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Corresponding Author:	Ruth Defrin Tel Aviv University Sackler Faculty of Medicine Tel Aviv, ISRAEL		
First Author:	Ruth Defrin		
Order of Authors:	Ruth Defrin		
	Tali Benromano		
	Chaim G Pick		
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Abstract:	We studied whether there exist variations in pain responses between different intellectual and developmental disability (IDD) etiologies. Self-reports and facial expressions (Facial Action Coding System=FACS) were recorded during experimental pressure stimuli and compared among 31 individuals with IDD – 13 with cerebral palsy (CP), 9 with Down syndrome (DS), 9 with unspecified origin (UIDD) – and among 15 typically-developing controls (TDCs). The CP and DS groups had higher pain ratings and FACS scores compared to the UIDD and TDC groups, and steeper stimulus-response functions. The DS group exhibited the most diverse facial expressions. There were variations in the foci of facial expressions between groups. It appears that different IDD etiologies display distinct pain responses.		

Unique Pain Responses in Different Etiological Subgroups of Intellectual and Developmental Disabilities

Abstract

We studied whether there exist variations in pain responses between different intellectual and developmental disability (IDD) etiologies. Self-reports and facial expressions (Facial Action Coding System=FACS) were recorded during experimental pressure stimuli and compared among 31 individuals with IDD – 13 with cerebral palsy (CP), 9 with Down syndrome (DS), 9 with unspecified origin (UIDD) – and among 15 typically-developing controls (TDCs). The CP and DS groups had higher pain ratings and FACS scores compared to the UIDD and TDC groups, and steeper stimulus-response functions. The DS group exhibited the most diverse facial expressions. There were variations in the foci of facial expressions between groups. It appears that different IDD etiologies display distinct pain responses.

Keywords: Intellectual disability, experimental pain, IDD etiology, pain measurement, facial action, self-report

Introduction

The challenges entailed in pain assessment among individuals with an intellectual and developmental disability (IDD) are widely acknowledged (de Knegt and Scherder, 2011; Barney et al., 2020A). They may be limited in their ability to comprehend the implications of an injury or pain and to adequately communicate it. Nevertheless, individuals with IDD are more exposed to painful conditions. Studies have noted higher rates than normal of injuries, falls, and accidents in IDD (Finlayson et al., 2010, Ho et al., 2019). Furthermore, the etiology of IDD may lead to specific painful complications. For example, individuals with Down syndrome (DS) may experience pain due to diabetes, obesity, osteoporosis, temporomandibular disorder, and atlantoaxial instability (Kinnear et al., 2018; Tsou et al., 2020). Individuals with cerebral palsy (CP) are exposed to a plethora of painful musculoskeletal problems due to exaggerated reflexes, flaccidity/rigidity, and unsteady walking (Tervo et al., 2006; van der Slot et al., 2020; Van Gorp, 2020). Individuals with Prader-Willi syndrome frequently experience pain due to scoliosis (Butler et al., 2002).

Apart from the varied sources of pain in different IDD etiologies, the clinical and physiological differences between IDD etiologies may reflect differences in the function of the pain system, hence in individuals' pain responses. Facial expressions and body gestures (e.g., Shinde et al., 2014; Benromano et al., 2017A; Barney et al., 2020B; Defrin et al., 2021) as well as pain-evoked potentials (EPs) (Benromano et al., 2017B) and autonomic variables (Barney et al., 2015; Benromano et al., 2017A) have been used to record pain responses following experimental stimuli among individuals with IDD. Although mostly increased responses compared to those found among typically-developing controls (TDCs) were noted, potentially indicating an increased vulnerability to noxious stimuli in IDD, these studies focused on a particular IDD etiology. Consequently, it is unclear whether there exist unique, identifiable pain responses among etiologically different IDD groups.

In addition, sensory testing assessing the function of the pain system has been mostly performed among individuals with a particular IDD etiology. For example, as compared to TDCs, pain thresholds were lower among people with DS (Valkenburg et al., 2015) and CP (Riquelme et al., 2014) but higher among individuals with Prader–Willi syndrome (Priano et al., 2009). It is therefore unclear whether there exist variations in pain sensitivity within subpopulations of IDD. In a previous study,

pain threshold of individuals with IDD was lower than that of TDCs; however, within the IDD group, males with DS had lower pain thresholds than did those with unspecified IDD (Defrin et al., 2004). This finding may point toward possible variations in pain sensitivity related to IDD etiology.

Importantly, although the prevalence of chronic pain is higher among individuals with IDD compared to that of TDCs (Oberlander, 2006; McGuire et al., 2010; van der Slot, 2020), they receive less treatment for pain than do TDCs (Walsh et al., 2011; Axmon et al., 2018; Segerlantz et al., 2019). Possible variations in pain responses between different IDD etiologies may further complicate pain management for these individuals. For example, individuals of certain IDD etiologies may exhibit vigorous facial and body movements to noxious events, whereas individuals of other IDD etiologies may have limited behavioral responses due to paresis/paralysis, which may deem them as experiencing weaker pain. Individuals of other IDD etiologies may also freeze in response to pain, and consequently may mistakenly be considered indifferent to pain. Therefore, various response types should be recognized in order to optimize pain assessment, and in order to provide proper, individually-based pain care.

In this study, we compared for the first time behavioral responses to pain among three IDD groups. Innocuous and noxious experimental stimuli were used to test whether the three IDD groups differed from each other and from TDCs in their: 1) subjective pain reports and 2) facial responses.

Materials and Methods

1. Participants

The study included 46 adults: 31 individuals with IDD and 15 TDCs. The IDD group comprised three subgroups: participants with CP (n=13), participants with DS

(n=9), and participants with an unspecified IDD origin (UIDD; n=9). Individuals with IDD were recruited from two daycare centers for people with IDD (the daycare centers belong to two organizations for people with disabilities: Alin and Elwyn). IDD was diagnosed according to clinical assessment and standardized testing of intelligence (including the Wechsler Intelligence Scale for Children-Revised and the Wechsler Preschool and Primary Scale of Intelligence) performed by a team from the Ministry of Social Affairs and Social Services, which supervises all services related to IDD. The individuals had an estimated level of mild or moderate IDD, and the ability to understand their mother tongue. Medical and other information on participants with IDD was obtained from their primary caregiver and the daycare center physician, and if needed also retrieved from their medical records by their legal guardian. TDCs were students and employees of the university or the daycare centers. Exclusion criteria for all the participants were: acute or chronic pain, bruises or injuries in the testing regions, and idiosyncratic behaviors such as self-injury and moaning (among the individuals with IDD). Acute or chronic pain conditions were excluded as the purpose of the present study was to analyze pain behavior in a controlled environment following experimental pain, namely controlled and quantifiable stimuli (i.e., experimental pain), so that the focus would be on the nuances of pain behavior related to IDD etiology. Notably, pain introduces a significant, strong confounder with respect to the evaluation methods used in the present study and the inclusion of individuals with acute and chronic pain would require tripling the sample size, an extremely difficult task in the case of IDD and this particular experimental protocol, considering the required approvals and consents. Moreover, the confounding effect of acute and chronic pain should be controlled, for example by including only a single clinical condition and recruiting people with typical development who suffer from the

same condition, a task that was beyond the scope of the present study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the university (3012/2012), the institutional review board of Israel's Ministry of Social Affairs and Social Services (201323-01), and by the legal guardians of the participants with IDD. Prior to the study, written informed consent was obtained from all the TDCs and from the legal guardians of all the individuals with IDD, after the study's aims and protocols had been explained. In addition, the protocol was explained to the participants with IDD and their escorts upon their arrival to the lab, and each step of the protocol was carried out only after their oral consent was obtained.

2. Instruments

Pressure stimuli were delivered using a hand-held pressure algometer (Somedic Sales AB, Algometer type II, Sweden) with an accuracy of \pm 3%. The algometer operates by exerting increasing pressure (at a constant rate) that is monitored on an electronic screen by the built-in pressure transducer. The size of the tip of the algometer that is pressed against the skin was 1 cm².

Subjective pain ratings following pressure stimuli were obtained using the Pyramid Pain Scale. The scale comprises a graphical rectangular plastic ruler, 20 cm long and 7 cm wide, on which 5 color pyramids of different increasing sizes are situated on a horizontal base, each representing the amount of pain. The area of the base with no pyramid above it (the left endpoint) signifies no pain (= 0) and the highest pyramid (the right endpoint) signifies the worst possible pain (= 5) (Benromano et al., 2017A).

Facial expressions to pressure stimuli were analyzed using the Facial Action Coding System (FACS). The FACS consists of a list of universal facial actions (action units or AUs) that are based on the movement of specific muscles or groups of

muscles of the face (Ekman and Friesen, 1978). We used 14 AUs that have been found to provide valid, reliable, and sensitive indications of pain (Prkachin and Mercer, 1989; Benromano et al., 2017A; Kunz et al., 2019). The UAs were: brow lowerer (AU4), cheek raiser (AU6), lid tightened (AU7), nose wrinkler (AU9), upper lip raiser (AU10), lip corner puller (AU12), lip stretcher (AU20), lip presser (AU24), lips part (AU25), jaw dropper (AU26), mouth stretch (AU27), eyelid drop (AU41), eyes closed (AU43), blink (AU45).

The scoring of the FACS was done by two certified coders. The inter-observer agreement was reported in a previous study. Essentially, two independent raters analyzed the facial expressions of 85% of the participants separately, in order to prevent any influences between them. The agreement between them was computed twice: 1) with the Ekman and Friesen conservative FACS reliability formula = number of actions on which Coder 1 and Coder 2 agreed X number of actions scored by the two coders, and 2) with interclass correlation (ICC). Both calculations obtained high agreement levels which varied according to the population tested and the condition. For example, 86.7 and 79.2 for typically developing participants and IDD participants, respectively, at baseline, and 90.1 and 75.3, respectively, for 200 kPa (for more information please see (Benromano et al., 2017A).

3. Procedures

The experimental protocol was designed by the experimental pain working group of the European Cooperation in the Field of Scientific and Technical Research (COST) program, termed "Pain assessment in patients with impaired cognition, especially dementia" (action TD1005). The aims of this international group are to raise awareness of the subject of pain among individuals with cognitive impairment and to develop a pain assessment tool-kit for this population. The protocol was

previously tested on healthy volunteers prior to testing individuals with IDD in order to verify the intensity of the pressure stimuli and the ability to endure them for the required duration (Benromano et al., 2017A).

Prior to actual testing, all the participants underwent a training session. The training session included familiarization with the pressure algometer and scoring with the pyramid scale. During training, the participants received various intensities of pressure stimuli in the thigh region (which was not stimulated later on). After each stimulus, they were asked to report whether the stimulus was painful or not, and if they said yes, they were asked to look at the pyramids on the scale and point to the pyramid that matched their pain. There was a learning curve. As this procedure was repeated several times, we could teach participants that the base of the pyramid scale (=0) corresponded to no pain, namely no stimulation or the 50 kPa stimulus, whereas increasing levels of stimuli corresponded with the increasing sizes of the pyramids. The examiner did not proceed to the study until she believed in the participant's ability to grasp the proportions of the pyramids.

After a five-minute break, the experiment began. Figure 1 presents the experimental set-up. The examiner stood behind the participant in order not to interfere with videotaping and to properly administer the stimuli. Each participant received a total of 6 pressure stimuli to the upper mid part of the trapezius muscle (halfway between the neck line and the shoulder line). The stimuli were administered alternately to the right and left side (3 stimuli on each side) at intensities of 50, 200, and 400 kPa. These intensities were chosen in order to evoke one innocuous, one mildly noxious, and one moderately noxious pressure sensation, respectively (Benromano et al., 2017A). Each stimulus rose from a baseline of 0 kPa to the designated intensity and lasted 7 seconds: a 2-second increase and 5 seconds at the

destination intensity. The participants were asked to rate their pain after each stimulus, using the pyramid scale by pointing with their finger to the pyramid that best fitted their pain.

The inter-stimulus interval (ISI) between sides was 2 minutes, and the ISI on the same side was 4 minutes. The examiner moved the stimulation site by about 0.5 cm when returning to a previous location. These ISIs were chosen in order to allow a proper pain rating and avoid carry-over between stimuli, due to our decision not to randomize the stimulation intensities. The reason for lack of randomization was that individuals with IDD, who due to randomization in a preliminary study, 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 participants could easily tolerate the entire protocol.

4. Recording and analysis of the facial 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, prior to the start of each stimulus, to keep their gaze on a fixed point: a green "X" shape that hung on the wall across from them (Figure 1). The facial expressions were analyzed retrospectively, using the slowmotion option. At baseline, the participants were not engaged in any specific activity, and a random 7-second segment was sampled for analysis. During pressure stimulation, the analysis commenced as soon as the examiner started the stimulus, and it lasted 7 seconds. The video segments of the different conditions (rest, the innocuous, and the two noxious stimuli) were presented to the raters in a random order to prevent biases related to stimulation order.

The intensity of most of the FACS AUs was coded on a 6-point intensity scale, ranging from 0 (= no action), through 1 (= minimal action/trace), to 5 (= maximum action). The intensity coding of AU43 (eyes closed) was binary – that is, 0 or 5 – and the intensity coding of AU45 (blink) 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 of the 14 AUs combined (Prkachin and Mercer, 1989). We were unable to code facial actions during 400 kPa stimulation of two individuals with CP and one individual with DS as they turned their heads away from the stimulus when stimulation commenced.

5. Data analysis

Data were processed with IBM SPSS statistics software (version 25). The normal distribution was evaluated using the Kolmogorov-Smirnov test. First, the values of the FACS and pain ratings that were obtained from the right and left shoulder were compared, with body side as the within-group factor. As there were no body side effects, data from the two shoulders for each variable separately were averaged for use in subsequent analyses. Since each subject underwent the same protocol this is a repeated measure design where the subjects were nested within four groups. Therefore, repeated measure analysis of variance (ANOVA) and Generalized Estimation Equations (GEE) with two main effects (group type and condition) and their interaction were used to measure the effect of group (CP, DS, UIDD, and TDC) and of condition (baseline, 50, 200, and 400 kPa) on the dependent outcome measures: FACS and pyramid scale scores, respectively. Additionally, parametric and non-parametric one-way ANOVAs were used to evaluate group effect within each condition. Post hoc tests were corrected for multiple comparisons. The correlation

between variables was calculated with Pearson's or Spearman's r, depending on the variable type. P-values <0.05 were considered significant.

Results

1. The study groups

Table 1 presents the four study groups. None of the groups differed in age or sex distribution. The IDD groups did not differ from one another in the level of IDD or in medication intake. Individuals in the CP group had various levels of physical disability, which none of the other groups had (Table 1).

2. Self-ratings

Figure 2 presents the pyramid scores in response to pressure stimulation for the four groups. Table 2 summarizes the analyses. Generalized Estimation Equations revealed a significant global effect of group type [Wald $\chi^2(3,6)=9.93$, p<0.05] and of condition [Wald $\chi^2(2,6)=42.28$, p<0.0001]. The interaction group X condition was also significant [Wald $\chi^2(3,6)=19.45$, p<0.01], suggesting that the increase in pain scores with the increase in stimulation intensity was not uniform across the four groups. The Kruskal–Wallis test revealed a significant group effect in 50 kPa [H(3)=12.58, p<0.01] and in 200 kPa [H(3)=15.30, p<0.01], and a borderline group effect in 400 kPa [H(3)=6.63, p=0.07]. There was no group effect at baseline. Corrected post hoc comparisons revealed that participants of the CP and DS groups rated the innocuous 50 kPa stimulus as painful whereas the vast majority of the participants of the UIDD and TDC groups rated it as non-painful (CP vs. UIDD: Z=-1.58, p=0.08; CP vs. TDC: Z=-3.27, p<0.01; DS vs. UIDD: Z=-2.01, p<0.05; DS vs. TDC: Z=-2.73 p<0.01). The CP and DS groups had similar pain ratings, and the UIDD and TDC groups had similar pain ratings. The pain scores for the noxious 200 kPa among both the CP and DS groups were significantly higher than those of both

the UIDD and TDC groups (CP vs. UIDD and TDC: Z=-2.46 and -3.18, respectively, p<0.01 for both; DS vs. UIDD and TDC: Z=-2.43 and -2.49, p<0.01 for both), who had similar ratings. In 400kPa, the pain scores of the CP and DS groups were significantly higher than those of the UIDD group (Z=-2.21 and -2.22, p<0.05 for both) but not compared to the TDC group (Z=-1.19 and -1.21, p=0.1 for both) (Figure 2).

Among each group separately, the pyramid scores correlated with stimulation intensity, suggesting a significant stimulus-response relation for pain (r=0.72, p<0.0001; r=0.60, p<0.001; r=0.65, p<0.0001 and r=0.85, p<0.0001 for the CP, DS, UIDD, and TDC group, respectively), as also suggested by the significant aforementioned condition effect. Figure 2 shows that all the groups exhibited a gradual increase in the pyramid scores with the increase in stimulation intensity; however, the slopes of the CP and DS groups were steeper than those of the UIDD and TDC groups (1.17 and 1.18 vs. 0.96 and 0.66, respectively).

3. Facial expressions

Figure 3 presents the sum of the FACS scores in response to pressure stimulation for the four groups. Table 2 summarizes the analyses. A repeated measures ANOVA revealed a significant global effect of group type [F(3,35)=10.54, p<0.0001] and of condition [F(3,105)=18.77, p<0.0001] on the FACS scores. The interaction group type X condition was not significant [F(9,105)=0.94, p=0.45], suggesting that all the groups exhibited an increase in FACS scores with the increase in stimulation intensity. A one-way ANOVA revealed a significant group effect within every stimulation condition [F(3)=4.72, p<0.01 for baseline; F(3)=11.40, p<0.0001 for 50 kPa; F(3)=10.95, p<0.0001 for 200 kPa; and F(3)=3.56, p<0.05 for 400 kPa]. Corrected post hoc comparisons revealed that at baseline, the FACS scores of the CP group were slightly higher but not significantly so than those of the DS group (p=0.13), and both of these groups had significantly higher FACS scores than did the UIDD group (p<0.05) and the TDC group (p<0.001). At 50 kPa, the FACS scores of the CP and DS groups were also similar, and both had higher scores than did the UIDD group (p<0.001 and p<0.05, respectively) and the TDC group (p<0.001 and p<0.05, respectively) and the TDC group (p<0.001 and p<0.05, respectively). Similarly, at 200 kPa, the FACS scores of the CP and DS groups were similar, and both had higher scores than did the UIDD group (p<0.01). At 400 kPa, only the FACS scores of the CP group were significantly higher than those of the UIDD (p<0.05) and the TDC group (p<0.01), although the FACS scores of the CP and DS were similar. The scores of the DS group showed only a trend toward being higher than those of the UIDD and TDC groups (p<0.08) (Figure 3).

Among each group separately, the FACS scores correlated with stimulation intensity, suggesting a significant stimulus-response relation for the FACS (r=0.43, p<0.01; r=0.50, p<0.01; r=0.47, p<0.05 and r=0.42, p<0.01 for the CP, DS, UIDD, and TDC group, respectively), as also indicated by the significant condition effect. Yet the slopes of the stimulus-response functions were different among the groups so that the slope of the CP and DS groups were much steeper (6.73, R²=0.99 and 7.78, R²=0.92, respectively) than those of the UIDD and TDC groups (3.48, R²=0.56 and 3.96, R²=0.73, respectively) (Figure 3).

4. Single AU analysis for the noxious stimulation

Table 3 presents the frequency of individuals in each group who exhibited each AU for the noxious pressure stimuli (200 and 400 kPa). At 200 kPa, the most expressive group was the DS group where 7 of the AUs were expressed by the majority of the group. These AUs included actions around the lips and mouth. Both the CP group and the majority of the DS group expressed AU7 (eyelids tightened). Lastly, both the UIDD group and the majority of the TDC group exhibited AU45 (blinked). At 400 kPa, the CP and DS groups showed more similarities in that the majority of both these groups expressed AU7, AU10 (upper lip raiser), and AU25 (lips part). The UIDD group also expressed AU7 but in addition uniquely exhibited AU43 (eyes closed). Finally, the majority of the TDC group exhibited AU41 (eyelid drop) and AU45 (blink).

5. Correlations between self-ratings and the FACS

Among each group separately, the self-ratings with the pyramid scale correlated moderately with the FACS scores: CP r=0.46, p<0.001; DS r=0.37, p=0.051; UIDD r=0.60, p<0.001; TDC r=0.47, p<0.001.

Discussion

The study's aim was to explore distinct pain responses among etiologically different IDD groups. Individuals with CP and those with DS had increased selfreported pain and FACS scores compared to individuals with UIDD and TDC, with some variations between the IDD groups in the facial AUs.

Behavioral responses to pain

A distinct behavioral pattern appeared in that self-reports of individuals with DS and those with CP were higher than those with UIDD, not only for noxious stimuli (200 and 400 kPa) but also for innocuous stimuli (50 kPa). Similarly, the DS group and in particular the CP group had increased facial reactivity during both noxious and innocuous stimuli, compared to that of the UIDD. Interestingly, the UIDD group's self-reports of pain were almost indistinguishable from those of the TDC group, as were the slopes of their stimulus-response function. We may therefore conclude that the IDD etiology matters with respect to pain perception and expression and that the IDD population cannot be regarded as homogenous in this respect.

Previous studies have reported increased pain behavior following experimental (noxious) stimuli among individuals with IDD, often of a particular etiology. For example, eight adolescents with neuronal ceroid lipofuscinosis exhibited increased facial and body responses to repeated application of a von Frey monofilament compared to their siblings (Barney et al., 2015). Thirteen individuals with CP and IDD had increased facial expressions and self-reported pain following noxious pressure stimuli compared to individuals with CP without IDD and controls (Benromano et al., 2017A). Twenty individuals with global developmental delays exhibited increased body reactivity compared to controls to pin prick and repeated von Frey (Barney et al., 2017). Although these experimental studies agree that individuals with IDD respond more strongly to noxious stimuli compared to TDCs, the current study comparing etiologically different IDD subgroups revealed nuances in the response patterns, suggesting the possibility of distinctive, etiologically-related pain behaviors.

Specifically, although all four groups exhibited facial activity around the eyes and mouth, the DS group had the most diverse facial activity compared to the CP, UIDD, and TDC groups, and the TDC group was the least active. The CP and DS groups were similar in their foci of facial actions, mostly with opening or widening of the mouth/lips and tightening of the eyelids; however, raising the cheeks and dropping the jaws were unique to the DS group. The UIDD group showed facial expressions only in the eyes, including being the only IDD group to close their eyes and/or to blink in response to pain. Although these AUs have previously been observed among individuals with IDD (e.g., La Chapelle et al., 1999; Breau et al., 2001; Symons et al.,

2010; Defrin et al., 2006; Rattaz et al., 2013; Bergström-Isacsson et al., 2013), rarely have they been analyzed following calibrated noxious stimuli.

Possible explanations for increased pain behavior in CP and DS

The increased behavioral responses of individuals with DS and CP compared to those of the UIDD group may result from observers' bias. Observers may be subject to biases related to the physical attractiveness of the observed (Hadjistavropoulos et al., 1990; LaChapelle et al., 1999) and stereotyped beliefs or preexisting knowledge about the observed (Prkachin and Craig, 1995; Breau et al., 2009; Hampton et al., 2018). Given that members of the DS and CP groups could be distinguished from the TDC and UIDD groups based on their appearance (although this was not always the case for the latter) it is possible that the observers were influenced by this bias. However, this eventuality seems unlikely, as the DS and CP groups also differed from the UIDD and TDC groups in their self-reports- responses unrelated to the observers. Also, the FACS was coded by trained, independent coders and the observed behaviors exhibited high reliability and agreement between the coders.

The increased responsivity in the DS and CP group is, however, supported by previous reports recording lower pain thresholds among these individuals than among TDCs (Defrin et al 2004; Valkenburg et al 2015; Riquelme et al., 2010;2015). Individuals with autism spectrum disorder also had increased sensitivity to thermal pain (Cascio et al., 2008), however, in contrast, individuals with Prader–Willi syndrome (Priano et al., 2009) had higher pain thresholds compared to TDCs. Interestingly, the DS group described herein had increased pain responses despite previous reports showing prolonged reaction time (Defrin et al., 2004) and somatosensory EPs latency (Chen and Fang, 2005). This apparent dissonance was demonstrated when pain thresholds of individuals with DS were measured either with,

or without, a reaction time component. Whereas the former method induced a higher pain threshold than normal, the latter method induced a lower pain threshold (Defrin et al., 2004). Similarly, children with DS were pain hypersensitive compared to their siblings only when measured with a reaction time-independent method (Valkenburg et al., 2015). Thus, the increased sensitivity and reactivity to noxious stimuli of individuals with DS or CP is exposed when voluntary reaction times are excluded from the assessment or via FACS scores and self-reports.

This increased behavioral reactivity may result from a reduced capacity of descending pain inhibition. Imaging studies have revealed reduced activation of the prefrontal cortex in individuals with DS compared with controls (Vega et al., 2015; Wilson et al., 2019), as well as decreased white matter volume in the brain stem (Shiohama et al., 2019) and additional brain regions involved in pain processing (deKnegt and Sherder, 2011). These data may explain the lack of sufficient control over nociceptive input in individuals with DS, which may also be evident in their increased pain EPs (Benromano et al., 2017B). A general reduction in white matter volume was also observed among individuals with CP (Pannek et al., 2014) as well as altered functional connectivity within the sensorimotor, frontoparietal, and salience networks (Qin et al., 2018), all of which may affect the processing of nociceptive information.

Notably, several observational studies have come to an opposite conclusion. Hyposensitivity to pain was concluded for individuals with DS based on delayed responses to touching an ice cube (Hennequin et al., 2000) and for individuals with UIDD based on proxy reports concerning their responses to potentially painful situations (Biersdorff et al., 1994). However, despite delays in behavioral and biological responses to invasive procedures in newborns with DS compared to

controls, when pain was finally perceived, it persisted for a longer duration among the former (Aguilar Cordero et al., 2015). This finding therefore supports an increased pain susceptibility in individuals with DS and suggests that the timing of their responses is misleading. The notion of reduced pain sensitivity in those with IDD based on their self-injurious behavior (SIB) has also been undermined by the increased facial expressions to various stimuli of individuals expressing SIB as compared to those without SIB (Symons et al., 2010). In the same vein, a large survey of families enrolled in the Australian Rett Syndrome Database concluded that a common feature of Rett syndrome is decreased pain sensitivity (Downs et al., 2010). However, the increased innervation density of epidermal nerve fibers stained for calcitonin gene-related protein in adolescents with Rett Syndrome compared to controls may suggest otherwise (Symons et al., 2019). Quantitative pain assessment is thus imperative in order to recognize pain sensitivity in IDD; otherwise, insufficient knowledge may lead to insufficient pain management and unnecessary suffering (e.g., Barney et al., 2017A).

Summary and implications

To our knowledge, this is the first comparison of behavioral responses to calibrated noxious stimuli between several IDD etiologies. The results suggest that compared to individuals with UIDD, those with CP and DS perceive painful stimuli as more intense and express increased facial expressions to both innocuous and noxious stimuli. Furthermore, individuals with DS exhibit more diverse facial expressions in response to pain than do individuals with CP and UIDD.

Several limitations should be considered. First, the results are specific and relevant to the specific IDD etiologies included in the study. Future studies may wish to compare clinical pain behavior between different IDD etiologies. Exploring distinct pain responses in additional IDD etiologies and comparing pain-free individuals with those suffering from pain is warranted. Second, the results are limited to individuals with mild-moderate IDD. Third, although individuals with non-genetic IDD etiologies comprise at least 50% of all people with mild-moderate IDD (e.g., Huang et al., 2016), the results of the participants with UIDD in the current study may not be applicable to all the individuals with unspecified IDD or global developmental delay. Fourth, although the groups did not differ significantly in IDD level, its none equivalent distribution may have affected the results. Fifth, facial expressions may also indicate distress; the recorded FACS responses may reflect a combination of pain and distress. Nevertheless, the increased responses recorded among individuals with CP and DS, along with their potential health hazards, may render them more vulnerable to noxious stimuli than individuals with UIDD, although individuals with UIDD are in no way pain hyposensitive. Thus, all individuals with IDD require careful monitoring of any possible sign of distress/pain and the administration of pain alleviation medication accordingly. As caregivers often rely on pain behavior for detecting pain (Genik et al., 2017), and considering the variance in facial expressions between IDD etiologies and potential biases, caution should be exercised when interpreting such behaviors.

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Figure legends

- **Figure 1:** The experimental setup: Pressure stimuli were applied to the shoulder region with a pressure algometer during which time self-reports were obtained following each stimulus. Facial expressions were continuously videotaped and then analyzed offline.
- Figure 2: The Pyramid pain scores of the DS group were significantly higher compared to those of the UIDD group (1) and TDC group (2) in both the innocuous and noxious conditions. Similarly, the Pyramid pain scores of the CP group were higher than those of the UIDD (3) and TDC (4) groups (^p=0.06, *p<0.05; **p<0.01). The UIDD and TDC groups had similar pain ratings. The values denote the group mean±SEM (raw data).</p>
- Figure 3: The FACS scores of the CP group were significantly higher compared to those of the UIDD group (1) and TDC group (2) in all of the stimulation conditions including at rest. The FACS scores of the DS group were higher than those of the UIDD (3) and TDC (4) groups during both innocuous and noxious stimulation (^p=0.08, *p<0.05; **p<0.01, ***p<0.001). The values denote the group mean±SEM (raw data).

Figure 1



Figure 2



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Figure 3



Table 1

Characteristics of the four study groups

	Cerebral palsy	Down syndrome	Unspecified origin	Typically developing controls	p-value#
Number	13	9	9	15	
Females (n, %)	7(53.8)	7(77.7)	4(44.4)	8(53.3)	.128
Age (M, SD)	34.4(4.5)	33.5(2.2)	38.8(9.4)	31.3(7.7)	.181
IDD level (n, %):					.305
Mild	9(69.2)	2(22.2)	5(55.5)		
Mild-moderate		4(44.4)	3(33.3)		
Moderate	4(30.7)	3(33.3)	1(11.1)		
Medications					.819
Psychotropic	3(23.1)	2(22.2)	2(22.2)		
Antiepileptic	2(15.4)	0	0		
Muscle relaxants	2(15.4)	2(22.2)	2(22.2)		
Antihypothyroidism	0	6(66.6)	2(22.2)		
Physical disability	13(100)*	0(0)	0(0)	0(0)	<.001

Note. #parametric one-way ANOVA for continuous variables/Kruskal Wallis for non-parametric variables, *p<0.001 compared to all other groups.

Table 2.

Summary of the analyses

Main effects and their interaction						
	Model	Group effect	Condition effect	Group*Condition interaction		
Self-report	Generalized	χ2(3,6)=9.93	χ2(2,6)=42.28	χ2(3,6)=19.45		
	Estimation	07	0001	0.1		
	Equations	p<.05	p<.0001	p<.01		
FACS	repeated measures	F(3,35)=10.54	F(3,105)=18.77	F(9,105)=0.94		
	ANOVA	p<.0001	p<.0001	p=.45		
One way ANOVAs for group effect within stimulation condition						
		Trends of post-hoc		Trends of post-hoc		
	Self-report	between-group tests	FACS	between-group tests		
Baseline	H(3)=1.53		F(3)=4.72			
	P=.21	CP,DS,UIDD,TDC	p<.01	CP,DS > UIDD,TDC		
50kPa	H(3)=12.58		F(3)=11.40			
	p<.01	CP,DS >UIDD,TDC	p<.0001	CP,DS > UIDD,TDC		
200kPa	H(3)=15.30		F(3)=10.95			
	p<.01	CP,DS >UIDD,TDC	p<.0001	CP,DS > UIDD,TDC		
400kPa	H(3)=6.63		F(3)=3.56			
	p=.07	CP,DS,TDC >UIDD	p<.05	CP,DS > UIDD,TDC		

Note. Each subject underwent the same protocol and therefore the subjects were nested within four groups in the repeated measure design. ANOVA= analyses of variance, FACS=facial action coding system, CP=cerebral palsy, DS= Down syndrome, UIDD= unspecified intellectual and developmental disability, TDC= typically-developing controls.

Table 3

The frequency (%) of each AU among the groups during noxious stimulation

	<u>200 kPa</u>			<u>400 kPa</u>				
	СР	DS	UIDD	TDC	СР	DS	UIDD	TDC
Brow lowerer (AU4)	5(38.5)	6(66.6)	2(22.2)	4(22.2)	5(38.5)	4(44.4)	3(33.3)	6(33.3)
Cheek raiser (AU6)	6(46.2)	6(66.6)	2(22.2)	1(5.55)	6(46.2)	5(55.5)	4(44.4)	6(33.3)
Lid tightened (AU7)	7(53.8)	7(77.7)	4(44.4)	4(22.2)	8(61.5)	6(66.6)	5(55.5)	7(38.8)
Nose wrinkle (AU9)	3(23.1)	4(44.4)	1(11.1)	0	3(23.1)	3(33.3)	2(22.2)	3(16.6)
Upper lip raiser (AU10)	6(46.2)	6(66.6)	1(11.1)	1(5.55)	7(53.8)	5(55.5)	4(44.4)	5(27.8)
Lip corner puller (AU12)	6(46.2)	6(66.6)	1(11.1)	0	6(46.2)	5(55.5)	3(33.3)	5(27.8)
Lip stretcher (AU20)	5(38.5)	6(66.6)	1(11.1)	1(5.55)	5(38.5)	3(33.3)	3(33.3)	6(33.3)
Lip pressor (AU24)	2(15.4)	2(22.2)	3(33.3)	2(11.1)	4(30.8)	2(22.2)	3(33.3)	4(22.2)
Lips part (AU25)	6(46.2)	7(77.7)	2(22.2)	0	7(53.8)	7(77.7)	3(33.3)	3(16.6)
Jaw dropper (AU26)	5(38.5)	6(66.6)	2(22.2)	0	5(38.5)	5(55.5)	2(22.2)	3(16.6)
Mouth stretch (AU27)	4(30.8)	4(44.4)	0	0	4(30.8)	3(33.3)	2(22.2)	2(11.1)
Eyelid drop (AU41)	4(30.8)	2(22.2)	4(44.4)	6(33.3)	3(23.1)	1(11.1)	4(44.4)	9(50.0)
Eyes closed (AU43)	4(30.8)	4(44.4)	3(33.3)	3(16.6)	6(46.2)	4(44.4)	5(55.5)	7(38.8)
Blink (AU45)	4(30.8)	2(22.2)	5(55.5)	17(94.4)	1(7.7)	0	3(33.3)	18(100)

Note. CP=cerebral palsy, DS= Down syndrome, UIDD= unspecified intellectual and developmental disability, TDC= typically-developing controls. In bold are marked those AUs exhibited by more than 50% of the members in each group