

MORPHINE EFFICACY IN MECHANICALLY VENTILATED PRETERM NEONATES; AN ITEM RESPONSE THEORY ANALYSIS

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Objectives

To assess the efficacy of morphine in preterm neonates undergoing endotracheal suctioning, using item response theory modeling and item-level data from multiple pain scales.

Methods

Data:

- 140 (preterm) mechanically ventilated neonates, placebo/morphine in a double-blind study design[1].
- Rescue analgesia allowed for both groups.
- Pain was quantified with items from
 - COMFORT scale (CMT), grade range 1-5.
 - Premature Infant Pain Profile (PIPP), grade range 0-3.
 - Neonatal Infant Pain Scale (NIPS) compound scores, score range 0-7.
 - VAS scores, range 0-10.

Modeling:

- An existing PK model [2]
- Sequential estimation with individually predicted PK parameters (IPP) [3].
- Graded response models of the IRT framework [4].
- Uninformative items were omitted from the final analysis.
- VAS scores included as continuous data.
- Drug effect: linear, power and (sigmoidal) EMAX models.
- Covariates tested: post-conceptual age, postnatal age and bodyweight.

Results

- The latent variable was successfully quantified (Figure 1).
- Linear effects of morphine (Table 1, Figure 2A) and postnatal age on pain (Table 1, Figure 2B)
- Baseline pain was separately quantified before, during and after suctioning (Table 1, Figure 2).

Discussion and conclusions

The effect of morphine on endotracheal suctioning related pain, experienced by newborns, was quantified. Increasing postnatal age was associated with more signs of pain. These results suggest a modest but definite pain-reducing effect of morphine.

Table 1. Parameter estimates from final model and bootstrap (n=1000).

Parameter	Symbol	Value (SE)	Bootstrap 5 th -95 th percentiles
Baseline pain, before suction	$\theta_{bl,1}$	-0.263 (0.052)	-0.386 to -0.156
	$\omega_{bl,1}$	0.54 (0.022)	0.47 to 0.62
Baseline pain, during suction	$\theta_{bl,2}$	1.14 (0.056)	1.02 to 1.25
	$\omega_{bl,2}$	0.60 (0.024)	0.53 to 0.67
Baseline pain, after suction	$\theta_{bl,3}$	-0.398 (0.054)	-0.513 to -0.295
	$\omega_{bl,3}$	0.56 (0.0233)	0.49 to 0.64
Morphine effect slope (ng/mL) ⁻¹	θ_2	-0.0103 (0.00076)	-0.0136 to -0.00665
Postnatal age effect parameter d ⁻¹	θ_3	0.0469 (0.0046)	0.0194 to 0.0795

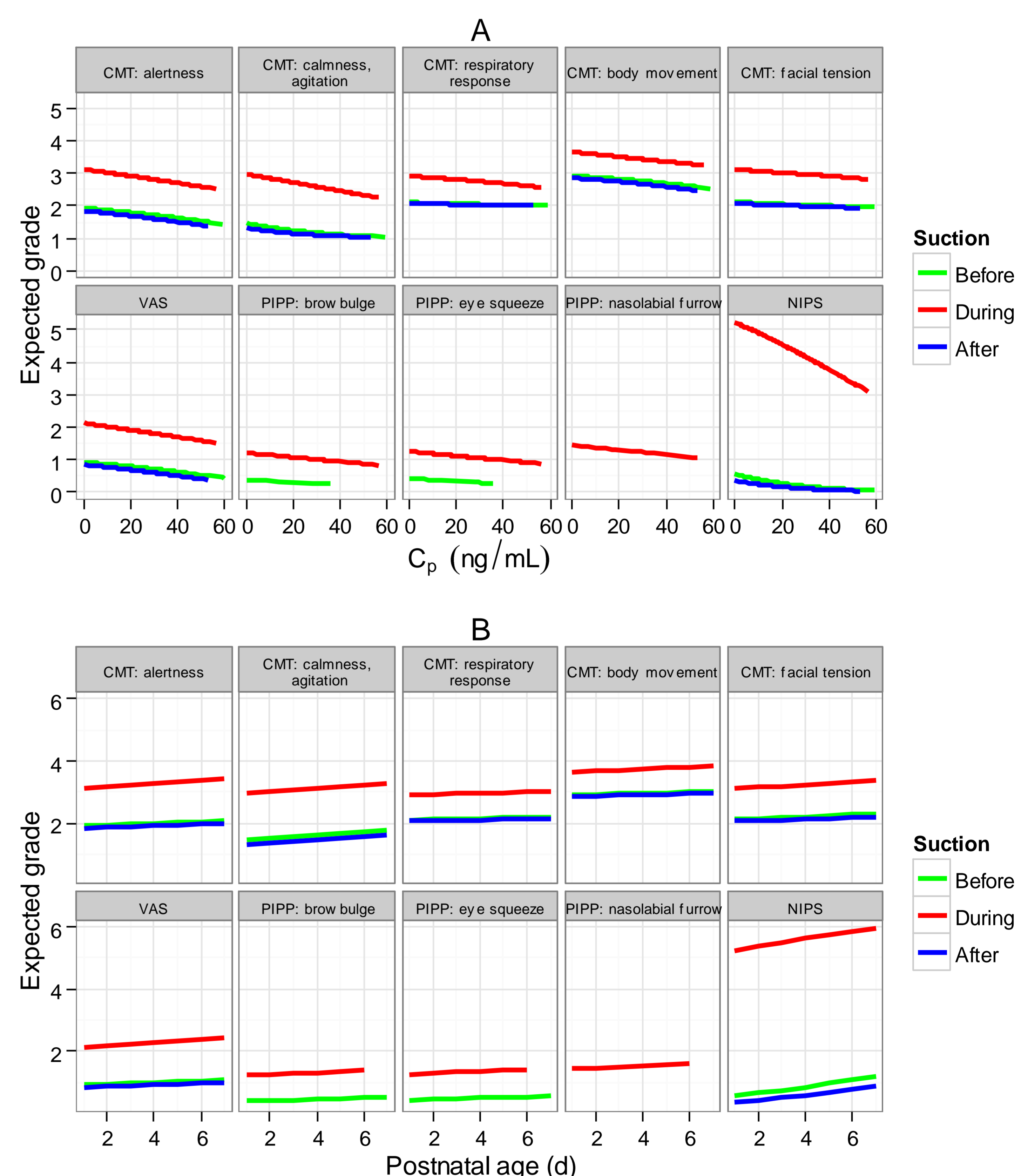


Figure 2. The predicted mean grades of the available COMFORT, NIPS, PIPP and VAS scores A) as a function of morphine concentrations when postnatal age is 1 and B) as a function of postnatal age, when morphine concentration is zero (the placebo group).

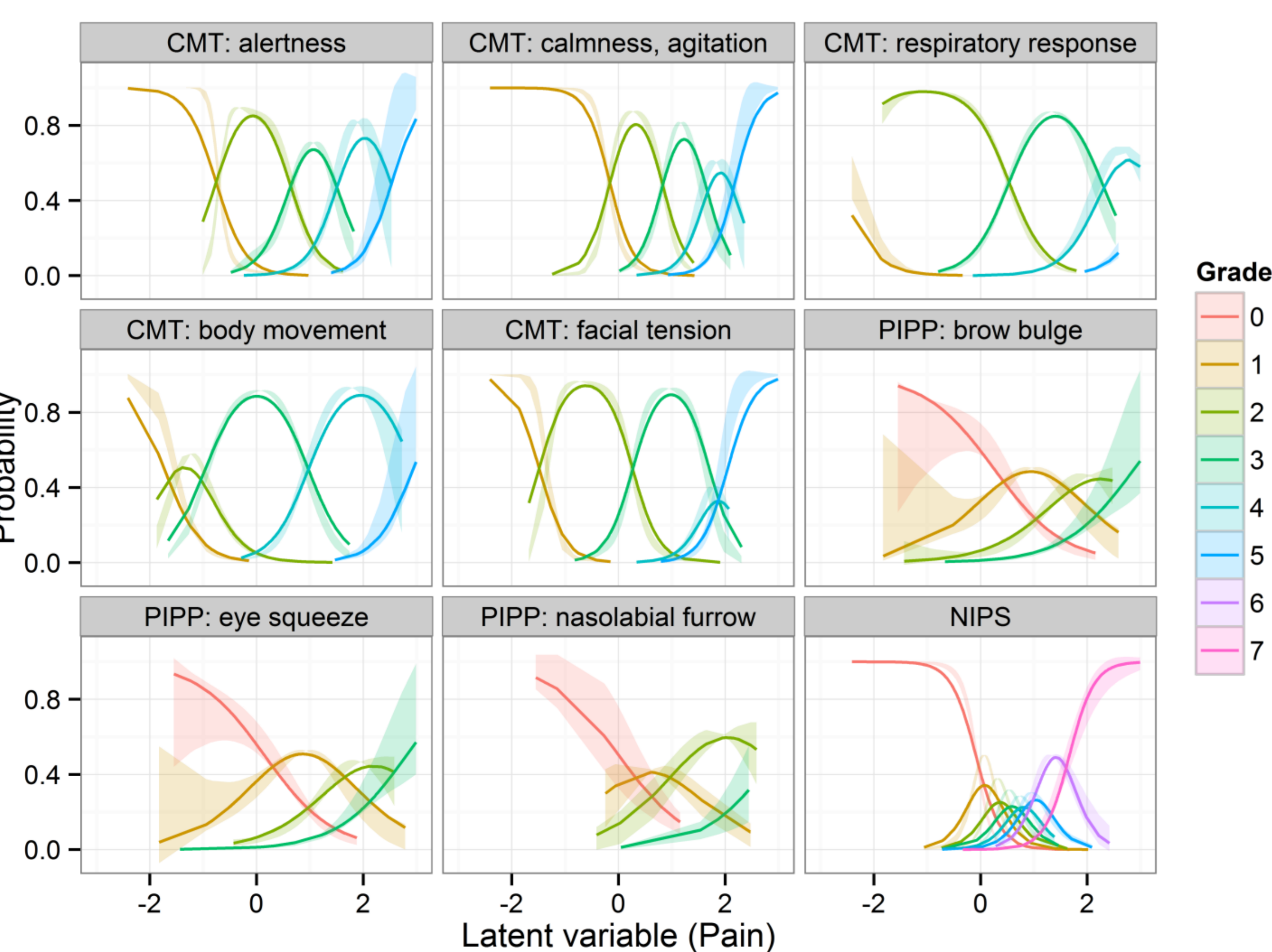


Figure 1. Model-predicted item characteristic curves (solid lines) and 95% confidence intervals for smoothed occurrence densities of the observed data (shaded areas). Colours denote different grades of the item (COMFORT and PIPP) or the compound score (NIPS).

References

1. Simons *et al.* JAMA. 2003;290(18):2419
2. Knibbe *et al.* Clin Pharmacokinet. 2009;48(6):371
3. Zhang *et al.* J Pharmacokinet Pharmacodyn. 2003;30(6):387
4. Samejima. Psychometrika 1970;35(1):139