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Pilot Study of Intensive Pain Rehabilitation, Sleep, and Small-World Brain Networks in Adolescents with Chronic Pain

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Abstract: Background: Approximately 25% of adolescents live with chronic pain, with many reporting symptoms of functional impairment and poor sleep quality. Both chronic pain and poor sleep quality can negatively impact brain functional connectivity and efficiency. Better sleep quality may improve pain outcomes through its relationship with brain functional connectivity. **Methods:** This pilot prospective cohort study used data from 24 adolescents with chronic pain (aged 10–18 years) participating in an Intensive Interdisciplinary Pain Treatment (IIPT) at the Alberta Children's Hospital. Data were collected within the first couple of weeks prior to starting IIPT and on the last day of the 3-week IIPT program. Sleep quality was assessed using the modified Adolescent Sleep-Wake Scale. Resting-state functional MRI data were obtained, and graph-theory metrics were applied to assess small-world brain networks. Questionnaires were used to obtain self-reported functional disability data. Paired t-tests were applied to evaluate changes in outcomes from pre- to post-IIPT, and moderation analyses were used to examine the relationships between sleep, small-world brain network connectivity, and functional disability. **Results:** Total sleep quality ($p = 0.005$) increased, and functional disability ($p = 0.020$) decreased, between baseline and discharge from IIPT. Small-world brain networks did not change pre- to post-IIPT ($p > 0.05$). Unlike adolescents with high small-worldness ($p = 0.665$), adolescents with low to moderate small-world brain characteristics (1*SD* below or at the mean) who reported better sleep quality reported less functional disability (all $p \leq 0.001$) over time. **Conclusions:** The IIPT program was associated with improvements in sleep quality and functional disability. Better sleep quality together with greater small-worldness was associated with less pain-related disability. This suggests that it is equally important for IIPTs to target sleep problems in adolescents with chronic pain, as this may have a key role in producing long-term improvements in pain outcomes.

Keywords: brain efficiency; pediatric pain; pain treatment; sleep; youth

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1. Introduction

Chronic pain is a major public health problem that affects approximately 25% of Canadian adolescents [1]. For a significant subset of these adolescents (~26%), pain-related impairment interferes with several aspects of daily life, such as attending school, socializing with peers, and participating in extracurriculars [2]. Unfortunately, current

pain treatments for adolescents provide limited benefits in some patients [3]. It is of the utmost importance to optimize the treatment of persistent pain and related disability in this vulnerable population.

Intensive Interdisciplinary Pain Treatments (IIPTs) are pain management programs that consist of psychotherapy, physiotherapy, and medical care delivered in inpatient units or day-hospital settings for 3–4 weeks [4]. Participation in IIPTs is linked to significant improvements in self-reported pain interference and quality of life for patients with pain problems that were not sufficiently managed by previous outpatient and/or inpatient programs [5]. The lasting effects of IIPTs on pain symptoms beyond discharge suggest that these programs may alter the biological mechanisms of pain modulation and perception.

Changes to functional brain networks are associated with a variety of pain symptoms, such as pain intensity, severity, bodily spread, and disability [6]. Of growing interest is the implication of pain on brain efficiency and organization of small-world networks (e.g., decreased normalized clustering coefficient and characteristic path length) [7,8]. IIPTs have been shown to rapidly alter brain structural and functional connectivity in the brain in areas implicated in sensation, emotion, cognition, and pain modulation [9]. However, it remains unclear how IIPTs alter small-world brain networks.

One mechanism by which IIPTs may alter small-world networks is through sleep. More than half of pediatric chronic pain patients report some form of sleep disturbance [10]. By contrast, sufficient sleep can enhance the biological and psychological mechanisms of pain recovery [11]. Improvements in both self-reported and actigraphic sleep have also been observed in IIPT patients, including less daytime sleepiness, fewer insomnia symptoms, and more consistent sleep patterns [12]. Given this evidence, it is suggested that IIPT-related improvements in sleep quality may underlie improvements in pain disability by way of brain functional connectivity.

This pilot study assessed whether improvements in sleep quality together with greater small-world brain functional connectivity were associated with less pain-related disability between baseline (pre-IIPT) and discharge from IIPT (post-IIPT). We hypothesized that (1) both sleep quality and (2) small-world network connectivity would increase between baseline and discharge, and (3) improvements in sleep quality and greater small-world brain functional connectivity would be associated with decreased functional disability following IIPT.

2. Materials and Methods

An ongoing study exploring "clinical outcomes for children and adolescents with complex pain" was approved by the University of Calgary's Conjoint Health Research Ethics Board (REB14-0162 and REB20-1464) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant aged 14 and older. Written assent was obtained from adolescents aged 13 and below, and written informed consent was also obtained from one of their parents.

2.1. Participants

For this pilot prospective cohort study, thirty participants were required to reach an 80% power given a moderate effect size (Cohen's d = 0.5). Accounting for the possibility of 25% missing data (n = 8), 38 adolescents with chronic pain (ages 10–18 years) were recruited from the Intensive Pain Rehabilitation Program, an IIPT program at the Alberta Children's Hospital (ACH), between August 2016 and June 2022. These same adolescents were included in previous publications by our group [5,13–15]. Because of the intensity and coordination required for this program, a limited number of patients could be seen at a given time. Therefore, only 2–4 adolescents were treated per quarter, requiring an extended recruitment window. Admission to the IIPT program at the ACH required a referral from a physician or nurse.

2.1.1. Inclusion Criteria

To participate in the program, patients had to be 10–18 years old, have had the necessary medical work-up, and be experiencing significant pain interference (i.e., poor physical functioning, sleep, or mood) that has been resistant to other evidence-based outpatient pain therapies.

2.1.2. Exclusion Criteria

Patients excluded from the IIPT program were adolescents with significant developmental delay, brain damage, functional neurological conditions, or conversion disorders; those who required opioid tapering; and those who needed significant medical care and/or had untreated psychiatric disorders that would interfere with their ability to complete the IIPT program. Further, patients with MRI contraindications (e.g., metallic implants) were excluded from the brain imaging component of the study.

2.2. The Intensive Pain Rehabilitation Program

The IIPT is an outpatient program at ACH that consists of three to six weeks (Monday through Friday) of daily intensive rehabilitation encompassing approximately 8 h of therapy each day. Program interventions included, but were not limited to, physiotherapy, individual psychology, family therapy, psychology education, and occupational therapy.

2.3. Measures

2.3.1. Demographics

Participants completed a demographic questionnaire that included questions pertaining to their age, gender identity, and pain type. Regarding their pain type, participants were asked to select their primary pain concern from the following: (1) abdominal pain, (2) nerve (neuropathic) pain (e.g., complex regional pain syndrome), (3) headache, (4) pelvic pain, (5) musculoskeletal pain, and (6) other with the option to specify.

2.3.2. Functional Disability Questionnaire

To assess how pain had limited the participants in their daily lives, the Functional Disability Inventory (FDI) was completed [16]. This 15-item questionnaire prompted participants to rate the difficulty of completing daily activities across a variety of settings (e.g., school, home) using a 5-point Likert scale (0 = "no trouble" to 4 = "impossible") and summed to create a total score (range: 0–60), with higher scores implying greater pain-related disability. The FDI has been reported to have a high internal consistency ($\alpha = 0.90$) and good convergent validity to related constructs such as the Abdominal Pain Index ($r = 0.33$, $p < 0.001$), Faces Pain Scale ($r = 0.35$, $p < 0.001$), and Children's Somatization Inventory ($r = 0.59$, $p < 0.001$) [16,17].

2.3.3. Sleep Questionnaires

Participants completed the Revised Adolescent Sleep–Wake Scale (ASWS) at baseline and discharge [18]. This 10-item questionnaire was used to rate the frequency of different sleep behaviors within the last month on a 6-point Likert scale (range: 1 = "always" to 6 = "never"). The ASWS yields a total sleep quality score, with higher scores indicating better sleep quality. In adolescents, good internal consistency has been reported for the total questionnaire ($\alpha = 0.72$) [19].

2.4. Brain Imaging

2.4.1. Acquisition Parameters

Adolescents underwent 3T MRI scans at baseline and discharge using a 32-channel head coil on a GE 3T Discovery MR750w (GE, Milwaukee, WI, USA) system at the ACH. T1-weighted structural images were obtained using an FSPGR BRAVO sequence (flip angle = 10°, 226 slices, TR/TE = 6.8 ms/3.00 ms, 0.8 mm × 0.8 mm × 0.8 mm resolution, matrix size = 512 × 512, inversion time = 540 ms). Resting-state functional images

were acquired using a gradient echo-planar imaging sequence (flip angle = 60°, 38 slices, TR/TE= 2 s/30 ms, 3.59 mm × 3.59 mm × 3.6 mm resolution, matrix size = 64 × 64, 150 vol, total scan time 5:10 min). During the resting-state functional MRI, adolescents had their eyes open and were asked to look at a black crosshair on a white screen while thinking about nothing in particular. Total scan time was approximately 45–60 min.

2.4.2. Image Preprocessing

The preprocessing procedure used in this study was modified from Long et al. 2019 [20]. Preprocessing was completed in FSL and AFNI [21,22]. Brain extraction, image segmentation, slice timing, head motion detection and correction, co-registration, and spatial normalization and smoothing were performed in FSL, version FSL_6.0.5 [22]. Removal of nuisance signals, band-pass filtering, and linear trend removal were completed in AFNI, version AFNI_21.3.13 [21].

For each participant, the T1-weighted images were manually skull-stripped and segmented into grey matter, white matter, and cerebral spinal fluid (CSF) masks, which were then co-registered to their fMRI space. Total brain volume was calculated by adding the gray and white matter volumes of each image and controlled for during graph-theory calculations. The data were corrected for slice timing and head motion. A 36-parameter matrix was created by averaging the signals from the whole brain mask, CSF mask, white matter mask, and six head motion parameters and their temporal derivatives and quadratic term signals. Volumes with spikes (framewise displacement, FD > 0.3 mm) were used to form a spike matrix. The 36-parameter matrix and the spike matrix were combined and regressed from the fMRI signals. If a dataset had spike volumes longer than four minutes, the participant's data were excluded from the study. There were 9 participants whose data were removed from analysis because of high head motion at baseline. Data from 13 participants were removed because of high head motion at discharge. A bandpass filter (0.009–0.08 Hz) was applied to the data, and the linear trend was removed. The signals were transformed to a standard pediatric Montreal Neurological Institute (MNI) brain template constructed for patients aged 13 to 18.5 years [23] and were spatially smoothed with a 4 mm full-width Gaussian kernel at half maximum.

2.4.3. Functional Connectome Construction

The Automated Anatomical Labeling (AAL) template was applied to divide each brain into 90 regions, excluding the cerebellum [24]. The average rs-fMRI time series was computed for each region, and Pearson's correlation coefficients (captures linear correlation; linear trend was removed as the last processing step) were calculated between the averaged time series of each of the AAL regions. The correlations were z-transformed and used to yield a 90 × 90 connectivity matrix.

2.4.4. Calculating Graph-Theory-Based Metrics

The 90 × 90 connectivity matrices were thresholded ($r = 0.16$ at $p < 0.05$) [25]. The threshold r = 0.16 was significant at $p = 0.05$ with the degree of freedom 148, which is the number of volumes (i.e., 150) minus 2. Graph-theoretical measurements were calculated for each connectivity matrix within the full resting-state fMRI (all timepoints/volumes). The GRETNA toolbox was used to perform whole-brain network analysis [26,27]. Graph-theory metrics were obtained for each matrix: (1) normalized clustering coefficient, the ratio of clustering coefficients across real and random networks (gamma); (2) normalized characteristic path length, the ratio of characteristic path lengths across real and random networks (lambda); and (3) small-worldness, the ratio between clustering coefficient and characteristic path length between real and random networks (sigma). A small-world network has a mean path length comparable to the mean path in a random network (lambda ≈ 1) but has a higher clustering coefficient (gamma > 1).

2.5. Statistical Analysis

IBM SPSS Statistics Version 28.0 was used for data analysis [28]. Data were assessed for violations in normality using the Shapiro–Wilk test. The following variables were found to deviate from normality: age and the normalized clustering coefficient. Listwise deletion of missing data was implemented. All analyses were conducted using two-tailed hypothesis testing.

Demographic characteristics of participants and the three small-world metrics at baseline and discharge were compared using paired-sample t-tests or chi-square, where appropriate, to determine if there were any significant changes in outcomes over the course of their participation in the IIPT at the ACH. In cases of non-normality, the Wilcoxon signed-rank test was applied. Linear mixed models were used to examine the interactions between sleep quality and small-world metrics in relation to changes in functional disability between baseline and discharge. Secondary exploratory analyses of the conditional effects at focal predictors were conducted using the PROCESS macro [29] in order to explore signification interactions and determine the direction of the relationships.

3. Results

3.1. Participant Characteristics

A participant flow chart is depicted in Figure 1. Three participants did not complete the protocol (n = 35 at discharge); see Supplementary Table S1 for cohort characteristics of all participants enrolled in IIPT from August 2016 to June 2022. Data from 24 adolescents were used in this analysis, with the average time between baseline and discharge being 24 days (SD = 10). Adolescents who did not complete the study were not statistically different from participants in terms of pain interference (χ^2 = 1.17, p = 0.557), pain-related functional disability (χ^2 = 0.77, p = 0.681), sleep quality (χ^2 = 5.17, p = 0.880), or small-worldness (χ^2 = 2.21, p = 0.137).

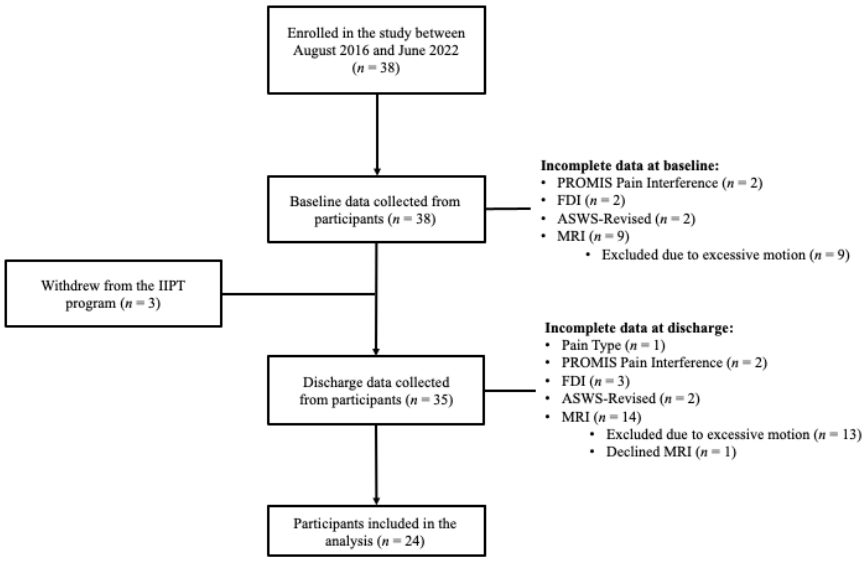

Figure 1. Participant flowchart. This flowchart shows the progression of participants in the study. The regression analyses used in the present study allow for some missingness. Of the 38 participants enrolled in the study, 20 had complete data at both timepoints and were included in the models. Furthermore, 4 participants were missing only the MRI data at discharge and were included in the models. Thus, 24 participants were included in the analyses. All other participants with incomplete data were excluded because of excessive data missingness. ASWS = Adolescent Sleep–Wake Scale; FDI = Functional Disability Inventory; IIPT = Intensive Interdisciplinary Pain Treatment; MRI = magnetic resonance imaging; PROMIS = Patient-Reported Outcomes Measurement Information System.

Data from 24 adolescents were used in this analysis (see Table 1). The majority (83.3%) of participants identified as female (n = 20), and the median age of the adolescents was 17 years old. The pain concern most reported by participants was neuropathic pain (n = 9). Functional disability scores did not significantly improve for adolescents included in the analysis ($t(21) = 1.69$, $p = 0.105$, Cohen's d = 0.36; see Table 1); however, significant improvements in functional disability scores over the course of the program were found in the overall sample ($t(29) = 2.46$, $p = 0.020$, Cohen's d = 0.45; see Supplementary Table S1). Additionally, participants experienced improvements in total sleep quality ($t(22) = -2.25$, $p = 0.035$, Cohen's d = 0.47) between baseline and discharge. Small-world brain metrics did not change significantly between baseline and discharge from IIPT (all $p > 0.05$).

Table 1. Cohort characteristics of study participants.

Characteristic	Baseline (n = 24)	Discharge (n = 24)	p-Value	Cohen's d or Effect Size
Age, Median (IQR), y	17.00 (16.00–17.00)	-	-	-
Gender (female), n (%)	20 (83.3)	-	-	-
Pain Type, n (%)			0.977	0.1
Abdominal	1 (4.2)	1 (4.3)		
Nerve/Neuropathic	9 (37.5)	9 (39.1)		
Headache	8 (33.3)	6 (26.1)		
Musculoskeletal	4 (16.7)	4 (17.4)		
Other	2 (8.3)	3 (13.0)		
Functional Disability, M (SD)	27.33 (12.77)	23.14 (13.24)	0.105	0.36
Sleep Quality, M (SD)	3.11 (0.89)	3.41 (0.90)	0.035	0.47
Normalized Clustering Coefficient, M (SD)	1.84 (0.13)	1.82 (0.14)	0.63	0.11
Normalized Characteristic Path Length, Median (IQR)	1.26 (1.23–1.28)	1.25 (1.23–1.30)	0.9	0.14
Small-Worldness, M (SD)	1.46 (0.10)	1.44 (0.10)	0.39	0.19

Missing data at discharge: pain type = 1; pain interference = 1; functional disability = 2; sleep quality scores = 1; graph-theory metrics = 3.

3.2. Total Sleep Quality, Small-World Brain Networks, and Functional Disability

There was a significant interaction between sleep quality and small-worldness in relation to functional disability (unadjusted: $F(1,43) = 7.80$, $p = 0.008$, R^2 change = 0.11) between pre- and post-IIPT (adjusted: coefficient = 0.41, 95% confidence interval = −0.13, 0.70, $p = 0.005$, $R^2 = 0.38$; see Table 2). This relationship was driven by an interaction between sleep quality and the normalized clustering coefficient (unadjusted: $F(1,43) = 3.82$, $p = 0.059$, R^2 change = 0.06; adjusted: coefficient = 0.28, 95% confidence interval = 0.01, 0.55, $p = 0.042$, $R^2 = 0.32$), as opposed to an interaction with normalized characteristic path length (unadjusted: $F(1,43) = 0.12$, $p = 0.732$, R^2 change = 0.002; adjusted: coefficient = 0.01, 95% confidence interval = −0.25, 0.27, $p = 0.941$, $R^2 = 0.28$). When examining the conditional effect at focal predictors of the moderator, it was found that among adolescents with low (1SD below the mean small-worldness: 1.361, effect: −11.99, 95% confidence interval: −16.87, −7.10, $p < 0.001$) to moderate (mean small-worldness: 1.458, effect: −6.55, 95% confidence interval: −9.66, −3.44, $p = 0.001$) small-worldness, greater sleep quality was associated with lower functional disability (see Figure 2). However, for adolescents with higher small-worldness (1SD above the mean: 1.556, effect: −1.11, 95% confidence interval: −6.23, 4.01, $p = 0.665$), greater sleep quality was not associated with a significant improvement in functional disability.

Table 2. Relationships between total sleep quality, small-world brain networks, and functional disability.

	Functional Disability		
Factors	**Coefficient**	**Confidence Interval**	***p*-Value**
Total Sleep Quality	−0.51	−0.73, −0.28	<0.001
Small-Worldness	−0.25	−0.50, −0.01	0.044
Small-Worldness X Total Sleep Quality *	0.41	0.13, 0.70	0.005
R^2 Value		0.38	

* Unconditional interactions associated with functional disability ($F(1,43) = 7.80$, $p = 0.008$, R^2 change = 0.11).

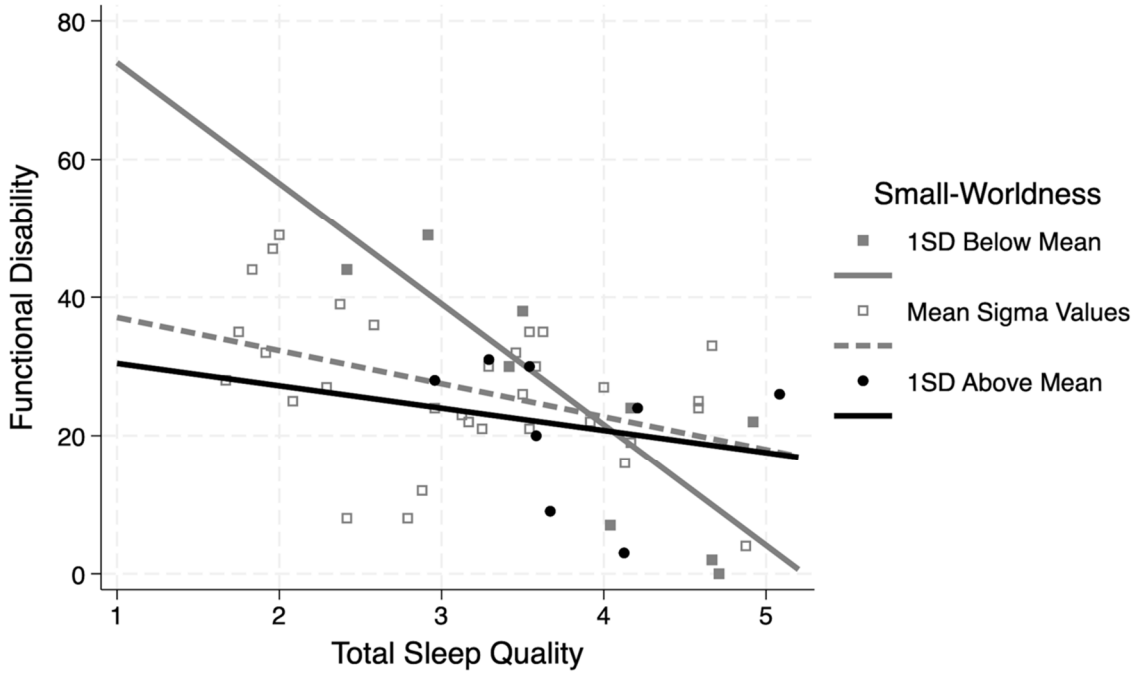

Figure 2. Small-worldness moderated the relationship between sleep quality and functional disability following IIPT. Displayed are the conditional effects at the mean (hollowed squares and dashed trend line), 1*SD* below the mean (grey squares, grey trend line) and 1*SD* above the mean (black circles, black trend line) for small-worldness on functional disability in relation to sleep quality. Moderate to low but not high small-worldness were associated with less functional disability with greater sleep quality. IIPT = Intensive Interdisciplinary Pain Treatment; *SD* = standard deviation.

4. Discussion

This pilot study assessed the relationships between IIPT-related sleep improvements, small-world brain networks, and pain-related disability in adolescents. Significant improvements in sleep quality were found between baseline and discharge from IIPT. Functional disability scores did not significantly change for the subset of participants analyzed in this study, but they did for the overall cohort. No changes in small-world brain networks were observed from pre- to post-IIPT. However, among adolescents with lower small-world properties, greater sleep quality was associated with decreases in functional disability from pre- to post-IIPT. This would suggest that moderate to high brain network efficiency is a protective factor against functional disability, regardless of sleep quality. However, among those with lower brain network efficiency, greater sleep quality can improve functional disability over time. Therefore, IIPTs should aim to address sleep problems in adolescents with chronic pain, as this may have a key role in producing long-term improvements in pain outcomes for adolescents with higher functional disability.

Correspondingly to the existing literature, we demonstrated short-term improvements in sleep quality following IIPT [12,30]. Sleep problems are common among adolescents with chronic pain [10]. Although IIPTs often do not directly address sleep problems in adolescents, participation in IIPT may have indirect benefits to sleep quality. The highly structured nature of the program may result in more stabilized sleep/wake patterns that contribute to more positive perceptions of sleep quality by participants [31]. Further, some of the individual treatments offered within the IIPT program have been reported to indirectly improve sleep quality. Physiotherapy uses various forms of physical intervention to remediate disability and promote mobility and function for patients with chronic pain [32]. A randomized controlled trial found that 8 weeks of physiotherapy sessions for adults with chronic low back pain were associated with significant improvements in sleep quality and insomnia symptoms [32]. Similarly, psychotherapies, such as cognitive-behavioral therapy, are often incorporated into IIPT programs and teach patients strategies to reduce physiological arousal and maladaptive beliefs [33]. These strategies may be generalized to sleep, which may explain the improvements in sleep quality often reported by IIPT patients [33].

The associations between poor sleep quality and pain symptoms have been well established [34]. Further, there is evidence to suggest that IIPT-related improvements in sleep are correlated to long-term reductions in self-reported pain interference and functional disability for participants [12,30]. However, the mechanisms by which this is achieved have yet to be established. This study explored the role of small-world brain networks within this relationship.

Unfortunately, none of the small-world brain metrics changed from pre- to post-IIPT. Therefore, we were unable to identify the mechanism through which improvements in sleep lead to decreases in functional disability in adolescents undergoing IIPT. In contrast, a previous study conducted in adolescents with complex regional pain syndrome was able to demonstrate rapid treatment-induced changes in functional connectivity [9]. However, this study focused on regionally specific changes, as opposed to global network changes, as in the present study. Therefore, future studies examining regionally specific changes in small-world networks may be able to detect early changes in brain efficiency. Longitudinal follow-up studies are necessary to determine whether global changes to small-world brain networks can be detected after IIPT.

Previously, it has been demonstrated that adolescent patients with narcolepsy had disrupted small-world network properties, including decreased small-worldness and normalized clustering coefficients compared to healthy controls [35]. Loss of sleep and poor-quality sleep may result in a large-scale loss of segregation within neural networks [36]. Indeed, in the present study, adolescents who had sigma values 1*SD* above the mean had sleep quality scores in the range of 2.96 to 5.08. In contrast, adolescents with mean sigma values or lower had sleep quality scores in the range of 1.67 to 4.92. Participants with higher small-world network properties and moderate to high sleep quality generally reported less functional disability across IIPT. Therefore, it was only the participants with low to moderate small-world network properties who saw improvements in self-reported functional disability with improvements in self-reported sleep quality.

Ideal networks are efficient at communicating information and are highly segregated. Highly segregated networks are implicated in greater emotional awareness and regulation [37]. The improved capacity to regulate emotions via a more segregated network topology may explain why better sleep quality is associated with less pain-related disability [12]. Therefore, among adolescents who are more biologically vulnerable to emotion dysregulation, improvements in sleep quality may be linked to more positive attitudes, leading to more positive perceptions of pain [12]. Indeed, emotion processing and regulation are important for mitigating the effects chronic pain may have on daily life.

This pilot study had several limitations despite providing insights into the relationships between sleep quality and pain outcomes for adolescents participating in IIPT programs. The acquisition time of the resting-state fMRI was short (5 min 10 s). There are new

methods of fMRI processing that consider the possibility of nonlinear relationships between the averaged time series and brain templates [38]. This study is a first step of looking into traditional small-world connectivity features (i.e., linear) within the context of treatment in a pediatric pain population. Exploring the possibility of nonlinear metrics warrants study on its own. Additionally, this study exclusively relied on self-reported measures to assess sleep. As such, future research could consider using more objective measures of sleep (e.g., actigraphy, polysomnography) in conjunction with these self-reports to better assess sleep quality. This study was a pilot study; therefore, the sample size used in this study was relatively small, which may limit the generalizability of the results. Within this sample, a variety of different pain types were represented by patients, which may yield different prognoses. Moreover, although IIPT offered promising outcomes for adolescents with chronic pain, the 3-week duration of the program limited our capacity to understand more long-term improvements in sleep and small-world brain networks. Therefore, the next steps will be to recruit more adolescents into this IIPT study and follow their recovery up to 3 years post-IIPT to determine the long-term relationships between sleep, small-world brain network efficiency, and functional disability, particularly among individual subgroups of adolescents with chronic pain.

5. Conclusions

In summary, the findings of this pilot study extend previous work on the association between sleep improvements and less pain-related impairment following participation in IIPT [12,30,31]. Consistent with literature linking functional networks to better sleep and pain recovery [9,36], our findings support the idea that adolescents with greater network segregation report better sleep quality and less functional disability [39,40]. However, among adolescents with lower small-world properties, improvements in sleep quality may lead to less functional disability. Overall, these findings suggest that sleep may be important to address in IIPT for adolescents with chronic pain.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/anesthres1030018/s1. Table S1: Characteristics of the full IIPT cohort.

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Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. King, S.; Chambers, C.T.; Huguet, A.; MacNevin, R.C.; McGrath, P.J.; Parker, L.; MacDonald, A.J. The epidemiology of chronic pain in children and adolescents revisited: A systematic review. *Pain* **2011**, *152*, 2729–2738. [CrossRef] [PubMed]
2. Perquin, C.W.; Hazebroek-Kampschreur, A.; Hunfeld, J.A.M.; Bohnen, A.M.; van Suijlekom-Smit, L.W.A.; Passchier, J.; van der Wouden, J.C. Pain in children and adolescents: A common experience. *Pain* **2000**, *87*, 51–58. [CrossRef] [PubMed]
3. Rosenbloom, B.N.; Rabbitts, J.A.; Palermo, T.M. A developmental perspective on the impact of chronic pain in late adolescence and early adulthood: Implications for assessment and intervention. *Pain* **2017**, *158*, 1629–1632. [CrossRef] [PubMed]
4. Hechler, T.; Kanstrup, M.; Holley, A.L.; Simons, L.E.; Wicksell, R.; Hirschfeld, G.; Zernikow, B. Systematic Review on Intensive Interdisciplinary Pain Treatment of Children with Chronic Pain. *Pediatrics* **2015**, *136*, 115–127. [CrossRef]
5. Hurtubise, K.; Blais, S.; Noel, M.; Brousselle, A.; Dallaire, F.; Rasic, N.; Camden, C. Is It Worth It? A Comparison of an Intensive Interdisciplinary Pain Treatment and a Multimodal Treatment for Youths With Pain-related Disability. *Clin. J. Pain* **2020**, *36*, 833–844. [CrossRef]
6. Argaman, Y.; Granovsky, Y.; Sprecher, E.; Sinai, A.; Yarnitsky, D.; Weissman-Fogel, I. Resting-state functional connectivity predicts motor cortex stimulation-dependent pain relief in fibromyalgia syndrome patients. *Sci. Rep.* **2022**, *12*, 17135. [CrossRef]
7. Liu, J.; Zhang, F.; Liu, X.; Zhuo, Z.; Wei, J.; Du, M.; Chan, Q.; Wang, X.; Wang, D. Altered small-world, functional brain networks in patients with lower back pain. *Sci. China Life Sci.* **2018**, *61*, 1420–1424. [CrossRef]
8. Li, K.; Liu, L.; Yin, Q.; Dun, W.; Xu, X.; Liu, J.; Zhang, M. Abnormal rich club organization and impaired correlation between structural and functional connectivity in migraine sufferers. *Brain Imaging Behav.* **2017**, *11*, 526–540. [CrossRef]
9. Erpelding, N.; Simons, L.; Lebel, A.; Serrano, P.; Pielech, M.; Prabhu, S.; Becerra, L.; Borsook, D. Rapid treatment-induced brain changes in pediatric CRPS. *Brain Struct. Funct.* **2016**, *221*, 1095–1111. [CrossRef]
10. Palermo, T.M.; Wilson, A.C.; Lewandowski, A.S.; Toliver-Sokol, M.; Murray, C.B. Behavioral and psychosocial factors associated with insomnia in adolescents with chronic pain. *Pain* **2011**, *152*, 89–94. [CrossRef]
11. Lewin, D.S.; Dahl, R.E. Importance of sleep in the management of pediatric pain. *J. Dev. Behav. Pediatr.* **1999**, *20*, 244–252. [CrossRef] [PubMed]
12. Boggero, I.A.; Krietsch, K.N.; Pickerill, H.M.; Byars, K.C.; Homan, K.J.; Williams, S.E.; King, C.D. Improvements in Sleep Correlate With Improvements in Clinical Outcomes Among Adolescents Undergoing Intensive Interdisciplinary Pain Treatment. *Clin. J. Pain* **2021**, *37*, 443–453. [CrossRef] [PubMed]
13. Pigott, T.; McPeak, A.; de Chastelain, A.; DeMayo, M.M.; Rasic, N.; Rayner, L.; Noel, M.; Miller, J.V.; Harris, A.D. Changes in Brain GABA and Glutamate and Improvements in Physical Functioning Following Intensive Pain Rehabilitation in Youth with Chronic Pain. *J. Pain* **2023**, *24*, 1288–1297. [CrossRef]
14. Epp, S.; Walker, A.; Boudes, E.; Bray, S.; Noel, M.; Rayner, L.; Rasic, N.; Miller, J.V. Brain Function and Pain Interference After Pediatric Intensive Interdisciplinary Pain Treatment. *Clin. J. Pain* **2024**, *40*, 393–399. [CrossRef]
15. Long, R.D.; Walker, A.; Pan, S.C.; Miller, J.V.; Rayner, L.; Vallely, J.; Rasic, N. Baseline Factors Associated with Pain Intensity, Pain Catastrophizing, and Pain Interference in Intensive Interdisciplinary Pain Treatment for Youth. *Children* **2023**, *10*, 1229. [CrossRef] [PubMed]
16. Walker, L.S.; Greene, J.W. The functional disability inventory: Measuring a neglected dimension of child health status. *J. Pediatr. Psychol.* **1991**, *16*, 39–58. [CrossRef]
17. Claar, R.L.; Walker, L.S. Functional assessment of pediatric pain patients: Psychometric properties of the functional disability inventory. *Pain* **2006**, *121*, 77–84. [CrossRef]
18. Essner, B.; Noel, M.; Myrvik, M.; Palermo, T. Examination of the Factor Structure of the Adolescent Sleep-Wake Scale (ASWS). *Behav. Sleep Med.* **2015**, *13*, 296–307. [CrossRef]
19. Sufrinko, A.M.; Valrie, C.R.; Lanzo, L.; Bond, K.E.; Trout, K.L.; Ladd, R.E.; Everhart, D.E. Empirical validation of a short version of the Adolescent Sleep-Wake Scale using a sample of ethnically diverse adolescents from an economically disadvantage community. *Sleep Med.* **2015**, *16*, 1204–1206. [CrossRef]
20. Long, X.; Kar, P.; Gibbard, B.; Tortorelli, C.; Lebel, C. The brain's functional connectome in young children with prenatal alcohol exposure. *Neuroimage Clin.* **2019**, *24*, 102082. [CrossRef]
21. Cox, R.W. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* **1996**, *29*, 162–173. [CrossRef] [PubMed]
22. Jenkinson, M.; Beckmann, C.F.; Behrens, T.E.; Woolrich, M.W.; Smith, S.M. Fsl. *Neuroimage* **2012**, *62*, 782–790. [CrossRef] [PubMed]
23. Fonov, V.; Evans, A.C.; Botteron, K.; Almli, C.R.; McKinstry, R.C.; Collins, D.L.; Brain Development Cooperative, G. Unbiased average age-appropriate atlases for pediatric studies. *Neuroimage* **2011**, *54*, 313–327. [CrossRef] [PubMed]
24. Tzourio-Mazoyer, N.; Landeau, B.; Papathanassiou, D.; Crivello, F.; Etard, O.; Delcroix, N.; Mazoyer, B.; Joliot, M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **2002**, *15*, 273–289. [CrossRef] [PubMed]
25. Wozniak, J.R.; Mueller, B.A.; Mattson, S.N.; Coles, C.D.; Kable, J.A.; Jones, K.L.; Boys, C.J.; Lim, K.O.; Riley, E.P.; Sowell, E.R.; et al. Functional connectivity abnormalities and associated cognitive deficits in fetal alcohol Spectrum disorders (FASD). *Brain Imaging Behav.* **2017**, *11*, 1432–1445. [CrossRef]
26. Xia, M.; Wang, J.; He, Y. BrainNet Viewer: A network visualization tool for human brain connectomics. *PLoS ONE* **2013**, *8*, e68910. [CrossRef]

27. Wang, J.; Wang, X.; Xia, M.; Liao, X.; Evans, A.; He, Y. GRETNA: A graph theoretical network analysis toolbox for imaging connectomics. *Front. Hum. Neurosci.* **2015**, *9*, 386. [CrossRef]
28. IBM. *IBM SPSS Statistics for Macintosh*, 28th ed.; IBM: Armonk, NY, USA, 2021.
29. Hayes, A.F. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*, 3rd ed.; Guilford Publications: New York, NY, USA, 2022.
30. Logan, D.E.; Sieberg, C.B.; Conroy, C.; Smith, K.; Odell, S.; Sethna, N. Changes in sleep habits in adolescents during intensive interdisciplinary pediatric pain rehabilitation. *J. Youth Adolesc.* **2015**, *44*, 543–555. [CrossRef]
31. Krietsch, K.N.; Beebe, D.W.; King, C.; Homan, K.J.; Williams, S.E. Sleep among Youth with Severely Disabling Chronic Pain: Before, during, and after Inpatient Intensive Interdisciplinary Pain Treatment. *Children* **2021**, *8*, 42. [CrossRef]
32. Eadie, J.; van de Water, A.T.; Lonsdale, C.; Tully, M.A.; van Mechelen, W.; Boreham, C.A.; Daly, L.; McDonough, S.M.; Hurley, D.A. Physiotherapy for sleep disturbance in people with chronic low back pain: Results of a feasibility randomized controlled trial. *Arch. Phys. Med. Rehabil.* **2013**, *94*, 2083–2092. [CrossRef]
33. Fales, J.; Law, E.; Claar, R.; Palermo, T. Sleep outcomes in adolescents with chronic pain: Findings from a multi-site randomized clinical trial of web-based cognitive behavioral therapy for pediatric chronic pain. *J. Pain* **2013**, *14*, S99. [CrossRef]
34. Valrie, C.R.; Bromberg, M.H.; Palermo, T.; Schanberg, L.E. A systematic review of sleep in pediatric pain populations. *J. Dev. Behav. Pediatr.* **2013**, *34*, 120–128. [CrossRef] [PubMed]
35. Fulong, X.; Spruyt, K.; Chao, L.; Dianjiang, Z.; Jun, Z.; Fang, H. Resting-state brain network topological properties and the correlation with neuropsychological assessment in adolescent narcolepsy. *Sleep* **2020**, *43*, zsaa018. [CrossRef]
36. Farahani, F.V.; Fafrowicz, M.; Karwowski, W.; Douglas, P.K.; Domagalik, A.; Beldzik, E.; Oginska, H.; Marek, T. Effects of Chronic Sleep Restriction on the Brain Functional Network, as Revealed by Graph Theory. *Front. Neurosci.* **2019**, *13*, 1087. [CrossRef]
37. Smith, R.; Sanova, A.; Alkozei, A.; Lane, R.D.; Killgore, W.D.S. Higher levels of trait emotional awareness are associated with more efficient global information integration throughout the brain: A graph-theoretic analysis of resting state functional connectivity. *Soc. Cogn. Affect. Neurosci.* **2018**, *13*, 665–675. [CrossRef]
38. Mohanty, R.; Sethares, W.A.; Nair, V.A.; Prabhakaran, V. Rethinking Measures of Functional Connectivity via Feature Extraction. *Sci. Rep.* **2020**, *10*, 1298. [CrossRef] [PubMed]
39. Logan, D.E.; Carpino, E.A.; Chiang, G.; Condon, M.; Firn, E.; Gaughan, V.J.; Hogan, M.; Leslie, D.S.; Olson, K.; Sager, S.; et al. A day-hospital approach to treatment of pediatric complex regional pain syndrome: Initial functional outcomes. *Clin. J. Pain* **2012**, *28*, 766–774. [CrossRef]
40. Becerra, L.; Sava, S.; Simons, L.E.; Drosos, A.M.; Sethna, N.; Berde, C.; Lebel, A.A.; Borsook, D. Intrinsic brain networks normalize with treatment in pediatric complex regional pain syndrome. *Neuroimage Clin.* **2014**, *6*, 347–369. [CrossRef]