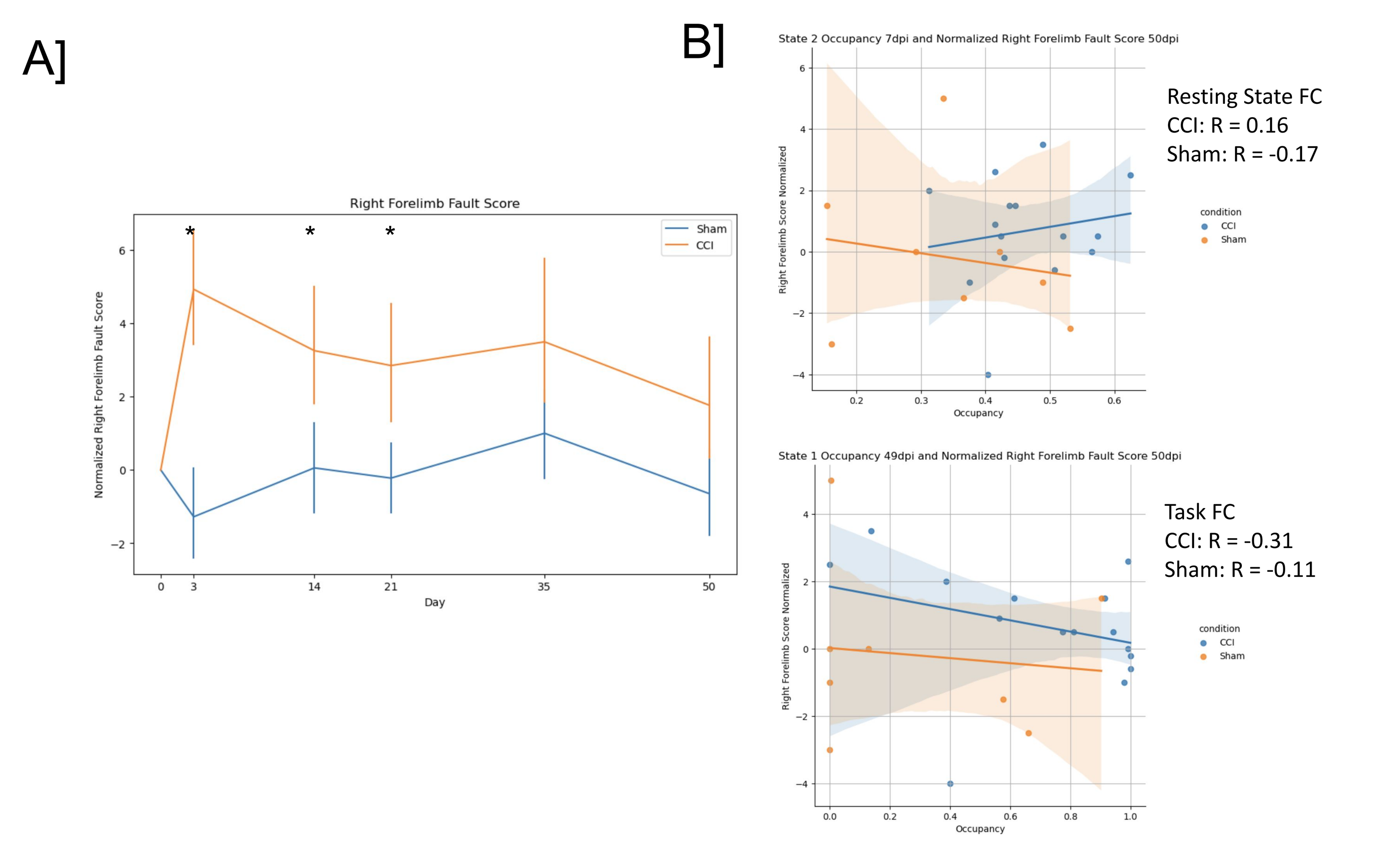
B] Kruskal-Wallis test did not reveal any group x time difference in state transition probabilities at task, raising questions about potential intrinsic network differences within CCI and Sham that might be masked due to large group variance, as seen in other state metrics such as dwell times and occupancy.

DYNAMIC FUNCTIONAL CONNECTIVITY AND BEHAVIORAL TESTING



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SUMMARY AND CONCLUSIONS

- dFC computed using LEiDA demonstrated increased state occupancy in sensorimotor states during task, and mild differences in transition probabilities between groups and across time after injury
- Intrinsic network differences between CCI and Sham could contribute to large variations in dFC metrics and behavioral associations
- Further investigation is necessary to determine the value of dynamic versus static FC in displaying regional and global changes after injury

References:
Cabral et al; 2007 Sci Rep:7(1):5135

Funding: UC Brain Injury Research Center