Studies on circadian rhythm disturbances and melatonin in delirium

de Jonghe, A.-M.

Citation for published version (APA):
Chapter 4
Rest-activity patterns in patients with delirium

Miranda van Uitert, Annemarieke de Jonghe, Swana de Gijsel, Eus J.W. van Someren, Sophia E. de Rooij, Barbara C. van Munster

Abstract
Objective: Delirium is a frequent syndrome in elderly hospital patients. Symptoms typically show a fluctuating course during the day with patients exhibiting disturbances of their sleep wake rhythm. Delirium is frequently underdiagnosed, especially the so-called hypoactive subtype. Devices measuring 24h motor patterns could contribute to the recognition of delirium. The purpose of this paper is twofold. First, the results of a pilot study are presented, in which 24h motor patterns of delirious patients are measured with a wrist-actigraph. Second, studies reporting 24h motor patterns in delirious patients are systematically reviewed.
Methods: The pilot study included nine patients, 65 years or older, with a hip fracture in need of surgical repair. For the review, MEDLINE and Embase were searched for studies on motor activity assessment in delirious patients.
Results: In the pilot study, the 24h activity rhythm was severely disturbed during delirium, and most actigraphic sleep parameter estimates indicated significantly worse sleep during delirious nights. The systematic search resulted in ten papers. In three papers, the sleep wake rhythm of delirious patients was significantly different than that of non-delirious patients. In five papers, delirious patients could be classified into delirium subtypes. In the two remaining papers, 24h motor patterns of delirium subtypes were not significantly different.
Conclusion: Activity patterns revealed differences between delirious and non-delirious patients and between the different subtypes, even in small samples of patients. Future studies, with preferably larger sample sizes, should confirm the potential of activity pattern measuring devices in the early detection of delirium.
Introduction

Delirium is a frequent syndrome in elderly patients and is associated with increased morbidity and mortality and a prolonged hospital stay (1, 2). Even after hospital discharge, delirium is associated with a higher risk for cognitive impairment, higher institutionalization rate, a threefold increase in mortality risk, and increased health care costs (1, 3). The syndrome of delirium is best described as an acute neuropsychiatric syndrome, which is characterized by deranged consciousness, concentration, attention and cognition (4, 5). Symptoms typically show a fluctuating course during the day with serious symptoms during the night. As such, patients exhibit disturbances in their circadian rhythm or, in other words, in their sleep wake rhythm, which are reflected in their 24 h motor activity behavior. Unfortunately, the delirium diagnosis is frequently missed.

Three clinical subtypes of delirium are known, mainly based on their level of arousal: hyperactive, hypoactive, and a mixed subtype (6-8). In the hyperactive subtype, psychomotor activity is increased, and agitation is prominent. In the hypoactive subtype, psychomotor activity is decreased, and the chance of remaining undetected as delirium is increased. Hypoactive subtypes have the highest prevalence among elderly patients and, at the same time, exhibit the worst prognosis (9, 10). Different subtyping scales have been developed in small study cohorts based on observations, but a gold standard is lacking (11). Better characterization and identification of delirium subtypes will assist the clinician in the choice of treatment. In addition, it will facilitate research into the biochemical and molecular pathways leading to delirium because the pathophysiology may differ between subtypes (12).

Devices that are capable of measuring the 24 h motor activity might be helpful in determining more objective criteria for delirium subtypes and the early recognition of delirium. Three different devices are known to study motor activity patterns, the activPAL™ (PAL Technologies Ltd, Glasgow, UK) (13-16), a discrete accelerometer-based device (such as the ADXLS22 from Analod Devices Inc.) (13, 14, 16-18), and the Actiwatch® (Cambridge Neurotechnology Ltd, Cambridge, UK) (19-23). The activPAL attached to the thigh records activity every 0.1 second (>2 g acceleration), and the software is designed to evaluate activity measurements. The discrete accelerometer-based device is similar to the commercial monitor activPAL, is attached to the thigh and records at a sampling frequency of 50-Hz and at a resolution of 12 bits. The actigraph placed on the wrist of the non-dominant hand records every 1 minute (>0.05 g acceleration), and the software aims at determining circadian rhythm and sleep wake rhythm.

Several researchers have studied the relationship between 24 h motor patterns and delirium or delirium subtype with these devices. Most of these studies were conducted in small populations, and they differed in their primary research question. To evaluate the results obtained so far and to review whether any of our questions have yet been answered, we have conducted a systematic review of the available literature. In addition, we report the results of a pilot study using the actiwatch. Instead of investigating whether
the presence of delirium influences the 24 h motor activity pattern using one or several preselected parameters, we are searching for specific sleep wake rhythm parameters that are influenced by the presence of delirium. There is no consensus on the parameters, and hence, the results will aid us in choosing the most suitable parameters that need to be reported in future studies.

Therefore the aim of this review is twofold: (1) to determine, in a pilot study, which of the sleep wake rhythm and circadian rhythm parameters measured by the actigraph are associated with delirium in a population of elderly hip fracture patients; and (2) to combine these current data with data from former studies in a complete overview with recommendations for future studies.

Methods

Methods for the pilot study

Patients and procedures

The study was conducted at the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Nine patients aged 65 years or older, acutely admitted to the Department of Orthopedic Surgery or Traumatology with a hip fracture and scheduled for surgery, were included in the study. Informed consent was obtained from all patients or from substitute decision-makers in cases of cognitive impairment. Patients were excluded if they were unable to speak or understand Dutch or English. The institutional medical ethics committee approved the study. The Actiwatch® was placed on the non-dominant wrist, in compliance with the manufacturer’s guidelines, and was worn continuously for five to seven days. The presence of delirium was assessed daily by a geriatrician using the Confusion Assessment Method (CAM). The CAM is a validated instrument that is based on the DSM criteria and extensively used by researchers in the field of delirium (24, 25).

Possible confounding factors, such as demographics, fracture characteristics, type of anesthesia, type of surgery and postoperative complications (including infectious events), were registered for all patients. Global cognitive functioning was based upon anamnensis, medical history, Informant Questionnaire on Cognitive Decline-Short Form (IQCODE-SF) (26), and the Mini-Mental State Examination (MMSE) (27). To measure physical functionality, patients, or their closest relatives in cases of cognitive impairment, were asked to complete the 15-item Katz Index of Independence in Activities of Daily Living (Katz-ADL) (28, 29) based on the situation two weeks before the hip fracture.

This pilot study was related to a larger study, of which the procedures are described in more detail in previous publications (30).

Data analysis

Estimates of sleep parameters were obtained from the Sleepwatch sleep analysis software (Cambridge Neurotechnology Ltd). Defining nighttime to be from 2300 to 0700, we calculated the following sleep parameters: the Actual sleep time (the difference between
the Assumed sleep time and the Actual awake time, in hours); the Sleep efficiency (the percentage of Actual sleep time during nighttime); the Sleep latency (the time it takes to fall asleep, in minutes); the Duration of sleep bouts (the Actual sleep time divided by the number of sleep bouts, in minutes); and the Duration of wake bouts (the Actual awake time divided by the number of wake bouts, in minutes). In addition, we calculated the following circadian rhythm parameters (31): the IV (Intradaily Variability, which represents the frequency and extent of transitions between rest and activity); the L5 (the Least active 5 h period in the average 24 h pattern); the M10 (the Most active 10 h period in the average 24 h pattern); and the Relative Amplitude (RA), which is equal to (M10-L5)/(M10+L5). Note that the RA yields a value between 0 and 1; the closer this value was to 1, the larger the difference was between the major periods of rest and activity.

To determine the influence of the presence of delirium on each of these different sleep and circadian rhythm parameters, a multilevel regression model was used. In this model, the presence or absence of delirium, as diagnosed by the geriatrician, was modeled as a 0/1 dummy variable. The analysis was conducted using the software package MLwiN (Center for Multilevel Modeling, University of Bristol).

Methods for the systematic review
Search strategy
We searched MEDLINE (1985 to March 2011) and Embase (1980 to March 2011) for studies on motor activity measuring devices that have been used with delirious patients. In addition, we searched the references of the relevant articles that we found. The following search strategy was used:

(actigraph* OR acceleromet* OR polysomnograph* OR “Motor activity”[mh] OR “Monitoring, Physiologic” [mh]) AND delir*.

Study selection
Inclusion criteria were original research articles in English, patients with delirium, and measurements of the 24 h motor activity pattern using a measurement device.

Results
Results pilot study
Due to technical problems, data from one patient could not be used in the analysis, leaving eight patients for the analysis. The characteristics of the patients can be found in Table 1. There are no significant differences between patients that develop delirium and patients that do not develop delirium. However, some trends are visible; for instance, patients that develop delirium more often exhibit a preadmission functional and cognitive impairment.

The results of the actometer registrations are shown in Table 2. We had 53 days available for our analysis, of which 24 were non-delirious and 29 were delirious. All of the sleep parameters but one are influenced significantly by delirium, meaning that the sleep...
Chapter 4

The pattern of patients with delirium is severely disturbed. The actual sleep time (p-value 0.006), the sleep efficiency (p-value 0.005) and the duration of sleep bouts (p-value 0.04) decrease, whereas the sleep latency (p-value 0.05) increases. Similar results are obtained for the circadian rhythm. Two of the four parameters representing the circadian rhythm are significantly influenced by the presence of delirium, the IV (p-value 0.001) and the RA (p-value 0.001), and the influence on L5 (p-value 0.07) is close to significant. The IV and the L5 increase, whereas the RA decreases, which means that the circadian rhythm is disturbed as well due to the presence of delirium.

Table 1: Baseline characteristics of the study population in the pilot study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delirium (n=5)</th>
<th>No delirium (n=3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (SD)</td>
<td>90.6 (8.7)</td>
<td>85.3 (7.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Male (%)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>0.38</td>
</tr>
<tr>
<td>Living at home (%)</td>
<td>1 (20)</td>
<td>2 (67)</td>
<td>0.46</td>
</tr>
<tr>
<td>Preadmission functional impairment (number of ADL disabilities)</td>
<td>9 (8-11)</td>
<td>5 (3-6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Preadmission cognitive impairment (%)</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Spinal anesthesia (%)</td>
<td>2 (40)</td>
<td>2 (67)</td>
<td>1</td>
</tr>
<tr>
<td>Fracture characteristics / type of surgery (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck / Hip replacement</td>
<td>4 (80)</td>
<td>2 (67)</td>
<td></td>
</tr>
<tr>
<td>Intertrochanteric / Internal fixation</td>
<td>1 (20)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Any postoperative complication (%)</td>
<td>3 (60)</td>
<td>1 (20)</td>
<td>1</td>
</tr>
<tr>
<td>Infection (%)</td>
<td>2 (40)</td>
<td>1 (20)</td>
<td>1</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>18 (9-29)</td>
<td>10 (9-11)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

For "Age," the mean values (SD) are given, with the t-test used to determine the p-value. For "Preadmission functional impairment" and "Length of stay," the median values (25% quantile to 75% quantile) are given, with the Mann-Whitney test used to determine the p-value. For the other variables, the absolute values (percentages) are shown, with the Fisher exact test used to determine the p-value.

Table 2: Results of the pilot study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-delirious night (n=24)</th>
<th>Delirious night (n=29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual sleep time (hours)</td>
<td>6.17 (0.35)</td>
<td>4.87 (0.59)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>77.11 (4.35)</td>
<td>60.79 (7.28)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sleep latency (minutes)</td>
<td>4.72 (11.08)</td>
<td>30.33 (17.13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of sleep bouts (minutes)</td>
<td>36.18 (6.37)</td>
<td>21.08 (9.84)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of wake bouts (minutes)</td>
<td>6.76 (1.68)</td>
<td>8.42 (2.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>IV</td>
<td>0.83 (0.08)</td>
<td>1.16 (0.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>L5</td>
<td>10.7 (2.93)</td>
<td>17.4 (4.72)</td>
<td>0.07</td>
</tr>
<tr>
<td>M10</td>
<td>47.62 (2.75)</td>
<td>44.41 (4.01)</td>
<td>0.27</td>
</tr>
<tr>
<td>RA</td>
<td>0.7 (0.05)</td>
<td>0.49 (0.09)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

For all parameters, the mean values (SD) and p-values are computed using multi-level linear regression models. IV: Intradaily Variability; L5: Least active 5 h period in the average 24 h pattern; M10: Most active 10 h period in the average 24 h pattern; RA: Relative Amplitude, which is equal to (M10-L5)/(M10+L5).
Results systematic review
The search strategy resulted in 240 studies in PubMed. Searching in Embase did not provide additional relevant articles. We screened the titles and abstracts of all 240 articles for patients with delirium whose motor activity pattern was measured by a measurement device. We found 11 studies that fulfilled the inclusion criteria. The references from relevant articles did not produce other studies.
In Tables 3 and 4, an overview of the 12 studies identified is represented. This total included 11 studies from the systematic search and the previously described (unpublished) pilot study. Five of the 11 articles reported on the same set of 34 patients (13-15, 17, 18). These five studies differed in their statistical methodology used to identify delirium subtypes based on the activity data. A pilot study for these five studies, with a subset of three of the 34 patients, is described in (16). In Tables 3 and 4, we only show the details of (15), because most of the details of the other studies are exactly the same, except for the statistical framework. We also note that the study population of (19, 20) is the same. However, different subgroups are made for the analyses. In (20), three subgroups are defined based on the duration of delirium, whereas in (19), delirious patients are compared to non-delirious patients.

Table 3: Characteristics of the study population

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Sample size (D and ND)</th>
<th>Study population</th>
<th>Age (years) (SD/range)</th>
<th>Diagnosis of delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osse (2009a)</td>
<td>79 (D=33, ND=46)</td>
<td>Elective cardiac surgery (coronary bypass graft, valve surgery or both)</td>
<td>D short-term: 75.2 (4.1) D sustained: 72.9 (4.9)</td>
<td>DSM-IV-TR criteria and CAM-ICU</td>
</tr>
<tr>
<td>Osse (2009b)</td>
<td>70 (D=38, ND=32)</td>
<td>Elective cardiac surgery (coronary bypass graft, valve surgery or both)</td>
<td>D: 76.0 (4.9) ND: 73.0 (4.6)</td>
<td>CAM-ICU of the first day</td>
</tr>
<tr>
<td>Eeles (2009)</td>
<td>16 (D=16, ND=0)</td>
<td>Medical and surgical hospital patients with delirium</td>
<td>D: median 85 (76-95)</td>
<td>DRS-R-98</td>
</tr>
<tr>
<td>Jacobson (2008)</td>
<td>13 (D=6, ND=7)</td>
<td>Major surgery patients</td>
<td>D: 81 (6.7) ND: 77 (7.9)</td>
<td>DSM-IV-TR criteria</td>
</tr>
<tr>
<td>Honma (1998)</td>
<td>8 (D=8, ND=0)</td>
<td>Demented inpatients in mental hospital</td>
<td>D: 84.9 (7.8)</td>
<td>Not known</td>
</tr>
<tr>
<td>Godfrey (2009a)</td>
<td>34 (D=25, ND=9)</td>
<td>Palliative care patients in a hospice palliative care centre</td>
<td>Not known</td>
<td>DSM-IV</td>
</tr>
<tr>
<td>Pilot study</td>
<td>8 (D=5, ND=3)</td>
<td>Acutely admitted to the hospital with a hip fracture</td>
<td>D: 92.2 (7.16) ND: 84.7 (6.7)</td>
<td>CAM</td>
</tr>
</tbody>
</table>

D: delirious patients, ND: non-delirious patients; short-term delirium is < 4 days; sustained is 4 days or longer; for age, the mean (std) is given, except for Eeles (2009), where the median (range) is given. CAM: Confusion Assessment Method [24] and [25], DRS-R-98: Delirium Rating Scale-R-98 [32] and [33], CAM-ICU: Confusion Assessment Method for the Intensive Care Unit [41].
Table 4: Details of included studies

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Device</th>
<th>Length of study</th>
<th>Output parameters</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osse (2009a)</td>
<td>Actiwatch</td>
<td>First 5 days postoperatively</td>
<td>During nighttime and daytime: • Mean activity per minute • Number of minutes immobile • Restlessness index • Activity amplitude</td>
<td>For non- or short-term delirious patients, significantly lower: • Activity amplitude • Daytime activity per minute • Daytime restlessness • Daytime number of immobility minutes No difference in night-time motor activity between the three groups</td>
</tr>
<tr>
<td>Osse (2009b)</td>
<td>Actiwatch</td>
<td>First postoperative day and night</td>
<td>During nighttime and daytime: • Mean activity per minute • Number of minutes immobile • Restlessness index And: • Mean activity of the 5 h with the least activity in 24 h • Mean activity of the 10 h with the highest activity in 24 h</td>
<td>In delirious patients: • Lower mean activity levels during the night • Reduced restlessness during the day</td>
</tr>
<tr>
<td>Eeles (2009)</td>
<td>Actiwatch</td>
<td>Not known</td>
<td>Average activity per minute Day-to-night ratio of activity</td>
<td>No correlation with psychomotor subtypes</td>
</tr>
<tr>
<td>Jacobson (2008)</td>
<td>Actiwatch</td>
<td>24 hours, for which the DRS-R-98 score was highest</td>
<td>During nighttime and daytime: • Total number of minutes active • Total number of minutes resting • Mean activity count And: • Total time resting in 24 h • The 24-h amplitude of the activity</td>
<td>Abnormal rest-activity patterns in delirious patients No correlation of activity parameters with delirium severity</td>
</tr>
<tr>
<td>Honma (1998)</td>
<td>Actiwatch</td>
<td>10 days</td>
<td>• Average 24 h activity chart • Day to day variation in activity • Activity rhythm with periodogram</td>
<td>Four delirium subtypes were found</td>
</tr>
<tr>
<td>Godfrey (2009a)</td>
<td>activPAL*</td>
<td>24 hours</td>
<td>Amount of time spent • Sitting or lying • Standing • Stepping Number of postural transitions</td>
<td>Discriminant features between subtypes: time spent standing and postural transitions</td>
</tr>
<tr>
<td>Pilot study</td>
<td>Actiwatch</td>
<td>All available data</td>
<td>• Actual sleep time • Sleep efficiency • Sleep latency • Duration of sleep bouts • Duration of wake bouts</td>
<td>Delirium influences: • Actual sleep time (negatively) • Sleep efficiency (negatively) • Sleep latency (positively) • Duration of sleep bouts (negatively)</td>
</tr>
</tbody>
</table>

*The activPAL is used in [13], [14], [15] and [18], and a discrete accelerometer-based device is used in [13], [14], [16], [17] and [18].

We next describe the studies according to their principal research questions.
The first research question, which was the main focus of three studies, involved the correlation between delirium subtypes and activity patterns. The relationship between symptoms and activity patterns was investigated in eight demented patients with delirium (23). Based on a daily average activity pattern, four types were identified visually: A) severe nocturnal delirium; B) remarkable wanderings and prominent activity elevation during daytime; C) delirium in the late afternoon and early evening and hypobulia (lack of willpower); and D) preferred lying down and delirious at random. The same question was addressed in a study involving 16 patients with delirium (seven hyperactive, two hypopactive and seven mixed) (21). None of the activity parameters calculated by the authors were found to correlate with delirium subtype. Delirium subtype was scored using the validated Delirium Rating Scale-R-98 (DRS-R-98) (32, 33) on days one, two, three, five, and seven. In addition, items concerning psychomotor activation and retardation were used (6). In the third study on this topic, 34 palliative care patients were monitored with the activPAL (15), a discrete accelerometer-based device (17, 18), or both (13, 14, 16). The data were used to build a so-called “classifier”, a software tool that is able to classify a patient based on his or her activity data in one of the subgroups of hyperactive, hypoactive or mixed. Subgroups are determined using the Delirium Motoric Checklist (DMC) (34), the DRS-R-98 and the Memorial Delirium Assessment Scale (MDAS) (35). In each of the papers, a different method is used to train and validate the classifier, such as standard Matlab® classification software or wavelet theory. The best classifiers were able to classify roughly 70% to 90% of the patients correctly in a validation set.

The second research question, addressed in three studies, is to investigate whether the actigraph is able to characterize the sleep wake rhythm of delirious patients compared to that of non-delirious patients. In the first study, six delirious patients and seven non-delirious patients were monitored for 24 hours after major surgery using the actigraph (22). Significant differences are found between delirious and non-delirious patients for the number of nighttime minutes at rest (lower with delirium, p-value 0.0006), the number of minutes at rest over the 24-hour period (lower with delirium, p-value 0.031), the mean activity count at night (higher with delirium, p-value 0.0023), and the amplitude of change in mean activity from day to night (smaller with delirium, p-value 0.012). In addition, significant correlations between each of these parameters and the severity of delirium, as measured by the DRS-R-98, were found (p-values 0.0007, 0.05, 0.009, 0.0066, respectively).

The second and third studies are related because they consider the same study population. The second study (19) focuses on the early diagnosis of delirium by investigating the first postoperative night and day in delirious and non-delirious patients. It is shown that during the first postoperative night, the mean activity level was significantly lower (p-value 0.05) in delirious patients compared to non-delirious patients. During the following day-period, the restlessness was significantly lower (p-value 0.03), the number of immobility minutes was higher (p-value 0.09) and the mean activity level was lower (p-value 0.08) for the delirious group compared to the non-delirious group. The
L5, the mean activity of the 5 h period with the lowest activity within the first 24 h, was significantly lower (p-value 0.01) for delirious patients. In the third study (20), three patient groups are distinguished, and five postoperative consecutive nights and days are analyzed. The aim of this study was to investigate the duration of delirium in relation to the recovery of circadian rest-activity patterns. The three groups of patients were as follows: patients who were not delirious (including those that were only delirious during the first postoperative day), patients who were delirious for a short term only (for two or three days directly following surgery), and patients who had sustained delirium (for four days or more). The so-called activity amplitude can be used as an indicator of recovery from disturbed rest-activity behavior and is computed as the difference between L5 and M10 (starting at 1900 h on the day of surgery). The activity amplitude turned out to be higher for both short-term and non-delirious patients compared to the sustained delirium group and also increased more in short-term and non-delirious patients (p-values 0.044 (group effect), <0.001 (time effect) and 0.019 (interaction effect)). During the daytime, both activity per minute and the restlessness index were higher in the short-term and non-delirious groups compared to the sustained delirium group, and the number of immobility minutes was higher for the sustained delirium group. Only the time effect was significant, with a p-value <0.001 for all three parameters, and the group effect was not significant. One of the main results was that the wrist actigraph is capable of separating the group of patients with short-term delirium from the group with sustained delirium.

Discussion

Pilot study
The pilot study has shown, using the actigraph, that the presence of delirium is significantly related to both the sleep quality and the circadian rhythm of the patient. All sleep parameters but one are significantly affected, and hence, it takes delirious patients longer to fall asleep; they sleep for shorter intervals and get less sleep during the night as a whole. For two out of the four circadian rhythm parameters, IV and RA, a significant difference is obtained. The fact that the IV is larger for delirious patients means that they experience more transitions between rest and activity. The smaller RA for delirious patients shows that the major period of rest is not very different from the major period of activity, whereas for the non-delirious patients, there is a clear difference.

Systematic review
We have reported on six original studies that measured the 24 h motor activity pattern in patients with delirium or at risk for delirium. The most popular device to measure the 24 h motor activity pattern was the wrist-actigraph, which all researchers with the exception of one (15) have used. All three devices: the wrist-actigraph, the discrete accelerometer-based device and the activPAL were, in general, well tolerated by the patients.
Three papers investigated whether the actigraph is able to capture the principal determinants of the sleep wake rhythm or the circadian rhythm of delirious patients (19, 20, 22). Indeed, it is shown that parameters exist that are different for delirious versus non-delirious patients. In one of the papers (20), parameters were found that differed between patients with short-term delirium and with sustained delirium, namely the activity amplitude, the daytime activity per minute, the restlessness index (all three parameters were higher for short-term delirium) and the daytime number of immobility minutes (lower for short-term delirium).

Three papers addressed the question of whether a measurement of the 24 h motor activity pattern could be helpful to determine delirium subtypes (15, 21, 23). In the first paper (23), the actigraph data were represented in graphical summaries showing that delirious patients could be categorized into four groups. Although these categories appear to be related to the established delirium subtypes, the authors do not mention them nor relate to them. The second paper could not identify subtypes, perhaps due to the small sample size, the selection of variables, or the choice of model (21). In the third paper, the authors managed to build relatively accurate classifiers for subtyping patients based on activPAL data (15). This result implies that there is certainly some correlation between the output parameters of the activPAL software and delirium subtypes.

**Limitations**

*Sample size*

One of the limitations of all seven studies is the small sample size that mostly shows trends but no definite results. The pilot study, for instance, had data available for eight patients and showed trends in baseline characteristics between delirious and non-delirious patients, such as a difference in pre-existing cognitive and functional impairment. However, it was not possible to show whether these have any effect on the sleep quality or the circadian rhythm. In another paper, 34 patients were available, of which 25 were delirious (15). Subtyping analysis required that the group be split up further into hyperactive (six patients in this case), mixed (eight patients) and hypoactive (11 patients), resulting in small sample sizes per subtype. In addition, a proper classification experiment requires a validation population that is different from the training population, meaning that the groups need to be split up even further. Hence, it is hard to draw definite conclusions from these results.

*Confounders*

Most studies lack models where appropriate confounders are taken into account. Important confounders for sleep and circadian rhythm disruption are medication, cognitive impairment and mental health in general (36, 37), abnormal light exposure, and general discomfort and pain (38). In addition, aging itself results in circadian rhythm changes (39).
Chapter 4

Future work
One of the most important lessons that can be drawn from this review is that future studies should include larger numbers of patients. Well-powered studies would allow for trends, which became visible in the small studies, to be shown as true or false. In addition, larger studies are necessary to take confounders into account. Interestingly, most authors had chosen the actigraph to measure the 24 h motor pattern, except for one study in which the activPAL is used. Recently, a new device was developed that is able to measure 24 h motor patterns: the Everon™ system (Earlsense LTD, Israel) (40). Like the actigraph, the sensor of the Everon system contains a piezo-electric crystal that records acceleration. A key feature of the Everon system is that it contains a non-contact sensitive mechanical sensor that is placed under the patient’s mattress. In delirious patients, this type of device may be advisable because of the absence of any extra burden for the delirious patient. Because there is currently no gold standard available for subtyping, future studies should focus on defining objective criteria for delirium subtypes based on 24 h motor patterns. At the same time, it should be kept in mind that analyses of activity patterns have to be made in real time to use the results in daily clinical practice. Hence, despite these promising results, the most significant challenge is to find sleep and circadian rhythm parameters that can be computed in real time per subtype that are relatively robust with respect to patient characteristics and can be used in clinical practice to screen for patients with a delirium. We propose that future studies continue with the sleep and circadian rhythm parameters that were found to be significantly different in the pilot study.

Conclusion
The studies discussed in this review show that measuring 24 h motor activity patterns of patients at risk for delirium is a promising method of screening for delirium. Activity patterns revealed relevant differences between delirious and non-delirious patients and between the different subtypes, despite small sample sizes. All of the studies have taken important initial steps, but there are major hurdles that need to be overcome before such devices can be integrated in clinical practice. Future well-powered studies should show the potential of activity pattern measuring devices in delirium subtyping and in the early detection of delirium symptoms, especially in relation to the pathophysiological studies investigating biomarkers.
Rest-activity patterns in delirium

Reference List

Chapter 4


