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p. 1

Title: Coherence between sleep detection by actigraphy and polysomnography in a multi-center, in-patient cohort of individuals with traumatic brain injury

Running head: Actigraphy-determined sleep in TBI

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Abstract

Introduction: Sleep is increasingly recognized as a crucial component to rapid and successful rehabilitation, especially from traumatic brain injuries (TBI). Assessment of longitudinal patterns of sleep in a hospital setting, however, are difficult and often the expertise or equipment to conduct such studies are not available. Actigraphy (wrist worn accelerometry) has been used for many years as a simple proxy measurement of sleep patterns, but its use has not been thoroughly validated in individuals with TBI.

Objective: To determine the validity of different sensitivity settings of actigraphy analysis to optimize its use as a proxy for recording sleep patterns in individuals with a traumatic brain injury (TBI).

Design: Comparison of actigraphy to criterion standard polysomnographic (PSG)-determination of sleep on a single overnight study.

Setting: Six rehabilitation hospitals in the TBI Model System

Participants: 227 consecutive, medically stable individuals with a TBI

Interventions: Not applicable

Main Outcome Measure: Concordance between PSG- and actigraphy-determined sleep using different sensitivity threshold settings (low, medium, high, automated).

Results: Bland-Altman plots revealed increasing error with increasing amounts of wake during the sleep episode. Precision-recall statistics indicate that with less sensitive actigraphy thresholds, episodes identified as 'wake' are usually 'wake', but many true episodes of 'wake' are missed. With more sensitive actigraphy thresholds, more episodes of 'wake' are identified, but only some of these are true episodes of 'wake'.

Conclusions: In hospitalized patients with TBI and poor sleep, actigraphy underestimates the level of sleep disruption and has poor concordance with PSG-determined sleep. Alternate methods of scoring sleep from actigraphy data are necessary in this population.

Key Words: traumatic brain injury, sleep, actigraphy, polysomnography

Introduction

While the criterion standard of determining sleep states is the use of polysomnography (PSG), the conduct of such studies is difficult for both the individual being studied and the technical team doing the examination. The extended time required to apply multiple skin electrodes to the face and scalp, coupled with the effort required to translate these electrical signals into stages of sleep (i.e., sleep scoring), minimizes the utility of PSG to track multiple nights of sleep. To overcome this limitation, many studies examining longitudinal changes in sleep use actigraphy (ACG) as a proxy for sleep.¹ ACG consists of a wrist-worn accelerometer that stores movement data in finite epochs (typically 30 or 60 seconds) that can be rapidly scored as “sleep” or “wake” through validated algorithms.

Algorithms to convert an actigraphic signal into “sleep” and “wake” epochs occurs by determining when a sufficient amount of movement has occurred during a known sleep opportunity such that this movement is likely associated with wake.² In patient populations, however, these algorithms might be inappropriate to accurately impute sleep and wake, especially in populations in which sleep is highly fragmented and abnormal movement might occur. Both of these situations can occur in individuals with a traumatic brain injury (TBI). In actigraphy-based studies of sleep individuals with TBI, evidence of significant changes to sleep is often evident.³⁻⁹ To date, only one study has validated actigraphy against PSG in individuals with TBI¹⁰ and it reported that nightly summary statistics (e.g., sleep efficiency, total sleep time) were reasonably well associated between ACG and PSG recordings. Epoch-by-epoch analysis of

sleep scoring and the accuracy of various algorithms to convert ACG data into sleep/wake states, however, has never been reported. The purpose of the present analysis was to examine the utility of ACG data, using different sensitivity thresholds, to accurately impute sleep and wake in a large, prospective cohort of individuals with TBI.

Methods

Participants

As part of a part Patient-Centered Outcomes Research Institute (PCORI)-funded clinical trial, consecutive, medically stable individuals with TBI who were enrolled in the TBI Model Systems between May 2017 and January 2019 at one of the six centers (Tampa FL, Seattle WA, Dallas TX, Columbus OH, Denver CO, Philadelphia PA) were recruited for this study. Full details of the cohort have been previously published.¹¹ Participants were at least 16 years of age and had sustained damage to brain tissue as a result of an external force. Participants needed to have had an alteration of consciousness of > 24 hours or a loss of consciousness > 30 minutes following the TBI, or an emergency room Glasgow Coma Scale (GCS)¹² score of 3-12, or intracranial abnormalities on neuroimaging regardless of GCS score. Potential participants were excluded if they averaged less than two hours per night of sleep in the rehabilitation ward prior to the scheduled PSG or had an external physical limitation to participating in a sleep study (e.g., full body cast or unable to be decannulated prior to the PSG).

All participants or their legally authorized representative provided informed consent. All methods conformed to the principles laid out in the Declaration of Helsinki and were approved by local Institutional Review Boards.

Procedure

As part of a larger study examining different measurement tools for determining sleep apnea in individuals with TBI,¹¹ data were collected during a single overnight sleep study on an inpatient rehabilitation ward with contemporaneous polysomnography (PSG) and wrist actigraphy. The units used to collect ACG and PSG data were synchronized through device initiation on the same computer. Questionnaires (see Subgroups below) were administered upon admission to the rehabilitation ward as well as immediately prior to PSG. Medical record abstraction was conducted by trained TBI Model System research assistants.

Measures

PSG-Derived Sleep/Wake: Criterion Standard. PSG was performed with an Alice 6 LDx Diagnostic Sleep System (Philips Respironics, Murrysville PA). A standard clinical recording montage was used to collect information on electroencephalographic (C3/C4, F3/F4, O1/O2),¹³ electromyographic (chin, intercostal), and electro-oculographic (left and right) signals, as well as breathing-related signals (snoring, heart rate, oxygen saturation, nasal cannula, chest and

abdominal effort). Between lights-out and lights-on time, 30-s epochs of PSG data were scored for sleep stages (N1, N2, N3, REM, wake) and apneic events by one of two registered PSG technicians at a single site (Tampa FL) according to American Academy of Sleep Medicine criteria.¹⁴ Interrater reliability between the two scorers was high.¹¹ All 30-s epochs identified as any stage of sleep (i.e., N1, N2, N3, or REM) were marked as “sleep”. From these “sleep” and “wake” epochs, nightly summary statistics were calculated, including the amount of wake after sleep onset (WASO; i.e., the total number of minutes of wake occurring after sleep initiation and before the final awakening), total sleep time (TST), and sleep efficiency (SE; i.e., TST/time in bed calculated from the lights-off to lights-on interval recorded by PSG technicians). The apnea-hypopnea index, a measure of the degree of sleep-disordered breathing, was also calculated from the PSG data.¹⁴

ACG-Derived Proxy Indices of Sleep/Wake. ACG data were acquired with an Actiwatch Spectrum Plus (Philips, Bend OR), set to record tri-axial arm movement in 15-s epochs. Following collection, ACG data were downloaded and scored using Actiware (v.6.0.9, Philips, Bend OR). Time in bed was set as lights-off to lights-on time. Each 15-s epoch was then assigned a value of “wake” or “sleep” based on a standard algorithm that compares whether the integrated activity of an epoch, weighted by the surrounding epochs, exceeds a threshold limit value (TLV). The activity in each epoch is a unitless measure derived from the integral of the vector amplitudes occurring during a 15-s epoch. As PSG-determined sleep was scored in 30-second epochs, we downsampled the ACG data. There are four possible configurations for this

downsampling: WW, SS, SW, and WS (such that “W” is a 15-s ACG-scored wake epoch and “S” is a 15-s ACG-scored sleep epoch). WW would be rescored as “wake”, SS would be rescored as “sleep”, and both SW and WS would be rescored as “wake” if the preceding epoch was scored as “wake” and would be rescored as “sleep” if the preceding epoch was scored as “sleep”. We examined four TLV (i.e., sensitivity settings) that are standard in the Actiware software: low (20 units), medium (40 units), high (80 units), and auto (units based on mean of daytime activity).² As noted, the TLV represents the point at which there is a sufficient amount of integrated activity that it is assumed that the activity is associated with wake, rather than the spontaneous activity that normally occurs during sleep. The lower the TLV, the higher the sensitivity, that is, the more likely that the movement would be deemed to be associated with wake. Based on categorization of each epoch as sleep or wake, the same nightly summary statistics as were produced for PSG were also calculated for ACG: WASO, TST, and SE.

Analyses

Nightly Summary Analytics. WASO, TST, SE as calculated from both PSG and ACG were compared with linear regression analyses and Bland-Altman plots.

Epoch-by-Epoch Comparison. The concordance between PSG- and ACG- determined “sleep” and “wake” 30-s epochs was examined with precision/recall analyses. As ACG is optimized to detect wake on a background of sleep, we set wake as the “positive” value and sleep as the

“negative” value. PSG was set as the criterion standard and ACG as the comparator. Using this nomenclature, the precision ($\frac{TP}{TP+FP}$) and recall ($\frac{TP}{TP+FN}$) [TP=true positive, FP=false positive, FN=false negative] were determined for each set of ACG/PSG data for each participant. Specificity, a measure of true negative (sleep) rate, was intentionally not calculated as the preponderance of sleep periods combined with the bias of the algorithms in assuming sleep as a default state limit the utility of this measurement in determining the goodness of the algorithms. Precision and recall were determined for each of the four ACG thresholding procedures (low, medium, high, and auto). To statistically determine which of the thresholding procedures was most accurate, the proportion of individuals in which a given threshold was best was calculated and presented with 95% confidence intervals.

Subgroup Analytics. Given that there are a variety of concomitant medical conditions and demographic variables that could theoretically influence the relationship between ACG and PSG, we examined precision and recall in nine different subgroups of individuals. We examined the following subgroups of participants for whom we had an *a priori* assumption that different thresholds might be necessary to more accurately determine sleep with ACG.

Subgroup 1 – TBI Severity: participants were classified based on their GCS score at admission to the emergency room following the TBI. Complicated mild (GCS: 13-15 with abnormal neuroimaging) and moderate (GCS: 9-12) were considered as one group, while severe (GCS: 3-8) were considered as a second group. We also analyzed the severe category while including individuals who were chemically paralyzed, sedated, or intubated upon admission.

Subgroup 2 – Cognitive Status: cognitive functioning was assessed in participants upon admission to the rehabilitation ward with the cognitive subscale of the Functional Independence Measure (FIM).¹⁵ Subgroups were determined with a median split (≤ 14 vs. > 14). FIM cognitive scores range 5 to 35 with higher scores being better.

Subgroup 3 – Agitation: prior to ACG, participants were rated on the Agitated Behavior Scale (ABS)¹⁶ by PSG technicians; participants were grouped as not agitated (ABS scores 0-21) or agitated (ABS scores ≥ 22).

Subgroup 4 – Motor Status: motor functioning was assessed in participants upon admission to the rehabilitation ward with the motor subscale of the FIM.¹⁵ Subgroups were determined with a median split (≤ 33 vs. > 33). FIM motor scores range 13 to 91 with higher scores being better.

Subgroup 5 – Limb Strength: manual muscle strength of the arm on which the actigraphy was placed was abstracted from the medical record.¹⁷ Individuals were parsed into groups with normal (4-5) and abnormal (0-3) scores.

Subgroup 6 – Wrist Site: while an actigraph is typically worn on the wrist contralateral to the dominant hand, in many individuals with a medical limitation, we were unable to place it on the contralateral wrist. Subjects were grouped according to ACG placement being on the dominant wrist (ipsilateral) or on the non-dominant wrist (contralateral).

Subgroup 7 – Age: we subdivided our population into three groups, ≤ 40 years, 41-59 year, or ≥ 60 years.

Subgroup 8 – Apnea: we subdivided our population into those who had no or mild sleep apnea (apnea-hypopnea index < 15) and those who had moderate or severe apnea (apnea-hypopnea index ≥ 15).¹⁸

Subgroup 9 – Time since Injury: groups were created as a median split of the duration between the TBI and the PSG recording (≤ 45 days, > 45 days).

Data are shown as mean \pm SD or median with interquartile range, as appropriate for normally and non-normally distributed data. Baseline comparisons are made with chi-square tests (categorical data) and t-tests with standardized mean difference (SMD) (continuous data). A SMD of 0.2 is considered small.¹⁹

Results

Participants. Of the 263 individuals who completed a single overnight sleep study, concomitant ACG was available in 227 individuals; 36 individuals were excluded due to failed ACG recordings. As compared to individuals who had completed ACG, those individuals who were excluded did not differ in their GCS severity ($X^2=1.83$, $p=0.40$), FIM Motor ($p=0.16$, t-test; SMD=-0.26) or Cognitive ($p=0.80$, t-test; SMD=0.048), agitation ($p=0.26$, t-test; SMD=-0.20), limb strength ($X^2=5.70$, $p=0.34$), age ($p=0.82$, t-test; SMD=-0.043), gender ($X^2=0.01$, $p=0.92$),

race ($X^2=0.29$, $p=0.59$), or time since injury ($p=0.52$, t-test; $SMD=0.054$). Of the remaining 227 participants, most were White, middle-aged men who had experienced a severe TBI, with PSG testing occurring a median of 1.5 months from the time of injury (Table 1). Due to problems with low limb mobility or injury, the ACG device was placed on the non-dominant wrist in 97 of the participants.

Whole-night summary statistics. Participants had 6.91 ± 1.31 hours of time in bed and had generally poor sleep (Table 2). ACG-derived sleep statistics (TST, WASO, SE) varied based on the TLV (Table 2). The higher the TLV (i.e., the more movement needed to be determined to be a wake episode), the less wake that was detected, resulting in greater TST and SE. In comparing the group averages, the PSG-determined statistics for TST, WASO, and SE were each highly divergent from the ACG data, with the low threshold being closest numerically. To examine the relationship between PSG- and ACG-derived whole night statistics, we plotted each ACG-determined statistic against the corresponding PSG-determined statistic (**Figure 1**). For each of the ACG thresholds, there was a linear relationship between the ACG- and PSG-determined statistic (adjusted $r^2=0.09\rightarrow 0.57$), but this linearity was significantly divergent from the line of unity for all but the lowest WASO, highest SE, and highest TST (**Figure 1**). In other words, in individuals who slept well, ACG-determined TST, WASO, and SE were reasonable proxies for those measures as determined by PSG. In individuals who slept poorly, however, the ACG-determined TST, WASO, and SE were highly divergent from the PSG determination.

To further visualize the relationship between the whole-night summary statistics generated by ACG analysis and the criterion standard PSG analysis, we used Bland Altman plots (**Figures 2-4**). In comparing TST calculated with each of the four thresholds, there is a common pattern of increasing error with increased amount of wake. Lower TST (**Figure 2**), lower SE (**Figure 3**), and greater WASO (**Figure 4**) are associated with a larger difference between PSG and ACG for each of the ACG thresholds. In the actual determination of wake (WASO), the ACG auto threshold produces the least spread in error with a consistent underestimation of the amount of wake, while the ACG low threshold produces a large spread that is both positive and negative, indicating that the low threshold both over- and under-estimates the amount of wake with greater WASO having larger error.

Epoch-by-epoch comparison. To more specifically examine the agreement between ACG and PSG, we examined the relationship between scores of individual 30-s epochs. To quantitate these relationships, we calculated recall and precision (Table 3). Recall, the percent of ACG-determined wake epochs that are actually wake epochs, was best in auto and progressively worse in high, medium, and low. Precision, the percent of time that PSG-determined wake is also estimated as ACG-determined wake, was almost always best in low, and was progressively worse in medium, high, and auto. Thus, under the auto threshold, wake that is determined by ACG is likely to be wake, but the auto threshold misses many of the wake episodes that are detected by PSG. Under the low threshold, many more of the PSG-determined wake episodes are detected, but there are also many episodes scored as wake that are scored as sleep by PSG.

Exploratory subgroup analyses. Given that there are a variety of concomitant medical conditions and demographic variables that could theoretically influence the relationship between ACG and PSG, we examined precision and recall in nine different subgroups of individuals. These groups were generated based on TBI severity, cognitive function, agitation during ACG recording, abnormal motor function, limb strength, ACG wrist placement, age, apnea, and time since injury. We did not observe any differences between the subgroups in terms of precision or recall (Supplemental Tables 1 and 2). In all subgroups, as with the complete sample, precision was best using the low ACG threshold and recall was best using the high ACG threshold.

Discussion

In this large, multi-center trial of individuals hospitalized with TBI, we examine the correspondence between sleep as determined by a PSG and a medical-grade actigraph. While ACG-determined sleep was a fair approximation of PSG-determined sleep in those with good sleep (i.e., SE>90%, WASO<60 minutes, TST>7hours), for those with poor sleep, actigraphy was very poor at estimating accurate sleep metrics and typically grossly overestimated the goodness of sleep. For example, individuals who slept only 25% of the night (as determined by PSG), would have been estimated to have slept 70%-90% of the night (as determined by ACG, depending on the threshold used) (Figure 1). While in good sleepers, the estimates of whole-night sleep statistics are more similar between ACG and PSG, there is no a priori or post hoc way to know if the individual being studied is a good sleeper by ACG data alone. For example,

individuals who appear to be sleeping well by ACG (e.g., SE>85%), could have a PSG-determined SE that ranges anywhere from 60%-100% if the low sensitivity threshold is used – with the auto sensitivity, this range is 5%-100%. In contrast, poor sleep quality metrics on ACG indicate poor sleep.

The failure of ACG to capture all-night sleep statistics is likely due to its inability to accurately determine wake epochs. We examined epoch-by-epoch agreement between PSG-determined sleep and wake with ACG-determined sleep and wake, further examining four different sensitivity settings. On the least sensitive setting (auto), ACG-determined wake was mostly correct, but this setting missed many epochs of wake. On the most sensitive setting (low), there were more epochs of ACG-determined wake, but many of the identified epochs were false positives (Figures 2-4).

Given the burdensome nature of PSG and the lack of its availability in many hospital settings, alternatives such as actigraphy have been used to objectively quantitating sleep.^{5, 10, 20-25} Kamper and colleagues reported good agreement between ACG and PSG in a Veteran sample (n=50) that was more chronic than the current sample.¹⁰ Across other populations, agreement between ACG and PSG has varied from good agreement between sleep/wake epoch classification to underestimation and/or overestimation of parameters as reported in this study.²⁶⁻²⁸ Our data agree with previous findings that the more wake that is present during sleep, the less accurate ACG is as a modality. ACG may have utility outside of determining sleep/wake states and has been used to examine the distribution of movement over the 24-hour day as a way to impute the strength of

the circadian organization of sleep.²⁹ Validation of these techniques in hospitalized patients with TBI, and if these measures are associated with clinically-relevant outcomes, is of critical importance to future research.

This study had several strengths including the use of a large, diverse (multi-center) cohort obtained as part of a PCORI-funded clinical trial that was well characterized in terms of time-elapsed post-TBI, injury severity, and degree of morbidity that may influence movement. There are, however, limitations. While we examined the relationship between ACG- and PSG-determined sleep in the context of a variety of potential confounds (TBI severity, general cognitive function, agitation prior to ACG recording, general motor behavior, limb strength, wrist placement, age, sleep apnea, time since injury), there may be other demographic or physical factors that were not included in these secondary analyses or part of the existing clinical trial. Furthermore, collection of multiple nights of PSG/ACG data from individual participants may have allowed us to better determine whether the coherence of the two data sets was dependent upon factors unique to individuals.

Conclusions.

Due to its practicality, the use of actigraphy to monitor sleep during inpatient rehabilitation for TBI is becoming more common, even for diagnostic purposes. Our data indicate that caution is warranted when interpreting actigraphy-inferred sleep indices in hospitalized moderate to severe TBI when sleep quantity metrics are normal. Given the limitations of alternative methods for

objectively and subjectively measuring sleep in this population, alternative approaches including examination of patterns of activity^{29, 30} should be explored in future work.

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Tables

Gender	187 (82%) Male, 40 (18%) Female
Age	median = 38 years (IQR: 27-58 years)
Race/ethnicity	
White	169 (75%)
Black/African-American	47 (21%)
Asian	6 (3%)
Native Hawaiian/Other Pacific Islander	3 (1.3%)
American Indian/Alaskan Native	1 (0.4%)
Latinx	29 (13%)
Glasgow Coma Scale severity <i>[missing = 26]</i>	
Complicated mild	53
Moderate	20
Severe	128
Time between TBI and PSG (days)	median = 46 (IQR: 22-88)
FIM Motor <i>[missing = 15]</i>	median = 34 (IQR: 17.5-50)
FIM Cognitive <i>[missing = 10]</i>	median = 14 (IQR: 8-20)
Limb Manual Muscle Testing Score <i>[missing = 6]</i>	abnormal = 22, normal = 199
Agitation Behavior Scale	agitated = 26, non-agitated = 201
Sleep apnea <i>[missing = 5]</i>	
None (AHI: 0-4.99)	125
Mild (AHI: 5-14.99)	43
Moderate (AHI: 15-29.99)	25
Severe (AHI: ≥ 30)	29
Table 1. Participant demographics and characteristics.	

	ACG				PSG
	Low	Medium	High	Auto	
TST (hrs)	6.00 ± 1.42	6.28 ± 1.37	6.50 ± 1.33	6.68 ± 1.32	5.20 ± 1.65
WASO (min)	49.2 ± 41.5	34.5 ± 30.4	22.7 ± 21.2	12.6 ± 12.5	71.5 ± 54.8
SE (%)	87.7 ± 10.5	91.4 ± 7.86	94.3 ± 5.43	96.8 ± 3.28	74.6 ± 18.0

Table 2. Comparison of actigraphy- (ACG) and polysomnography- (PSG) derived whole-night measures of sleep, including total sleep time (TST), wake after sleep onset (WASO), and sleep efficiency (SE).

	Low	Medium	High	Auto
Recall	0.74 ± 0.23	0.80 ± 0.24	0.85 ± 0.24	0.88 ± 0.23
% superior	17% (13-23%)	25% (19-31%)	45% (39-52%)	71% (65-77%)
Precision	0.35 ± 0.22	0.24 ± 0.19	0.16 ± 0.15	0.08 ± 0.09
% superior	100% (98-100%)	2.6% (1.1-5.9%)	0.44% (0.02-2.8%)	0.44% (0.02-2.8%)

Table 3. Recall and precision of different thresholds of ACG as compared to PSG. Below the recall and precision are the percent of participants, with 95% CI, in whom the specific ACG threshold was superior.

Figure Legends

Figure 1. Regression analysis between ACG- and PSG-determined wake after sleep onset (WASO, left), sleep efficiency (SE, middle), and total sleep time (TST, right). Linear regression lines with 95% confidence intervals (shaded grey) are plotted for both the auto ACG threshold (solid black line) and low ACG threshold (solid dark grey line). The line of unity, where ACG and PSG yield identical values, is plotted as a dotted line. The medium and high ACG thresholds are not plotted for clarity and are between the low and auto ACG thresholds.

Figure 2. Bland-Altman plots of total sleep time (TST). The x-axis represents the average value of the PSG- and ACG-determined TST in minutes, while the x-axis represents the difference between PSG and ACG in TST. The horizontal solid line is the bias and the dotted lines are the 95% confidence intervals ($\pm 1 \text{ SD} * 1.96$).

Figure 3. Bland-Altman plots of sleep efficiency (SE). The x-axis represents the average value of the PSG- and ACG-determined SE in percentage (x100), while the x-axis represents the difference between PSG and ACG in SE. The horizontal solid line is the bias and the dotted lines are the 95% confidence intervals ($\pm 1 \text{ SD} * 1.96$).

Figure 4. Bland-Altman plots of wake after sleep onset (WASO). The x-axis represents the average value of the PSG- and ACG-determined WASO in minutes, while the y-axis represents the difference between PSG and ACG in WASO. The horizontal solid line is the bias and the dotted lines are the 95% confidence intervals ($\pm 1.96 \text{ SD}$).

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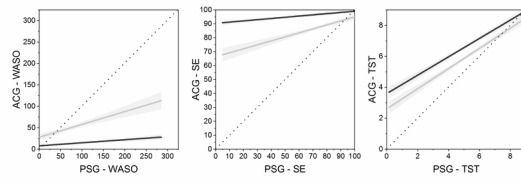
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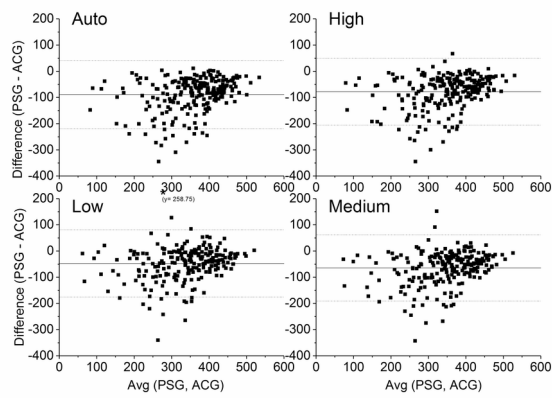
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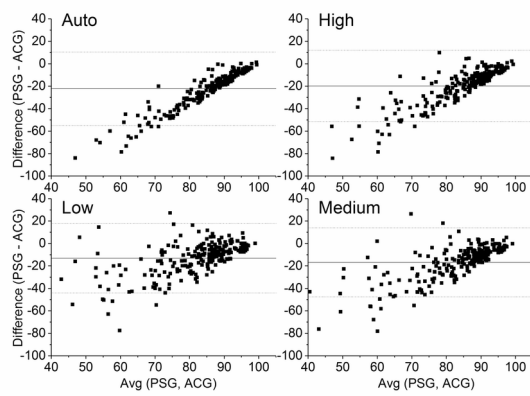
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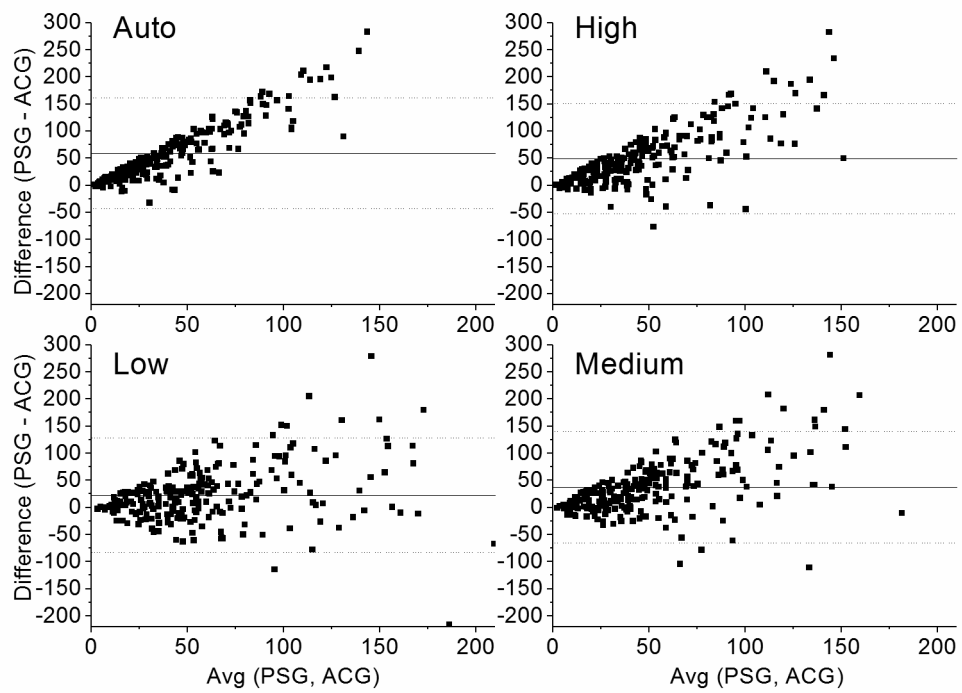
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Title: Coherence between sleep detection by actigraphy and polysomnography in a multi-center, in-patient cohort of individuals with traumatic brain injury

Running head: Actigraphy-determined sleep in TBI

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