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Cognitive performance in patients with implantable cardioverter defibrillators: Associations with objective sleep duration, age and anxiety

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Abstract

Sleep disturbance and anxiety are highly prevalent in patients with implantable cardiac defibrillators (ICDs). There is limited research, however, on the associations between cognitive performance and sleep parameters, age and anxiety. Forty-one patients with ICDs and self-reported sleep disturbance completed 14 days of actigraphy (M_{age} = 60.3, *SD* = 12.3) measuring total sleep time (TST), and a computerized cognitive test battery measuring processing speed and attention (i.e. simple reaction time and symbol digit modality task [SDMT]) and executive function (i.e. flanker task, letter series task and N-back task). Multiple regressions determined whether independent effects of TST, age and anxiety, as well as interactive effects of TST and age, predicted cognitive performance. TST predicted performance on two tasks of executive function (i.e. letter series and N-back task), as well as an attentional vigilance and processing speed task (i.e. SDMT), and this did not depend on patient age. On letter series, N-back and SDMT, longer TST predicted better performance. Increasing age was a predictor of worse performance on SDMT and flanker tasks. No other predictors were associated with task performance. Results show that sleep duration, not anxiety, may be an important predictor of higher-order cognitive functioning and lower-order tasks measuring processing speed and attention in ICD patients, with longer sleep duration showing greater benefit for performance.

KEYWORDS
ageing, cardiovascular disease, cognition, insomnia

1 | INTRODUCTION

Cardiovascular disease is the leading cause of death in the USA, accounting for approximately 500,000 deaths annually (Heron, 2017). Implantable cardioverter defibrillators (ICDs) are widely used in patients at high risk of sudden death or in those who have had a previous ventricular arrhythmia (Kusumoto et al., 2014). The ICD provides both low-energy pacing and high-energy shock to terminate ventricular arrhythmias. These shocks are known to be uncomfortable or painful to the patient (Dornelas & Sears, 2018). Up to 67% of patients with ICDs experience disturbed sleep (Berg, Higgins, Reilly, Langberg, & Dunbar, 2012; Habibović et al., 2018) and ICD use has also been associated with increased anxiety (Bilge et al., 2006; Pedersen et al., 2011; Sears, Hauf, Kirian, Hazelton, & Conti, 2011; Sola & Bostwick, 2005). Research also shows that patients with ICDs experience self-reported cognitive

disturbance (Kamphuis et al., 2004), as well as objective cognitive deficits across a wide range of tasks (Hałas et al., 2014), which is exacerbated with increasing age (Hałas et al., 2014). However, the effects of disturbed sleep and anxiety on cognitive functioning in ICD patients have not been established. Thus, examination of the impact of sleep and the potential moderating influence of age on cognitive performance of ICD patients is warranted (Moulaert, Wachelder, Verbunt, Wade, & Van Heugten, 2010).

Although sleep parameters, particularly sleep duration or total sleep time (TST), have been examined in other adult populations, there is a paucity of research documenting effects of disturbed sleep in ICD patients. For instance, self-reported TST (i.e. <6 hr) has been associated with worse performance on tests measuring higher-order or executive function in younger adults with insomnia (Khassawneh, Bathgate, Tsai, & Edinger, 2018), processing speed and executive function in middle-aged adults with insomnia (Fernandez-Mendoza et al., 2010), and worse global cognitive performance in older adults (Lo, Loh, Zheng, Sim, & Chee, 2014). Other research has found that objectively measured (i.e. via actigraphy) TST is associated with worse global cognitive performance in older adults (Blackwell et al., 2011). Given findings of associations between sleep and cognitive performance, and the well-known finding that cognitive performance declines with increasing age (Salthouse, 2009), in the present study we specifically examined how TST and age potentially interact in their prediction of cognitive performance in patients with ICDs. Such evidence could inform behavioural treatments aimed at improving primary sleep and secondary outcomes such as cognitive performance in these patients, with the goal of ultimately improving daytime functioning and increasing quality of life. Additionally, given the high prevalence of anxiety in ICD patients (Bilge et al., 2006) and the research documenting that greater anxiety can impair performance on tests measuring executive abilities (Derakshan & Eysenck, 2009), we also assessed the impact of self-reported general anxiety on cognitive function.

The goal of this study was to examine effects of associations between objective sleep duration and anxiety on cognitive functioning in patients with an ICD. We also examined whether sleep duration interacted with age in these associations with cognition. We predicted that longer TST would be associated with better cognitive performance on tasks requiring higher-order cognitive functioning (i.e. executive functioning tasks measuring reasoning, inhibition and working memory), but would not affect performance on tasks requiring lower-level cognitive processing (i.e. sustained attention and processing speed). We also predicted that these associations would be stronger with increasing age. Finally, we predicted that greater anxiety would be independently associated with worse cognitive performance on tasks requiring higher-order cognition.

2 | METHODS

2.1 | Participants

Participants were recruited as part of a larger randomized controlled trial (ClinicalTrials.gov Identifier: NCT02232204) through physician referral from a university-based cardiac clinic. Participants were included if they had (a) an implanted ICD device and (b) reported difficulty sleeping via a screening interview (i.e. responded "yes" to the question "Are you currently experiencing difficulty with your sleep?"). Participants were excluded if they demonstrated severe cognitive impairment (Mini-Mental State Examination scores of <23 [if participants had ninth grade education or higher] or <17 [if participants had less than ninth grade education]), were shift workers or did not complete 14 days of actigraphy or cognitive tests. Participants completed a clinical interview, where we obtained demographics, cardiac-specific health history and current use of prescription sleep medications. A formal review of medical records was conducted prior to the baseline visit to verify cardiovascular-specific history (i.e. date of ICD implantation and cardiac aetiology), as well as information regarding premorbid psychiatric diagnoses (e.g. depression and anxiety). The University of Florida Institutional Review Board approved all study procedures and participants provided informed consent.

2.2 | Sleep measures

Sleep was assessed through actigraphy. Participants wore an actigraphy watch (Actiwatch 2, Phillips Respironics, Bend, OR) on their non-dominant wrist 24 hr a day for the 14 days of baseline. Actigraphy is highly correlated with polysomnography on measures of TST in individuals with insomnia, with moderate correlations for nighttime wake variables (0.30 for sleep onset latency, SOL; 0.48 for wake after sleep onset, WASO) (Lichstein et al., 2006). The Actiwatch 2 records data on gross motor activity using a solid-state piezo-electric accelerometer. The accelerometer continually measures the intensity and frequency of wrist movement at a sampling rate of 32 cycles/s. The sum of all wrist movements within 30 s is recorded as an activity count. Activity counts were analysed using Actiware Sleep Analysis Software v.5.3.2, which classifies each 30-s epoch as sleep or wake using validated algorithms (Oakley, 1997). The high sensitivity setting was used because it provides good correlation with PSG for TST (0.70) in individuals with insomnia (Lichstein et al., 2006; Mccrae et al., 2005). As part of the parent clinical trial procedures, participants also completed daily sleep diaries (Lichstein, Riedel, & Means, 1999). Bed and wake times reported in sleep diaries that were recorded concurrent with actigraphy measurement were inserted into corresponding actigraph days to represent the time-in-bed period. Actiware determined the start of sleep by searching this time-in-bed period for the first 10-min interval during which no more than one epoch was scored as awake. Similarly, sleep end was signified by the last 10-min interval containing no more than one wake-state epoch. The average TST value across 14 days of baseline was the sleep parameter of interest in the present study.

The aetiology of self-reported sleep disturbance was determined by a board-certified sleep physician (R.B.B.) and sleep psychologist (C.S.M.), based on an in-depth clinical interview, 14 days of sleep diaries and one night of ambulatory polysomnography (PSG) testing. Sleep apnea and periodic leg movement disorder (PLMD) were

diagnosed in accordance with criteria of the International Classification of Sleep Disorders, 3rd edn (AASM, 2014), and insomnia criteria were consistent with DSM-5 criteria (American Psychiatric Association, 2013) and Research Diagnostic Criteria (RDC) (Edinger et al., 2004). Insomnia was diagnosed if participants reported: (a) >30 min of SOL (Lichstein, Durrence, Taylor, Bush, & Riedel, 2003), WASO, or waking up too early; (b) sleep that is chronically non-restorative or poor in quality; (c) items 1 and 2 occurring despite adequate opportunity and circumstances for sleep; (d) insomnia present 3+ nights/week for more than 1 month; (e) 1+ sleep-related daytime impairment (e.g. fatigue, cognitive disruption, social/vocational/educational disruption, mood disturbance/irritability, daytime sleepiness, motivation/energy/initiative reduction, being prone to errors/accidents at work or while driving, tension headaches, and/or gastrointestinal symptoms associated with sleep loss or a concern about sleep). Patients were diagnosed with sleep apnea if PSGs showed an apnea–hypopnea index (AHI; mean apnea/hypopneas or partial apneas per hour) >5 and they were diagnosed with PLMD if PSGs revealed myoclonus arousal >15/hr.

2.3 | Anxiety measure

Anxiety was assessed through the State Trait Anxiety Inventory Form Y (STAI-Y). (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), a 20-item questionnaire measuring general levels of anxiety. Items consist of self-descriptive statements (e.g. "I feel ____; calm, secure, upset") and participants are asked to rate their agreement on a 4-point Likert scale (1 = "not at all" to 4 = "extremely"). Total scores range from 20 to 80, with higher scores indicating greater maladjustment. To match the 2-week baseline period, STAI-Y instructions were modified to have participants respond based on the past 2 weeks. The STAI-Y demonstrates test–retest reliability exceeding 0.7 and reliably distinguishes patient and normal groups (Kabacoff, Segal, Hersen, & Van Hasselt, 1997; Spielberger et al., 1983).

2.4 | Cognitive tasks

As part of the larger aims of this project, a computerized cognitive battery was administered immediately after the 14 days of actigraphy to examine cognitive functioning. From this larger battery, tasks were chosen to represent a range of cognitive performance in both lower-order (i.e. attention and processing speed) and higher-order (i.e. executive functioning) domains: attention and processing speed (symbol digit modality test [SDMT] and simple reaction time [SRT]), executive functioning (flanker task, letter series and N-back task).

2.4.1 | SDMT

The SDMT (Smith, 1982) measures sustained attention and processing speed (Spreen & Strauss, 1998). In this task, participants are presented with a legend at the top of the computer screen consisting of nine digit/symbol pairs. A series of symbols with blank spaces are shown below the legend. Participants are instructed to enter the corresponding number (provided in the legend) for each symbol and to complete as many responses as possible within 90 s. The number of correct responses entered in the time limit was computed (i.e. total items with correct numbers that correspond with the symbol), with higher scores representing better performance.

2.4.2 | SRT

In the SRT task, participants are presented with a warning stimulus (***) followed by a signal stimulus (+) in the middle of the computer screen. Participants are instructed to press a designated key with their dominant hand as quickly as possible when the signal stimulus appears. Ten practice trials preceded the 50 test trials. Ten randomly arranged trials were then presented at each of five intervals separating the warning and signal stimuli (500, 625, 750, 875, and 1000 ms). The main outcome measure was the average reaction time in the 50 test trials, with higher scores indicating worse performance.

2.4.3 | N-Back

In this task, participants view a single letter in 48-point font in the centre of the computer screen and decide whether that letter matches a target letter presented in previous N trials, with N varying from zero to two trials. They are instructed to respond as fast and as accurately as possible. In the 2-Back condition, participants judge whether the current letter matches the letter presented two letters previously, indicating their response with designated "yes" or "no" keyboard keys. Letters remained visible until a response was made, with a 1 s inter-stimulus interval. The N-Back task measures working memory, which is considered an executive function (Cohen et al., 1997). The outcome measure of interest was the total number of correct 2-back trials, with higher scores representing better performance.

2.4.4 | Letter series

The letter series test (Thurstone & Thurstone, 1962) measures inductive reasoning, an executive function. Participants are presented with a letter series on the computer screen and instructed to choose the letter (from five possible choices) that would continue the established pattern. Participants are to complete as many of the series as possible in 4 min. The proportion of correct trials (# correct/total trials attempted) was computed as the outcome measure of interest, where higher scores indicate better performance.

2.4.5 | Flanker task

The flanker task (Eriksen & Eriksen, 1974) involves responding to a target in the presence of non-target stimuli "flanked" around the target. Non-target stimuli are either congruent (i.e. correspond to the same directional response as the target), incongruent (i.e. correspond to the opposite response to the target) or neutral (i.e. do not

correspond to any of the required responses regarding the target item). Our outcome of interest was the average reaction time for target response on incongruent trials. Performance on these trials measures the ability to inhibit irrelevant stimuli, an index of executive functioning (Eriksen & Eriksen, 1974). Higher scores indicate worse performance.

2.5 | Statistical analyses

Multiple linear regressions were carried out using the PROCESS macro (Hayes, 2016) in SPSS (Version 24). Criterion variables included cognitive measures: SDMT, SRT, N-back task, letter series and flanker task. Predictor variables included average TST (over 14 days of actigraphy), age, the TST by age interaction and STAI-Y anxiety scores. Significant TST by age interactions were clarified by calculating simple slopes of the association between TST and cognitive performance for sample-estimated age values characterized as follows: younger/middle-aged (1 *SD* below mean age, ~48 years of age), younger-older adults (~60 years of age) and older-older adults (1 *SD* above mean age, ~72 years of age).

3 | RESULTS

3.1 | Participant characteristics

Participant demographics and values for sleep and cognitive measures are provided in Table 1. A total of 41 participants (M_{age} = 60.3, *SD* = 12.3) had full data available for actigraphy, anxiety and cognition values and were included in the analyses. Twelve participants (29%) met trial-defined criteria for insomnia, five (12%) participants met criteria for sleep apnea (AHI > 5) and no participants met criteria for PLMD.

TABLE 1 Demographics and sleep outcomes of study sample of patients with implantable cardiac defibrillators (ICDs), with self-reported sleep disturbance (*n* = 41)

Variable	Mean (*SD*)	Range
Age	60.34 (12.32)	20.00–84.00
Sex (M:F)	23:18	–
Time since ICD implantation (years)	3.61 (3.14)	(0.08–13.00)
Medical conditions		
Coronary artery disease (*n*, %)	7 (17%)	–
Cardiomyopathy (*n*, %)	3 (7%)	–
Congestive heart failure (*n*, %)	14 (34%)	–
History of myocardial infarction (*n*, %)	6 (15%)	–
Atrial fibrillation (*n*, %)	19 (46%)	–
Psychiatric diagnosis (*n*, %)	12 (29%)	
Use of prescription sleep medications (*n*, %)	26 (63%)	–
MMSE	27.11 (1.82)	26.00–30.00
Anxiety score (STAI-Y)	36.15 (13.35)	20.00–72.00
Sleep measure		
TST actigraphy (min)	409.77 (74.77)	262.20–566.43
Cognitive measures		
Flanker task (RT, s)	710.78 (207.00)	227.40–1184.63
Letter series (proportion correct)	0.59 (0.29)	0.06–1.00
N-Back (2-back; number correct)	83.30 (19.11)	16.00–100.00
SDMT (number correct)	28.32 (11.36)	1.00–56.00
SRT (RT, s)	344.87 (121.21)	182.43–673.74

Note. Dx, diagnosis; MMSE, mini-mental state examination; STAI-Y, state-trait anxiety subscale form Y; TST, total sleep time; SDMT, symbol digit modality test; SRT, simple reaction time.

3.2 | Multiple regression

Results of models predicting performance for each cognitive test are presented in Table 2.

Findings were similar for analyses including and excluding patients who met criteria for sleep apnea.

3.2.1 | Processing speed and attention functioning

For SDMT, TST and age independently predicted performance. Longer TST was associated with better performance, regardless of participant age. In general, older age was associated with worse performance. Anxiety scores were not associated with SDMT performance. For SRT, cognitive performance was not associated with any predictors.

3.2.2 | Executive functioning

TST independently predicted performance on letter series task and N-back tasks. Longer TST was associated with better letter series and N-back performance, regardless of participant age. Age and anxiety did not predict performance in either cognitive task.

Age independently predicted performance on the flanker task. Older age was associated with worse performance. TST and anxiety did not predict performance on the flanker task.

3.3 | Exploratory analyses

To explore whether sleep fragmentation may have played a role in associations between TST and cognitive performance, we conducted additional separate multiple regressions, with WASO (mean = 50.2 min, *SD* = 26.5, range = 5.9–144.8) and sleep efficiency percentage (SE; calculated as time spent asleep/time spent in bed × 100%; mean = 77.9, *SD* = 9.5, range = 52.4–95.2), entered separately as predictors in the previously examined regression models. Results remained similar for associations between TST and performance across all tests. Furthermore, WASO and SE did not predict performance on any test (*p*s > 0.05).

TABLE 2 Actigraphic sleep determinants of cognitive performance in patients with implantable cardioverter defibrillators (ICDs) (n = 41)

Cognitive domain/measure	*B*	*SE*	*t*	*p*
Attention/processing speed				
SDMT[a]				
TST	0.05	0.02	2.37	0.02
Age	−0.42	0.14	−2.91	0.01
TST × age	−0.00	0.00	−0.85	0.40
Anxiety score	−0.11	0.13	−0.82	0.42
SRT[a]				
TST	−0.29	0.24	−0.17	0.25
Age	2.85	1.57	1.81	0.08
TST × age	0.01	0.03	0.28	0.78
Anxiety score	−2.79	1.46	−1.91	0.07
Executive functioning				
N-Back (2-back)[a]				
TST	0.10	0.04	2.53	0.02
Age	−0.08	0.26	−0.33	0.74
TST × age	−0.01	0.00	−1.44	0.16
Anxiety score	0.03	0.24	0.14	0.89
Letter series[a]				
TST	0.00	0.00	2.19	0.04
Age	−0.00	0.00	−1.10	0.28
TST × age	−0.00	0.00	−0.63	0.53
Anxiety score	0.00	0.00	0.34	0.74
Flanker task[a]				
TST	−0.38	0.40	−0.96	0.34
Age	8.81	2.56	3.43	<0.01
TST × age	−0.02	0.05	−0.35	0.73
Anxiety score	−0.87	2.39	−0.36	0.72

Note. *SE*, standard error; flanker task, mean reaction time on incongruent trials; TST, total sleep time; anxiety score, score on the state-trait anxiety subscale form Y (STAI-Y); SDMT, symbol digit modality test; SRT, simple reaction time.

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

4 | DISCUSSION

The present study evaluated the effects of associations between objective TST and its interaction with age, as well as the independent association of anxiety, on cognitive performance in patients with ICDs and self-reported sleep disturbances. Regardless of age, TST predicted higher-order cognition and performance on a lower-order cognitive task that measured processing speed and attention, whereas anxiety was not associated with cognition.

Our prediction that TST would be associated with performance on tests measuring higher-order cognitive functions was generally supported, but the type of cognitive task was important. For the reasoning and working memory tasks, associations between longer sleep duration and better performance agree with the direction of association reported in prior studies examining self-reported TST in adults without ICDs (Fernandez-Mendoza et al., 2010; Khassawneh et al., 2018). This suggests that patients with ICDs may receive cognitive benefits following increased sleep duration. The present results are generally consistent with prior research on older adults, which found similar associations with global cognitive performance for participants with long sleep duration (i.e. >8 hr) (Blackwell et al., 2011). Although we also predicted that TST associations would be strongest with increasing age, this was not supported. This may suggest that in patients with ICDs, the association between sleep duration and higher-order cognition may be a generalized relationship across the lifespan.

Our prediction that TST would not be associated with lower-level cognitive functioning in patients with ICDs was partially supported. The results showing no association between TST and SRT are not surprising given that sleep loss has been associated with the pre-frontal cortex (Horne, 1993), an area that is not likely to mediate this lower-level cognitive task. Additionally, given that cognitive outcomes were assessed at single time-points, sleep duration may not have as much of an impact on cognitive performance because participants were likely able to recruit the necessary cognitive resources to perform this task. It is possible that examination of repeated daily cognitive assessments may reveal different associations with sleep duration compared with the single-shot approach reported here, which is an important consideration for future research on patients with ICDs. However, we did observe that longer TST was associated with better SDMT performance. Given that SDMT measures attentional vigilance in addition to simple processing speed (Shum, Mcfarland, & Bain, 1990; Spreen & Strauss, 1998), it presumably requires additional cognitive resources to those required to conduct SRT. Thus, like the other higher-order cognitive tasks examined in the present study, SDMT may also be sensitive to disturbance following shorter sleep duration.

Interestingly, although all participants self-reported sleep disturbances, only a small proportion of patients met trial criteria for insomnia disorder or sleep apnea. Therefore, the present results demonstrate that even without the criteria met for these sleep disorders, patients with ICDs still might experience impairments that limit their daytime functionality. Furthermore, our finding that results remained similar whether patients with sleep apnea were or were not included in analyses agrees with prior research showing associations between objectively measured (i.e. through PSG) sleep duration and cognitive performance in middle-aged adults with insomnia, independent of sleep-disordered breathing (Fernandez-Mendoza et al., 2010). Thus, in general, sleep duration may be an important area for clinical monitoring or targets for intervention in patients with ICDs.

Although not a primary focus of the present study, our exploratory analyses showing no associations between cognition and other objective sleep parameters that capture wake time during the night (i.e. WASO and SE), as well as no change in associations between TST and cognition, are interesting. Although these exploratory analyses should be evaluated in larger samples, it is possible that longer

sleep, regardless of how fragmented, is more important for improving higher-order cognitive performance in patients with ICDs.

Contrary to our prediction, general anxiety scores were not associated with cognitive performance across any examined domain in patients with ICDs. These findings are surprising given the well-known negative association between anxiety and executive functions (Derakshan & Eysenck, 2009). We did not, however, examine associations between anxiety and all possible measures of executive function, but rather only three tests measuring reasoning, working memory and inhibition. Moreover, patients with ICDs may also have disease-specific anxiety, often termed *shock anxiety*, which could be more salient for this patient group (Ford et al., 2012). Therefore, it is possible that the pattern of results reported here may differ on other executive-ability measures or different disease-specific anxieties. Further, given that recommended cut-off scores for clinically meaningful anxiety on the STAI-Y are higher for older adults and the mean age of the present sample was in the older age range (i.e. ~60 years of age), anxiety scores in the present sample (mean of ~36) may not have been high enough to show the expected associations with higher-order cognition. Finally, given that we measured anxiety and cognitive performance at single time-points, it is possible that there are acute fluctuations in the associations between anxiety and day-to-day cognitive performance in patients with ICDs, which should be examined in future work.

The present study has several limitations. First, although findings are likely to be representative of patients with ICDs and self-reported sleep disturbance, whether results may generalize to patients without self-reported sleep disturbances remains unclear. Second, the sample size was small; therefore, findings should be replicated in larger patient samples. Larger samples would also allow for sufficient power (adhering to the recommended sample size of 10 participants per predictor variable in the regression model (Vanvoorhis & Morgan, 2007)) to explore other potential predictors (e.g. time since ICD implantation, medications and total number of shocks received) of cognitive performance. Third, as previously stated, given that we did not explore all possible test measures of each cognitive domain, it is possible that findings may not generalize to associations between sleep duration and performance on other cognitive tests. Fourth, given that the mean age of participants was approximately 60 years, results may not generalize to younger patients. Finally, as the present study did not compare findings with those of an age-matched control group of participants without ICDs, we cannot be certain that findings are specific to ICD patients.

To our knowledge, the present study is the first to examine associations between sleep and cognition in patients with ICDs. Results suggest that regardless of patient age, objectively assessed sleep duration may play an important role in the prediction of executive function and a lower-order task measuring attention and processing speed in patients with an ICD and self-reported sleep disturbance. Given that cognitive function is associated with quality of life in ICD patients (Moulaert et al., 2010), as well as functional independence in older adults (Mehta, Yaffe, & Covinsky, 2002), who were widely represented in the present analysis, the results may inform clinical applications related to sleep and ageing, and potentially facilitate the management of cognitive aspects of daytime functioning.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

AFC and AJR drafted the manuscript. AFC conducted analyses. JMD collected data. CSM and JMD drafted and carried out the protocol. All authors revised a draft of the paper.

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