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Sedation levels in dogs: a validation study

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Author contributions

Study design: MW, KGH, DSJP. Data collection: MW, DSJP. Data analysis: MW, KGH, DSJP. Manuscript preparation: MW, KGH, DSJP.

Conflicts of interest

The authors have no conflicts of interest.

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Abstract

The aim of this study was to assess validation evidence for a sedation scale for dogs. We hypothesized that the chosen sedation scale would be unreliable when used by different raters and show poor discrimination between sedation protocols.

A sedation scale was used to score 62 dogs scheduled to receive sedation at two veterinary clinics in a prospective trial. Scores recorded by a single observer were used to assess internal consistency and construct validity of the scores. To assess inter-rater reliability, video-recordings of sedation assessment were randomized and blinded for viewing by 5 raters untrained in the scale. Videos were also edited to allow assessment of inter-rater reliability of an abbreviated scale by 5 different raters.

Both sedation scales exhibited excellent internal consistency and very good inter-rater reliability (full scale, $ICC_{single} = 0.95$; abbreviated scale, $ICC_{single} = 0.94$). The full scale discriminated between the most common protocols: dexmedetomidine-hydromorphone (11 [1-18], n = 20) and acepromazine-hydromorphone (5 [0-15], n = 36, p = 0.02).

The hypothesis was rejected. Full and abbreviated scales showed excellent internal consistency and very good reliability between multiple untrained raters. The full scale differentiated between levels of sedation.

Key words: validity, reliability, canine, dexmedetomidine, anesthesia

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Introduction

Sedation describes a state where an animal's response to external stimuli is reduced and sedating animals is a common procedure, used to improve safety during handling and to facilitate minor procedures without general anesthesia. Before general anesthesia, sedation is an important component of pre-anesthetic medication, providing anxiolysis, contributing to balanced anesthesia, providing pre-emptive analgesia (if a sedative has analgesic properties) and producing a smooth recovery {Murrell, 2016, #67895}. During trials for drug licensing and toxicology, the presence of sedation is monitored and recorded.

However, measurement scales for quantifying sedation in dogs have not been formally assessed for validity and reliability of the scores. Existing scales vary considerably in the number and content of scale items and scales are frequently altered between studies, impeding the direct comparison of sedation data between studies {Young et al., 1990, #467; Grint et al., 2009, #3397; Hamlin and Bednarski, 1989, #51091; Kuusela et al., 2000, #92129; Kuusela et al., 2001, #63942; Kuusela et al., 2001, #68920; Vainio et al., 1989, #62644}.

Assessing validation and reliability provides information on whether a scale measures what it claims to measure (validity) and the degree of measurement error (reliability). In the context of measuring sedation, establishing evidence for the validity and reliability of the scores are essential to ensure appropriate scale sensitivity when evaluating levels of sedation and acceptable agreement between raters. Furthermore, using an appropriately developed scale facilitates comparing results between studies, thereby supporting reproducibility.

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The scale selected for evaluation was published by Grint et al. (2009) in a study describing the sedative properties of the alpha$_2$-adrenergic receptor agonist dexmedetomidine alone or in combination with the opioid meperidine to produce sedation in dogs. In reviewing the literature to trace the origin of the sedation scale evaluated in the study, it became apparent that the scale had evolved through numerous versions over approximately 27 years, with early versions having 4-5 items in common with the 7 items of the current scale, with varying ranges of scores for each item {Clarke and England GCW, 1989, #90506; England and Clarke, 1989, #23123; Grint et al., 2009, #3397; Hamlin and Bednarski, 1989, #51091; Kuusela et al., 2000, #92129; Kuusela et al., 2001, #63942; Kuusela et al., 2001, #68920; Vainio et al., 1989, #62644; Young et al., 1990, #467}. This evolution reflects iterative changes made by different authors but limits quantitative comparisons between studies: this acted as a stimulus to perform the study presented here.

The primary goal of this study was to gather evidence regarding the validity and reliability of the scores from the selected sedation scale by applying psychometric methods and, if the evidence was acceptable, to begin development of a simplified version of the scale. A secondary goal was to evaluate the psychometric performance of the full scale with a recently published scoring system for evaluating the quality of health measurement scale development {Barr et al., 2013, #48571}.

We hypothesized that the scale would perform poorly, with a limited ability to detect differences between levels of sedation and show poor inter-rater reliability when used by multiple raters.

Materials and methods

Animals

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This project received ethics approval from the University of Calgary Veterinary Sciences Animal Care Committee (AC13-0103), which operates in accordance with Canadian Council on Animal Care guidelines. Dogs scheduled to be sedated for a diagnostic procedure or before general anesthesia were enrolled over a 12 week period through two clinics following informed client consent. The choice of sedation protocol was at the discretion of the supervising veterinarian. Dogs were excluded if aggressive, had been given drugs with potential sedative effects earlier on the same day, were known to be deaf, or had an American Society of Anesthesiologists physical classification status > 2. Dogs were housed individually in kennels in the clinic.

Experimental procedure

A published scale was used to assess sedation at baseline (before drug injection) and 15 minutes after drug injection {Grint et al., 2009, #3397}. The scale included seven items: spontaneous posture, palpebral reflex, eye position, jaw & tongue relaxation, response to noise, resistance when laid into lateral recumbency, and general appearance/attitude (Appendix 1). Each item was assigned a score and scores summed to give a sedation score (range 0 to 21), with higher scores indicating a greater level of sedation. Response to noise was assessed with a clicker (i-Click Clicker, i-Click, Waltham, MA, USA) actuated approximately 150 cm from the head. For assessment of sedation each dog was taken to a quiet, empty room by the rater (MW). Assessments were also video-recorded (Hero 3+ GoPro camera, San Mateo, CA, USA).

All drugs used to provide sedation were combined into a single syringe and administered either intravenously (via cannula) or intramuscularly (lumbar epaxial muscles). Route of injection was at the discretion of the supervising veterinarian. Following injection, dogs were returned to their

kennel and left undisturbed. Twelve minutes after drug injection dogs were walked or carried to the assessment room with a long (200 cm) leash attached and two minutes allowed for adjustment to surroundings so that assessments were performed 15 minutes after injection. The scale items were assessed in the same order each time: observation for spontaneous posture (at a distance of 150 cm), response to noise, eye position, palpebral reflex, jaw tone (and if reduced, a tongue depressor was placed at the base of the tongue to assess tongue relaxation and the swallow reflex), resistance when laid in lateral recumbency, and a final observation of general appearance/attitude. After completing the post-injection assessment, each dog continued along its intended care pathway (diagnostic procedure or general anesthesia).

Following data collection, a subset of 15 videos was selected to represent different levels of sedation (little/no sedation; score 0-2, moderate sedation; score 4-11, heavy sedation; score 13+, n = 5 videos per group). These were used to assess inter-rater reliability. Five registered animal health technologists voluntarily and independently watched each video and provided a sedation score using the published scale {Grint et al., 2009, #3397}. No instruction was given in use of the scale (none had previous experience of the scale) and raters were blinded to treatment and time point.

Finally, the sedation scale was simplified by removing items felt to be more invasive or stressful to the dogs, or potentially increasing risk to personnel. These were items 2, 4 and 6: palpebral reflex, jaw and tongue relaxation, and resistance when laid into lateral recumbency. Assessment of these items was edited out of each of the 15 videos. Edited videos were scored by five different technicians or interns using the simplified version of the scale (abbreviated scale range

0 – 12). The new raters were also blinded to treatment and time point, and had no previous experience with the scale.

Statistical methods

Internal consistency, the degree to which scale items are inter-related, was determined by calculating Cronbach's alpha of the scores assigned by the primary rater (MW). This was done for the full scale (7 items) and simplified scale (4 items) using post-injection scores. Internal consistency was considered excellent if Cronbach's alpha was greater than 0.75 {Ponterotto and Ruckdeschel, 2007, #81241}.

Inter-rater reliability, agreement between raters, was determined by calculating the intraclass correlation coefficient (ICC). The ICC was calculated for the full and simplified scale and classified as: very good (ICC 0.81-1.0), good (ICC 0.61-0.80), moderate (ICC 0.41-0.60), fair (ICC 0.21-0.40), poor (ICC < 0.20) {Altman, 1991, #14899; Landis and Koch, 1977, #17898}.

The efficacy of sedation protocols was assessed by comparing baseline with post-injection sedation scores with a Wilcoxon matched-pairs signed rank test. Sedation scores were compared between the two most common protocols with a Mann-Whitney test. Values of $p < 0.05$ were considered significant. Analyses were performed with commercial software (IBM SPSS Statistics for Windows version 22.0, IBM Corp., Armonk, NY, USA and Prism v7.0, GraphPad Software, La Jolla, CA, USA). An overall assessment of the psychometric performance of the sedation scale was performed according to a recently developed scoring criteria for human sedation scales (Appendix 2) {Barr et al., 2013, #2809; Barr et al., 2013, #48571}. According to these criteria, scores are assigned to reflect assessment and reporting of validity, reliability and

feasibility. A total score of ≥ 12/20 is considered to reflect acceptable psychometric properties. The relationship between scores assigned by the primary observer (MW) and untrained observers was explored by calculating a Spearman correlation coefficient, with the median value of the 5 untrained observers used for calculation.

Results

Seventy-five dogs were enrolled in the study. Thirteen dogs were excluded for: poor video quality or technical complications with recording equipment (n = 3), aggression (n = 2), failure to adhere to time points (n = 7) and additional sedation given during assessment period (n = 1). Sixty-two dogs were included in the analysis (Table 1).

Table 1 here

Cronbach's alpha for the full sedation scale was excellent (alpha = 0.89). Inter-rater reliability was very good (ICC_{single} = 0.95; $ICC_{average}$ = 0.99).

Sedation level increased in the majority of dogs following injection ($p < 0.0001$, 97% CI [4 to 8] Fig. 1). Baseline scores ranged from 0 to 5 (median = 1). Post-injection scores varied greatly between individuals, ranging from 0 to 18 (median = 6).

Seven dogs (11.3%) did not show an increase in sedation score. These dogs received sedation via an intramuscular injection. Three of the dogs received acepromazine (0.03 mg/kg)-hydromorphone (0.05 mg/kg), two received dexmedetomidine (4.2-4.8 mcg/kg)-hydromorphone (0.05 mg/kg), one each received meperidine (2.9 mg/kg)-acepromazine (0.02 mg/kg) and morphine (0.5 mg/kg)-acepromazine (0.03 mg/kg).

Figure 1 here

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The two most commonly used sedation protocols were dexmedetomidine (2.5-9.9 mcg/kg)-hydromorphone (0.04-0.1 mg/kg, n = 20), and acepromazine (0.01-0.05 mg/kg)-hydromorphone (0.05-0.1 mg/kg, n = 36). In general, both drug combinations were effective at increasing levels of sedation (Fig. 2). Acepromazine-hydromorphone, baseline versus post-injection: $p < 0.0001$, 97% CI (3 to 6). Dexmedetomidine-hydromorphone, baseline versus post-injection: $p < 0.0001$, 96% CI (6 to 13). Baseline sedation levels were slightly higher in dogs given dexmedetomidine-hydromorphone than those receiving acepromazine-hydromorphone ($p = 0.02$, 95% CI [0 to 1]). At post-injection, dogs receiving dexmedetomidine-hydromorphone were significantly more sedated than dogs given acepromazine-hydromorphone ($p = 0.001$, 95% CI [2 to 9]).

Figure 2 here

Post-injection, seven of the sedated dogs (11.3%) had no jaw tone and did not swallow or show tongue movement when stimulated with a tongue depressor placed at the base of the tongue. Five of these dogs were given dexmedetomidine (3.9-9.9 mcg/kg)-hydromorphone (0.05-0.1 mg/kg), and two were given dexmedetomidine (9.6-14.4 mcg/kg)-hydromorphone (0.05-0.1 mg/kg)-ketamine (2.9-3.0 mg/kg). The sedation scores of the dogs without a swallow reflex were 17-18 out of 21 (dexmedetomidine-hydromorphone) and 18 out of 21 (dexmedetomidine-hydromorphone-ketamine). Dogs that received acepromazine-hydromorphone swallowed or showed tongue movement in response to stimulation.

No dogs showed an absence of palpebral reflex at fifteen minutes post-sedation. Of the dogs that lost jaw tone/gag-reflex, four had a slow palpebral reflex but with a full corneal sweep, and three maintained a brisk palpebral reflex.

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The psychometric properties of the sedation scale were considered acceptable, with a total weighted score of 14.8/20, when graded against a recently established set of criteria for assessing psychometric properties of health measurement scales (Appendix 2).(ref crit care x 2) The distribution of scores by item was as follows: Scale development; 0.8/2, Reliability; 6/6, Validity; 6/8, Feasibility; 2/2.

Abbreviated scale

The abbreviated scale (removal of 3 items: palpebral reflex, jaw and tongue relaxation, and resistance when laid into lateral recumbency) maintained excellent internal consistency (Cronbach's alpha = 0.84). Additionally, applying the abbreviated scale to edited video-recordings maintained very good inter-rater reliability (ICC_{single} = 0.94; $ICC_{average}$ = 0.99; Fig. 3). The time to complete assessment was approximately 3 times shorter for the abbreviated scale (40 [29-70] seconds) than the full scale (128 [63-206] seconds).

Figure 3 here

Table 2 here

Both full and abbreviated scale scores showed a high degree of correlation between the primary (MW) and untrained observers (Supplementary Fig. S1). The r value for the full sedation scale was 0.977 (95% CI 0.93 to 0.99, $p < 0.0001$) and for the abbreviated scale it was 0.990 (95% CI 0.97 to 1.0, $p < 0.0001$).

Discussion

These data show that: 1. the sedation scale studied shows excellent internal consistency and is able to discriminate between different levels of sedation, 2. both the full and abbreviated scale

versions show very good inter-rater reliability when applied by untrained raters, 3. high levels of sedation may be associated with loss of the swallow reflex, potentially increasing the risk of aspiration.

Internal consistency was excellent for both the full and abbreviated versions of the sedation scale. Internal consistency reflects the closeness of the relationship between scale items, the extent to which they measure the same general outcome (e.g. sedation) {Streiner and Norman, 2008, #28776}. Together with an ability to discriminate between levels of sedation, this shows that the studied scale measures, and appears to be sensitive to, changes in sedation.

Combining an alpha2 adrenergic receptor agonist with an opioid increases the depth and quality of sedation compared with an alpha2 adrenergic receptor agonist alone {England and Clarke, 1989, #23123; Grint et al., 2009, #3397}. These data reflect the findings of Grint et al. (2009), where the same sedation scale was used to assess the effect of medetomidine and pethidine and the resultant scores (approximately 15/21) were very similar to those reported here.

Using a 15 minute observation period successfully exploited pharmacodynamic differences between dexmedetomidine and acepromazine, allowing discrimination between the sedative effects of each drug. Peak sedation occurs between 10-20 minutes after administering (IM or IV) dexmedetomidine {Kuusela et al., 2000, #92129; Kuusela et al., 2001, #63942; Vainio et al., 1989, #62644}, but approximately 30 minutes after administering acepromazine (IM) {Bell et al., 2011, #16113; Herbert et al., 2013, #43585}{Grint et al., 2010, #56828}.

Scores from this study provide validation evidence for the use of the sedation scale and sedation protocols within our clinical context. That is, there is evidence to support that the scores measure

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what they are designed to measure, and scores from raters are able to detect changes in sedation between different sedation protocols and when compared with baseline.

Assessing and reporting inter-rater reliability is crucial when multiple raters are involved in data collection {Buisman et al., 2016, #49155; Hasiuk et al., 2015, #54738; Oliver et al., 2014, #48120; Streiner and Norman, 2008, #28776}. Doing so confirms agreement between raters, providing confidence that assigned scores are comparable. Several studies have shown rater reliability to vary considerably with experience (specialists versus trainees, changes over time) and between raters with similar training {Brondani et al., 2013, #62085; Hansson et al., 2009, #40724}. This inter-rater variability may negatively affect study outcomes and clinical case management by introducing data variability and reducing power, and influence the accuracy of diagnoses {Klinck et al., 2015, #44860; Wisner et al., 1993, #71472}{Hammarberg et al., 2016, #60259}.

The inter-rater reliability of the studied scale (full and abbreviated versions) was very good even though raters were untrained and unfamiliar with the scale prior to participating in the study. The observed consistency between raters suggests that scale-specific training may not be required, and that sedation scores may be comparable across studies. This shows promise for its application in research and clinical environments.

Seven dogs had no jaw tone, tongue movement or swallowing at the post-injection assessment. Those dogs received either dexmedetomidine-hydromorphone or dexmedetomidine-hydromorphone-ketamine. This was an unexpected and concerning finding as it indicates a potential loss of the cough reflex and consequent inability to protect the airway. Though the

cough reflex was not assessed directly by attempting orotracheal intubation, the ability to perform orotrachal intubation has been reported in dogs receiving an alpha2 adrenergic agonist alone or in combination with an opioid {England and Clarke, 1989, #23123; Young et al., 1990, #467}. Twenty percent of dogs (5/20) receiving IM medetomidine (40 mcg/kg) could be intubated approximately 20 minutes after injection {Young et al., 1990, #467} and the addition of fentanyl (2 mcg/kg IV) 16-18 minutes after IM medetomidine (20 or 40 mcg/kg) allowed all dogs (n = 6) to be intubated {England and Clarke, 1989, #23123}. Furthermore, dogs without tongue movement and swallowing maintained a palpebral reflex, indicating that presence of a palpebral reflex may be a poor predictor of a maintained cough reflex.

Combining dexmedetomidine with a potent mu receptor agonist, such as hydromorphone, is a common protocol for sedation and premedication in dogs. In light of these and previous findings, the potential loss of protective airway reflexes should be considered when high levels of sedation are observed. The potent sedation created by medetomidine and dexmedetomidine exhibit a dose dependent duration {Kuusela et al., 2000, #92129}. Sedation lasting up to 240 minutes has been reported {Hamlin and Bednarski, 1989, #51091; Kuo and Keegan, 2004, #86834; Kuusela et al., 2000, #92129; Kuusela et al., 2001, #63942; Vainio et al., 1987, #87770}. This makes a strong argument for pharmacological antagonism of medetomidine or dexmedetomidine with atipamezole once the procedure is completed.

A recent study in cats suggests that when multimodal analgesia is employed, antagonism of dexmedetomidine does not compromise analgesia {Hasiuk et al., 2015, #54738}. Furthermore, a rapid return to normal function supports the concept of “enhanced recovery after surgery”

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whereby post-procedural morbidity and mortality is reduced through optimizing multiple aspects of patient care, including a rapid, smooth, pain-free recovery {Hasiuk et al., 2015, #54738; Kehlet, 1997, #15081}.

Interestingly, dogs that received the dexmedetomidine-hydromorphone combination had lower baseline sedation scores than those given acepromazine-hydromorphone, indicating that factors other than baseline behavior contribute to choice of a sedation protocol. These might include performing additional diagnostic procedures before induction of anesthesia, such as radiography.

The abbreviated scale was developed to shorten the assessment time, thereby improving feasibility and minimizing risk to personnel performing the assessment. Our preliminary assessment of the abbreviated scale shows it performs well, but further work is required to assess its ability to discriminate between levels of sedation.

The sedation scale performed well when evaluated against predetermined criteria established for evaluating the psychometric properties of health measurement scales in humans {Barr et al., 2013, #2809; Barr et al., 2013, #48571}. To our knowledge, this is the first report of a formal evaluation of a health measurement scale using this scoring system in veterinary medicine. While acceptable, the performance of the scale against the scoring system indicates that further work is required. Practical implementation (feasibility) of the scale in a clinical setting, with diverse raters, remains to be fully determined. Convergent validation, comparison of the scale against an alternative measure of sedation, is possible though potentially challenging, as typical measures might include a form of electroencephalography. Finally, while scale items have clearly been

adjusted through numerous iterations by experimenters with considerable experience, there is an absence of explicit description of how the scale items came to be selected.

This study was designed to assess the validity and reliability of a sedation scale, rather than compare different sedation protocols. Hence, routes of administration were not controlled and the time between injection and beginning the scheduled procedure was determined by the participating clinics. The latter restricted the post-injection assessment to 15 minutes. In combination with different routes of injection, it is likely that peak sedation was not achieved in many dogs that received acepromazine.

It was not possible for the primary observer (MW) to be blinded to treatment or time point. However the significant correlation with scores from the untrained observers for both the full and abbreviated scale indicates that scoring was unbiased.

The ability of an assessment scale to perform in varied settings reflects generalizability, a feature that can only be assessed by reporting psychometric properties (validity and reliability) in these situations {Buisman et al., 2016, #49155; Oliver et al., 2014, #48120}. Therefore the population studied (age, breed, sex, mass) and setting (sedation protocols, raters, physical environment) should not be taken as a guarantee of scale performance in all settings {Barr et al., 2013, #2809; Buisman et al., 2016, #49155; Oliver et al., 2014, #48120; Streiner and Norman, 2008, #28776}. However, the diversity of breeds, sedation protocols and use of untrained raters indicates that the scale is likely to perform well in a range of settings and that data collected with the same scale could be compared across studies.

Conclusion

311 Scores from the sedation scale provided evidence for excellent internal consistency and very
312 good inter-rater reliability and these characteristics were maintained with the abbreviated scale. It
313 was robust to the heterogenous population and study parameters indicating that it has good
314 generalizability to a range of settings, potentially allowing a direct comparison of data between
315 studies.
316
317 **Figure legends**
318 Figure 1: sedation scores recorded before (baseline) and 15 minutes after injection of sedative
319 drugs (post-injection). Box and whisker plots show median (central horizontal line), inter-
320 quartile range (box boundaries) and Tukey whiskers.
321 Figure 2: sedation scores recorded before (baseline) and 15 minutes after injection (post-
322 injection) of the two most common sedation protocols. Acepromazine-hydromorphone, n = 36.
323 Dexmedetomidine-hydromorphone, n = 20. Box and whisker plots show median (central
324 horizontal line), inter-quartile range (box boundaries) and Tukey whiskers. Identical letters
325 indicate statistically significant differences. See text for presentation of p values and 95% CI.
326 Figure 3: Sedation scale scores for the full (A) and abbreviated (B) scale, showing scores from 5
327 representative videos (15 videos scored in total). Same 5 videos shown in A and B. Inter-rater
328 reliability was very good for both the full scale (A; $ICC_{single} = 0.95$) and abbreviated scale (B;
329 $ICC_{single} = 0.94$).

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Table 1. Demographic data for dogs from the two most common sedation protocols. Data are median (range).

Sedation protocol	Acepromazine - hydromorphone	Dexmedetomidine - hydromorphone
Number of dogs	36	20
Age (years)	3 (0.25 - 11)	3 (0.58 - 10)
Sex	18 females, 11 males, 6 spayed females, 1 neutered male	7 females, 6 spayed females, 4 neutered males, 3 males
Mass (kg)	15.7 (2.4 - 40.2)	19.3 (1.57 - 47.0)
Breed	12 Mixed breed, 9 Pitbull types, 2 Miniature Pinschers, 2 Shih Tzus and 11 other pedigree breeds	13 Mixed breed, 2 Labrador Retrievers, 2 Chihuahuas, 3 other pedigree breeds

Table 2: demographic data for dogs included in the 15 videos scored by the animal health technicians and interns. Data are median (range).

Number of dogs	14
Age (years)	4 (0.17-10)
Sex	5 males, 4 females, 3 female spayed, 2 male neutered
Mass (kg)	7.8 (2.4 - 28.8)
Breed	3 Mixed breed, 3 Pitbull types, 2 Pomeranian, Pug, Chihuahua, Pyrenees mountain dog, English Bulldog, Bichon Frise, Cocker Spaniel
Sedation	Baseline (n = 4), acepromazine-hydromorphone (n = 7), dexmedetomidine-hydromorphone-ketamine (n = 2), acepromazine (n = 1), dexmedetomdine-butorphanol (n = 1)

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Figure 1

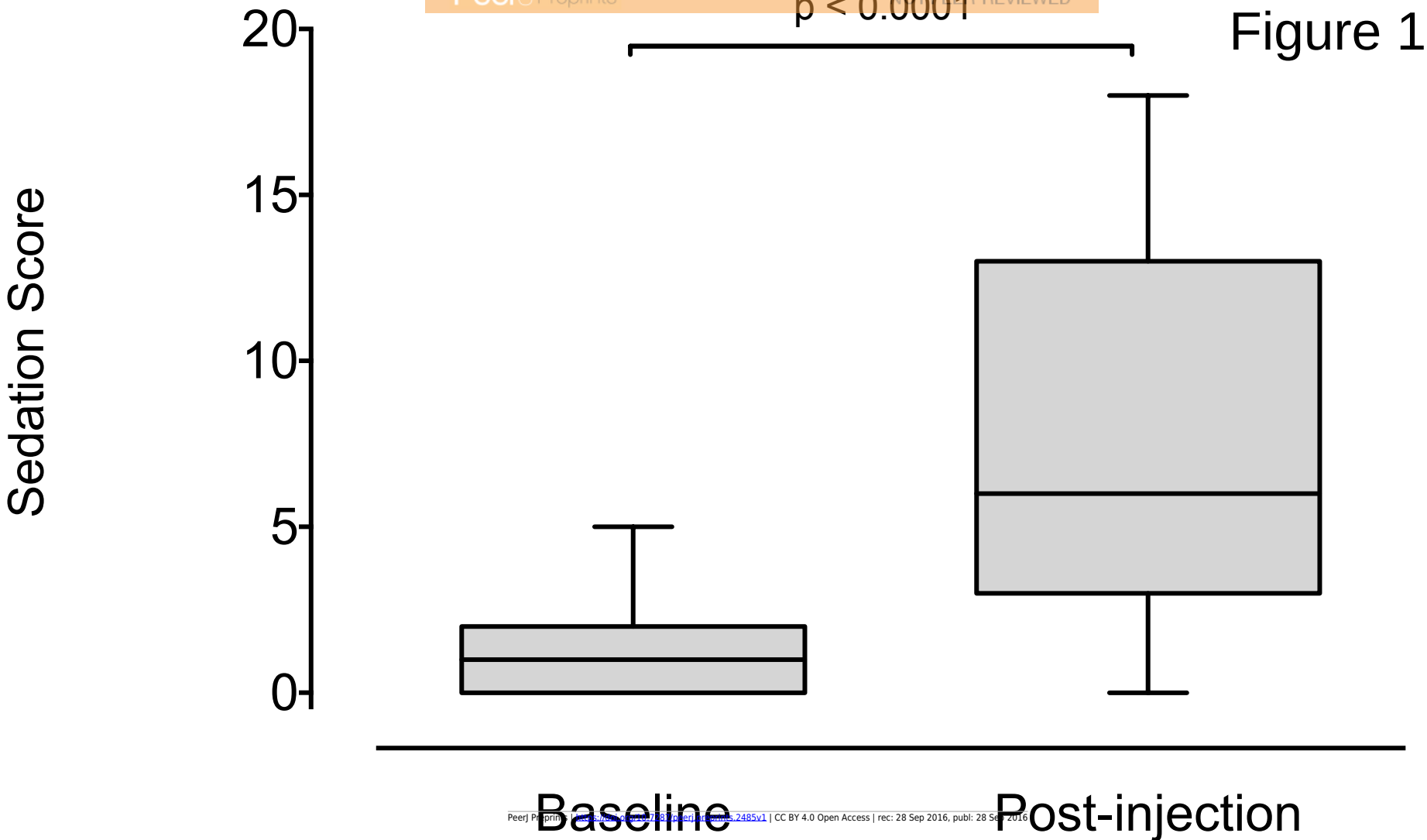

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Figure 2

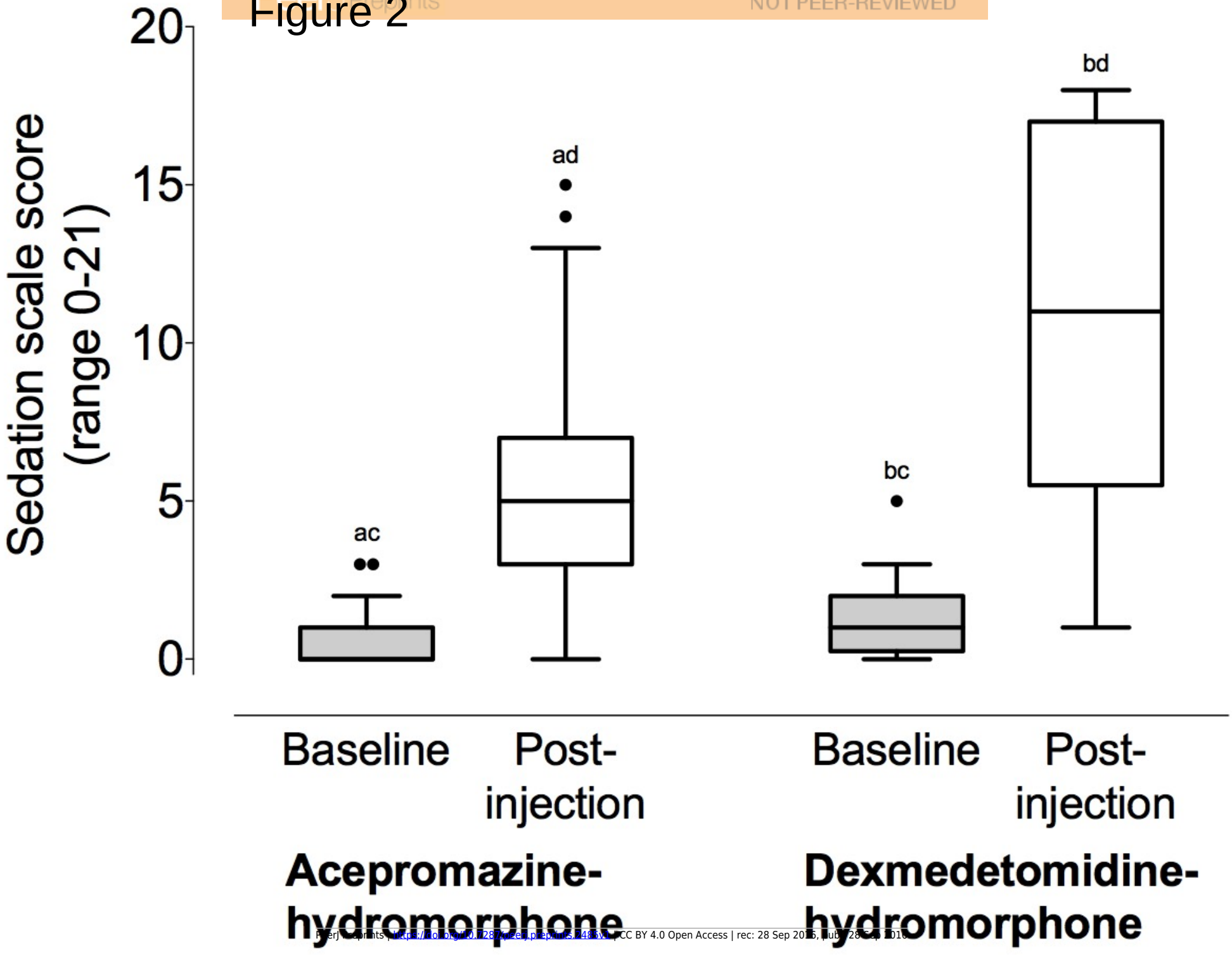

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Figure 3

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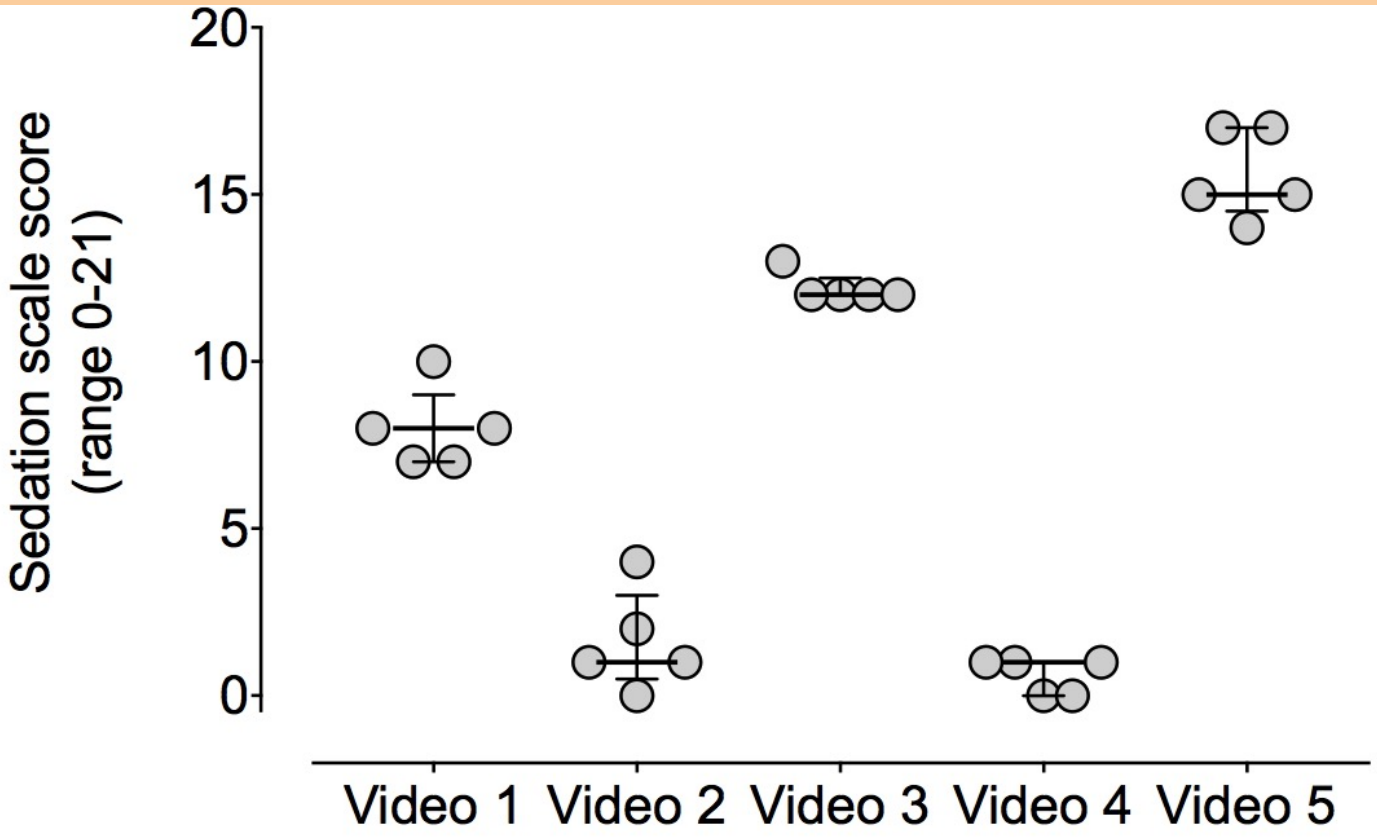

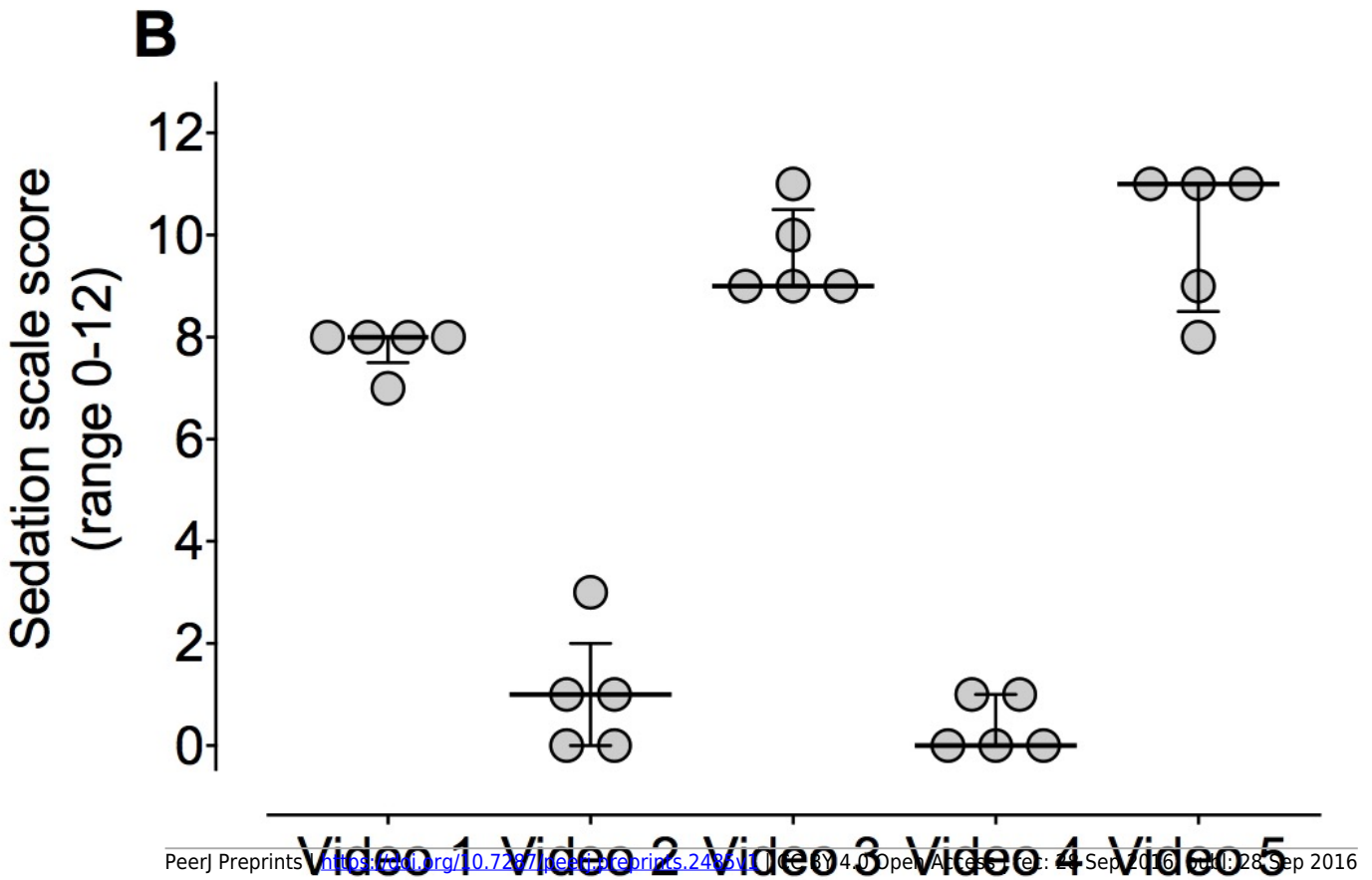

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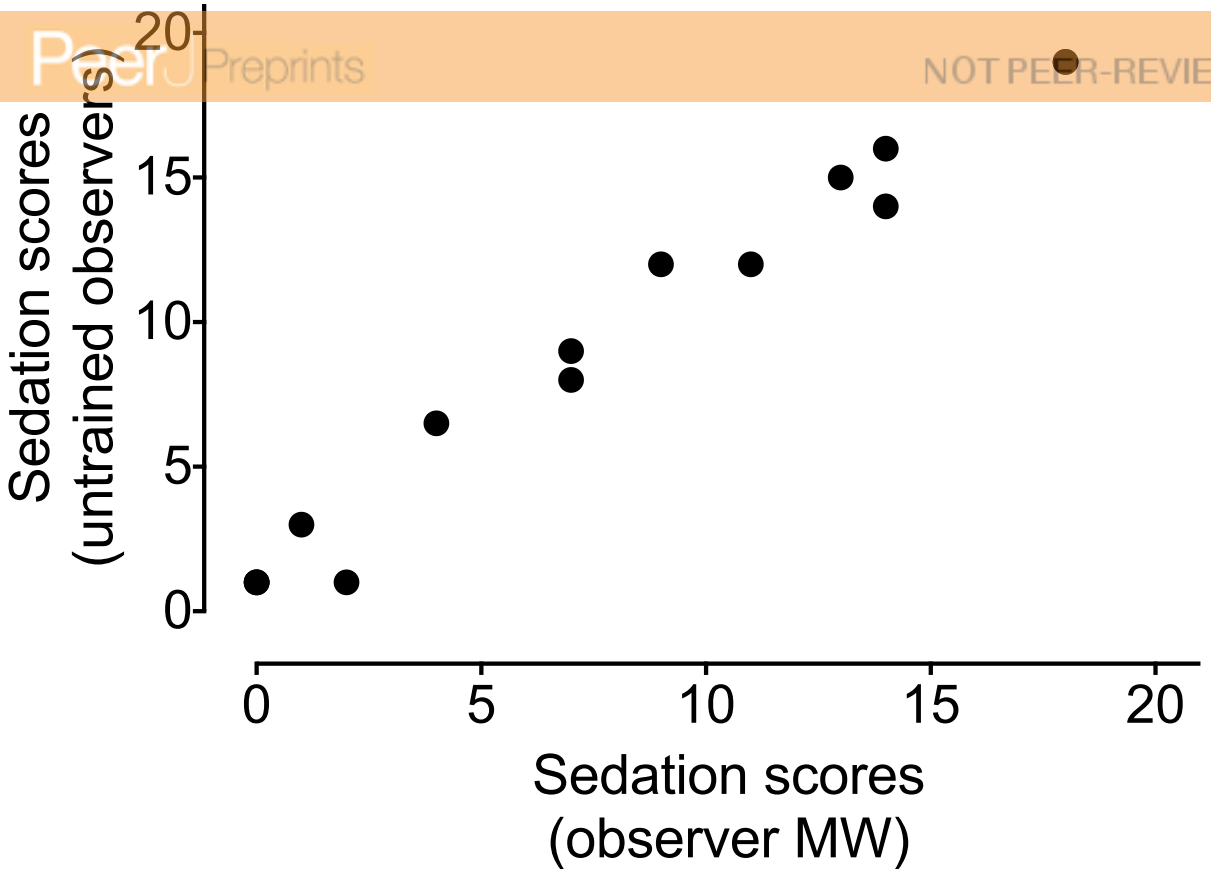

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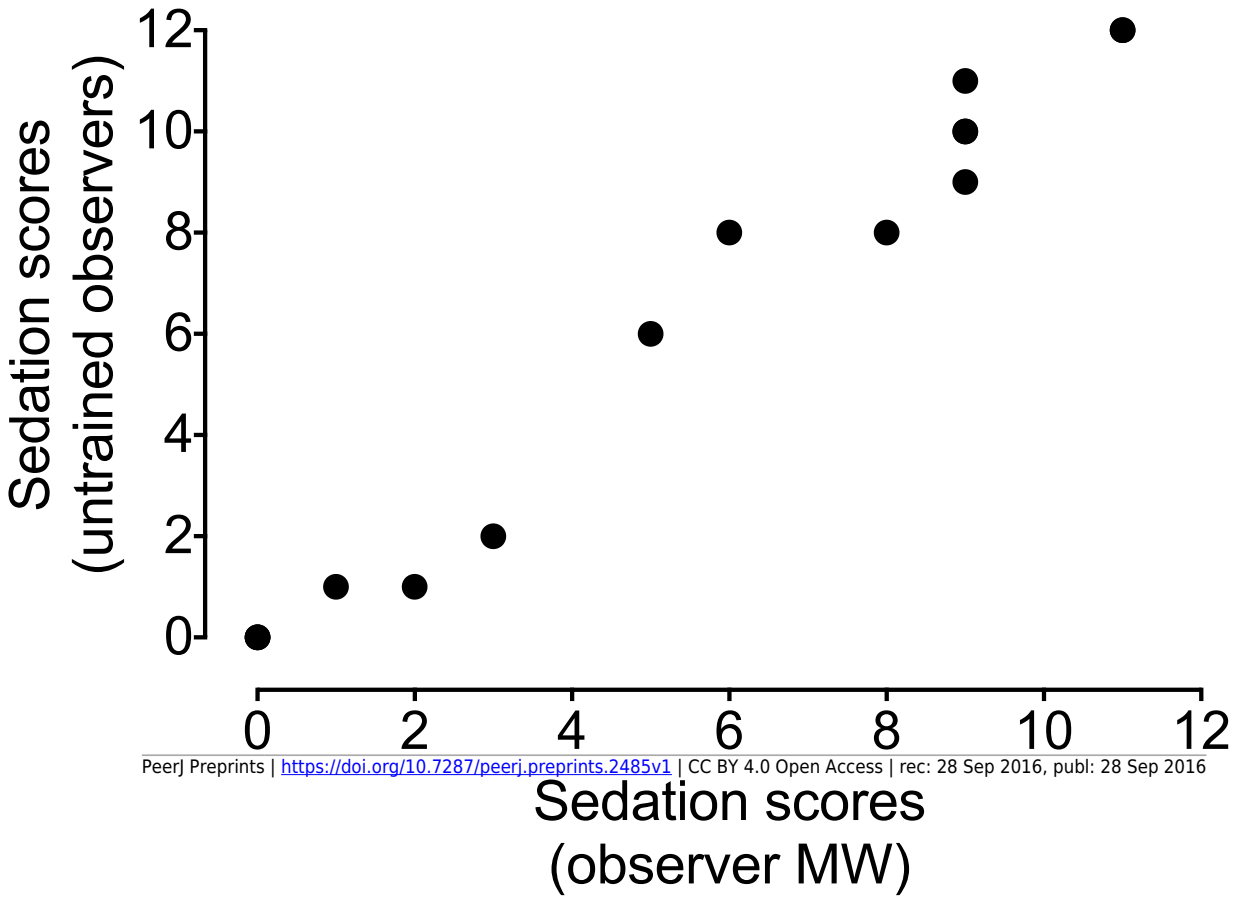

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