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Behavioral changes in brain-injured critical care adults with different levels of consciousness during nociceptive stimulation: an observational study

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Abstract *Purpose:* The primary objective of this study was to describe the frequency of behaviors observed during rest, a non-nociceptive procedure, and a nociceptive procedure in brain-injured intensive care unit (ICU) patients with different levels of consciousness (LOC). Second, it examined the inter-rater reliability and discriminant and concurrent validity of the behavioral checklist used. *Methods:* The non-nociceptive procedure involved calling the patient and shaking his/her shoulder. The nociceptive procedure involved turning the patient. The frequency of behaviors was recorded using a behavioral checklist. *Results:* Patients with absence of movement, or stereotyped flexion or extension responses to a nociceptive stimulus displayed more behaviors during turning (median 5.5, range 0–14) than patients with localized responses (median 4, range 0–10) or able to self-report their pain (median 4, range 0–10). Face flushing, clenched teeth, clenched fist, and tremor were more frequent in patients with absence of movement, or stereotyped responses to a nociceptive stimulus. The reliability of the checklist was supported by a high intra-class correlation coefficient (0.77–0.92), and the internal consistency was acceptable in all three groups (KR 20, 0.71–0.85). Discriminant validity was supported as significantly more behaviors were observed during nociceptive stimulation than at rest. Concurrent validity was confirmed as checklist scores were correlated to the patients' self-reports of pain ($r_s = 0.53$; 95 % CI 0.21–0.75). *Conclusion:* Brain-injured patients reacted significantly more during a nociceptive stimulus and the number of observed behaviors was higher in patients with a stereotyped response.

Keywords Pain measurement · Brain injuries · Adult · Consciousness · Intensive care · Psychometrics

Introduction

Intensive care patients often experience pain, with an incidence rate as high as 56 % at rest [1]. In brain-injured patients, pain is a major concern as it can alter cerebral perfusion and therefore increase the risk of brain damage [2]. In order to provide adequate pain relief, sedatives and analgesics must be administered; however, these drugs can mask clinical signs of neurological complications [2, 3]. Therefore, it is essential to accurately assess pain in order to achieve adequate pain relief without jeopardizing neurological assessment.

Several studies have validated behavioral pain assessment tools recommended and adapted for the general intensive care unit (ICU) population unable to self-report [4–8]. The implementation of these assessment

tools improves pain management and patient outcomes [9, 10]. The few validated tools available for the assessment of pain in ICU adult patients [11, 12] may not be appropriate for brain-injured patients as they exhibit different pain behaviors [8, 13, 14]. In a study comparing behavioral and physiological pain responses between conscious and unconscious ICU patients, a subgroup of brain-injured patients showed different facial expressions and more variability in their physiological parameters when compared to other patients [13]. In another study, patients in a vegetative state showed less complex behaviors to a nociceptive stimulus than patients in a minimally conscious state, leading to lower scores on the nociception coma scale revised (NCSR), an instrument that assesses behavioral responses to nociceptive pain in comatose patients [15]. However, the authors did not precisely describe the nature of the differences between groups. Recently, Arbour and colleagues [14] described pain behaviors in 45 critically ill traumatic brain-injured (TBI) patients according to their level of consciousness (LOC). However, because this study was limited to TBI patients, it is necessary to further describe specific behaviors of pain in brain-injured ICU patients in order to improve pain assessment in this vulnerable population.

The present study fills this need by describing the frequency of behaviors observed at rest, during a non-nociceptive procedure (calling the patient and shaking his/her shoulder), and during a nociceptive procedure (turning) in brain-injured ICU patients with different LOC. It also tests the psychometric properties of the checklist used to record these behaviors (i.e., inter-rater reliability; discriminant and concurrent validity).

Materials and methods

Settings and participants

This prospective observational psychometric study took place in two adult ICUs in two university hospitals in Western Switzerland. A convenience sample of 116 patients were recruited during a 7-month period between March and October of 2011. Further demographic information can be found in Table 1. Patients over 18 years old were eligible if they had brain injury less than 4 weeks prior to enrolment in the study, and if they had an ICU stay of more than 24 h. Patients were excluded if they were being investigated for brain death, were receiving neuromuscular blocking agents, had impaired sensory transmission to peripheral nerves (i.e., tetraplegia), were pacemaker-dependent, or suffered from dysautonomia or hypothermia.

To compare behaviors between patients with different LOC, patients were divided into three groups according to their motor response to a nociceptive stimulation. The first group (self-report) included patients able to self-report their pain and follow commands. The second group (localized group) included patients who demonstrated a localized response to a nociceptive stimulus. A localized response was considered a distinguishing feature of the ability to perceive pain in patients with a LOC [16]. The third group (stereotyped group) included patients with stereotyped flexion/extension of the extremities, or an absence of response to a nociceptive stimulus. Automatic reflexive responses seen in the stereotyped group suggest a reaction to a noxious stimulation with no pain perception [16].

The study was approved by the ethics committee of the two participating institutions and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Informed consent was waived for unconscious patients.

Measures

A 33-item pain behavioral checklist was developed on the basis of an integrative review of the literature [17] and consultation with 12 nurses and six physicians. Content validity was established through consultation with 14 European experts [18]. Further selection of the behaviors was carried out and described in Electronic Supplementary Material (ESM) 1.

Following the selection of behaviors, two checklists were constructed (ESM 1): (a) a 20-item checklist specific to intubated patients with four indicators (facial expression, movements, muscle tension, and mechanical ventilation); (b) a 19-item checklist for vocal patients where behaviors linked to mechanical ventilation were replaced by vocal signs. Each behavior was either present or absent and scored with a 1 or 0, respectively.

With patients able to self-report their pain, pain intensity was measured using a numeric rating scale (NRS) with a possible score between 0 (no pain) and 10 (worst possible pain). The absence or presence of pain was assessed with a simple yes/no question (e.g., “do you presently feel pain?”), a satisfactory measure of pain in critical care [19].

LOC was measured with the full outline of unresponsiveness (FOUR) scale, developed to assess the LOC of intubated and ventilated patients in critical care [20]. It includes four sections: eye response, motor response, brain stem reflexes, and respiration. Each is scored from 0 (no response) to 4 (full response); the total score range is 0–16 [20].

The criterion measure of consciousness—the Glasgow coma scale (GCS)—was also used to assess LOC even though its verbal score is not adapted for intubated or aphasic patients [21]. In this study, a verbal score of 1 was designated to all intubated patients.

Level of sedation was assessed with the Richmond agitation-sedation scale (RASS) [22], a 10-point scale

Table 1 Variables and characteristics of patients ($N = 116$)

Variable	Self-report group ($n = 46$), n (%)	Localized group ($n = 33$), n (%)	Stereotyped group ($n = 37$), n (%)	p[a]
Endotracheal tube or tracheostomy	11 (25)	28 (85)[a]	35 (95)[a]	<0.001
No mechanical ventilation	40 (87)	6 (18)[a]	2 (5)[a]	<0.001
Etiology of brain injury				
Intracranial hemorrhage	29 (63)	18 (55)	19 (49)	0.592
Postanoxic	4 (9)[a]	6 (18)[a,b]	12 (32)[b]	0.026
Ischemic stroke	5 (11)	5 (15)	3 (8)	0.649
Brain tumor	8 (17)	2 (6)	0	0.014
Meningitis	0	2 (6)	3 (8)	0.171
Medication				
Vasoactive drugs	3 (7)	10 (30)[a]	15 (41)[a]	<0.001
Antihypertensive drugs	16 (35)[a,b]	17 (52)[a]	7 (19)[b]	0.017
Opiates (morphine iv, fentanyl iv, sulfentanyl iv)	13 (28)	20 (61)[a]	25 (68)[a]	0.026
Sedative (diprivan infusion, midazolam infusion, lorazepam iv)	2 (4)	15 (46)[a]	19 (51)[a]	<0.001
	Median (IQR)	Median (IQR)	Median (IQR)	p[b]
SAPS II	27.5 (18–43)	42 (34–52)[a]	51 (41–60)[a]	<0.001
GCS on hospital admission	8.5 (4–14)	5 (3–10)[a]	3 (3–6)[a]	<0.001
Measures on data collection day				
Number of days in ICU	2 (1–3)	3 (1–6)	3 (1.5–5)	0.112
RASS	0 (−1 to 0)	−4 (−4 to 1)	−4 (−3.5 to −5)	<0.001
FOUR	16 (14–16)	11 (6–14)	6 (4–8)	<0.001
FOUR motor subscale	4 (4−4)	3 (3−3)	0 (0−1)	<0.001
Glasgow coma scale	14 (13–15)	9 (7–10)	3 (3–5)	<0.001

Parameters in each row that share superscripts do not differ significantly (Mann–Whitney U test; $p < 0.016$; Bonferroni corrected p value threshold)

SAPS II simplified acute physiology score II, *RASS* Richmond agitation sedation scale, *GCS* Glasgow coma scale, *ICU* intensive care unit, *FOUR* full outline of unresponsiveness scale, *IQR* interquartile range

[a] Fisher exact test

[b] Kruskal–Wallis rank test

with four levels of agitation (1–4) where the highest score is indicative of combativeness, one level for calm or alert (0), and five levels of sedation (−1 to −5) where the highest negative score is indicative of not being aroused (−5).

Severity of illness was assessed with the simplified acute physiology score II (SAPS) [23], a disease severity scoring system with 12 variables done within the first 24 h after ICU admission.

The following demographic and clinical characteristics were collected: age, gender, GCS at admission, diagnosis, and therapeutic regimen of analgesics, sedatives, and hypnotics.

Procedure

Following study enrolment, patients' clinical data were collected from medical notes. Patients were assessed by a member of the research team at three different times: at rest (T1), during a non-nociceptive procedure (shaking of the shoulder and calling the patient's name as described in the RASS testing procedure) (T2) [22], and during turning an empirically based nociceptive procedure (T3) [24]. Before T1, a 10-min period with no patient stimulation or intervention was respected. Patients were observed for 1 min at each observation period by members of the research team not involved in the patients' care. Immediately after T2, patients were evaluated for their level of sedation with the RASS, and their level of consciousness with the GCS and FOUR. The ICU nursing staff would then provide routine standard care and turn the patient. T3 started when the nursing staff turned the patient. All three assessments were completed within 60 min. To examine inter-rater reliability, patients were assessed by two independent raters blinded to each other's scores.

Patients able to self-report were asked if they had experienced pain during the procedure and to score their pain intensity using the NRS. In the self-report group, it was not possible to differentiate between rest and non-nociceptive stimulation, as the patient was stimulated as soon as he/she was asked to self-report his/her pain. Therefore, there were only two observation sequences: T1 and T3.

Data analysis

Patients were classified into three groups according to the FOUR motor response sub-score [20]. The self-report group included patients able to follow command

(FOUR-motor = 4), the localized group included patients with a localized response to a nociceptive stimulus (a compression of the temporomandibular joint) (FOUR-motor = 3) and the stereotyped group included patients with a reflexive response to a nociceptive stimulus (FOUR-motor = 2, 1, or 0). Descriptive statistics were calculated for all variables. Because the presence of behaviors was unequal between the observations, comparisons between patient groups were conducted using exact tests.

Inter-rater reliability was examined for vocal and intubated patients by the ICC. Internal consistency was determined using the Kuder–Richardson 20 coefficient (KR 20) for binomial variables, and tested for each patient group. Values of at least 0.7 were expected for an instrument in development [25].

Discriminant validity was determined by comparing the checklist total scores at rest, during non-nociceptive stimulation, and during nociceptive stimulation, to elucidate whether the checklist was able to detect increases in the number of behaviors following a nociceptive procedure, and to demonstrate no change in the number of behaviors occurring at rest and following a non-nociceptive stimulation. Differences between the conditions were compared with the Wilcoxon signed-rank test.

Concurrent validity was determined by measuring the relationship between the checklist scores and the patients' self-report of pain (the criterion measure of pain). The Mann–Whitney *U* test was used to compare total scores on the behavioral checklist between patients reporting pain and those reporting no pain at rest (T1), and during nociceptive stimulation (T3). Spearman's rank correlation analysis was used to examine the association between the NRS and the number of behaviors observed. All data were analyzed with PASW version 18 (SPSS Inc., Chicago).

Results

Of the 116 patients included in the study, 46 were able to self-report, 33 had a localized response to a nociceptive stimulus, and 37 had a stereotyped response. Patients included were mostly men ($n = 66$, 57 %) with a mean age of 56.2 years old (SD = 1.6). Among the patients with stereotyped responses, 20 (64.5 %) had a FOUR-motor score of 0, corresponding to no motor response. Ten patients with no motor response were receiving sedatives or opiates.

Comparison of behaviors between patient groups

During the delivery of nociceptive stimulation (i.e., turning), the most frequently observed behaviors in the stereotyped group were ventilator asynchrony (71 %), coughing (61 %), eye movements (54 %) and frowning/brow lowering (51 %). Statistically significant differences were found between patient groups at rest, during non-nociceptive and nociceptive stimulation (Table 2). During turning, frowning/brow lowering, orbit tightening, and muscle rigidity were observed statistically more frequently, than at rest, in the self-report and stereotyped group (Table 3). All behaviors linked to ventilation were statistically more frequent during turning in the stereotyped group. In the localized group, none of the behaviors changed significantly during the nociceptive stimulation.

Reliability

Inter-rater agreement was measured in 46 patients (17 stereotyped, 11 localized, and 18 self-reporting patients). High ICCs were obtained at rest (0.77; 95 % CI 0.56–0.88) and during nociception (0.92; 95 % CI 0.86–0.96). The checklist had good internal consistency when tested with patients showing a stereotyped response to pain (KR 20 = 0.85; 95 % CI 0.78–0.89) and those with a localized response (KR 20 = 0.83; 95 % CI 0.74–0.88). The coefficient was lower with patients able to self-report (KR 20 = 0.71; 95 % CI 0.59–0.79).

Discriminant validity

The checklist total scores were significantly higher during the nociceptive procedure than at rest for all three groups (see Fig. 1 and ESM 2). Significant differences were found between rest and nociceptive stimulation for the total checklist score in all patient groups (Fig. 1). Muscle tension sub-scores significantly differed only in the stereotyped and self-report groups (ESM 2). The movement sub-score did not differ between rest and nociceptive stimulation in any group.

Concurrent validity

The self-report group reported pain significantly more (χ^2 (1, $n = 40$) = 4.00, $p = 0.04$) during the nociceptive procedure (61.9 %; $n = 26$) than at rest (44 %; $n = 18$). Self-reporting patients who answered "yes" to the question about pain scored significantly higher on the behavioral checklist than patients who answered "no" (Table 4).

The NRS scores of the self-report group were significantly associated with the total behavioral checklist scores during nociceptive stimulation ($r_s = 0.53$; 95 % CI 0.21–0.75; $n = 30$) but not at rest ($r_s = 0.33$; 95 % CI −0.05 to 0.63; $n = 27$).

Table 2 Frequencies of behaviors during rest, non-nociceptive stimulation, and nociceptive stimulation between groups

Behaviors	Rest (T1)				Non-nociceptive stimulation[a] (T2)			Nociceptive stimulation (T3)		
	Self-report *n* (%)	Localized *n* (%)	Stereotyped *n* (%)	p^b	Localized *n* (%)	Stereotyped *n* (%)	p^b	Self-report *n* (%)	Localized *n* (%)	Stereotyped *n* (%)	p^b
Frowning/brow lowering[c]	14 (29)	5 (16)	6 (16)	0.25	7 (23)	13 (35)	0.42	30 (63)	9 (29)	19 (51)	0.02
Orbit tightening[c]	5 (10)	2 (7)	6 (16)	0.45	4 (13)	9 (24)	0.36	21 (44)	8 (26)	18 (47)	0.14
Closing eyes[c]	26 (54)	11 (36)	3 (8)	0.00	15 (48)	8 (22)	0.02	35 (73)	20 (65)	13 (35)	0.00
Eye movements[c]	26 (54)	12 (39)	8 (22)	0.01	16 (51)	13 (35)	0.14	31 (65)	17 (55)	19 (54)	0.45
Fixation, staring[c]	2 (4)	2 (7)	0	0.30	6 (19)	0	0.01	4 (8)	8 (26)	6 (16)	0.11
Upper lip raising[c]	1 (2)	1 (3)	1 (3)	1.00	3 (10)	3 (8)	1.00	3 (6)	2 (7)	3 (3)	0.58
Clenched teeth and tense jaw[c]	2 (4)	0	1 (3)	0.78	2 (7)	6 (16)	0.45	3 (6)	2 (7)	11 (30)	0.01
Face flushing[c]	1 (2)	0	0	1.00	1 (3)	2 (5)	1.00	10 (21)	6 (19)	16 (43)	0.04
Protective movements[d]	1 (2)	1 (3)	0	0.73	0	0	–	6 (13)	4 (13)	1 (3)	0.22
Touching/rubbing the pain site[d]	11 (30)	1 (3)	0	0.00	3 (10)	0	0.08	14 (29)	2 (7)	2 (4)	0.00
Flexion withdrawal[d]	8 (17)	3 (10)	2 (5)	0.30	10 (32)	3 (8)	0.01	10 (21)	8 (26)	4 (11)	0.26
Muscle rigidity[e]	4 (8)	7 (23)	4 (11)	0.20	7 (23)	9 (24)	1.00	17 (35)	15 (48)	12 (32)	0.36
Resistance to movements[e]	4 (8)	4 (13)	4 (11)	0.80	5 (16)	7 (19)	1.00	7 (15)	9 (29)	8 (22)	0.28
Shaking and twitching[e]	2 (4)	1 (3)	7 (19)	0.04	4 (13)	9 (24)	0.36	6 (13)	3 (10)	8 (22)	0.38
Tremor[e]	0	1	2 (5)	0.27	0	6 (16)	0.03	0	0	6(15)	0.00
Clenching fist[e]	0	0	2 (5)	0.17	0	4 (11)	0.13	3 (6)	1 (3)	4 (11)	0.59
Ventilator asynchrony[f]	2 (50)	1 (3)	1 (3)	0.02	1 (3)	5 (14)	0.21	3 (75)	9 (32)	25 (71)	0.00
Coughing[f]	2 (50)	1 (3)	5 (14)	0.05	1 (3)	9 (24)	0.03	3 (75)	6 (21)	22 (61)	0.00
Ventilation impossible[f]	0	0	1 (3)	1.00	0	1 (3)	1.00	1 (25)	2 (7)	9 (25)	0.03
Biting endotracheal tube[f]	1 (25)	0	2 (5)	0.09	3 (10)	4 (11)	0.12	3 (75)	2 (7)	9 (25)	0.01
Groaning and moaning[g]	9 (21)	0	–	1.00	0	–		12 (29)	1 (33)	–	1.00
Screaming and howling[g]	0	0	–		0	–		3 (7)	0	–	1.00
Sighing[g]	3 (7)	0	–	1.00	0	–		4 (10)	0	–	0.13

[a] No observation in the self-report group during non nociceptive stimulation at T2
[b] Fisher exact test
[c] Facial expression
[d] Movements
[e] Muscle tension
[f] Mechanical ventilation ($n = 68$)
[g] Vocal signs ($n = 45$)

Table 3 Comparison of behaviors between rest (T1), non-nociceptive stimulation (T2), and nociceptive stimulation (T3) for each patient group

Behaviors	Self-report group[a] ($n = 46$)	Localized group ($n = 33$)			Stereotyped group ($n = 37$)		
	T1−T3 p	T1−T2 p	T2-T3 p	T1−T3 p	T1−T2 p	T2−T3 p	T1−T3 p
Frowning/brow lowering	<0.001	0.250	1.000	0.375	0.008	0.039	<0.001
Orbit tightening	<0.001	0.375	0.625	0.070	0.125	0.002	<0.001
Closing eyes	0.096	0.031	0.687	0.057	0.016	0.227	0.002
Eye movements	0.388	0.039	0.754	0.227	0.031	0.109	0.002
Fixation, staring	0.625	0.375	0.687	0.109	–[b]	0.125	–[b]
Upper lip raising	0.500	0.375	0.625	0.375	0.500	0.453	0.063
Clenched teeth and tense jaw	–[b]	–[b]	1.000	–[b]	0.063	0.065	<0.001
Face flushing	–[b]	–[b]	0.500	–[b]	–[b]	<0.001	–[b]
Protective movements	0.063	–[c]	–[c]	0.375	–[b,c]	–[c]	–[b]
Touching/rubbing the pain site	0.850	0.500	1.000	0.625	–[b,c]	–[c]	–[b]
Flexion withdrawal	0.549	0.008	0.388	0.508	1.000	0.500	0.250
Muscle rigidity	<0.001	0.375	0.344	0.092	0.063	0.125	0.002
Resistance to movements	0.375	0.375	1.000	0.344	0.250	0.625	0.063
Shaking and twitching	0.500	0.250	1.000	0.375	0.250	1.000	0.687
Tremor	–[b]	–[b,c]	–[c]	–[b]	0.375	1.000	0.375
Clenching fist	–[b]	–[b,c]	–[c]	–[b]	0.500	0.500	0.500
Ventilator asynchrony[d]	–[e]	1.000	0.063	0.070	0.219	<0.001	<0.001
Coughing[d]	–[e]	1.000	0.250	0.219	0.219	<0.001	<0.001
Ventilation impossible[d]	–[e]	–[e]	–[e]	–[e]	1.000	<0.001	0.002
Biting endotracheal tube[d]	–[e]	–[e]	–[e]	–[e]	0.625	0.039	0.004
Groaning and moaning[f]	0.344	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]
Screaming and howling[f]	0.250	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]
Sighing[f]	0.500	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]

McNemar test (exact test), Bonferroni p corrected value threshold of $p < 0.025$

[a] No observation in this patient group at T2

[b] Was not observed at rest

[c] Was not observed during non nociceptive stimulation

[d] $n = 68$

[e] No observation in this patient group for this behavior

[f] $n = 45$

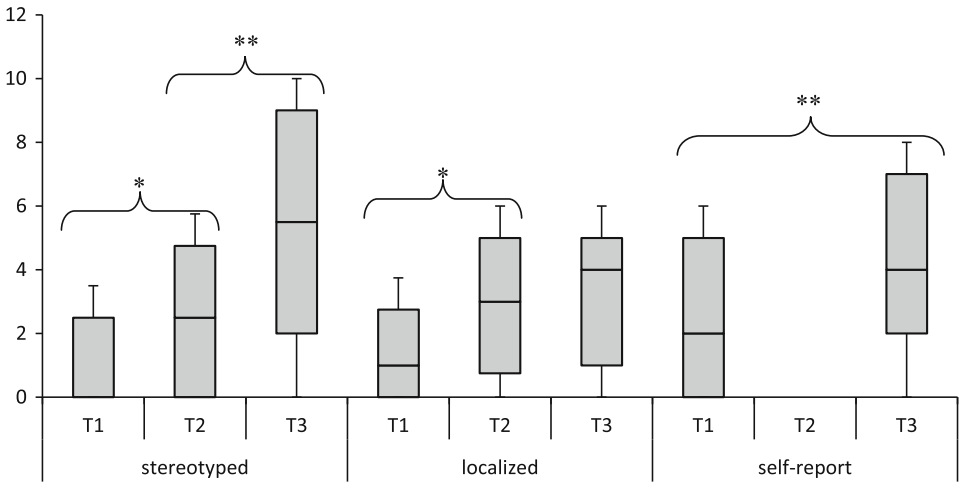

Fig. 1 Median total behavioral checklist scores, interquartile range, and minimum–maximum scores found for each observation period for all three patient groups: self-report, localized, and stereotyped. *Asterisks* mark significant difference between measures ($N = 110$) *T*1 at rest, *T*2 non-nociceptive stimulation, *T*3 nociceptive stimulation; $*p < 0.016$ and $**p < 0.000$; Bonferroni corrected p value threshold

Discussion

This study investigated behaviors in brain-injured adult ICU patients with different LOC, and tested the psychometric properties of a checklist measuring these behaviors. Reliability was good as internal consistency was above 0.70 for all groups and inter-rater reliability was high for all assessments, comparing well with other studies of pain assessment tools [4, 7].

Patients displayed different behaviors according to their motor response on the FOUR scale. Some behaviors,

Table 4 Comparison of total scores on the behavioral checklist between patients reporting pain and those reporting no pain at rest (T1) and during nociceptive stimulation (T3)

Observation	Pain			No pain			*Z*
	n	Md	IQR	*n*	Md	IQR	
At rest (T1)	17	5	2–6.3	22	1	0–3.3	2.614[a]
Turning (T3)	24	5	3–7	14	2.5	0.8–4	2.852[a]

Md median, *IQR* interquartile range

[a] Mann–Whitney *U* test $p < 0.025$; Bonferroni corrected *p* value threshold

displayed during turning, have not been described in other ICU patients (i.e., closing the eyes or face flushing). Although Chatelle and colleagues [15] described differences in responses to nociceptive stimulation measured with the NCSR according to patients' LOC, they only reported total scores and did not describe differences found in observed behaviors. In an observational study of 45 intubated TBI patients, Arbour and colleagues [14] found results comparable to ours, with facial expressions being the most frequently observed.

It is noteworthy that in patients who exhibited localized responses, none of the behaviors changed significantly, and the total checklist score did not increase significantly between non-nociceptive stimulation and nociceptive stimulation, even though these patients had a higher LOC than patients with a stereotyped response, as attested by the FOUR and GSC scales. These results suggest that this patient group reacted to the stimulation and not to the nociception. Several hypotheses can account for this: (1) these patients were not in pain during nociceptive stimulation (turning); (2) the behaviors were not pertinent for this group.

It must be noted that patients with stereotyped responses to nociceptive stimulation had higher scores than other patients, even if four patients in this group displayed none of the behaviors included in the checklist at T1, T2, or T3. These results contradict those of Gelinas and Johnston [7] where the scores measured with the critical care pain observation tool (CPOT) were lower in patients with severe brain injury compared with those with moderate brain injury. Chatelle and colleagues [15] found similar results with the NCSR. These differences may be explained by the measurement method as the CPOT and NCSR assign a score to specific behaviors. For example, the NCSR scores localization to painful stimulation with a value of 3, whereas flexion withdrawal receives a score of 2 [15]. In the present study, the tool used was a checklist, and each behavior was assigned a score with equal weight. This method of scoring showed that patients with stereotyped responses to a nociceptive stimulus displayed different, not fewer, responses.

Higher total scores were recorded during nociceptive stimulation than during rest or non-nociceptive stimulation, supporting the discriminative validity of the current checklist. In addition, patients who reported pain at rest and during nociceptive stimulation displayed more behaviors than those who reported no pain. It must be pointed out that 44 % of self-reporting patients had pain at rest. Yet high prevalence of pain at rest has been previously described in studies of pain assessment tools [1, 11].

The behaviors included in the movement sub-score did not significantly change between T1 and T3 or T2 and T3. These behaviors could be excluded, as their validity for the assessment of pain in brain-injured adult ICU patients is lacking. These results confirm those found by Arbour and colleagues [14], where 87 % of unconscious patients (GCS $\leq$ 8) and 52.4 % of patients with an altered LOC (GCS 9–12) had an absence of body movement during turning.

Correlations with patients' self-reported pain intensity scores and the checklist were moderate during nociceptive stimulation, and non-significant at rest. However, only few patients were able to provide NRS scores and statistical power may have been insufficient. Nevertheless, correlation coefficients between 0.60 and 0.80 are considered acceptable, as self-reports and behavioral tools do not exactly assess the same construct [26]. Self-reports integrate patients' subjective pain experience, which may be cognitively mediated, whereas pain behavioral tools are based on patients' reaction to pain, which reflect expressive automaticity that requires lower mental processing [27].

This study has several limitations. First, the study population was heterogeneous with regard to the etiology of the brain injury. Second, patients were sedated, as it would have been harmful to remove the sedation, but we did not control for sedation in the analysis. Third, the nociceptive stimulus was based on a single situation where pain was assumed to be present; we did not examine other situations. Furthermore, the nociceptive stimulation chosen (i.e., turning) could cause ventilator asynchrony and explain some of the observed behavior. However, the majority of pain assessment studies in ICUs have chosen turning as a form of nociceptive stimulation [4–6] because it is regularly performed and described as painful [24]. Fourth, similar to other studies [4, 7, 15], investigators were not blinded and the measurements might have been influenced by their knowledge and beliefs concerning pain in adult brain-injured patients. Yet, behaviors included in the checklist were selected according to their inter-rater reliability, limiting investigator-dependent results. Finally, concurrent validity could only be determined in the group with the highest LOC; there was no objective pain measurement reference for the other groups.

Studies are needed to validate the behaviors elicited with different nociceptive stimuli, such as a mechanical pressure in the fingernail or comparing scores after an analgesic treatment [15, 28]. Further development would

include testing a shortened version of our checklist excluding behaviors linked to movement, and comparing it to other recommended and validated pain scales (CPOT or behavioral pain scale) [8]. The results of behavioral assessments should be compared with more objective measures, such as neuroimaging, to ensure concurrent validity of this checklist for brain-injured patients with different LOC.

Despite its limitations, the present study offers the insight that brain-injured patients display signs of pain that differ according to their LOC. Behaviors linked to facial expression, muscle tension, ventilation, or vocal signs are reliable and responsive to pain. They could be used either to develop a specific instrument for the adult brain-injured ICU population, or for inclusion in an existing tool.

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Conflicts of interest M.-J. Roulin and A.-S. Ramelet have no conflict of interest to declare.

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