Physiological and Behavioral Responses to Calibrated Noxious Stimuli Among Individuals with Cerebral Palsy and Intellectual Disability

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Abstract

Objective. As individuals with intellectual disability (ID) due to cerebral palsy (CP) are at high risk of experiencing pain, measuring their pain is crucial for adequate treatment. While verbal reports are the gold standard in pain measurements, they may not be sufficient in ID. The aim was to detect behavioral/autonomic responses that may indicate the presence and intensity of pain in individuals with CP and ID, using calibrated stimuli, here for the first time.

Subjects. Thirteen adults with CP and ID (CPID), 15 healthy controls (HC), and 5 adults with CP with no ID (CPNID).

Methods. Subjects received pressure stimuli of various intensities. Self-reports (using a pyramid scale), facial expressions (retrospectively analyzed with Facial Action Coding System = FACS), and autonomic function (heart rate, heart rate variability, pulse, galvanic skin response) were analyzed.

Results. Self-reports and facial expressions but not the autonomic function exhibited stimulus-response relationship to pressure stimulation among all groups. The CPID group had increased pain ratings and facial expressions compared with controls. In addition, the increase in facial expressions along the increase in noxious stimulation was larger than in controls. Freezing in response to pain was frequent in CPID.

Conclusions. 1) Individuals with CP and ID have increased responses to pain; 2) facial expressions and self-reports, but not autonomic variables can reliably indicate their pain intensity; 3) the pyramid scale is suitable for self-report in this population. Although facial expressions may replace verbal reports, increased facial expressions at rest among these individuals may mask pain, especially at lower intensities.

Key Words. Cognitive Impairment; Perception; Experimental Pain; Pain Behavior; Autonomic Function

Introduction

Intellectual disability (ID) is the most common developmental disability, affecting about 1–3% of the population [1]. ID is characterized by impairments of general mental abilities that impact adaptive functioning in the...
conceptual, social, and practical domain. The conceptual domain includes skills in language, reading, writing, math, reasoning, knowledge, and memory. The social domain refers to empathy, social judgment, interpersonal communication skills, the ability to make and retain friendships, and similar capacities. The practical domain centers on self-management in areas such as personal care, job responsibilities, money management, recreation, and organizing school and work tasks [2].

One of the etiologies with relatively high prevalence of ID is cerebral palsy (CP). CP is a group of movement, muscle tone, and/or posture disorders. CP causes impaired movement associated with exaggerated reflexes, flaccidity or rigidity of the limbs and trunk, abnormal posture, involuntary movements, unsteadiness of walking, or some combinations of these [3]. Apart from motor signs and symptoms that appear during infancy or preschool years, CP is often accompanied by disturbances of communication, sensation, perception, and cognition [3]. The prevalence rate of ID varies from 23–44% depending on the type of CP and the presence or absence of epilepsy [4].

In general, individuals with ID are exposed to many potentially painful conditions related to the etiology of ID and its secondary and tertiary consequences [5–7]. Higher rates than normal of injuries, falls, and accidents—all of which are sources of pain—are characteristic of individuals with ID [8]. In light of the severe motor and postural disorders characteristic of CP, individuals with CP and ID in particular, are at a greater risk of pain [3,9–11]. At the same time, these individuals may be hypersensitive to pain as reflected by their lower pain thresholds [12–14], an additional perpetuating factor for pain.

Successful pain management requires the measurement of pain, verbal report being its gold standard. Yet, the limited cognitive and communication capabilities of individuals with ID present a challenge in identifying the presence of pain, diagnosing the source of pain, and evaluating the magnitude of pain and suffering [15,16]. Therefore, an indirect method to evaluate pain that does not necessitate verbal reports is called for. Facial expressions and physiological responses are potential candidates for this purpose.

Indeed, many studies have recorded increased facial/bodily expressions compared with baseline among individuals with ID during painful clinical conditions, such as vaccination, surgery, venipuncture, and dental care (e.g., [17–27]). In addition, autonomic variables such as oxygen saturation, heartbeat, and blood pressure were increased in some, but not in all individuals with ID following the aforementioned clinical conditions [26,28,29]. However, only in the minority of the studies these were individuals with CP included and therefore the response properties of this unique group have not been fully documented. Furthermore, the stimuli eliciting pain in the previously tested clinical instances cannot be controlled nor measured. Therefore, the extent to which behavioral and autonomic variables can reliably differentiate between nonpainful and painful stimuli, and also between different levels of pain is still not clear.

Experimental pain can be standardized and measured, and enables a systematic examination of the association between stimulation intensity and pain response. We found only two pioneer studies that analyzed behavioral responses following experimental stimuli. The authors administered innocuous stimuli of various sensory modalities to adults with severe-profound ID and found a similar increase in facial and body reactions compared with baseline, regardless of the stimulation modality [30,31]. Thus, the manner with which these individuals respond to painful stimuli remained unanswered. To the best of our knowledge, autonomic responses following experimental (painful) stimuli among individuals with ID have not been analyzed as well. Thus, controlled experimental studies assessing pain responses in ID, let alone among individuals with ID due to CP who seem especially susceptible to pain are lacking and needed.

The aims were thus to test whether facial and autonomic reactions to pain in individuals with CP and ID: 1) are increased compared with controls, 2) can indicate pain intensity and replace subjective, verbal reports.

Methods

Participants

The study included 33 adults; 13 individuals with CP who had mild-moderate ID (CPID group, age 34.5 ± 4.9 years), 15 healthy subjects (HC group, 31.3 ± 7.7 years) as a first control group, and five individuals with CP with no ID (CPNID) (CPNID group, 24 ± 4.2 years) as a second control group. The latter were chosen in order to control for the possible effect of physical disabilities on pain behavior. Individuals from the CPID were recruited from a day care center for people with ID. ID was diagnosed according to clinical assessment and standardized testing of intelligence (including the Wechsler Intelligence Scale for Children-Revised, the Wechsler Preschool and Primary Scale of Intelligence) by the team of the Ministry of Social Affairs and Social Services. Individuals in this group had an estimated level of mild or moderate ID, and the capability to understand their mother tongue. Individuals from the CPNID group were recruited from independent residential communities. Healthy controls were students and workers of Tel-Aviv University. Exclusion criteria for all the participants were: known acute or chronic pain, bruises, or injuries in the testing regions. The study was approved by the Tel-Aviv University ethical committee, by the institutional review board of the Ministry of Social Affairs and Social Services, and by the legal guardians. A written informed consent was obtained from all cognitively intact individuals and from the legal guardians of the individuals with
Instruments

Pressure Algometer

Pressure stimuli were delivered, using a hand-held pressure algometer (Algometer type II, Somedic Sales AB, Horby, Sweden). The algometer has a built-in pressure transducer, an electronic recording, and display unit, a power supply, and subject-activated push button connected via a cable to the instrument. It has an accuracy of ±3% and its unit of measurement is the kilopascal (kPa). The principle of operation of the algometer is the exertion of a constantly increasing rate of pressure that is monitored by a cursor presented on the display. The size of the tip of the algometer that is pressed against the skin was 1 cm². The algometer was calibrated before each measuring day.

Facial Action Coding System (FACS)

Facial expressions to noxious stimuli were analyzed using the Facial Action Coding System (FACS). The FACS consists of a list of facial actions (action units [AUs]) based on the movement of specific muscles or group of muscles of the face [32] as indicative of pain. In the present study, we used 14 AUs that were previously found to be characteristic of pain [33–38]. The AUs were: Brow lowerer (AU4), cheek raiser (AU6), lid tightened (AU7), nose wrineker (AU9), upper lip raiser (AU10), oblique lip puller (AU12), lip stretcher (AU20), lip pressor (AU24), mouth opener (AU25), jaw dropper (AU26), mouth stretcher (AU27), eyelid dropper (AU41), eyes closer (AU43), and blink (AU45). The intensity of the AUs was coded on a 6-point intensity scale, ranging from 0 = no action, through 1 = minimal action/trace to 5 = maximum action [37]. The intensity coding of AU43 was essentially binary; that is, 0 or 5 and the intensity coding of AU45 was based on the frequency of blinking. The FACS score for each participant for subsequent analysis was the sum total of the intensity (or frequency) scores of all the 14 AUs. In addition, for the purpose of analyzing the location of the pain-related AUs, we calculated the frequency of each AU for the most painful stimulation (400 kPa).

The Freezing Item

In our previous study, we found that in addition to the aforementioned AUs, individuals with ID often respond with “freezing” to noxious stimuli [18]. Weiner et al. (1999) have also identified freezing (“stillness”) among individuals with cognitive impairment during chronic pain [39]. Therefore we added this item to the analysis of the behavior and coded it in a binary format (yes/no). For this purpose, freezing was defined as stillness, lack of facial and upper body movement for at least 3 seconds. Note that in some subjects freezing followed the changes in facial actions whereas in others freezing was dominant.

Self-Report Rating Scale

Subjective pain ratings were obtained with a pyramid pain scale (Figure 1). This is a graphical rectangular plastic ruler, 20 cm long and 7 cm wide, on which five color pyramids of different increasing sizes are situated on a horizontal base. The area of the base with no pyramid above it (the left end of the scale) signifies no pain = 0.
The sizes of the pyramids represent the amount of pain and the highest pyramid (the right end of the scale) signifies the worst possible pain = 5.

As this scale is less common, we first tested its validity in measuring pain sensation in a group of 15 control subjects. The subjects received three stimuli of 50, 200, and 400 kPa in a random order, and were asked to rate the intensity of their pain using the pyramid scale and a visual analog scale (VAS). The VAS consisted of a plastic ruler 10 cm long with two anchor points; 0 = no pain sensation and 10 = the most intense pain imaginable. We then compared the pain ratings obtained with the pyramid scale to those of the VAS. Analysis of variance revealed lack of effect of scale type on the pain ratings and a lack of interaction between stimulation intensity and scale type. Interclass correlation coefficient between the two scales was 0.83 (P < 0.0001). After this validity procedure, we used the pyramid scale thereafter.

PMD-100 System for Recording Physiological Signals

The response of the sympathetic system to noxious stimuli was evaluated by measuring the changes in heart rate (HR), heart rate variability (HRV), pulse amplitude (PA), and galvanic skin response (GSR). The physiological signals were recorded, sampled, and stored with a personal computer, using the PMD-100 TM™ system (Medasense Biometrics Ltd., Ramat Gan, Israel) through a finger probe. A 1-lead electrocardiogram signal was sampled with a frequency of 500 Hz, and a reflectance-mode photoplethysmogram (PPG) signal from the right-hand index finger was sampled at a frequency of 500 Hz. Skin conductance (measured in micro-Siemens, μS) was measured, using two electrodes positioned on the volar pads of the distal phalanx in the middle and ring fingers of the right hand, and was sampled with a frequency of 31.25 Hz. The recorded signals were synchronized and processed off-line, using MATLAB R2010 scientific software (The MathWorks, Inc., Natick, MA, USA).

Procedures

Training and Stimulation Protocol

The experimental protocol was designed by the experimental pain working group of the European Cooperation in the Field of Scientific and Technical Research (COST), termed “Pain assessment in patients with impaired cognition, especially dementia” (action TD1005). Authors TB, CGP, and RD of the present study are part of this group. The protocol was designed based on preliminary experiments done prior to the present experiment. In these experiments, 12 healthy controls were administered series of pressure stimuli ranging from 50–500 kPa (at a random order) at a rate of 50 kPa/sec and an inter-stimulus interval of 60 seconds. The subjects were asked to rate their perceived pain using a 10 unit numerical rating scale (NRS) after each stimulus. The NRS was set as 0 = “no pain sensation” and 10 = “the most intense pain sensation.” This procedure was repeated twice for each subject in order to test reliability. Individual stimulus-response functions for pressure-pain were then constructed and the stimuli of 50, 200, and 400 kPa were chosen based on the ratings and defined as nonpainful, mildly painful, and moderately painful, respectively.

Prior to actual testing in the present experiment, all the participants were familiarized with the algometer and underwent a training session. During training the participants received pressure stimuli in the thigh region (which was not stimulated further during testing) at the intensities used during testing and were instructed how to use the pyramid rating scale. In addition the subjects were instructed on how to maintain their faces so that their expressions would be best captured by the camera.

After a short break, the experiment started. The examiner stood behind the subject in order not to interfere with videotaping and in order to properly administer the stimuli. Each subject received a total of six pressure stimuli, applied to the upper mid part of the trapezius muscle, alternately to the right and left side (three stimuli on each side). The intensities of the pressure stimuli were: 50, 200, and 400 kPa. Each stimulus rose from a baseline of 0 kPa to the destination intensity in 2 seconds, and lasted for 5 seconds in destination (total duration 7 seconds). The reason for determining a fixed rise time was to maintain a similar stimulation duration (hence similar duration for recording facial expressions and autonomic responses) for all the stimulation intensities. The inter-stimulus-interval between sides was 2 minutes and the inter-stimulus-interval on the same side was 4 minutes. These relatively long intervals were maintained in order to avoid carry over between stimuli, due to our decision not to randomize the stimulation intensities and to allow proper pain rating. In addition, the examiner moved the stimulation site by about 0.5 cm when returning to a previous location.

The reason for lack of randomization in pressure intensity was based on preliminary trials. In these trials, individuals with ID who, due to randomization, received the strongest stimulus first were alarmed and anxious and immediately withdrew from the experiment. In contrast, when stimuli were administered in an increasing order, the subjects could easily receive the entire protocol.

The participants were asked to rate their pain after each stimulus, using the pyramid scale by pointing out with their finger onto the pyramid that best fitted their pain. For those participants who could not use their finger to point on the scale due to motor disability, the examiner pointed out for them and asked whether the pyramid
fitted their pain. Physiological signals were recorded continuously throughout the entire protocol duration and the values were extracted off-line for each condition (rest, 50, 200, and 400 kPa).

Recording and Analysis of Behavioral Responses

The participants were videotaped throughout the entire protocol. The camera was situated on a tripod 0.5 meter in front of the participant. In order to ensure an optimal position of the face, the participants were asked to keep their gaze on a fixed point that was a green “X” shape that was hanging on the wall in front of them.

The behavioral responses of the participants during baseline and during pressure stimulation were analyzed retrospectively using frame-by-frame analysis and the slow motion option. During baseline, the subjects were not engaged in any specific activity, and analysis of facial expressions and of freezing were conducted for a random 7-seconds segment. During pressure stimulation, the analysis commenced at the very second the examiner started the stimulus and lasted 7 seconds. The video segments of the different conditions (rest, innocuous and noxious stimuli) were presented to the raters in a random order to prevent any biases due to the immediate comparison between subsequent conditions.

Inter-Rater Reliability and Agreement

Two independent raters analyzed the facial expressions and freezing of 85% of the participants for the purpose of inter-rater reliability analysis. One coder was a certified FACS coder and the other was trained by the certified coder. The two raters conducted their analysis separately to prevent any influences between them.

Data Analysis

Data were analyzed with the IBM statistics 21 software. The internal consistency of the FACS was assessed with the α-Cronbach test. Repeated measure analysis of variance (ANOVA) with body side as the within group factor was conducted on the values of the FACS; pain ratings, and autonomic variables in order to test whether there is a significant effect of body side on these dependent variables. As no body side differences were found, data collected from the right side were averaged with data collected on the left side for subsequent analyses. Fixed effects models with interactions were used to evaluate the effect of group (CPID, HC) and of stimulation intensity (baseline, 50, 200, and 400 kPa) on the dependent outcome measures: sum total of the FACS scores, frequency of FACS AUs (400 kPa only), pain ratings with the pyramid scale, and the autonomic variables: HR, HRV, PA, and GSR. Due to the size of the CPNID group, we used the Mann-Whitney test to compare the aforementioned outcome measures between the CPID and the CPNID groups. Post hoc tests were corrected for multiple comparisons using the Tukey correction. The agreement between the two raters for the FACS was computed with the Ekman and Friesen conservative FACS reliability formula = (number of actions on which coder 1 and coder 2 agreed X 2)/(number of actions scored by the two coders) [40] for one shoulder of a random sample of 85% of the subjects. In addition, agreement between raters was also assessed with interclass correlation (ICC). All P values presented are two-tailed significant. P < 0.05 was considered significant.

Results

Characterization of the Study Groups

Table 1 describes the three study groups. The CPID group did not differ in age from the HC group but both were slightly older than the CPNID group (P = 0.063). The two CP groups did not differ in motor disability, frequency of epilepsy, and medication intake.

Facial Expressions (FACS)

Figure 2 presents the sum of FACS scores in response to pressure stimulation for the three groups: CPID, HC, and CPNID. Repeated measure ANOVA for groups CPID and HC revealed a significant global effect of group type (F(1,75) = 20.95, P < 0.0001) and of stimulation intensity (F(3,75) = 15.24, P < 0.0001) on the FACS scores. The interaction between group and stimulation intensity was not significant (F(3,75) = 1.02, P = 0.38). Post hoc tests revealed that the FACS scores of the CPID group were significantly higher than those of HC and those of the CPNID group except for baseline (Figure 2). Despite the higher FACS values of CPID at baseline, the increase in FACS values from baseline to 50 and the increase from baseline to 200 kPa were higher in this group compared with that of the HC (P < 0.05 for both) and CPNID groups (P < 0.05 for both). Pearson’s tests revealed a significant positive correlation between the FACS scores and the stimulation intensity among all the groups (CPID: r = 0.42, P < 0.001; HC: r = 0.48, P < 0.0001; CPNID: r = 0.54, P < 0.01).

In summary, although all three groups exhibited an increase in facial expressions with the increase in stimulation intensity, the CPID group had overall greater facial expressions than both HC and CPNID groups and a steeper increase in the facial expressions.

Table 2 presents the frequency of each AU in 400 kPa stimulation. In general, the AUs most frequently appearing in the CPID group were AUs 4, 7, 10, 12, 20, 25, 26, and 41, showing that most activity was located in the eyes and mouth areas. AUs 10, 12, 20, 26, 27...
were significantly more frequent among the CPID group compared with the two control groups and AU25 was characteristic of the two CP groups (Table 2).

**Pain Ratings**

Figure 3 presents the self-reported pyramid pain scores in response to pressure stimulation for the three groups: CPID, HC, and CPNID. Repeated measure ANOVA for groups CPID and HC revealed no significant main effect of group type ($F(1,75)=1.80, P=0.18$) but a significant effect was found for stimulation intensity ($F(3,75)=75.20, P<0.0001$). The interaction between group and stimulation intensity was also significant ($F(3,75)=6.81, P<0.01$). Post hoc tests revealed that the pain scores of the CPID group were significantly higher than those of both the HC and CPNID groups in 50 kPa, and higher than HC in 200 kPa pressure intensity. The scores in baseline and in 400 kPa were similar for all the groups (Figure 3). Pearson’s tests revealed a significant positive correlation between the pyramid scale score and stimulation intensity among all the groups (CPID: $r=0.63$, $P<0.0001$; HC: $r=0.91$, $P<0.0001$; CPNID: $r=0.83$, $P<0.0001$).

In summary, although all three groups exhibited an increase in pain ratings with the increase in stimulation intensity, the CPID group had greater pain ratings than the two control groups in the low intensity range.

**Autonomic Function**

Figure 4 presents the autonomic variables in response to pressure stimulation for the three groups: CPID, HC, and CPNID. Repeated measure ANOVA for groups CPID and HC revealed that none of the variables was the effect of stimulation intensity significant (HR:...
Correlations Between Behavioral and Autonomic Variables in the CPID Group

Table 3 presents the correlations between behavioral and autonomic variables in the CPID group. A significant, positive correlation was found between the FACS scores and the pyramid pain scores. A significant correlation was also found between the FACS scores and three of the autonomic variables; HR, PA, and GSR. However, the pyramid pain ratings did not correlate with any of the autonomic variables.

Post hoc tests revealed that the CPID group had higher PA values than the HC group throughout all stimulation intensities and also higher values than the CPNID group except in 400 kPa. In summary, the autonomic variables did not significantly change with the increase in stimulation intensity in any of the groups; however, the CPID group had overall higher PA values and lower GSR values than the control groups.

Figure 3 The pyramid pain scores increased with the increase in stimulation intensity. The pyramid scores of individuals with CPID were significantly higher compared with both the HC (A) and CPNID (B) groups in 50 kPa, and higher than the HC group in 200 kPa pressure intensity. CPID = individuals with cerebral palsy (CP) and intellectual disability; HC = healthy controls; CPNID = individuals with cerebral palsy with no intellectual disability. *P < 0.05; **P < 0.01. Values denote group mean ± SEM.

Table 2 Mean frequency (SD) of appearance of each FACS AU in 400 kPa among the three groups

<table>
<thead>
<tr>
<th>Action units (AUs)</th>
<th>CPID</th>
<th>HC</th>
<th>CPNID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brow lowerer (AU4)</td>
<td>0.83(0.38)</td>
<td>0.46(0.51)</td>
<td>0.60(0.55)</td>
</tr>
<tr>
<td>Cheek raiser (AU6)</td>
<td>0.66(0.49)</td>
<td>0.40(0.51)</td>
<td>0.20(0.45)</td>
</tr>
<tr>
<td>Lid tightened (AU7)</td>
<td>0.83(0.38)</td>
<td>0.46(0.51)</td>
<td>0.80(0.55)</td>
</tr>
<tr>
<td>Nose wrinkle (AU9)</td>
<td>0.66(0.49)</td>
<td>0.33(0.48)</td>
<td>0.20(0.45)</td>
</tr>
<tr>
<td>Upper lip raiser (AU10)</td>
<td>0.91(0.29)</td>
<td>0.40(0.51)</td>
<td>0.40(0.55)</td>
</tr>
<tr>
<td>Oblique lip puller (AU12)</td>
<td>0.91(0.29)</td>
<td>0.40(0.51)</td>
<td>0.40(0.55)</td>
</tr>
<tr>
<td>Lip stretcher (AU20)</td>
<td>0.83(0.39)</td>
<td>0.40(0.51)</td>
<td>0.20(0.45)</td>
</tr>
<tr>
<td>Lip pressor (AU24)</td>
<td>0.66(0.49)</td>
<td>0.40(0.51)</td>
<td>0.20(0.45)</td>
</tr>
<tr>
<td>Mouth opener (AU25)</td>
<td>0.83(0.39)</td>
<td>0.26(0.45)</td>
<td>0.80(0.55)</td>
</tr>
<tr>
<td>Jaw dropper (AU26)</td>
<td>0.83(0.39)</td>
<td>0.20(0.41)</td>
<td>0.20(0.45)</td>
</tr>
<tr>
<td>Mouth stretcher (AU27)</td>
<td>0.75(0.45)</td>
<td>0.20(0.41)</td>
<td>0</td>
</tr>
<tr>
<td>Eyelid dropper (AU41)</td>
<td>0.83(0.39)</td>
<td>0.53(0.51)</td>
<td>1(0)</td>
</tr>
<tr>
<td>Eyes closer (AU43)</td>
<td>0.66(0.49)</td>
<td>0.33(0.48)</td>
<td>0.40(0.55)</td>
</tr>
<tr>
<td>Blink (AU45)</td>
<td>0.75(0.45)</td>
<td>1(0)</td>
<td>1(0)</td>
</tr>
</tbody>
</table>

SD = standard deviation; FACS = Facial Action Coding System; AU = action unit; kPa = kilopascal; CPID = cerebral palsy and intellectual disability; CPNID = cerebral palsy with no intellectual disability; HC = healthy controls. Between-group comparisons: 1 = CPID vs HC, 2 = CPID vs CPNID. 

F(3,60)=0.97, P = 0.41; HRV: F(3,60)=2.4, P = 0.06; PA: F(3,60)=1.32, P = 0.27; GSR: F(3,60)=1.71, P = 0.17. Accordingly, there were no significant correlations between the autonomic variables and stimulation intensities (see also Table 3). The effect of group type was not significant for HR (F(1,60)=2.6, P = 0.11), HRV (F(1,60)=0.84, P = 0.36), and GSR (F(1,60)=5.3, P < 0.32) but was significant for PA (F(1,60)=7.4, P < 0.01). The interactions between stimulation intensity and group type were not significant for any of the variables.

In summary, the autonomic variables did not significantly change with the increase in stimulation intensity in any of the groups; however, the CPID group had overall higher PA values and lower GSR values than the control groups.
Inter-Rater Agreement

According to the Ekman and Friesen reliability formula, the overall agreement between raters was high. The agreement between raters for the HC group was higher than the CPID group except for 400 kPa as follows: 0 kPa 86.7 vs 79.2%, respectively, $P = 0.08$; 50 kPa: 92.4 vs 77.9, $P < 0.001$; 200 kPa: 90.1 vs 75.3, $P < 0.001$; 400 kPa: 86.2 vs 77.6, respectively, $P = 0.14$. ICC revealed moderate inter-rater agreement in the baseline scores ($r = 0.67$, $P < 0.0001$) whereas the agreement between the raters was rather high in the stimulation conditions; 50 kPa ($r = 0.81$, $P < 0.0001$), 200 kPa ($r = 0.92$, $P < 0.0001$) and 400 kPa ($r = 0.84$, $P < 0.0001$).

Freezing

Table 4 presents the frequency of freezing in response to pressure stimulation within each group. Post hoc tests revealed a significantly higher frequency of freezing in the CPID group than in the HC group across all the stimulation intensities.

Discussion

The aim was to detect behavioral/autonomic responses that may indicate the presence/intensity of pain in individuals with CP and ID, using calibrated pressure stimuli. Self-reports and facial expressions but not autonomic variables correlated with pressure stimulation among both individuals with CP and ID and controls; however, the former group exhibited increased responses to pain.

Facial Expressions Among Individuals With CP and ID

This is the first study in which facial expressions of pain were analyzed following calibrated noxious stimuli of various intensities. The results show that individuals with
**Disability, HC:** Disability, HC

Decreased children and adolescents with CP, some of which had

Table 3 Pearson’s correlation coefficients between behavioral and autonomic variables in the CPID group

<table>
<thead>
<tr>
<th>GSR</th>
<th>PA</th>
<th>HRV</th>
<th>HR</th>
<th>Pyramid pain scale</th>
<th>FACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.22</td>
<td>-0.09</td>
<td>-0.06</td>
<td>0.12</td>
<td>0.63***</td>
<td>0.42**</td>
</tr>
<tr>
<td>0.31*</td>
<td>0.41**</td>
<td>-0.05</td>
<td>0.42**</td>
<td>0.49***</td>
<td>-</td>
</tr>
<tr>
<td>0.24</td>
<td>-0.02</td>
<td>-0.15</td>
<td>0.11</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*P < 0.05.

**P < 0.01; CPID = individuals with cerebral palsy and intellectual disability, FACS = Facial Action Coding System, HR = heart rate, HRV = heart rate variability, PA = pulse amplitude, GSR = galvanic skin response.

Table 4 Frequency (%) of subjects exhibiting freezing in response to pressure stimulation within each group

<table>
<thead>
<tr>
<th>Group</th>
<th>CPNID</th>
<th>CPID</th>
<th>Stimulation intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>1 (6.7)</td>
<td>2 (40)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>CPNID</td>
<td>5 (38.5)*</td>
<td>7 (53.8)**</td>
<td>9 (61.5)**</td>
</tr>
</tbody>
</table>

CPID = individuals with cerebral palsy and intellectual disability, CPNID = individuals with cerebral palsy with no intellectual disability, HC = healthy controls.

*P < 0.05.

**P < 0.01 between CPID and HC.

CP and ID exhibit increased responses to pain compared with both individuals with CP and intact cognition and healthy controls. In addition, despite increased facial expressions at baseline (rest), the increase in facial expressions with the increase in stimulation intensity was larger among individuals with CP and ID compared with the two control groups, as observed in the slope of the stimulus-response function. Therefore, not only individuals with ID have increased facial expressions to pain in general, they respond stronger than controls to each increase in stimulation intensity. These results corroborate previous studies in which pressure-pain threshold of children and adolescents with CP, some of which had ID, was lower than that of controls [13,14]. Decreased pain threshold was also observed among individuals with Down syndrome and individuals with unspecified ID [12]. Our results may correspond with imaging studies showing alterations in brain structures responsible for pain processing/modulation among individuals with CP [41,42] and individuals with ID [43]. Thus, increased facial expressions due to noxious stimuli may well result from increased sensitivity to pain among individuals with CP and ID, a conclusion that bears significant clinical implications.

The results also showed that facial expressions correlated with stimulation intensity among individuals with

CP and ID, suggesting that the FACS may encode not only the presence of pain but also the intensity of pain. Namely, the magnitude of change in facial expressions (a particular AU or a group of AUs) may be used to monitor changes in pain intensity while following up aggravation of pathological conditions or alternatively, pain alleviation therapies. This is particularly important given that the objective indicators, namely the autonomic variables, did not correlate with stimulation intensity as discussed below. Such a suggestion is, however, subject to future research that will examine the use of the FACS as an indicator for pain intensity on an individual basis considering its repeatability and inter-subjects’ variability in facial expressions. Importantly, the lower inter-rater reliability for FACS scores in the CPID group as compared with controls may reflect either the diversity of responses of these individuals to pain, the difficulty in identifying pain among them, or both.

The sample size in the present study is not sufficient to conclude on specific AUs that best represent the subjects’ pain. However, the frequency of AUs during 400kPa stimulation, the highest stimulation intensity, suggests that activity in the mouth area (AUs 10, 12, 20, 26, and 27) is characteristic of subjects with ID in particular. It is noteworthy that AU25 seem characteristic of CP in general, as it was equally frequent among the two CP groups and significantly more frequent than in the HC group. Yet, individuals with CP and ID exhibit in a much greater extent the subsequent/adjoining AU26–27 than cognitively intact individuals with CP. Most of these AUs were also reported by other authors as most frequently observed among individuals with ID and/or as differentiating between painful and nonpainful stimuli (AU 4, 6, 7, 10, and 25) [30,31].

We could find only two studies in which facial and bodily reactions were analyzed following experimental stimuli among individuals with ID of unspecified etiology. Symons and coworkers found increased pain behavior during stimulation with innocuous heat, cold, pressure, and touch stimuli as well as during pin prick compared with rest, with no differences between these stimuli [30,31]. The addition of two control groups in the present study enabled us to show that facial expressions of pain among individuals with CP and ID are increased...
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already at baseline compared with controls, presenting a challenge in identifying mild pain. In addition, the use of calibrated stimuli enabled us to differentiate between responses to pain vs rest and between responses to mild vs moderate pain.

It is noteworthy that studies assessing pain responses in clinical settings have also demonstrated increased facial expressions among individuals with ID compared with controls [e.g., 17–27]. Although experimental pain may not necessarily predict acute and chronic pain responses in clinical setting, taken together, the previous and present results suggest that individuals with CP and ID may be more vulnerable to both experimental and clinical pain and that careful monitoring of their conditions is pertinent in order to maintain their health and well-being.

Self-Report Abilities of Individuals With CP and ID

In accordance with the facial expressions, self-ratings of pain obtained from CP individuals with ID using the pyramid scale exhibited a stimulus-response relationship with stimulation intensity. This relationship that likewise occurred in controls suggests that individuals with mild-moderate ID can successfully use the pyramid scale. Note, however, that there was a discrepancy between subjective ratings (using the pyramid scale) and facial expressions in 400 kPa; whereas group differences in self-reports disappeared, they were maximal for facial expressions at this stimulation intensity. This could be due to the lower sensitivity level of the pyramid scale (6 categories) compared with the FACS (14 categories with six frequencies each) and to the cognitive capacity of the person using the scale. However, the discrepancy may also stem from the nature of the two measures. Self-reports seem to be more under the influence of higher mental processes than facial expressions, thus are more subject to purposeful distortion [15,16].

Studies are inconsistent with regard to the ability of individuals with ID to provide adequate pain self-reports using scales. For example, in some studies individuals with ID of etiologies other than CP were able to use faces scales in order to rate their clinical pain [44,45]; whereas in other studies they could not provide an appropriate report [18,46]. Similarly, numerical rating scales and colored visual analog scales were found suitable for individuals with ID in some studies [47,48] but not in others [21,27,44]. However, the cube and box scales enabled responses from these individuals [46,49].

Obviously, the degree of ID plays an important role in the ability of individuals to use self-report scales; however, it appears that concrete/graphical scales that can symbolize the amount of pain are easier for them to grasp. The use of the Pyramid scale herein that was validated both among controls in a preliminary study and herein among individuals with ID, using calibrated stimuli, seems highly appropriate in detecting pain intensity in this population. The pyramids symbolize pain intensity by their size and their gradual increase, enabling better understanding of the concept of intensity. Further studies are needed to test the use of the pyramid scale by individuals with ID in clinical conditions.

Autonomic Variables as Pain Indicators

None of the autonomic variables correlated with stimulation intensity, suggesting the lack of their validity as indicators of experimental pain among CP adults with mild-moderate ID. There is evidence, however, that individuals with ID due to autism or CP present elevated HR during venipuncture and removal of tracheostomy compared with unimpaired individuals [26,50]. It is possible that the pressure stimuli administered in the present study were not strong enough to evoke an autonomic reaction such as the clinical insults. It is also possible that the sample was not sufficient to test the validity of the autonomic variables as pain indicators due to their inherent variability.

Despite the lack of correlation between stimulation intensity and the autonomic variables, we found group differences; PA was significantly higher and GSR significantly lower in CP individuals with ID than controls. These findings are in line with previous reports on alterations in the autonomic function in CP [51–53]. It should be pointed out, however, that the CP individuals without ID exhibited values similar to healthy controls, suggesting perhaps that the autonomic function may also be influenced by the cognitive status. Not mutually exclusive is the possibility that individuals of the CP and ID were more alert or apprehensive throughout the experiment compared with the two control groups, affecting their level of arousal.

Freezing

It was interesting to find that despite enhanced facial expressions, the majority of individuals with CP and ID also exhibited freezing in response to noxious compared with innocuous stimuli. Freezing among individuals with ID of other etiologies was already observed in our previous study during vaccination, especially among individuals with severe-profound ID [18]. Weiner et al. (1999) was the first to report that freezing (stillness) was frequent among individuals with cognitive impairment who suffered from chronic pain [39]. Symons et al. (2010) found no difference in freezing between sham and active stimulation; however, the active stimuli were generally innocuous [31]. Thus, freezing is characteristics of ID regardless whether the etiology is CP or other.

During freezing, the individuals might appear detached and not bothered by the pain. This may give a wrong impression of not being in pain and may therefore prevent proper care [54,55]. Considering the high frequency of freezing and the discrepancy between facial actions and freezing, it might be helpful to incorporate “freezing” as an item in behavioral checklists and use it...
as an additional indicator of pain. It should be pointed out, however, that while freezing might indeed be a specific indicator of pain it might also be indicative of fear, surprise, paying attention, or other phenomena that need further study.

Limitations and Clinical Implications

This study provides novel information on the validity of behavioral and physiological responses as pain indicators; yet several issues should be considered. First, the results apply to individuals with mild-moderate ID due to CP. Similar tests should be performed among those with more severe ID and other ID etiologies. Second, due to communication problems it is difficult to discern the pain responses from that of stress/anxiety and therefore the facial reactions observed may reflect a combination of pain and anxiety. Although this possibility is unlikely due to the use of FACS items that are considered pain specific, some of them may also indicate anxiety.

Based on both the facial expression and self-reports, the results of this study suggest that individuals with CP and ID may perceive painful stimuli as more intense than normal. Thus, while individuals with ID and specifically those with the combination of ID and CP are at high risk of experiencing pain due to congenital and acquired pathologies, they may suffer to a greater extent and in addition they may have difficulties in verbally expressing their pain. Therefore, pain alleviation means should be administered to these individuals, considering their increased sensitivity and responsiveness to pain.

Caregivers face great challenges in identifying and quantifying pain among their patients with ID in order to provide an appropriate care. Craig has outlined the complexity of the pain experience and its evaluation in the Social Communication Model of Pain [16,56] which takes into account the biological and psychosocial predispositions, contexts, and consequences. From the perspective of caregivers, the model pertains that pain assessment and subsequently pain management is influenced by all of these factors. This is particularly important when the communication capabilities of persons in pain are limited as in the case of intellectual disability. Considering that each pain measure contributes unique information on the individual the use of various measures is beneficial.

The results of this study show that self-reports of pain can be successfully obtained from individuals with mild-moderate ID, using the pyramid scale. In such instances, facial expressions provide a supplement mean to assess the individual’s pain. However, among individuals with ID who cannot provide adequate self-reports, facial expressions but not autonomic variables may be the single pain measurement used. Until more optimal tools are available for this purpose, caregivers should also take into consideration unexpected and sometimes seemingly unsuitable responses to painful incidents (e.g., freezing).

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