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Associations between Pain, Objective Sleep Efficiency and Cognition in Patients with Implantable Cardioverter Defibrillators

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Abstract

Introduction: Patients with implantable cardioverter defibrillators (ICDs) frequently experience sleep disruption. Prior work shows associations between objective (actigraphic) sleep and cognition in these patients, but whether pain affects associations between measures of sleep fragmentation (e.g., sleep efficiency, SE) and cognition is unknown. The present study examined independent and interactive associations between objective SE and pain on cognitive performance in patients with ICDs.

Methods: Thirty-seven patients with ICDs (M_{age}=60.0, SD=12.4) and self-reported sleep disturbance completed 14 days of actigraphy. Average SE was computed [(average total sleep time/average time in bed)x100%]. Patients completed the Short Form 36 Health Survey pain section, and computerized tasks measuring executive functioning (letter series, n-back task), sustained attention/processing speed (symbol digit modalities test, SDMT), and simple reaction

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Author Credit Statement

Ashley Curtis: Conceptualization, Statistical Analysis, Original draft preparation. **Alicia Roth:** Data Collection, Writing – Reviewing and Editing. **Samuel Sears:** Conceptualization, Writing- Reviewing and Editing. **Jamie Conti:** Writing – Reviewing and Editing. **Richard Berry:** Writing – Reviewing and Editing. **Joseph Dzierzewski:** Data Collection, Writing – Reviewing and Editing. **Christina McCrae:** Conceptualization, Supervision, Writing – Reviewing and Editing.

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time. Multiple linear regressions examined whether SE independently predicted or interacted with pain ratings to predict cognitive performance.

Results: SE interacted with pain to predict SDMT performance, accounting for 12% unique variance. In patients reporting worse pain, higher SE was associated with better SDMT performance. Similar patterns of association on SDMT were not observed in patients with average or low pain. SE and pain ratings did not independently predict SDMT performance. Performance on other cognitive tasks was not associated with any predictors.

Conclusion: Better sleep efficiency may play an important role in improving sustained attention/processing speed in patients with ICDs and perceived severe pain. Future research should examine whether interventions aimed at improving sleep fragmentation provide benefit to lower order cognition, particularly in patients with worse pain.

Keywords

insomnia; implantable cardioverter defibrillators; cognition; pain, sleep efficiency

1. Introduction

Compared to healthy adults in which 30% experience disturbed sleep (Ancoli-Israel & Roth, 1999), ~67% of patients with implantable cardioverter defibrillators (ICDs) experience sleep disruptions (Habibović et al., 2018). Reasons underlying high prevalence of disturbed sleep in ICD patients are unclear. Hypervigilance related to potential ICD discharge and/or sleep-related breathing changes following ICD shocks (Grimm et al., 2009) may be important factors. Additionally, poor sleep quality is associated with worse pain in ICD patients (Berg, Higgins, Reilly, Langberg, & Dunbar, 2012). Although both poor sleep and worse pain independently predict cognitive disturbance in other disorders such as insomnia (Fortier-Brochu & Morin, 2014) and chronic pain (Iezzi, Duckworth, Vuong, Archibald, & Klinck, 2004), research regarding sleep/pain/cognition associations in patients with ICDs is limited. Given the high prevalence of sleep disturbance and its association with increased pain, ICD patients may be particularly vulnerable to associated cognitive consequences of worse sleep/pain.

We recently reported that longer sleep predicted better executive function and attention/processing speed in ICD patients (Curtis et al., 2018). Associations between sleep fragmentation (e.g., sleep efficiency) and cognitive performance in these patients are unknown. Although previous research in fibromyalgia patients suggests subjective sleep quality and pain interact to predict attention performance (Fang, Wu, Chen, Teng, & Tsai, 2019), whether pain impacts objective sleep/cognition associations in ICD patients is not established. This information is critical to understanding consequences of sleep disruption and pain to aspects of daytime functioning in these patients, who may be at greater risk of worse cognition due to higher prevalence of disturbed sleep than their healthy counterparts. This study examined whether objective sleep efficiency (measured by actigraphy) independently predicted or interacted with pain to predict cognitive performance in patients with ICDs.

2. Methods

2.1. Participants

Participants recruited through physician referral (parent trial:NCT02232204) in Gainesville, Florida. Inclusion criteria were: 1)implanted ICD, 2)self-reported sleep disturbance (answered "yes" to "are you currently experiencing sleep difficulty?"). Exclusion criteria were: 1)Mini-Mental State Examination (MMSE) score <23 (≥9th grade education) or <17 (<9th grade education), 2)shift-worker, 3)did not complete 14 days of actigraphy/cognitive tasks. Clinical interviews determined cardiac history, sleep medication use. Board-certified sleep physician (R.B.B) and sleep psychologist (C.S.M.) determined sleep disturbance etiology via clinical interview, sleep diaries (14 days), and single-night polysomnography (PSG). Sleep conditions diagnosed according to diagnostic/research criteria: insomnia [1)>30 minutes sleep onset latency, wake time after sleep onset, or waking too early; 2)chronically non-restorative/poor quality sleep; 3)1&2 occur despite adequate sleep opportunity; 4)symptoms 3+ nights/week >1 month; 5)1+ sleep-related daytime impairment (e.g., cognitive disruption/mood disturbance, (Association, 2013; Edinger et al., 2004))], sleep apnea (PSG-apnea hypopnea index>5), periodic leg movement disorder (PLMD; PSG-myoclonus arousal>15/hour). Participants provided written informed consent. University of Florida Institutional Review Board approved procedures.

2.2. Objective Sleep

Participants wore an Actiwatch 2 (Phillips Respironics, Bend, OR) for 14 days (on nondominant wrist). This records gross motor activity using solid-state, piezo-electric accelerometer measuring wrist movement intensity/frequency at 32 cycles/second. Total wrist movements/30s recorded as activity count, and analyzed in Actiware (v.5.3.2), classifying 30s epochs as sleep/wake using validated algorithms. Participants completed daily sleep diaries (Lichstein, Riedel, & Means, 1999). Diary-reported bed/wake times used to compute time-in-bed period. Sleep start/end time computed as first (start) or last (end) 10-minute interval within time-in-bed with ≥1 "awake" epoch. Sleep efficiency (SE) calculated as: (Time Spent Sleeping/Time-in-Bed)x100%. Average SE across 14 days was sleep parameter of interest. Higher values represent less fragmented sleep.

2.3. Pain Measure

Participants completed the Short Form 36 Health Survey. Scaled scores (0–100) measuring 8 health domains (e.g., mental health, bodily pain) were computed. Lower scores indicated greater dysfunction. Scaled score of bodily pain ["How much bodily pain have you had in the last 4 weeks" (none-very severe), "During the past 4 weeks, how much did pain interfere with your normal work? (not at all-extremely)] used as pain index. Lower scores indicate worse pain.

2.4. Cognitive Tasks

Participants completed computerized tasks: Symbol Digit Modalities Test (SDMT), Simple Reaction Time Task (SRT), Letter Series, and N-back.

2.4.1. SDMT.—SDMT (Smith, 1982) measures sustained/selective attention and processing speed (Spreen & Strauss, 1998). A legend of nine digit/symbol pairs is presented, with symbols underneath. Participants provide corresponding legend number for each symbol for 90 seconds. Proportion of correct responses computed. Higher scores represented better performance.

2.4.2. SRT.—A warning stimulus (***) is presented at the screen center and participants respond with designated key press (using dominant hand) to target stimulis (+). After ten practice trials, 50 tests trials are presented at varying warning-signal/stimulus intervals: 500/625/750/875/1000ms. Outcome of interest was average response time (ms) for 50 test trials. Quicker reaction times indicated better performance.

2.4.3. N-Back.—N-Back measures working memory [executive function;(Cohen et al., 1997)]. Participants view a 48-font letter at the screen center and indicate (as quickly/accurately as possible; “yes”/”no” key response) whether the letter matches a target letter presented N trials previously. Letters remain visible until response selection, with one second inter-stimulus intervals. Outcome of interest was total number correct 2-back trials. Higher scores represented better performance.

2.4.4. Letter Series.—Letter series (Thurstone & Thurstone, 1962) measures inductive reasoning (executive function). Participants are presented with letter series and choose the correct letter (from five choices) that completes the established pattern (for a duration of four minutes). Outcome of interest is proportion of correct trials (# correct/total trials attempted). Higher scores indicate better performance.

2.5. Statistical Analyses

Multiple linear regressions conducted in SPSS (Version 24). Separate regressions carried out for each criterion variable: SDMT, SRT, N-Back, Letter Series scores. Predictor variables included: SE, pain, and SE by pain interaction. Significant interactions clarified by calculating simple slopes of association between SE and cognition at sample-estimated SE/pain values. SE values characterized as: low SE (1 SD below mean, ~68%), average/moderate SE (mean, ~78%), high SE (1 SD above mean, ~87%). Pain values characterized as: low pain (1 SD above mean, ~82), average/moderate pain (mean, ~59), high pain (1 SD below mean, ~36). Following statistical recommendations (Bender & Lange, 2001), given the paucity of studies on pain/sleep/cognition, particularly in ICD patients, and our subsequent lack of directional hypothesis, we accepted the false positive risk and applied no familywise error correction. Regression results evaluated at an alpha level of $p<.05$.

3. Results

3.1. Participant Characteristics

Forty-nine participants underwent screening/baseline assessments. Thirty-seven participants (M_{age}=60.3, SD=12.3; Males:21/Females:16) had full data available for analyses. Average time since ICD implantation was 3.62 years (SD=3.18), average number of lifetime shocks was 1.50 (SD=4.50), and average months since last shock was 1.00 (SD=2.41). Frequency

(*n*,%) of medical conditions were: coronary artery disease (6, 16%), cardiomyopathy (3, 18%), congestive heart failure (12, 32%), history of myocardial infarction (5, 14%), atrial fibrillation (17, 46%), psychiatric diagnosis (10, 27%). Average MMSE was 27.11 (*SD*=1.82). Twenty-three participants (62%) used sleep medications. Average values on other variables were: SE (*M*=77.63%, *SD*=9.51; Range=52.36–95.24), Pain (*M*=59.12, *SD*=23.90; Range=10–100), SDMT (*M*=.94, *SD*=.08; Range=.73–1.00), SRT (*M*=346.18ms, *SD*=125.41, Range=182.43–673.74), Letter Series (*M*=.57, *SD*=.30; Range=.06–1.00), N-back (*M*=82.83, *SD*=20.01; Range=16.00–100.00). Number of participants (*n*,%) meeting sleep disorder criteria were: insomnia (11, 30%), apnea (3, 8%), PLMD (0, 0%).

3.2. Multiple Regression

Table 1 displays results. For SDMT, SE and pain did not independently predict performance. SE interacted with pain to predict SDMT performance. For individuals with high pain, higher SE predicted better SDMT scores (*B*=.004, *SE*=.002, *p*=.03; Figure 1). SE did not predict SDMT performance for individuals with moderate/average or lowest pain (*ps*>.05). For SRT, Letter Series, and N-Back, there were no significant predictors.

4. Discussion

This study investigated independent and interactive associations of objective SE and pain with cognition in ICD patients with disturbed sleep. Findings show SE and pain interact to predict performance on a sustained attention/processing speed task (SDMT), but not other tasks (SRT, Letter Series, N-Back).

Similar to previous research on subjective sleep in fibromyalgia (Fang et al., 2019), we found no independent associations between objective SE or pain on cognition. It may be only in the context of worse pain where sleep fragmentation/lower level cognition associations arise. Absence of associations between SE/pain and higher order cognition (reasoning, working memory) is somewhat surprising, given previous findings of associations between objective sleep duration and these tasks in ICD patients (Curtis et al., 2018). However, research suggests sleep fragmentation is uniquely associated with brain regions associated with attention (Kingshott, Cosway, Deary, & Douglas, 2000), and there is substantial overlap between these neural regions and pain processing (Forn et al., 2009; Torta & Cauda, 2011). We speculate that more fragmented sleep may exacerbate pain-related attention deficits in patients with disturbed sleep and more severe pain. It is possible that ICD patients with worse pain may benefit most in aspects of cognitive functioning (greater improvement in attention/processing speed) from interventions (e.g., Cognitive Behavioral Therapy for Insomnia) aimed at improving SE.

There are several limitations in this study. First, although we adhered to the rule of thumb for regression analyses of examining 1 explanatory variable per 10 cases (Harrell Jr, 2015), larger samples would allow for examination of other potentially important predictors/covariates (e.g., medications, ICD duration). Although this work could be considered preliminary given the small sample, and we accepted the false positive risk, we recommend that findings be examined in future confimatory studies with larger patient samples. Additionally, future work should examine the impact of SE/pain on additional cognitive

tasks before any conclusions can be made regarding SE/pain/cognition associations. Prospective longitudinal studies are also needed to evaluate temporal relationships between variables. Results may not generalize to ICD patients without sleep disturbance. Comparison of results to age-matched controls will determine whether findings are specific to ICD patients.

In ICD patients with sleep disturbance, associations between objective SE and cognition may depend on pain level. ICD patients with worse pain may be most vulnerable to effects of worse sleep fragmentation on sustained attention/processing speed. Pain level should be considered in the understanding and treatment of daytime dysfunction related to poor sleep in these patients.

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Highlights

- In ICD patients, sleep and pain interact to predict attention/processing speed
- In patients with worse pain, better sleep efficiency predicted better performance
- Sleep efficiency, pain, or their interaction did not predict executive function
- In ICD patients, pain may moderate sleep efficiency/lower order cognition association

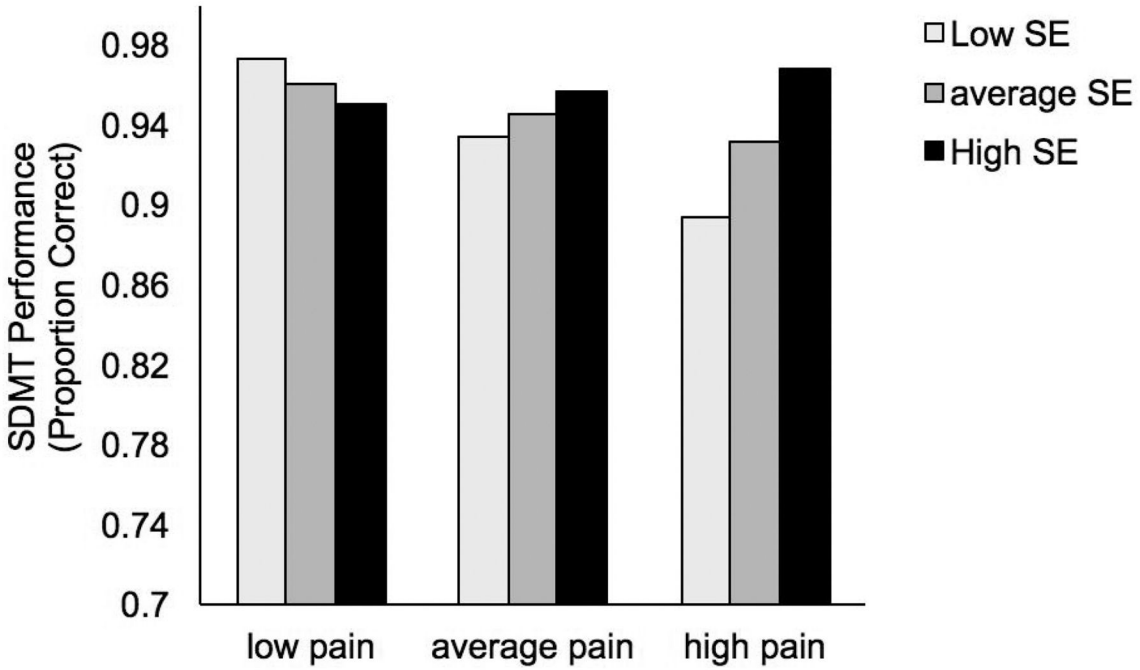

Figure 1.

Actigraphic sleep efficiency and pain interact to predict SDMT performance in patients with ICDs. Note. SE = sleep efficiency; SDMT = Symbol Digit Modalities Test.

Table 1

Actigraphic sleep efficiency and pain determinants of cognitive performance in patients Implantable Cardioverter Defibrillators (ICDs) (n=37)

Cognitive Domain/Measure	*B*	*SE*	*t*	*p*
Attention/Processing Speed				
SDMT[a]				
SE	.001	.00	.98	.33
Pain	.0006	.00	1.19	.24
SE x pain	−.0001	.00	−2.18	.04
SRT[a]				
SE	−3.23	2.14	−1.51	.14
Pain	1.69	.85	1.98	.06
SE x pain	−.01	.08	−.15	.88
Executive Functioning				
N-Back (2-back)[a]				
SE	.44	.35	1.24	.23
Pain	.17	.14	1.20	.24
SE x pain	.001	.01	.10	.92
Letter Series[a]				
SE	−.08	.06	−1.25	.22
Pain	.03	.03	1.08	.29
SE x pain	.001	.00	.38	.70

Note. *SE* = Standard error; SE= actigraphic Sleep efficiency SDMT = Symbol Digit Modalities Test; SRT = Simple Reaction time.

[a]Regression analyses were also conducted with participants who met sleep apnea criteria (AHI > 5, n = 3) removed. Results remained similar across all cognitive tasks, therefore these participants were retained in the study sample.