Author's response to reviews

Title: Actigraphy Assessments of Circadian Sleep-Wake Cycles in the Vegetative and Minimally Conscious States

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Author's response to reviews: see over
Dear Dr. Tree-Booker,

We would like to thank the editorial team and two Reviewers (Dr. Zasler and Dr. Birbaumer) for providing us with the opportunity to revise our submission to *BMC Medicine*. We were pleased to see that the Reviewers were very positive about our manuscript, and have made many constructive suggestions. Please find attached our revised submission which we feel is improved as a result. We also include a point-by-point response to each of the Reviewers’ comments.

Briefly, at the request of the Reviewers, our revised manuscript includes a number of clarifications and new discussion points, along with a new table, which provides details regarding the patients’ injuries and prescribed medications. We have also included three new middle authors (Marie-Aurélie Bruno, Olivia Gosseries, and Audrey Vanhaudenhuyse) in order to reflect their contributions to the data collection and preparation of clinical information contained in our revision.

Again, we would like to thank you, and Dr. Zasler, and Dr. Birbaumer, for agreeing to receive our revised manuscript, and look forward to hearing from you in the near future.

All the best,

Damian Cruse and colleagues.
Reviewer's report

Title: Actigraphy Assessments of Circadian Sleep-Wake Cycles in the Vegetative and Minimally Conscious States

Version: 1 Date: 5 September 2012
Reviewer: Nathan Zasler

Reviewer's report:
The article by Cruse, et al. is a very interesting, unique and methodologically sound contribution to the acquired brain injury literature in general and particularly as related to sleep medicine. The title of the paper adequately represents the study conducted. The study provides a solid abstract that adequately covers the background, methods, results and conclusions of the study. The writing style overall is excellent aside from not using “person first” language (that is “person with a brain injury,” as opposed to “brain injury person”). Relevant literature is reviewed in the background information section of the paper. The methods are well described in terms of the study population.

- We thank the Reviewer for their positive comments about the study.

I would suggest that the use of the term “informed assent” be changed to “informed consent,” as the term informed assent is typically utilized as related to a person’s willingness to participate in research when they are too young to give informed consent, but old enough to understand the proposed research in general relative to its risks and benefits.

- As suggested, this statement has been changed to ‘informed consent’ (see Methods: Patients).

I would note that the authors discuss, towards the beginning of the article, the use of actigraphy in similar patient populations and to validate its use of the current population of persons with DOC by quoting literature in persons with tetraplegia, however the quoted Israeli article by Stivak et al. did not look at high level tetraplegics but rather at tetraplegics at C4 and below. I do not think that this group of patients can necessarily be considered “motorically parallel” to persons in a minimally conscious state, and even more so to persons in a vegetative state. This issue is partly addressed in the context of the discussion (page 2 of that section... top full paragraph) in the author’s notation that there is a need for caution in the use of actigraphy for assessing circadian to do weight rhythm since they relay on motor output for the rhythm to be detected. Therefore, if there is any weakness methodologically in the paper it is with regard to the assumption that the use of the technique in tetraplegic patients (C4 and below as noted above) is somehow comparing apples to apples when it comes to assessing patients in DOC with actigraphy relative to their circadian cycles. I think the authors should expound on this particular issues as if there is any fault in the article this would be the area of most consternation.
We understand the Reviewer’s concern that C5-C7 tetraplegia (as described by Stivak et al.) is not an ideal comparison with VS/MCS patients motoric state. In the revised manuscript, we now include a closing paragraph in which we describe the potential problems with drawing parallels between tetraplegia and VS/MCS, and argue that what is needed is a validation of the relationship between actigraphy and polysomnography in these patient groups. This revision can be found at the end of the Discussion section:

“**A final caveat is that the apparent absence of reliable circadian rhythms in some of our patients may be a result of a lack of sensitivity of the actigraphy method, rather than the true absence of those rhythms.** While wrist actigraphy has been validated for sleep assessment in patients with C5-C7 tetraplegia [23], these patients are nevertheless capable of small but purposeful wrist movements. Patients in the VS, however, are by definition unable to produce purposeful movements, although spontaneous movements are common. Similarly, due to the heterogeneity of brain injuries of these patients, it is not clear whether the presence of actigraphy-detected waking is necessarily indicative of concurrent cerebral waking. Future validation of the relationship between polysomnography and actigraphy measures of sleeping and waking in VS and MCS patients is needed in order to fully characterize the nature of their circadian rhythms**”.

Another concern this reviewer has regarding the article is the authors lack of mention regarding anything about prescribed medications having a potential effect on motor behavior during sleep whether during REM or non-REM periods. This point should be further addressed in the article.

We thank the Reviewer for raising this important point. Indeed, medications will have an effect on all measures of circadian rhythms, including actigraphy and polysomnography. Since there are few guidelines regarding pharmacological interventions, VS and MCS patients receive a wide variety of medications with unknown effects on circadian rhythms. This makes successfully controlling for their effects and interactions essentially intractable in almost all studies involving these patient groups. In order to provide more information, however, we now include in the revised manuscript a new table containing the daily medications administered to each individual patient. We also include a paragraph in the Discussion in which we describe this problem, and argue for future controlled trials in VS and MCS research:

“**Some prescribed medications may also have an effect on actigraphy-detected circadian rhythms.** For example, treatment for spasticity (e.g. with Baclofen) is common in VS/MCS patients and may increase the amount of movement that will be detected with actigraphy, while psychoactive medications (e.g.
Amantadine may also serve to exogenously modulate a patient’s level of arousal. Caution in this regard is not limited to actigraphy, however, since psychoactive medications will also alter the resting EEG of a patient, thereby modulating the level of wakefulness that will be inferred from polysomnography. Due to differences in the wishes of families and physicians, a wide variety of medications are prescribed to VS and MCS patients (see Table 2 for details). As a result, it is not possible to statistically control for each of these drugs individually, nor for their many interactions. Nevertheless, there is no reason to believe that prescribed medications would systematically differ between VS and MCS groups due to the paucity of treatment recommendations for all patients with disorders of consciousness. Future controlled clinical trials are needed in order to provide insights into the effects of specific medications not only on circadian rhythmicity, but also on VS/MCS patient outcome in general.”

In general, based on my review of the article relevant standards of reporting and data deposition were met and the discussion and conclusions are well balanced and adequately supported by the data. Where the authors become theoretical in terms of speculative commentary, there should be a greater acknowledgement of same. For example, their theory that more purposeful eye movements to those scoring more highly on the visual subscale might allow for differing levels of light to reach the retina, perhaps, through a greater ability to orient toward light should be clarified.

- We agree that our commentary in this regard is only speculative, but highlights a biologically interesting result. At the suggestion of the Reviewer, in order to clarify the nature of our argument, the following has been included in the Discussion section (page 2 of section, 2nd paragraph):

- “The more purposeful eye-movements of those scoring highly on the visual subscale may allow for differing levels of light to reach the retina – perhaps through a greater ability to orient toward light or to maintain eye-opening for longer periods – and consequently result in a strengthening of the rhythm via the SCN. The predictive value of the visual subscale could therefore be considered to be consistent with our understanding of the biological generators of sleep-wake rhythmicity. This conclusion is necessarily speculative, however, since it is unclear whether high visual functioning is associated with a greater degree of orientation toward light or longer periods of eye-opening. Further investigation of this relationship will contribute to our understanding of the exogenous queues that drive circadian rhythms in VS/MCS patients.”

The authors also bring up the point in the later section of their discussion regarding the potential for some contamination of actigraphy recordings through exogenous activity, yet do not provide the reader with sufficient information to
know whether all patients were treated the same with regards to the risk for such activity (i.e. if certain patients had skin pressure wounds then it would seem likely that they would be turned more frequently than persons without pressure wounds, as one example of the potential for such variability). The authors should address this point further.

- We now include more detail in the Methods: Patients section in which we emphasise that all patients were subject to the same levels of exogenous activity:

  - “During their admission, all patients were manually turned in their beds 4-times per day. No patient had skin pressure sores that required more frequent manual turning. No patient required mechanical ventilation. All patients were admitted as part of the same research protocol, and completed the same tasks across each day e.g. behavioural tests, positron emission tomography (PET), and magnetic resonance imaging (MRI).”

Overall, I think the conclusions follow from the data provided and that the statistical interpretations are apropos. As far as the circadian sleep rhythm differences between DS and MCS of non-TBI and TBI patients. With that being said, I am not sure that the data strongly supports the use of actigraphy for sleep assessment per se, although I do not disagree that it is both less expensive and less invasive than other forms of sleep/wake monitoring. By the authors own data, there appeared to be consternations about the sensitivity of this technique for assessing sleep/wake cycles and circadian rhythm. The authors may want to clarify this latter point further in their conclusion.

- We agree that the relationship between actigraphy and sleep/wake monitoring with polysomnography is currently not entirely understood for VS and MCS patients. Alongside the new paragraph included at the end of the Discussion section (see response above), we now include the following to the Conclusion section at the suggestion of the Reviewer:

  - “Future validation of the relationship between actigraphy and polysomnography measures of sleeping and waking in VS and MCS patients will allow for a more complete understanding of the physiological nature of their circadian rhythms.”

I do believe that the data suggests by extension at least, that the potential for actigraphy to serve as a way of assessing overtime when a particular patient is “most active” and this may have implications on when to schedule other types of assessments whether neurobehavioral or neurodiagnostic. Clearly, there is also potential, as noted, for actigraphy data to potentially be used for prognostic purposes; however, at this point in time there is no data to truly support such a
contention. Overall, I feel that the authors have some issues to address in the context of a revision. In particular, the issues noted regarding medications, nursing care and the sensitivity of the technique in persons with very little movement (as seen in persons in DOC). This is a very important article looking at a new application of existing technology in this patient population that I believe warrants publication in BMC medicine.

- Again, we thank the Reviewer for their positive and constructive comments, and look forward to hearing their views on the revised manuscript.
Reviewer's report
Title: Actigraphy Assessments of Circadian Sleep-Wake Cycles in the Vegetative and Minimally Conscious States
Version: 1 Date: 28 September 2012
Reviewer: Niels Birbaumer

Reviewer's report:
The authors should describe in the introduction with reference to controlled quantitative studies, the correlation with actigraphy and EEG-defined sleep-wake cycles or any other physiological correlates of sleep-wake cycle i.e. EOG (see Hobson).

- We now describe the relationship between actigraphy and polysomnography as employed in healthy participants in the Introduction. Briefly, actigraphy is used in two primary ways in order to detect sleep-wake cycles. The first is an algorithmic method that predicts sleep/wake on a minute-by-minute basis, but has not been validated with concurrent polysomnography in VS/MCS patients. The second is a more conventional cosinor method that detects circadian rhythmicity across far longer time-scales (several days). We argue that this approach makes fewer assumptions, and so is more appropriate in the current circumstances:

- “A number of algorithms have been developed in order to produce minute-to-minute estimations of sleeping/waking from short-term variations in actigraphy data in healthy individuals. Broadly, these algorithms judge an individual to be awake or asleep at a given sample point by weighting the amount of movement in a number of preceding sample points by a set of predefined constants. Such approaches have reported between 88-97% concordance with polysomnography in healthy individuals (see de Souza for a full review). However, none of these approaches have been validated with VS or MCS patients by means of concurrent polysomnography and actigraphy recordings. Nevertheless, a circadian sleep-wake rhythm – i.e. more activity during waking hours and less activity during sleeping hours – can be readily identified from raw actigraphy recordings, and makes fewer assumptions than these unvalidated algorithms.”

A single-measure-approach such as the one adopted here demonstrates variability as all the other measures (i.e. EEG, eye-movements, EMG). The statement of variability in VS and MCS does not assist the diagnostic procedure. In the contrary, it assists those who claim that VS and MCS are diagnostically uniform unities. These authors know that's not the case, therefore they should emphasize the unreliability of these syndrome-definitions.

- We agree with the Reviewer's comment that VS and MCS are not diagnostically uniform entities, and would argue that our finding of significant differences between VS and MCS patients emphasizes this well.
We now include the following in our Conclusions in order to highlight the importance of this observation:

- “Our analyses indicate a greater impairment of circadian sleep-wake cycling in patients in the VS compared with those in the MCS, and in those with non-TBI compared with TBI. The significant differences observed between VS and MCS patients support the conclusion that these are diagnostically distinct entities. However they also suggest that despite periods of eye-closure and eye-opening, sleep-wake cycles are not necessarily present despite the clinical criteria for these conditions.”

The ms should describe how actography correlates with sleep-waking cycle in general: is it just more activity during waking?

- As the Reviewer says, put simply, the correlation with circadian sleep/wake cycling is indeed ‘more activity during waking’, and is sufficient to identify a rhythm with a circadian period. A body of research has endeavoured to develop algorithms that can estimate sleeping/waking on a minute-to-minute basis (e.g. Cole et al., Sadeh et al.). However, these have not been validated in VS or MCS patients. Nevertheless, more slowly varying activity rhythms – i.e. those with a circadian period – can be readily identified with conventional rhythmometry analyses under the assumption that there is ‘more activity during waking’ (e.g. Brown et al., Girardin et al.). This is now clarified in our addition to the Introduction (penultimate paragraph) described above.

How can they exclude that patients were moved passively during the day and left alone at night? (i.e. wheelchair, more social activity, visits etc. during day).

- As we note in the Discussion of our manuscript, it is impossible to exclude the contribution of exogenous activity to the patients’ data. However, we argue that since all patients were admitted for the same research protocol, and had the same daily schedule, the potential exogenous noise is uniformly distributed across all patients. We conclude that simultaneous video-recordings are one way in which future studies may rule out the contributions of exogenous activity. We now also include greater detail in the Methods: Patients section regarding the exogenous activity in patients:

- “During their admission, all patients were manually turned in their beds 4-times per day. No patient had skin pressure sores that required more frequent manual turning. No patient required mechanical ventilation. All patients were admitted as part of the same research protocol, and completed the same tasks...”
across each day e.g. behavioural tests, positron emission tomography (PET), and magnetic resonance imaging (MRI)."

How are amplitude, acrophase, and mesor in actography defined? No methodological details are described.

- The definitions of these three parameters are now clarified in Methods: Circadian Rhythm Analyses:

  - "The amplitude of the fit refers to half the distance between the peak and the trough of the fitted wave – in effect describing the amount of movement produced during periods of activity. The acrophase describes the point in the cycle at which activity is maximal. Finally the mesor (an acronym for midline-estimating statistic of rhythm[26]) describes the rhythm-adjusted mean of the wave, or the value around which the fitted wave oscillates. For equidistant data samples (as employed here), the mesor is equivalent to the arithmetic mean of the fitted wave, or the average amount of activity produced across the recording period."

It seems trivial to state that more activity is related to increased wakefulness, but in VS and MCS that simple relationship may not apply: patients may be cerebrally asleep but peripherally more active, a phenomenon seen in epilepsy and other disorders of sleep-wake cycles (i.e. disorders of respiration and pulmonary functions, apnoe for example). The reviewer assumes that many or some of the patients were artificially respirated or had disorders of respiration which would produce artificially more short awakenings during the day because of respiratory problems but cerebral sleep! (A table with exhaustive clinical information of all patients is mandatory). Only EEG (not fMRI) may shed light on cerebral activity in the S-W-cycle.

- To address the Reviewer's first point, no patients were included who required mechanical ventilation (this is now noted in Methods: Patients).

- Second, we agree with the Reviewer that since we can only speculate about the relationship between actigraphy and polysomnography in VS/MCS patients, it is not possible to determine whether cerebral sleep accompanies the peripheral signs of sleep we observe in the actigraphy. We now emphasise the importance of future concurrent use of EEG (polysomnography) and actigraphy in order to determine their relationship in this difficult patient group (Discussion):

  - "Similarly, due to the heterogeneity of brain injuries of these patients, it is not clear whether the presence of actigraphy-detected waking is necessarily indicative of concurrent cerebral waking. Future validation of the relationship between polysomnography and actigraphy measures of sleeping and waking in
VS and MCS patients is needed in order to fully characterize the nature of their circadian rhythms.”

- Finally, we have included a new table (Table 2) that details the specific cause of each patient’s diagnosis, along with their prescribed medications during their admission in order to provide a greater level of clinical information.

- We thank the Reviewer for their time and constructive comments, and look forward to hearing their views on our revised manuscript.