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Variability in infant acute pain responding meaningfully obscured by averaging pain responses

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ABSTRACT

Given the inherent variability in pain responding, using an "average" pain score may pose serious threats to internal and external validity. Using growth mixture modeling (GMM), this article first examines whether infants can be differentiated into stable groups based on their pain response patterns over a 2-minute post-needle period. Secondary analyses, to specifically address the issue of averaging pain scores to represent a sample, qualitatively described clinically meaningful differences between pain scores of the discerned groups and the overall mean (irrespective of groups). Infants were part of Canadian longitudinal cohort naturalistically observed during their 2-, 4-, 6-, and/or 12-month immunization appointments (N = 458 to 574) at 3 pediatrician clinics between 2007 and 2012. At every age, GMM analyses discerned distinct groups of infants with significantly variable patterns of pain responding over the 2 minutes post-needle. Our secondary suggested that the overall mean pain score immediately post-needle reflected most groups well at every age. However, for older infants (6 and 12 months, especially), the overall mean pain responses at 1 and 2 minutes post-needle significantly over or underestimated groups that contained 48% to 100% of the sample. These results combined highlight the significant variability of infant pain responding patterns between groups of infants and furthermore, calls into question the validity of using an overall mean in research with older infants during the regulatory phase post-needle.

1. Introduction

A recent Cochrane Review addressing behavioral and/or cognitive pain management techniques for healthy infants older than 1 month demonstrated that not one technique had sufficient evidence for procedural pain [15,16]. In addition, the vast majority of parents do not use pharmacological strategies for acute procedural pain in infancy [13,23], despite demonstrated efficacy, suggesting infant acute pain management is cause for concern.

These findings subsume an important need for a greater quantity of research on healthy infants' pain management over the first year of life. In developed nations, infancy is the time when most infants receive the most immunization needles [17]. Needle phobias, health care avoidance, and increased pain reactivity are all implications of these experiences documented in the literature [22,25,26]. In addition, compared to infancy, no other period of development results in greater biological, psychological, and social change, suggesting greater implications of unrelieved pain during this formative period [14]. This steep development is often ignored in treatment studies exploring pain management by coarsely grouping infants of different ages [4–7].

Infant development researchers have long recognized the crucial influence of age and individual differences (such as temperamental predispositions to negative affect reactivity/regulation) on infants' reactions [3,19]. Infant pain researchers are just beginning to investigate the idea that pain reactions post-procedure may also be a function of temperamental predispositions and not simply the painful stimulus [8,10]. If pain reactions are due, in part, to reliable individual differences (such as stable patterns in how certain infant react or regulate from noxious stimuli), using a simple overall mean score (ie, averaged over all infants within a sample or treatment arm) may pose a serious conceptual flaw when conducting

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research involving infant pain management, as the efficacy of pharmacological and non-pharmacological strategies may vary along the continuum of such individual differences.

Taking a step in this direction, this study examined a longitudinal cohort of healthy infants followed over immunizations during the first year of life. The purpose was to determine whether individual differences regarding infants' pain responses post-needle (pattern of pain scores from immediately post-needle to 2 minutes post-needle) can be effectively discerned. After the groups are discerned, mean pain scores were calculated for each group separately and then each mean pain score was compared to the overall mean pain score (ie, collapsed over groups) to determine whether any of the groups differ from their respective overall mean in a clinically significant manner. First, we hypothesized that there would be sufficient heterogeneity in pain responses to describe individual differences using distinct groups. Second, we hypothesized that these reliably discerned groups would have clinically meaningful differences in pain responding when compared to the overall mean.

2. Methods

2.1. Study cohort

The data collection procedures and measures are described in detail elsewhere [1,14,18]; a synopsis is given below. Ethical approval was obtained through research ethics review boards at both the participating university and the associated pediatric hospital.

The data are part of our ongoing longitudinal study in which caregiver–infant dyads are recruited from 3 pediatric clinics in the greater Toronto area and followed in a cohort sequential design during immunizations over the first 12 months of a child's life and again at the preschool immunization. Data were collected between October 2007 and May 2012. Infants were recruited at 2, 4, or 6 months of age. The withdrawal rate for the infant waves was 3%. The sample included data from 747 different infants. Based on the analysis plan, a given infant's data were included in analyses if the infant was observed at any time point (2 months, n = 485; 4 months, n = 574; 6 months, n = 568; and 12 months, n = 458). Table 1 lists demographic characteristics. The infants are healthy, from middle-class families, at low risk, and developmentally typical. Caregivers were fluent in English and legal guardians of the studied infant.

2.2. Procedure

During each immunization appointment, infants' facial, vocal, and body movements were video recorded before and after the immunization. Parents filled in a short demographic questionnaire before each immunization appointment. First, infants were observed at different times over a single immunization appointment (immediately after final needle, 1-minute after the final needle, 2-minutes after the final needle); and second, they were observed at subsequent appointments through the first year of life. This is a naturalistic observational study, in that families were observed during their infant immunization appointments with little interference on the part of the research team, aside from the videotaping of the procedure.

2.3. Behavioral coding measures

The Modified Behavior Pain Scale (MBPS) [24] was used to assess the degree of infant pain-related distress. Coders rated the severity of distress reflected in 3 types of infant pain behaviors (facial expression, cry, and body movement) during 3 different 15-second epochs (15 seconds immediately after the needle [MBPS0], 1 minute after the needle [MBPS1], and 2 minutes after the needle [MBPS2]). For each epoch, all 3 behaviors were summed to calculate a pain score out of 10 (higher scores reflect greater pain). MBPS0 reflects the peak pain response that occurs right after the needle. A lowering of scores from MBPS0 to MBPS1 to MBPS2 would represent regulation from the peak distress (ie, a returning to baseline or pre-needle levels of pain). Moderate to high concurrent and construct validity as well as item-total and interrater reliability have all been demonstrated in the immunization context [24]. Our primary coders were blinded to the study hypotheses, and interrater reliability was high (with intraclass correlations ranging from 0.93 to 0.96).

After the groups were discerned statistically (primary analysis), to understand whether any of the group means on the MBPS at any of the epochs or ages differed notably from the overall mean (ie, pain scores collapsed over groups at each of the ages and/or epochs), clinical significance on the MBPS was considered (secondary analysis). Only differences greater than 1 point on the 10-point MBPS were considered clinically significant. This is in line with recently published meta-analytic work determining the effect of a known analgesic agent on immunization pain using MBPS [21].

2.4. Statistical analysis

To address our 2 research questions, two types of analyses were conducted. First, growth mixture modeling (GMM) is a technique used to summarize individual variation on a set of longitudinal repeated measures (ie, trajectories) using a small number of homogeneous subgroups within a sample [12]. We were interested in growth mixtures of pain responses both across age and within age across the first 2 minutes post-immunization. First, to model heterogeneity in immediate infant pain reactivity post-needle across age, we examined MBPS0 across 2, 4, 6, and 12 months of age (1 GMM model). Second, to model heterogeneity in how infants regulate from peak distress, we examined the trajectory of scores from MBPS0 to MBPS1 to MBPS2 separately within each of the 4 age groups (4 GMM models). In a GMM, infants are not assigned to groups deterministically; instead, each participant receives a score that represents the probability that she or he would be assigned to each of the discerned groups. Thus, for our secondary analyses, when reporting group means for any of the individual groups, only infants that had a probability of .9 or greater of belonging to 1 of the groups were used. For each GMM, we provide the proportion of infants that had a class probability score greater than .9. Only these infants were used to calculate the group means, described below. At all ages, this encompassed the vast majority of infants.

For each of the models, we first specified a single group and then tested a series of models formed by increasing the number of groups. Models with varying numbers of groups were compared using Akaike's Information Criterion (AIC) [2] and the Bayesian Information Criterion (BIC) [20]. Smaller values of AIC and BIC are associated with improved model fit. We systematically increased the number of groups until these model fit measures no longer justified the extraction of additional groups (or had obtained an improper model with a negative residual variance term). For brevity, AIC and BIC statistics will be provided only for the penultimate model and the final model. Although all groups will be shown on the graph for each GMM because they are a part of the best fitting solution, we will not discuss groups that contained less than 5% of the sample because they are unlikely to replicate in future studies [9].

After the groups were discerned for each of the 5 models, for the secondary analyses, group means from each model (ie, the mean of each group at a particular epoch and/or age) were compared to the