

Dynamic functional brain connectivity underlying temporal summation of pain in fibromyalgia

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Abstract

Objective: Abnormal central pain processing is a leading etiology underlying fibromyalgia (FM) pain and is perceptually characterized with the psychophysical measure of temporal summation of pain (TSP). TSP is the perception of increasingly greater pain to repetitive or tonic noxious stimuli. Previous neuroimaging studies have used static (i.e. summary) measures to examine the fMRI correlates of TSP in FM. However, functional brain activity rapidly and dynamically reorganizes across time, and TSP is similarly a temporally evolving process. A full understanding of the neural circuitry supporting TSP in FM thus requires a dynamic measure that evolves over time.

Method: We applied novel dynamic functional connectivity (dFC) methods to examine how TSP-associated fluctuations are linked to dynamic functional reconfigurations of the brain. We acquired high-temporal resolution fMRI data during a resting-state (REST) and during sustained cuff pressure pain applied to the leg (PAIN) in 84 FM patients and matched healthy controls (HCs).

Results: FM patients experienced greater TSP than HCs (FM: 17.93 ± 19.24 ; HC: 9.47 ± 14.06 ; $p = 0.028$), but TSP varied substantially between patients. In the brain, the presence versus absence of TSP in FM was marked by more sustained enmeshment between sensorimotor and salience networks during PAIN. Furthermore, dynamic enmeshment was more isolated in FM patients with high TSP, as interactions with all other brain networks were dampened during PAIN.

Conclusion: This study elucidates the dynamic brain processes underlying facilitated central pain processing in FM, and enables future work investigating dynamic symptomatology in FM.

Introduction

Pain and nociceptive processing are altered in many chronic pain disorders. For fibromyalgia (FM), clinical pain is debilitating, widespread, and is often dynamic and fluctuating, both temporally and spatially(1). Current understanding of FM etiology implicates abnormal amplification of pain within the central nervous system(1), bolstered by findings that FM patients often exhibit elevated temporal summation of pain (TSP)(2, 3)– the perception of increasingly greater pain intensity to repetitive or prolonged noxious stimuli(4). TSP may be centrally mediated by the “wind-up” phenomenon which has been characterized extensively in the spinal cord dorsal horn(5, 6) in preclinical models. “Wind-up” refers to the progressive excitability of dorsal horn neurons when C-nociceptive afferents are repetitively stimulated by noxious stimuli, a process mediated by the N-methyl-D-aspartate (NMDA) receptor(7). Notably, the clinical use of NMDA receptor antagonists such as ketamine has been shown not only to reduce TSP, but also muscle pain at rest in FM(8).

In the brain, the use of neuroimaging techniques in FM has demonstrated alterations in brain structure(9), functional stimulus-evoked activation(10-13), and functional connectivity (14-16). Functional connectivity assesses the degree of correlation in brain activity across different regions, with a higher correlation signifying greater functional connectedness. Using such an approach, we previously linked inter-subject variability in TSP in FM to variability in functional connectivity between sensorimotor and salience network regions (e.g., cross-network enmeshment)(15). However, the traditional approach of measuring functional connectivity uses the entire period acquired in the scanner to generate a summary metric, termed static functional connectivity (sFC). Yet, brain connectivity is known to vary substantially over time(17, 18), and the perception of TSP is similarly a temporally dynamic experience. Therefore, a full characterization of how abnormal central pain processing in FM is functionally represented in the brain must be sensitive to these temporal dynamics. Towards this goal, the use of dynamic functional connectivity methods (dFC)(17, 18) can capture how connectivity transiently changes throughout time, and how the brain functionally reorganizes as TSP evolves.

In this study, we investigated how temporal fluctuations in TSP are linked to dynamic changes in brain organization in FM. Of note, we used recent advances in multiband, simultaneous multi-slice fMRI to enhance the temporal resolution of the dataset. We also show how previously published sFC results for FM can be replicated and contextualized within this novel dynamic framework.

Materials and Methods

Experimental Subjects

Eighty-four female patients meeting the American College of Rheumatology (ACR) criteria for a diagnosis of fibromyalgia (FM)(19) ($\text{mean}_{\text{age}} \pm \text{SD} = 39.8 \pm 12.3$) and 38 female healthy control (HC) participants ($\text{mean}_{\text{age}} \pm \text{SD} = 38.8 \pm 12.9$) were recruited through Clinical Trials listings hosted by Partners Healthcare (clinicaltrials.partners.org) and by physician referral. The eligibility criteria were reported in the Supplementary. All participants were recruited as part of a trial evaluating the effects of cognitive-behavioral therapy (CBT) on brain circuitry supporting chronic pain (NIH R01-AR064367), and all data in this analysis were collected prior to any intervention. The protocol was approved by the Human Research Committee of Partners

Healthcare and Massachusetts General Hospital. All participants provided written informed consent prior to beginning study procedures.

Behavioral visit

All study participants completed a behavioral session on a separate day from the MRI scan. During this visit, both FM patients and HCs were introduced to study procedures, including the use of a 0-100 pain rating scale, and underwent a calibration procedure to determine appropriate pain stimulus intensities for the fMRI procedures (see Supplementary Methods).

MRI Session

Brain responses to deep tissue pain were examined using cuff pressure algometry, consistent with our previous studies with chronic pain populations, including FM(15, 20). During the MRI session, participants completed 6-minute resting state (REST) and 6-minute sustained cuff pressure pain (PAIN) fMRI runs. All MRI data were obtained on a 3.0T Siemens Skyra (Siemens Medical) equipped with a 32-channel head coil at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, between 2015 and 2019. T1-weighted structural images were obtained using a 3-dimensional magnetization-prepared rapid gradient-echo pulse sequence (MPRAGE; TR = 2530 ms, TE = 1.64 ms, flip angle 7°, FOV = 256x256 mm, spatial resolution 1x1x1 mm). Functional MRI data were obtained using a simultaneous multi-slice pulse sequence (acceleration factor 5, TR = 1250 ms, TE = 33 ms, flip angle 65°, approximate FOV = 196 x 196 mm, voxel dimensions = 2x2x2 mm, 75 axial slices with no gap, 288 volumes, total acquisition time = 6 minutes)(21). During both the REST and PAIN runs, subjects were instructed to relax and lie still with their eyes open while viewing a blank screen.

Physiological data

Physiological data, including cardiac (finger pulse) and respiration (pneumatic belt), were collected using an MRI-compatible recording system (BIOPAC) during all fMRI scans. These data were used for cardiorespiratory artifact correction in fMRI data (see Supplementary Methods).

Functional MRI data pre-processing

A non-modular pre-processing of the fMRI data was used to avoid re-introducing noise through sequential steps(22). Additional details were reported in Supplementary Materials. Several subjects were excluded from various analyses following quality control of the acquired psychophysical data, image acquisition, or healthy subject inclusion criteria (see Supplementary).

Temporal summation of pain

The stimulus intensity was percept-matched to elicit a 40/100 pain intensity level for each subject prior to the PAIN scan on a scale where 0 means “no pain” and 100 represents “the most intense pain imaginable”. However, when subjects reported their recalled cuff pain intensity for the first, middle, and last tertile of the PAIN scan, many subjects experienced TSP throughout the course of the scan. Specifically, since previous cuff algometry studies have indicated that self-reported sensations of pain are relatively stable over a 2-minute period (23, 24), subjects provided verbal pain intensity ratings from 0-100 for each of the 2-minute periods for the beginning, middle, and end of the 6-minute PAIN scan. The pain ratings were assessed retrospectively immediately after the PAIN scan to exclude any confounding neural activation related to rating procedures. To quantify TSP for each individual, the change in pain rating for the last 2 minutes versus the first 2 minutes during PAIN was calculated – i.e. positive values denote

TSP, while negative values suggest habituation. To exclude recall bias from retrospective pain ratings, we conducted additional analyses comparing moment-by-moment and retrospective pain ratings acquired during a separate task outside the scanner (see Supplementary), demonstrating that they are indeed highly correlated. To statistically test for a group by time interaction effect on the pain rating, a mixed ANOVA was performed. One sample t-tests were then conducted to determine statistical significance of TSP in FM and HC patient groups separately, and an independent samples t-test was used to compare between the two groups. In some of the following analyses, FM patients were split into three subgroups: no summation ($TSP \leq 0$), low summation ($0 < TSP < \text{median (positive TSP)}$), and high summation ($TSP > \text{median (positive TSP)}$) – see **Fig. S1**. The median value computed on 54 subjects was equal to 21.25. As stimulus intensities used to percept match during the PAIN scan could differ across groups, we conducted further analyses to determine any differences between groups and its implications on connectivity (see Supplementary Materials).

S1_{leg} to whole-brain static FC analyses

To replicate our previous findings of altered static S1_{leg} connectivity during a sustained cuff pain state (15), sFC was calculated between each subject's contralateral S1 representation of the left leg region to the whole brain during PAIN and during REST separately (Pearson's correlation). Non-parametric testing was used at the group level to contrast between PAIN and REST (Randomise, FSL(25)), and between FM and HCs. Statistical significance was set at a family-wise error (FWE) corrected p -value < 0.05 , with clusters determined by the Threshold-Free Cluster Enhancement (TFCE) option. Additional details were reported in the Supplementary.

S1_{leg} to whole-brain dynamic FC analyses

Instantaneous phase synchrony analysis (IPSA)(26) was used to determine dFC between the S1_{leg} region and all other voxels across the brain (see Supplementary material for more details). The mean values of the instantaneous dFC estimates from the last 2 minutes and first 2 minutes of the 6-minute PAIN scan for each subject were calculated on a voxel-wise basis and subtracted to identify meaningful variations in S1_{leg} connectivity over time (Δ dFC). Higher-level regression analysis was then performed across all subjects with TSP as a regressor of interest to determine where changes in S1_{leg} dFC during the PAIN scan were correlated with TSP (Randomise, FSL). Statistical significance was set at FWE-corrected p -value < 0.05 with TFCE to determine clusters.

Parcellation and ROI-to-ROI dFC analysis

To extend beyond a seed-based functional connectivity approach towards an approach with connectivity estimated between pairs of ROIs, a 200-area Schaefer parcellation of the brain was used(27). The right S1_{leg} ROI was separated out as its own parcel using the same 4-mm radius spherical seed as used in the previous voxel-wise analyses. Therefore, a total of 201 parcels were used in this approach. The IPSA method was then applied pairwise to the mean voxel-wise timeseries between each parcel, generating a 201 x 201 x 285 dFC matrix for each subject.

Multi-slice community detection analysis

A multi-slice community detection approach was then applied on dFC matrices to determine how brain networks are organized in communities which dynamically evolve over time(28-31). The partition estimation accounted for both the intra-slice connections between brain

regions at a single timepoint and the connections between adjacent slices in time (see Supplementary).

Network properties and community dynamics

The output of a multilayer community detection algorithm is a partition (each node/parcel is assigned to a community) for each given slice. Specific synthetic indices have been identified in order to quantify the main properties of the estimated communities and how they change over time.

Weighted agreement. The agreement matrix has dimension nodes by nodes (201 x 201) and each element indicates how many times a pair of parcels belongs to the same community over the course of the scan. We computed the agreement and weighted agreement index during PAIN and REST for each subject (see Supplementary). Group-level paired t-tests were then conducted across all FM patients and HC subjects separately to determine which regions spent a greater amount of time in the same community as the right $S1_{leg}$ region during PAIN versus REST. Independent samples t-test was used to compare HCs and FM patients. Results were corrected for multiple comparisons using false discovery rate (FDR)(32) correction, with the statistical threshold set at $q < 0.05$. To relate this measure with TSP in FM patients, changes in $S1_{leg}$ -TPJ weighted agreement (Δ Agreement) were correlated (Pearson's) with the TSP score. Δ Agreement was defined as the difference between the $S1_{leg}$ /TPJ weighted agreement in the last and first 2 minutes of the scan.

Recruitment and integration. These measures, recently applied to brain network analyses(33), quantify how frequently regions from conventional resting-state networks are assigned to the same module (community)(34, 35). Whereas *recruitment* represents the tendency of regions within the same network to remain in the same community over time, *integration* measures the tendency of regions from two different networks to be part of the same community over time. We divided the 201 parcels from the lateralized 17-network Schaefer parcellation(27) into 8 networks by combining each network across hemispheres. These networks included: visual, sensorimotor, temporal parietal, dorsal attention, salience, control, default, and limbic networks. We then calculated the recruitment of each network, and the integration between each pair of networks (see Supplementary).

Timeseries of $S1_{leg}$ -salience community structure

To visualize the differences between no TSP, low TSP, and high TSP groups in terms of community structure evolution throughout the scan, we focused our analyses on $S1_{leg}$ -ROI pairs where there was a statistically significant difference in agreement between PAIN and REST. For each ROI pair and for each subgroup, we plotted the percentage of subjects over time whose $S1_{leg}$ and that region were assigned to the same community. This was done for PAIN and REST separately (see Supplementary).

Salience and sensorimotor integration during sustained PAIN versus REST

Integration and recruitment indices were computed separately for each FM subgroup: no TSP, low TSP and high TSP. The values obtained for PAIN and REST scans were statistically compared using an independent samples *t*-test. Moreover, a one-way ANOVA was performed to contrast the variation of Salience and Sensorimotor integration (PAIN - REST) across subgroups. The salience and sensorimotor integration indices were obtained considering all the other

networks except for each other. These measures were then correlated with TSP scores across all FM patients (Pearson's correlation, $\alpha=0.05$)

Results

TSP was greater in FM compared to HCs

The average pain reported by FM patients in the first, second, and third two-minute windows of the PAIN scan were: 37.67 ± 16.19 , 49.13 ± 18.53 , and 55.60 ± 19.09 (Mean \pm SD), respectively. For healthy control (HC) subjects, their average pain for the first, second, and third two-minute windows of the PAIN scan were: 42.85 ± 16.29 , 47.69 ± 15.47 , and 52.32 ± 21.48 (Mean \pm SD), respectively. There were no statistically significant differences in average pain between FM patients and HCs for any of the 2-minute time windows of the PAIN scan. However, many subjects experienced TSP that we quantified as the change in pain rating from the beginning to the end of the PAIN scan (reported average pain during last two minutes minus first two minutes). Specifically, 78% and 74% of FM patients and HCs respectively had a TSP > 0 over the course of the PAIN scan. A mixed ANOVA revealed a statistically significant main effect of time over the PAIN scan ($F(1,111) = 52.16$, $p < 0.001$), no significant main effect of group ($F(1,111) = 0.08$, $p = 0.77$), and a significant time by group interaction ($F(1,111) = 804.85$, $p = 0.028$). Separately, both FM patients and HCs had a statistically significant TSP over the course of the PAIN scan (**Fig. 1**; FM: Mean \pm SD = 17.93 ± 19.24 , $t = 8.44$, $df = 81$, $p < 0.001$; HC: Mean \pm SD = 9.47 ± 14.06 , $t = 3.75$, $df = 30$, $p < 0.001$). However, FM patients as a group exhibited a greater degree of TSP compared to HCs (**Fig. 1**; $t = 2.23$, $df = 111$, $p = 0.028$).

S1_{leg} connectivity to salience regions was increased during sustained PAIN in FM

As our previous study found altered static S1_{leg} connectivity during a sustained cuff pain state for an independent FM cohort (15), we created an S1_{leg} seed around the leg somatotopic area of S1 on the right hemisphere (contralateral site of noxious cuff stimulation). A paired, whole-brain voxel-wise analysis investigated altered S1_{leg} sFC to the rest of the brain during PAIN versus REST. In both HCs and FM patients, S1_{leg} was less connected with other S1 areas during PAIN compared to REST (**Fig. 2A**). In HCs, there were no brain regions which were more highly connected with S1_{leg} during PAIN compared to during REST. In contrast, FM patients demonstrated greater sFC between S1_{leg} and brain regions known to be nodes of the salience or ventral attention network (**Fig. 2A**). These regions included the mid-cingulate cortex, right anterior insula, right anterior temporoparietal junction (TPJ), and right inferior frontal gyrus (IFG) (36, 37). Notably, these findings replicated our previous work from another FM dataset with different subjects, image acquisition parameters and pre-processing steps (15), supporting their generalizability. When the PAIN versus REST condition was contrasted between HCs and FM patients, no statistically significant clusters were found.

Change in S1_{leg} – TPJ and SII dFC during sustained PAIN was associated with greater TSP

Although both FM patients and HCs experienced a statistically significant TSP throughout the PAIN scan, HCs experienced a very low magnitude of TSP (mean = 9.47) and consisted of a smaller sample for correlational analysis. As such, dFC analysis with TSP was focused on the FM patient group. Specifically, we wanted to determine whether TSP in FM was dynamically tracked by S1_{leg} functional connectivity. We estimated dFC between S1_{leg} and every other voxel. We then averaged the dFC estimates within both the first and last 2-minutes of the PAIN scan for each

region pair separately, corresponding to the pain rating periods used to calculate TSP. A linear regression model then evaluated the association between TSP and the dFC difference between the final and initial 2-minute windows (final – initial; Δ dFC), for each region pair (**Fig 2B**). We found that for FM patients, greater Δ dFC between S1_{leg} and the right secondary somatosensory cortex (SII) anteriorly, and anterior TPJ posteriorly was associated with greater TSP. To demonstrate that the posterior extent of the cluster overlaps with the anterior TPJ, a TPJ parcellation was overlapped with the cluster (see Supplementary, **Fig. S4**)

Dynamics in S1_{leg} community structure extended prior sFC findings

As summarized in **Fig. 3**, we estimated dFC between region pairs, followed by the application of multi-slice community detection to show how brain regions are organized into different communities over time (29, 30) - i.e. how they evolve differently in time during PAIN versus REST. To link this approach with sFC findings, we first evaluated alterations for ROI pairs involving S1_{leg}. We found that for both HCs and FM patients, S1_{leg} spent a greater proportion of time in the same communities with other S1 areas during REST versus PAIN (**Fig. 4A**). However, in FM patients only, the S1_{leg} region spent a greater proportion of time in the same community as salience/ventral attention network brain regions (anterior insula, mid-cingulate, anterior TPJ, IFG) during PAIN compared to during REST. Notably, these findings were in general agreement with those obtained from the sFC analyses but demonstrated greater spatial extent of this effect within S1 and the salience network.

The community involving S1_{leg} and anterior TPJ had a similar spatial extent as the S1_{leg} to TPJ and/or SII dFC cluster found to be linked with TSP in FM (see **Fig. 2B**). Hence, we performed a similar correlation analysis using the S1_{leg} agreement and found that a greater increase in time spent by S1_{leg} in the same community as anterior TPJ and/or SII (Δ Agreement from the last to the first 2-minute time period) was associated with greater TSP in FM patients (**Fig. 4B**).

Both groups, HCs and FM patients, demonstrated decreased agreement between S1_{leg} and other S1 areas during PAIN compared to during REST. However, a greater decrease in agreement between these regions was found in HCs compared to FM patients. The brain maps obtained from this analysis were reported in the Supplementary Material (**Fig. S7**).

More sustained S1_{leg}-salience community structure existed in TSP versus no TSP groups

We next examined whether differences in TSP within the FM group would be reflected in different temporal dynamics of community structure of S1_{leg}. We split the FM patients into 3 subgroups: 1) no TSP (N = 15), 2) low TSP (N = 27), and 3) high TSP (N = 27). We then focused our analyses on S1_{leg}-ROI pairs which were statistically significant from the PAIN versus REST contrast (**Fig. 4A**). For each S1_{leg}-ROI pair and for each subgroup separately, we plotted the proportion of FM patients over time that demonstrated shared community structure between S1_{leg} and each ROI, both during PAIN and REST (**Fig. 5**). Whereas patients who exhibited pain summation (both low and high TSP subgroups, see Supplementary material for low TSP group) demonstrated persistent community structure between S1_{leg} and salience regions throughout the PAIN scan, patients who did not temporally summate exhibited intermittent gaps in this community structure. We defined gaps as time segments of at least 5 TRs where 0% of the subjects had a given region in the same community as S1_{leg} (**Fig. 5**, yellow arrows). These intermittent gaps were also observed during REST, regardless of the subgroup (**Fig. S8**, Supplementary material).

High TSP was marked by integration of the sensorimotor and salience networks at the exclusion of other networks

To examine interactions between communities of brain regions over time, we assessed measures of recruitment and integration separately for each group (no TSP, low TSP, high TSP). We found that during PAIN versus during REST, integration between sensorimotor and salience network regions was increased across all three TSP subgroups of FM patients (**Fig. 6A**). However, for the high TSP subgroup only, on average, the salience and sensorimotor networks decreased their integration with all other networks except for each other during PAIN. For example, when contrasting PAIN and REST, the dorsal attention network increased in integration with the salience and sensorimotor networks for both the no summation and low summation TSP group, but not for the high TSP group. Therefore, high TSP was marked by high integration between the sensorimotor and salience networks at the exclusion of other networks. In order to quantify this behavior, we reported the results of a one-way ANOVA performed to compare the three groups (**Fig. 6B**). The drop in salience network integration was significantly larger for the high TSP group ($F=4.1$, $p=0.02$). The same trend was also seen for integration of the sensorimotor network ($F=2.25$, $p=0.11$). Decrease in salience integration was negatively correlated with TSP score in FM patients, suggesting that a more isolated salience/sensorimotor cluster was associated with higher TSP (**Fig. 6C**). A similar correlation was observed for sensorimotor integration and reported in the Supplementary (**Fig. S9**).

Discussion

In this study, we demonstrated how TSP-related fluctuations are associated with concurrent dynamic brain changes in FM. We began by demonstrating that FM patients have abnormal central pain processing as they exhibit enhanced TSP relative to HCs(2, 3, 15). We then replicated our previous findings from an independent FM cohort (15) that sFC between $S1_{leg}$ and salience network brain regions is enhanced by tonic pressure pain within a large cohort of FM patients. As a novel extension, we contextualized these prior sFC findings within a dynamic framework by demonstrating that the corollary of increased sFC between these regions is a greater proportion of time spent within the same communities throughout the scan.

Using a dFC approach, we also showed that increased $S1_{leg}$ to anterior TPJ connectivity at the end compared to the beginning of the PAIN scan was associated with higher TSP in FM. Whereas anterior TPJ is a cardinal node of the salience or larger “ventral attention network”, posterior TPJ is known to be involved with mental state predictions(38, 39). Prolonged activation of anterior TPJ and ventral attention network have been demonstrated in response to tonically salient stimuli, such as that occurring with a prolonged painful stimulus (40). Within this conceptual framework, greater increases in sensory-salience connectivity, as reflected by somatotopically-specific $S1_{leg}$ and anterior TPJ connectivity throughout the PAIN scan, supports more profound TSP, in response to increased processing of an increasing and highly salient perception – tonic pain evoked at the leg.

Applying a community-based dFC approach, we demonstrated how the presence versus absence of TSP in FM patients is associated with more consistent $S1_{leg}$ to salience network community structure during PAIN. In fact, for a “no summation” FM group, we noted frequent temporal gaps during which there was a distinct lack of $S1_{leg}$ to salience network community structure. Early psychophysical research using repetitive noxious stimuli showed that a short break from stimulation “reset” pain perception back to baseline, relieving any temporal

summation(41). Furthermore, electrophysiological studies in the spinal dorsal horn demonstrated that spinothalamic tract neurons whose activity “winds-up” with TSP also exhibited the same reset phenomenon in activity during a gap in repeated pain provocation(42). In our study, no breaks in stimulation were provided during the PAIN scan. However, the representation of pain in the brain can shift spatially over the course of a scan/stimulation set. Therefore, the sustained sensorimotor and salience community structure observed in individuals who temporally summate may reflect a perceptual corollary of the wind-up occurring in the dorsal horn. Whereas in individuals who do not temporally summate, breaks in sensorimotor to salience community structure may reflect dynamic reconfigurations of brain organization towards other states, e.g., those associated with top-down pain or attentional modulation. Indeed, in differentiating FM patients who experience high TSP versus those who experience low/no TSP, a hallmark was the decrease in integration between the salience and all but the sensorimotor network. For example, in low/no but not high TSP FM patients, there was increased integration between the salience/ventral attention and dorsal attention network during PAIN. Communication between both the ventral and dorsal attention networks plays an integral role in attentional selection(43), and their interactions observed in low/no TSP patients may represent a greater ability to modulate attention away from pain.

A limitation of this study is that pain ratings were acquired retrospectively for each 2-minute block instead of continuously during the scan. Although this prevents confounding from rating-related brain activity, continuous ratings would have allowed for dFC estimates to be regressed against pain ratings using every single time-point. In addition, future dynamic community structure analyses should consider the inclusion of a subcortical parcellation, as well as investigate how results differ with higher resolution parcellations.

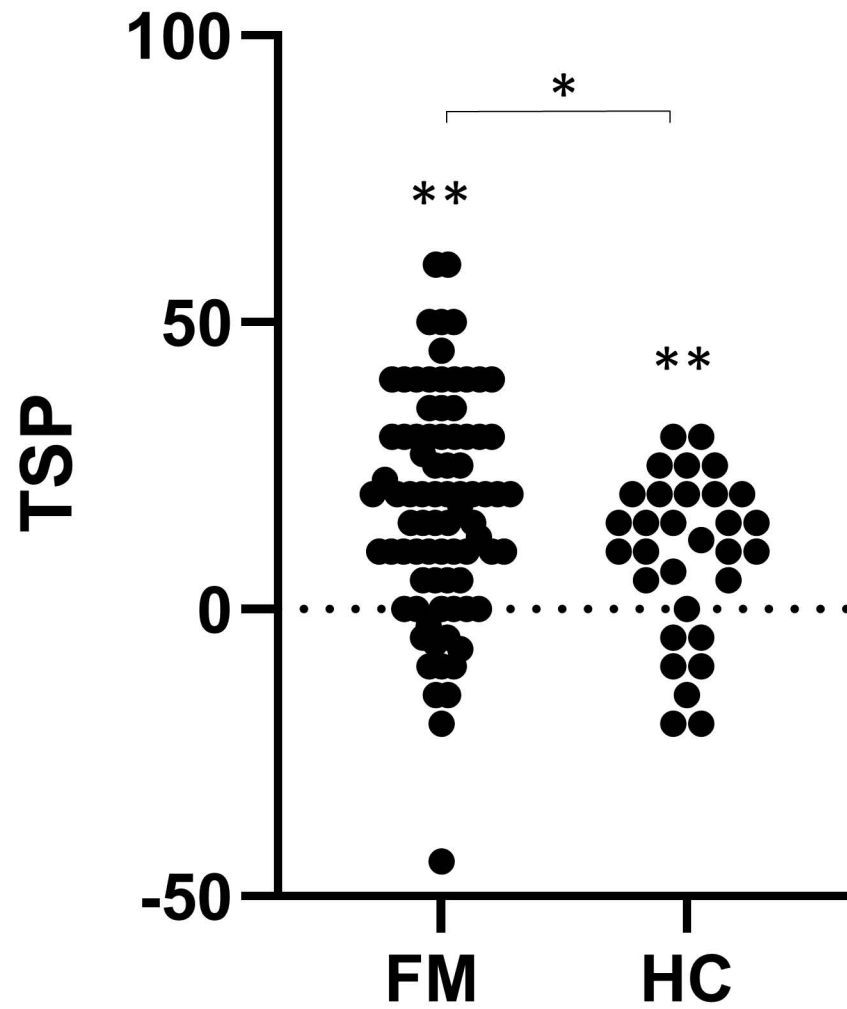
In conclusion, we showed how dynamic community structure between the sensorimotor and salience networks during tonic pain was enhanced in FM patients compared to HCs. We further demonstrated how FM patients with enhanced TSP exhibited longer and more consistent integration of the aforementioned networks during pain, with downregulated interactions with all other brain networks. These results elucidate the brain dynamics supporting TSP and suggest specific time-resolved alterations in pain processing underlying chronic pain.

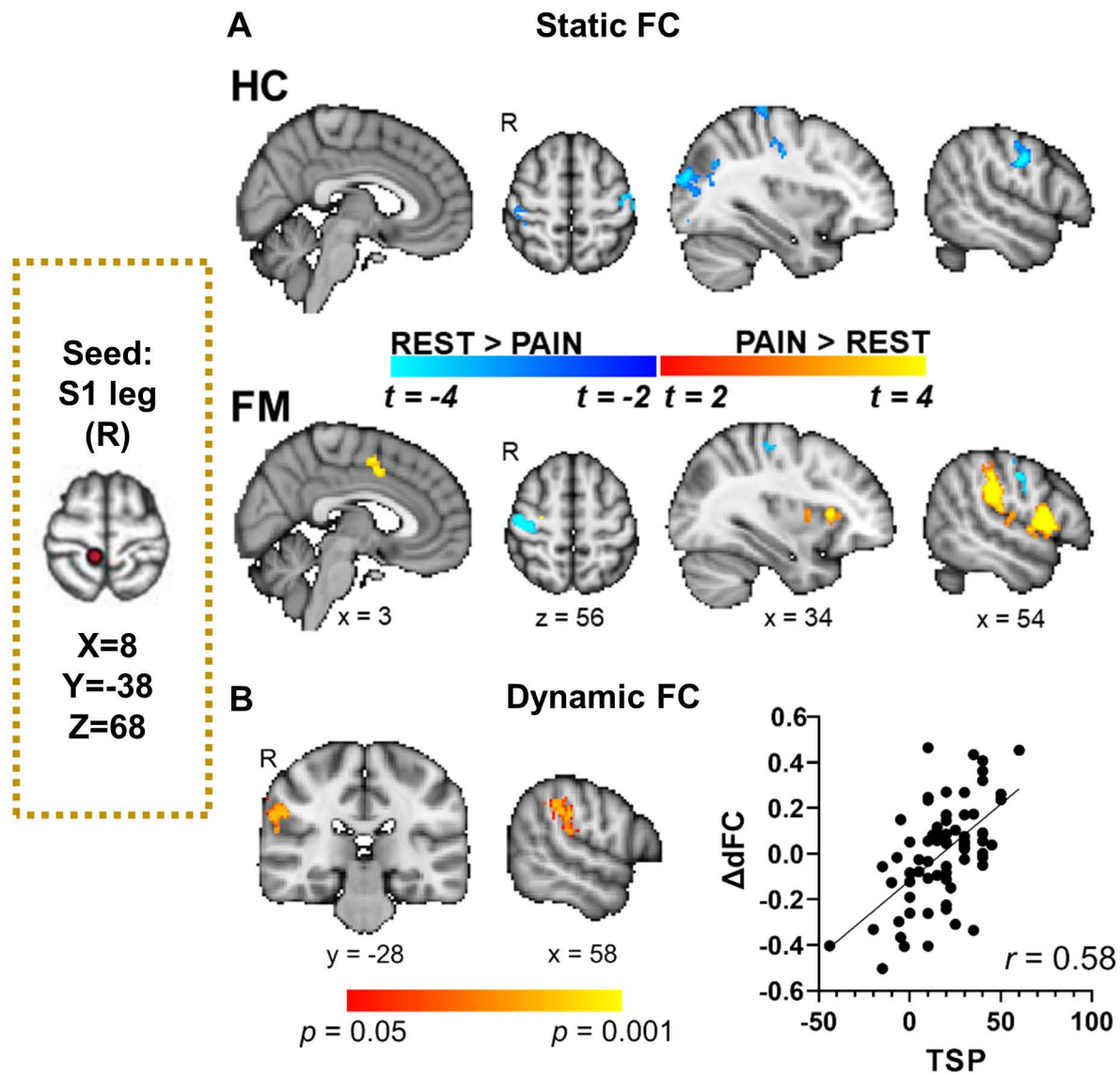
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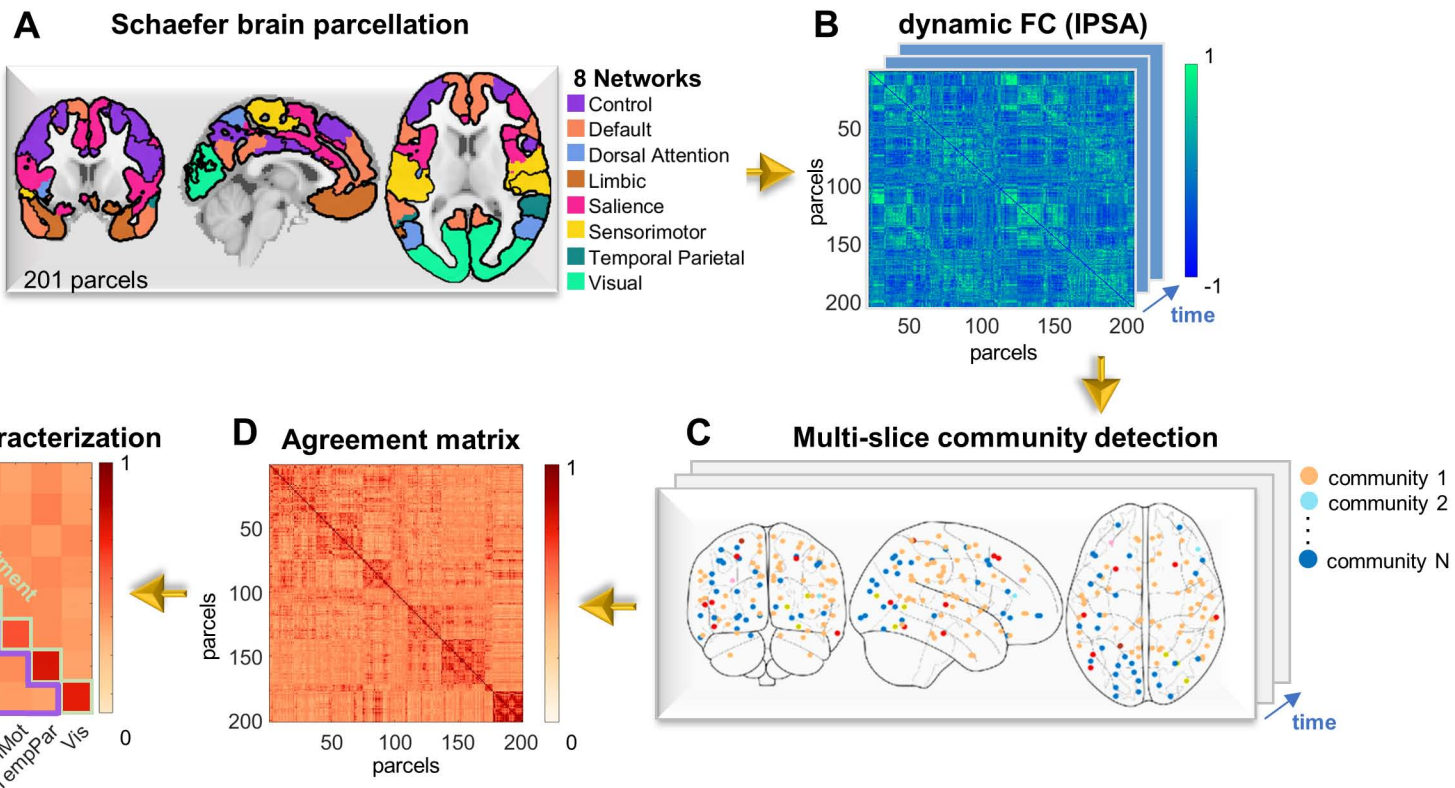
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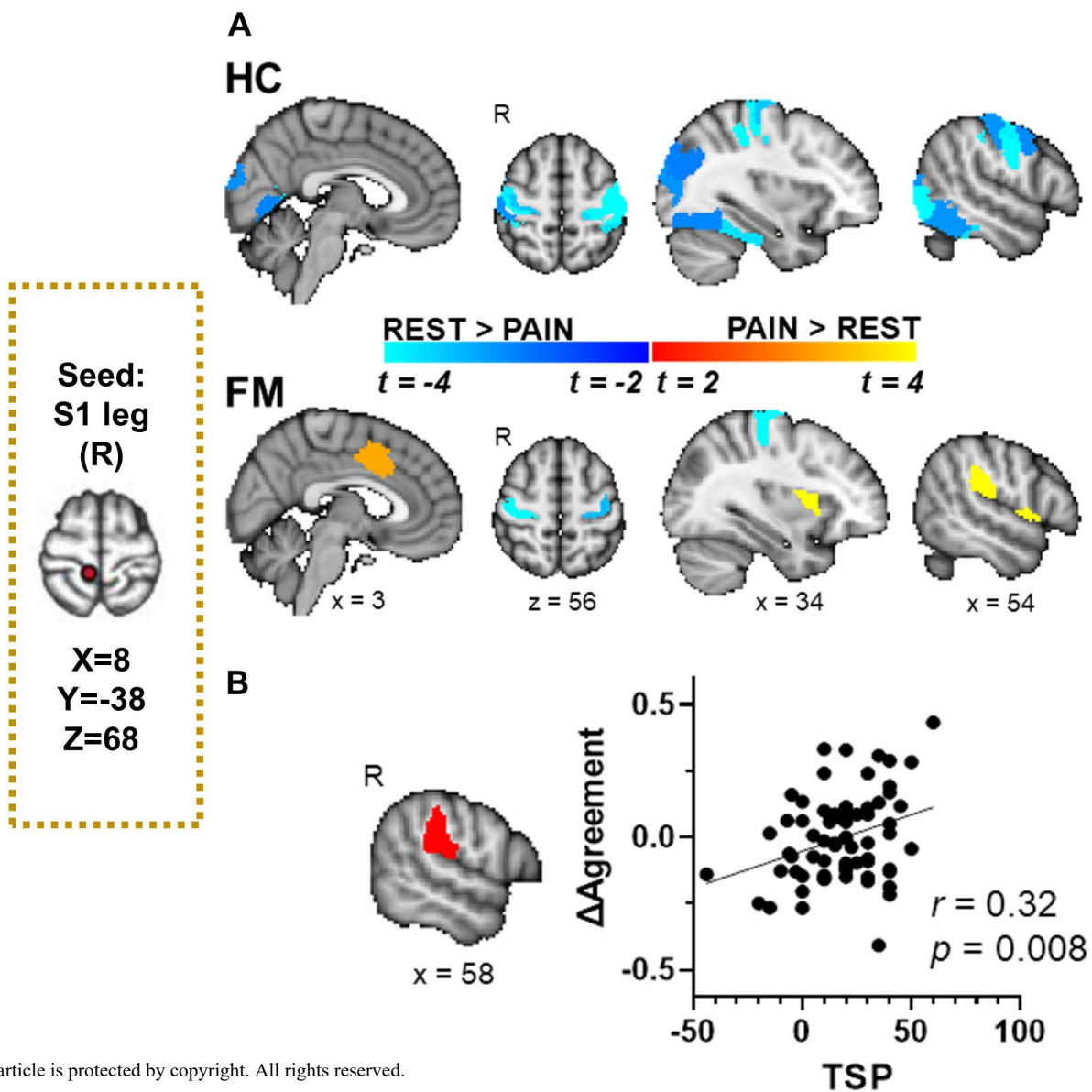
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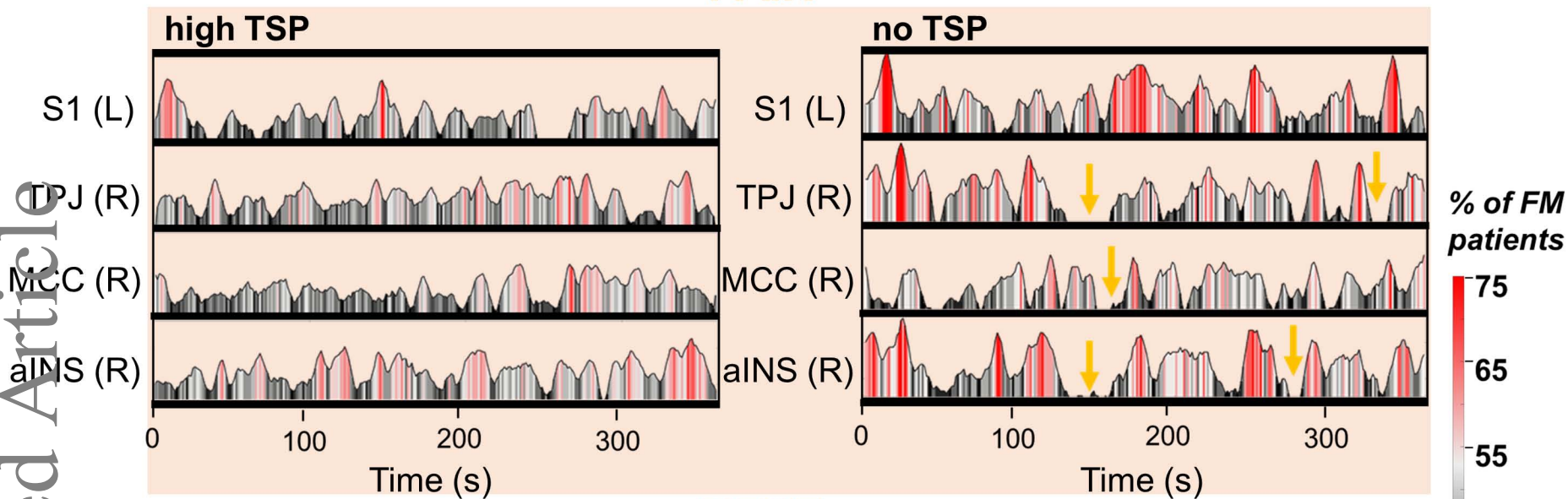




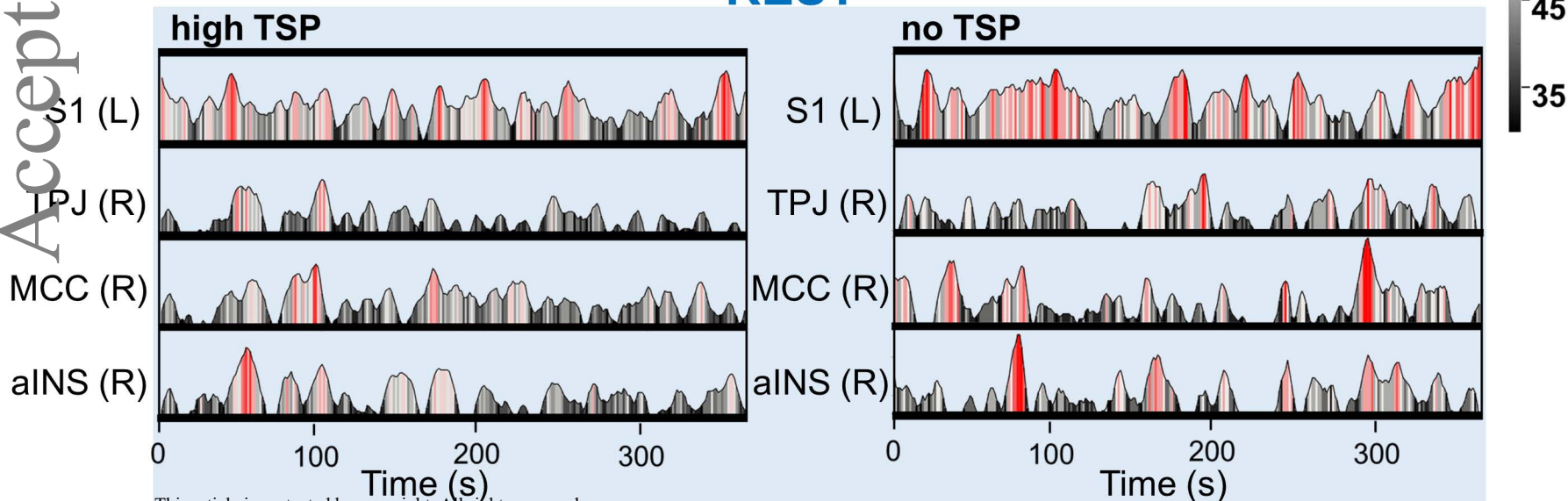




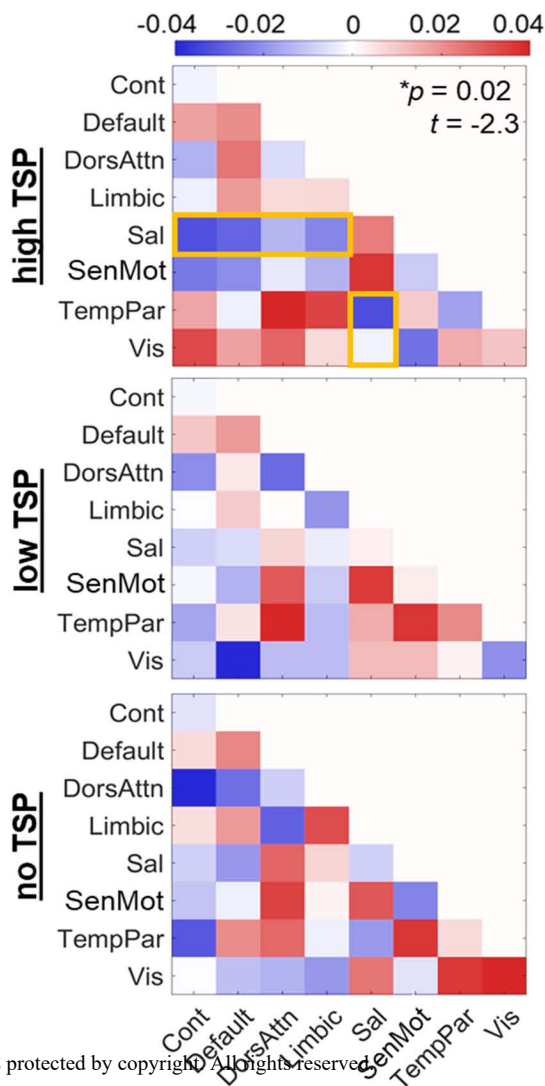
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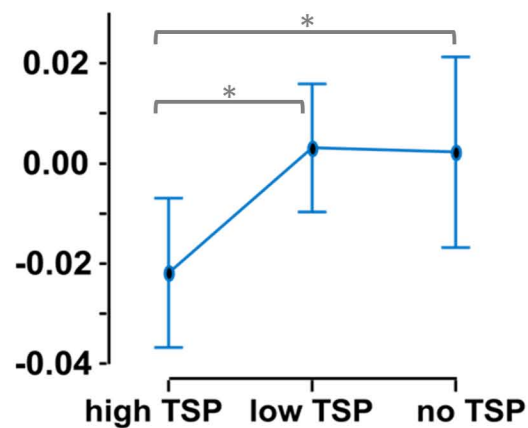
REST



A network integration/recruitment PAIN-REST



B salience network integration PAIN-REST



C salience network integration PAIN-REST

