Nociception Coma Scale Revised allows to identify patients with preserved neural basis for pain experience.

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The Nociception Coma Scale-Revised (NCS-R) was developed to help assessing pain in patients with disorders of consciousness (DOC). Several studies have shown its sensitivity in assessing responses to acute noxious stimuli. However, they failed to determine a reliable cut-off score that could be used to infer pain processing in these patients.

This retrospective cross-sectional study aimed to determine an NCS-R cut-off score supporting preserved neural basis for pain experience, based on brain metabolism as measured by fluorodeoxyglucose positron emission tomography (FDG-PET).

We included patient with unresponsive wakefulness syndrome confirmed by the FDG-PET (UWS) and looked at their highest NCS-R total scores. As the highest score was 4, we determined the cut-off of 5 and compared the brain metabolism of these patients with matched patients with DOC and with a cut-off score ≥ 5 (i.e., *potential pain*) and healthy subjects.

We found a higher global cerebral metabolism in healthy subjects compared with both patients' groups and also in patients with *potential pain* compared with FDG-PET confirmed UWS. We observed a preserved metabolism in the left insula and a preservation of the connectivity between the left insula and the medial frontal gyrus in patients with *potential pain* compared with FDG-PET confirmed UWS.

Perspectives: Our data suggest that using the cut-off score of 5 can be helpful to improve pain management in patients with DOC. Future studies should focus on patients showing scores below this cut-off to better characterize their profile and improve cares.

Keywords: nociception, pain, cut-off score, nociception coma scale-revised, disorders of consciousness.

Abbreviations: CRS-R = Coma Recovery Scale Revised, NCS-R = Nociception Coma Scale Revised, DOC = Disorders of Consciousness, UWS = Unresponsive Wakefulness Syndrome, MCS = Minimally Conscious State, MCS* = UWS with atypical cortical metabolism preservation, FDG-PET = Fluorodeoxyglucose Positron Emission Tomography

Introduction:

Assessing and treating pain in severely brain-injured patients unable to communicate is a real challenge. Cases like unresponsive wakefulness syndrome (UWS; eye opening periods and only reflexive movements [25,33]) and minimally conscious state (MCS; purposeful responses without functional communication [13,25]) bring major ethical and clinical concerns regarding their need for pain treatment. Neuroimaging studies have investigated cortical responses to noxious stimuli in UWS and MCS patients. These studies reported a preservation of thalamo-cortical connectivity and an activation of areas involved in the cognitivo-affective dimension of pain (insula, anterior cingulate cortex [ACC]) in MCS patients that seem to be impaired in UWS patients [2,17,19]. However, other neuroimaging data reported remaining activity within the emotional pain network in about 30% of in UWS patients [21], suggesting that residual sensory and emotional pain processing can remain active even if the patient is unresponsive at bedside. Among the different techniques used to better document the patient's covert abilities, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to be a strong complement to bedside examinations for patients with disorders of consciousness (DOC) [28–30,34]. A study about diagnostic precision of FDG-PET reported that 32 % of the behaviorally UWS patients showed signs of potential covert cognitive abilities, and 69% of them recovered signs of consciousness after 12 months [28]. Moreover, global metabolic rate of glucose have shown a good sensibility (95%, [30]) to distinguish UWS from MCS .

The Nociception Coma Scale-Revised (NCS-R) was developed to assess potential pain in patients with DOC [4,6,27]. Several studies have shown its sensitivity to nociception and to the level of consciousness [6,27]. A study using FDG-PET reported a significant correlation between NCS-R total scores and resting brain metabolism in the ACC [7], supporting that the higher the score, the higher the potential for cortical pain processing. If previous results support the experimental and clinical usefulness of this tool, there is currently no reliable cut-off score that has been defined to determine the potential experience of pain and the need for treatment [5,6].

The aim of this study was to determine an NCS-R cut-off score using an approach based on neuroimaging data. Using FDG-PET, we investigated the NCS-R score ranges obtained in "FDG-PET confirmed UWS patients". The diagnosis was based on behavioral assessment and visual examination of brain metabolism (i.e., a severe bilateral hypometabolism of the

associative frontoparietal cortex without preserved areas led to a diagnostic of UWS [28]). We hypothesize that patients with a global hypometabolism of the whole cortical area (including the network known to be involved in pain processing) cannot sustain conscious treatment of potentially painful stimuli. Therefore the highest behavioral responses observed in these FDG-PET confirmed UWS patients could be used as a conservative NCS-R cut-off score [6,28,30]. Then, we looked at the global and local differences in brain metabolism between FDG-PET confirmed UWS, patients with potential pain (i.e., patients with a NCS-R score equal or higher to the threshold defined in the study) and healthy subjects, all matched for age, gender, and etiology. We hypothesize that patients with perception of pain would have a minimal cortical preservation, particularly in areas involved in pain processing (i.e., ACC and insula [2]), as compared with patient without perception of pain. As pain processing requires also a preservation of cortical connectivity, we investigated differences in cortical connectivity in FDG-PET confirmed UWS and patients with potential pain [18,20].

Methods:

Participants:

This retrospective study included patients admitted to the intensive care and the neurology ward of the University Hospital of Liège. These patients were assessed as part of a week of diagnostic and prognostic assessment. Inclusion criteria were: (1) age ≥ 16 years, (2) no administration of neuromuscular function blockers and no sedation 24 h before assessment, (3) a diagnosis of unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS), based on the behavioral assessment performed using the Coma Recovery Scale-Revised (CRS-R [14]), (4) pain assessment performed with the NCS-R, and (5) brain metabolism data assessed by FDG-PET. Exclusion criteria were: (1) documented history of prior brain injury; (2) premorbid history of developmental, psychiatric or neurologic illness resulting in documented functional disability up to time of the injury; and (3) upper limb contusions, fractures or flaccid paralysis. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege and written informed consent was obtained by the healthy subjects and the patients' legal representatives.

For PET analyses, inclusion criteria for the healthy subjects were: (1) no history of neurologic or psychiatric disorders, (2) no head injuries, (3) absence of pregnancy, (4) absence of diabetes.

Different groups were used during this study, criteria of each group were:

- "FDG-PET confirmed UWS" group: (1) patients behaviorally diagnosed as UWS (2) with a global decrease of brain metabolism on FDG-PET based on visual examination of the FDG-PET Standardized Uptake Values (see below [28]).
- "Patients with potential pain" group: (1) patients behaviorally diagnosed as UWS or MCS with (2) a pain assessment performed by the NCS-R with a score equal or higher to the threshold defined before.

Materials:

We included data obtained with the NCS-R following experimental noxious stimulation (deep pressure on the left and right nailbed of the middle finger for 5 seconds [27]) The use of finger pressure as a noxious stimulation was used as it is widely used in different neurobehavioral scales to assess response to nociception [14,32]. To ensure we captured the highest response of the patient, we also looked at the NCS-R scores during mobilization. If mobilizations are not comparable to an experimental noxious stimulus, several studies reported that mobilizations (i.e., care or physiotherapy) could be potentially painful for patients with brain injury [11,12]. The NCS-R includes three subscales, each of them graded from 0 to 3, assessing motor, verbal, and facial expression with a total score ranging from 0 to 9.

The CRS-R was used to determine the clinical diagnosis of the patient. It consists of 23 hierarchically arranged items that comprise six subscales addressing arousal, auditory, visual, motor, oromotor/verbal and communication functions. The lowest item on each subscale represents reflexive activity while the highest item represents cognitively-mediated behaviors [14]. The assessment was performed at least 5 times during the same week (between day 1 and day 5) by different examiners to reduce the potential misdiagnosis [37] and the best diagnosis was used for final diagnosis.

Positron emission tomography was performed during resting conditions after intravenous injection of 5 to 10 mCi (185-370 MBq) FDG on a Gemini Big Bore PET/CT scanner (Philips Medical Systems, Best, Netherlands). Data were spatially normalized to a stereotaxic space and smoothed using a 14 mm full width at half maximum Gaussian kernel. To overcome the problem of big deformations due to brain lesions as well as the fact that SPM has a default template based on $H^{15}{}_2O$ data, the normalization was performed using a customized template using the procedure as described in [24]. Statistical analyses were performed using Statistical Parametric Mapping (SPM12; www. fil.ion.ucl.ac.uk/spm). The FDG-PET and the NCS-R assessment were performed the same day.

Determining the cut-off score

We used the FDG-PET Standardized Uptake Values (SUV) to assess the cerebral metabolic rate of glucose consumption: $SUV = \frac{(Decay\ corrected\ Voxel\ Intensity)}{\frac{Injected\ Dose}{Body\ Weight}}$ at single subject level. The SUV images were used to select FDG-PET confirmed UWS patients through visual observation by three different expert examiners (all blinded of the clinical diagnosis and other examiners assessment). Each expert (neuropsychologist and physiotherapist working with patients with DOC and PET imaging for at least 5 years) provided a diagnosis based on two illustrative examples of UWS and MCS (see Figure 1). Full agreement was observed for typical UWS.

Then, we looked at the NCS-R highest score in this subgroup of FDG-PET confirmed UWS to determine the cut-off score.

<<Insert Figure 1 around here >>

Brain metabolism and cut-off score

To investigate whether the cut-off score can be used to support preserved neural basis for pain experience, we used global and regional brain preservation. A group of patients with DOC and potential pain was selected based on their age, gender and etiology (diagnosis of UWS or MCS) to match with the FDG-PET confirmed UWS patients. A group of healthy subjects (also matched

for age and gender) was also included. We extracted the global mean value to compare global brain metabolism preservation between the three groups.

To look for regional differences, we used a design matrix including the FDG PET confirmed UWS patient, patients with *potential pain*, and the healthy subjects' scans. We identified brain regions with preserved metabolism in patients with *potential pain* vs FDG PET confirmed UWS patients and in patients with *potential pain* vs healthy subjects. We also identified brain regions with decreased metabolism in patients with *potential pain* vs healthy subjects and in FDG-PET confirmed UWS patients vs healthy subjects. Global normalization was performed by proportional scaling. Thresholding of results was done at $p < .05$ corrected for multiple comparisons within a priori defined regions of interest (using a 10-mm radius spherical small volume correction in SPM—at voxel and cluster level) centered on a priori coordinates for areas previously identified as the most frequently identified in pain processing (i.e., ACC and bilateral insula; respective coordinates $x = 12$, $y = 10$, $z = 36$; $x = -34$, $y = -24$, $z = 36$; and $x = 34$, $y = -24$, $z = 36$, were taken from two previous studies on pain perception [2,7]).

Cortical connectivity

Then, we used a psychophysiological interaction analysis to observe the cortical connectivity in patients with *potential pain* and in FDG-PET confirmed UWS patient [10]. The design matrix included the same scans as described above and considered group differences in mean levels of glucose consumption. Now the analysis looked for brain regions that experienced a significant difference in reciprocal modulation with/from the cortical regions most preserved in patients with *potential pain*. It included the most significant peaks obtained from the first analysis.

A posteriori, we looked at regional brain metabolism preservation in patients MCS* (i.e., behaviorally diagnosed in UWS but with an atypical cortical metabolism preservation [15] who showed potential pain (i.e., a score ≥ cut-off) at the single subject level, using the same approach as described above (compared with 33 healthy subjects, 18 men, mean age 43, SD 15 years).

Finally, we calculated the sensitivity (i.e., proportion of patients who have received noxious stimulation and have a NCS-R score equal or above the threshold defined in the study) and specificity (i.e., proportion of patients who have not received noxious stimulation and have a NCS-R score below the threshold) of the threshold defined for all the patients with MCS

assessed with the NCS-R since 2011 in order to assess the number of patients who might be underestimated by the identified threshold.

Results:

Out of the 209 patients included in the database, 50 patients were diagnosed in UWS with the CRS-R assessment. Out of these 50 patients, 26 showed a global cortical hypometabolism based on visual analysis (i.e., "FDG-PET confirmed UWS", see Figure 1 and 2) and 13 of these FDG-PET confirmed UWS patients were assessed with the NCS-R.

Determining the cut-off score

When looking at the range of NCS-R total scores for these 13 FDG PET confirmed UWS patients (8 men, range of age: 27-73 years, aetiology: traumatic (n=1), post-anoxic (n=7), subarachnoid hemorrhage (n=1), stroke (n=2) and mixed etiology (n=2), see Supplementary Table 1) found scores between 0 and 4 during potentially painful conditions (i.e., noxious stimulation and/or mobilisation). Therefore, we set the cut-off score at ≥ 5.

<<Insert Figure 2 around here >>

Brain metabolism and cut-off score

In a second step, these 13 FDG-PET confirmed UWS were matched with 13 patients with DOC presenting a *potential pain* (i.e., NCS-R score ≥ 5; see Supplementary Table 1) and 13 healthy subjects (18 men, mean age 43, SD 15 years). Out of the 13 patients with *potential pain*, 3 were unresponsive at bedside (i.e., MCS* = UWS with atypical cortical metabolism preservation [15]). The data were not normally distributed according to Shapiro-Wilk tests ($W < 1$, $p = 0.012$). A non-parametrical statistical analysis was performed using a Kruskal-Wallis test in order to compare global metabolism in FDG-PET confirmed UWS vs patient with potential pain vs healthy subjects. We found a higher global metabolism in healthy subjects compared to both patients' group ($\chi^2 = 33.8$; $df = 2$; $p < .0001$), and in patients with *potential pain* compared to FDG-PET confirmed UWS ($\chi^2 = 33.8$; $df = 2$; $p<.0001$; see Figure 3).

Locally, we observed a preservation in brain metabolism only in the left insula in patients with *potential pain* compared to FDG-PET confirmed UWS (Z= 3.31; corrected p= 0.016; MNI [Montreal Neurological Institute] coordinates x = -38, y = -20, z = 44; see Figure 3). This preservation was also observed in patient with *potential pain* when compared to healthy subjects (Z= 5.95; corrected p= 0.004; MNI coordinates x = -32, y = -32, z = 40). We did not observed a preservation in brain metabolism in the right insula.

<<Insert Figure 3 around here >>

A hypometabolism in the ACC was observed in FDG-PET confirmed UWS patients (Z= 5.06; corrected p= 0.011; MNI coordinates x = 6, y = 18, z = 36) compared to healthy subjects and between patients with *potential pain* and healthy subjects (Z= 4.01; corrected p= 0.012; MNI coordinates x = 4, y = 14, z = 32).

Cortical connectivity

A preservation of the connectivity between the left insula (MNI coordinates x = -38, y = -20, z = 44) and the medial frontal gyrus (Z= 5.06; corrected p= 0.011; MNI coordinates x = 6, y = 18, z = 36, see Figure 4) was observed in patients with *potential pain* as compared with FDG-PET confirmed UWS patients.

<<Insert Figure 4 around here >>

When focusing on the three MCS* showing a score ≥ 5, we observed a preservation in brain metabolism in the insula bilaterally in all 3 patients, and in the ACC in 2 patients (see Figure 4 and 5).

<<Insert Figure 5 around here >>

Finally, when accounting for all patients with MCS assessed with the NCS-R during an experimental noxious stimulation (n=65), we found a specificity of 98.46 % (n=64) and a sensitivity of 23.07 % (n=15) for detecting potential pain in this population.

Discussion:

The aim of this retrospective study was to determine a cut-off score at the NCS-R supporting preserved neural basis for pain experience, based on global and local brain metabolic activity.

First, we investigated the NCS-R score ranges obtained in FDG-PET confirmed UWS patients (i.e., patients with critically low cortical metabolic activity, no access to consciousness and therefore no access to conscious process of pain). According to our results, the highest behavioral responses observed during noxious stimulation and mobilization was associated with a NCS-R total score of 4. In other words, those results suggest that a score equal to or above 5 would require a certain degree of cortical processing of painful stimuli and a potential experience of pain. Therefore, we fixed the conservative NCS-R cut-off score at 5, suggesting that careful attention should be given to treat with analgesics patients with score equal or higher to 5.

As a second step, we compared the global brain metabolism between the FDG-PET confirmed UWS, patients with potential pain and healthy subjects. Patients with potential pain showed a significantly higher global metabolism than the FDG-PET confirmed UWS group. It goes in line with previous findings on reduced metabolism in UWS as compared with MCS [30].

As a third step, we looked at regional differences in brain metabolism in two areas known to be involved in pain processing, namely the insula (1) and the ACC (2).

(1) In the insula, we found a preservation only in the left insula in patients with potential pain compared to patients with FDG-PET confirmed UWS and healthy subjects [29]. Studies have suggested that this region could be involved in the affective dimension of pain by playing a mediating role between its posterior part (lateral system) and the rostral part of the ACC (median system) [8,23]. If some studies support a higher involvement of the right hemisphere in pain sensation [22,36], several of them have also shown a bilateral activation of the insula during a noxious stimulation [3,31].

(2) In the ACCs, however, a hypometabolism of the ACC was also observed in patients with *potential pain* and patients in UWS when compared to healthy subjects. In neuroimaging studies on pain processing, the ACC is one of the most frequent region to come up as being linked to pain. This region, most particularly the rostral part of the ACC, seems to be key for the affective dimension of pain processing [29,38]. Neuroimaging studies have

shown that the increase of brain activity in the ACC was correlated with an increased pain sensation [16,26]. Other studies demonstrated an activation of this region after a noxious stimulation in patients with MCS but also in some patients with UWS [1,2].

Then, we wanted to investigate and compare the cortical connectivity in patients with potential pain and in FDG-PET confirmed UWS patients. We found a preservation of the connectivity between the left insula and the medial frontal gyrus in patients with potential pain but not in FDG-PET confirmed UWS patients supporting that the threshold of 5 could be used for inferring preserved neural basis for pain experience [2,19].

If one could say that these results are mainly due to the MCS patients included in the group (i.e., higher brain metabolism in MCS than UWS [30]), single subject analysis of the 3 MCS* patients with potential pain supports the idea that these patients also had a preserved brain metabolism in areas involved in pain processing (i.e., ACC and insula). This also suggests that the score of 5 or higher could be used as a red flag for pain processing, even in patients behaviorally diagnosed in UWS, and by extension the presence of covert cognitive abilities in these patients [17].

Our approach justifies its origin in the fact that previous studies aiming at determining NCS-R cut-off scores failed in distinguishing reliably behavioral responses that could be elicited by non-noxious vs noxious stimulations [5,6]. In fact, a recent study [5] determined a cut-off score of 2, a total score that could be achieved only by purely reflexive/spinally-mediated behavior and that would inevitably lead to a large amount of false positive patients. Nevertheless, we are aware that our threshold of 5, despite its significant advantage to be specific for a cortical process of pain and usable independently of the clinical diagnosis of the patient, has the disadvantage, as we will discuss later on, to lead to a large lack of sensitivity.

These findings need to be interpreted in spite of several limitations: (1) the heterogeneity of the population (i.e., etiology : more anoxic patients in UWS than in MCS), time since injury); (2) this study is retrospective, so it was difficult to control for confounding factors such as pharmacological treatment, motor abilities, intensity of the noxious stimulation or heterogeneity in threshold for pain in each patient; (3) the use of neuroimaging in patient with severe brain damages targeting regions of interest may be challenging but also can be of limited interpretation due to normalization and smoothing issues; (4) we only had the opportunity to analyze resting state brain metabolism data, which is less sensitive and relevant than activation studies when

discussing about pain processing and could also account for differences with some previously mentioned studies. One could also argue that one of the conditions used may not be nociceptive (i.e., mobilization). However, our aim was to first determine the highest score that could be observed in FDG-PET confirmed UWS, and as mobilization can be potentially painful (especially in this population suffering from various physical pathologies such as spasticity [35]), we think it is relevant to use such data in this study. The fact that some of the patients included showed higher scores during mobilization than during experimental pain supports our approach. Despite these limitations, behavioral (i.e., cut-off score $\geq$ 5) and neuroimaging results (i.e., higher global brain metabolism and better preservation of the metabolism in the left insula) suggest that patients with a NCS-R score $\geq$ 5 are potentially able to perceive pain, or have, at least, the neural basis for experiencing it. However, this cut-off score needs to be interpreted with caution given its low sensitivity while being highly specific. Indeed, 74 % of patient with MCS displayed a score below this threshold following an experimental noxious procedure. If part of them could have an impairment in pain processing, it is also likely that for others the NCS-R could have failed to detect potential painful stimuli due to patients' motor issue.

In conclusion, this retrospective study allowed (1) to determine a cut-off score of 5 at the NCS-R that allows to identify patients with preserved neural basis for pain processing and which is in relation with a better preservation of global and local (left insula and ACC) cerebral metabolism and (2) to suggest that, at least, the preservation of the left insula and the left ACC are prerequisites to the conscious process of pain, supporting our hypothesis whereby behavioral responsiveness to pain necessitates a minimal preservation in regions involved in pain processing in patients with DOC. These data provide a first step towards providing better guidelines to clinicians for the management of pain in DOC. The very high specificity and low sensitivity of the score highlight the score currently proposed is very conservative and, if patients with a score of 5 or more should clearly be targeted as potentially in pain, it also shows that patients with a score below that threshold may still be in pain and in need of an appropriate treatment and should not be neglected.

Finally, this study also highlights the complex relationship between consciousness and pain processing. The use of the NCS-R in a clinical setting becomes clearer as we can now support that patients with a NCS-R score below 2 are not able to perceive a stimulus as being painful and

that, on the other side, patients who show a score of 5 or above are likely able to perceive a stimulus as painful. Future studies should focus on better characterizing pain processing in patients with a NCS-R score between 2 and 5, and develop non-behavioral/paraclinical biomarkers of pain processing in DOC.

Conflict of interest:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figure Legends:

Figure 1: Brain metabolism at PET-FDG in a) unresponsive patient (UWS) with a global hypometabolism, b) patient in minimally conscious state (MCS) and c) healthy control. The scale represents the cerebral metabolic rate of glucose (CMRglc; μmoL/g per minute) from 0 (blue) to 12 (red).

Figure 2: Flow chart representing the selection of patients in a) UWS with the CRS-R assessment and with a global hypometabolism at PET-FDG, b) MCS with potential pain defined based on threshold (LIS = Locked-in syndrom, eMCS = emergency minimally conscious state, UWS = Unresponsive wakefulness syndrom/vegetative state, MCS* = UWS with atypical cortical metabolism preservation).

Figure 2: Left: Global brain metabolism preservation in FDG-PET confirmed unresponsive patients (UWS) with NCS-R score < 5, patients with disorders of consciousness (DOC) with NCS-R score ≥ 5 and healthy subjects (CTRL; grey triangles represent patients behaviorally diagnosed as UWS). Right: Regional brain metabolism preservation in patients with a NCS-R score ≥ 5 compared to FDG-PET confirmed UWS. Preservation of the brain metabolism was observed in the left insula (x = -55mm, y = -20mm, z = 12mm).

Figure 4: Brain metabolism in the left insula (x = -55mm, y = -20 mm, z = 12 mm) and in medial frontal gyrus (x = 6mm; y = -18mm; z = 56mm; right panel) in patients with disorders of consciousness (DOC) with NCS-R score ≥ 5 (grey dots) compared to well documented unresponsive patients (UWS) with NCS-R score < 5 (black dots).

Figure 5: Coordinates of peak voxels (in standardized stereotaxic MNI space) showing preserved and impaired metabolism in patients behaviorally UWS with a NCS-R score ≥ 5 (MCS*) compared to healthy subjects (using a 10-mm radius spherical small volume correction in SPM—at voxel and cluster level, centred on a priori coordinates for areas previously identified as the most frequently identified in pain processing; i.e., ACC and bilateral insula; respective coordinates x = 12, y = 10, z =36; x = −34, y = −24, z = 36; and x = 34, y = −24, z = 36). P value corrected for multiple comparisons at cluster level.

Supplementary Table 1 : Demographic table of patients in UWS with the CRS-R assessment and with a global hypometabolism at PET-FDG, based on visual inspection and matched patients with NCS-R score ≥ 5. (F = Female, M = Male, TBI = Traumatic Brain Injury, SAH = Subarachnoid hemorrhage, UWS = Unresponsive Wakefulness Syndrome, MCS = Minimally Conscious State, MCS* = behaviorally UWS with atypical brain metabolism on FDG-PET. In red = highest score observed during the NCS-R).

Supplementary Figure 1 : PET-FDG showing the brain activation in the 13 well-documented UWS selected for the study. (MCS = Minimally Conscious State, CTRL = healthy subjects).