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Pain management decisions in emergency hospitals are predicted by brain activity during empathy and error monitoring

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Summary

Objective. Pain undertreatment, or *oligoanalgesia*, is frequent in the emergency department (ED), with major medical, ethical, and financial implications. Across different hospitals, healthcare providers have been reported to differ considerably in the ways in which they recognize and manage pain, with some prescribing analgesics far less frequently than others. However, factors that could explain this variability remain poorly understood. Here, we employed neuroscience approaches for neural signal modelling to investigate whether individual decisions in the ED could be explained in terms of brain patterns related to empathy, risk-taking, and error monitoring.

Methods. For fifteen months, we monitored the pain management behaviour of ED nurses at triage, and subsequently invited them to a neuroimaging study involving three well-established tasks probing relevant cognitive and affective dimensions. Univariate and multivariate regressions were used to predict pain management decisions from neural activity during these tasks.

Results. We found that the brain signal recorded when empathizing with others predicted the frequency with which nurses documented pain in their patients. In addition, neural activity sensitive to errors and negative outcomes predicted the frequency with which nurses denied analgesia by registering potential side effects.

Conclusions. These results highlight the multiple processes underlying pain management, and suggest that the neural representations of others' states and one's errors play a key role in individual treatment decisions. Neuroscience models of social cognition and decision-making are a powerful tool to explain clinical behaviour and might be used to guide future educational programs to improve pain management in ED.

MeSH Keywords

Pain Management; Neuroimaging; Decision Making

Introduction

The burden of unrelieved pain is a major unresolved public health problem, resulting in human suffering and economic costs. Unlike other medical conditions, pain is difficult to quantify objectively, and is mainly assessed using self-reports and indirect information about its intensity and aetiology, including medical history, previous experience, etc. As such, pain is frequently undertreated in hospitals (*oligoanalgesia*)[1,2], an issue which is exacerbated by the fact that healthcare providers vary widely in the willingness to prescribe analgesics, with only a fraction of this variability explainable by simple demographic characteristics (gender, age or professional experience)[3–7].

In the last years, Emergency Departments (ED) worldwide have introduced computerized protocols to guide nurses at diagnosing and managing pain. Although these approaches improved the overall quality of pain management[8–10], they did not counteract *oligoanalgesia*, as ED nurses still underestimated and undertreated patients' pain to a variable degree[11–14]. This begs for the introduction of new approaches to better understand the processes underlying individual pain management decisions, which could lead to appropriate training procedures to reduce practice variation.

In the present study we exploited recent advances in cognitive and affective neuroscience, which identified brain patterns related to personal affect and decision-making. In particular, a network involving the insula, cingulate cortex, and postcentral gyrus, was consistently implicated in empathizing with other people's pain[15,16]. In addition, a partially-overlapping network in the anterior cingulate, anterior insula, and lateral prefrontal cortex was systematically associated with monitoring errors and negative outcomes from one's

choices[17,18]. This growing knowledge about brain functions provided an opportunity to understand the processes underlying individual differences in pain management. In particular, we hypothesized that brain patterns related to empathy might explain individual differences in diagnosis, as healthcare providers who are less sensitive to others' suffering might report less the pain of their patients. Further, we predicted that brain patterns related to error-processing might also influence decisions at the bedside, as individuals most concerned about their performance might refrain from administering analgesics in fear their side effects.

Methods

Ethics Approval

The study was approved by the Ethical Commission of Canton Vaud (CER-VD N°95/13) and conducted according to the declaration of Helsinki. Each participant signed an informed consent form.

Nurse-Initiated Analgesia Protocol

This study took advantage of a nurse-initiated analgesia protocol implemented in 2013 in the ED of the Lausanne University Hospital (Switzerland). The ED receives around 40,000 patients annually, each of which is initially triaged through the Swiss Emergency Triage Scale[19]. Each nurse certified at using the protocol was prompted by an electronic health record (EHR) to report: (*a*) whether the patient was in pain (> 0 using a numeric rating scale ranging from 0 [no pain] to 10 [the worst pain imaginable]); (*b*) whether there were contraindications to analgesia; (*c*) whether the patient wished to receive analgesia; (*d*) whether an appropriate treatment (paracetamol, ibuprofen, tramadol) should be selected (Figure 1A). Importantly, as protocol

data were recorded at triage, the assignment of patients to nurses was based exclusively on personnel availability, without any preselection in terms of acuity/aetiology. Hence, the nurses' identity was independent from the cases examined.

Pain Management Measures

We used the EHR to retrieve information about the pain management decisions of each certified nurse for 15 months following the protocol implementation. Specifically, we focused on data from eligible patients (> 16 years old, in pain for less than 3 months, without history of drug/alcohol abuse, and no life-threatening condition) to estimate the following measures (see Figure 1A for more details):

1. *Treatment Application:* proportion of decisions to deliver analgesia on triaged patients.

This index was then broken down into two sub-indexes:

2. *Documentation Rate:* the proportion of pain documentations on triaged patients.
3. *Contraindication (CI) Rate*: the proportion of CIs to analgesia documented in those patients who were in pain.

Participants

Nine months after the protocol implementation, all certified nurses were invited to take part to a survey probing for demographic information, work experience, and the *anxiety from uncertainty* scale[20]. Subsequently, between 16-18 months after the protocol implementation, a subgroup was invited to take part to a study involving functional Magnetic Resonance Imaging (fMRI). This subgroup comprehended equal proportion of individuals from each tertile of the Treatment Application distribution obtained from a preliminary analysis of protocol data (6

months from the implementation). This selection ensured that the tested individuals would represent a broad spectrum of protocol use.

Neuroimaging Intervention

The neuroimaging study involved the following three experimental paradigms (see Supplements for more details).

1. *Empathy for pain task*[15,21]. Nurses saw pictures depicting hands in painful situations (wounded, pierced by a syringe, etc.), and control stimuli involving hands without any aversive feature. The task included 30 stimuli per condition, each presented for 2.5 sec and followed by an inter-stimulus interval ranging between 2.5-4.1 sec. This task lasted about 15 minutes.
2. *Balloon Analog Risk Task (BART)*[22,23]. Nurses had to adjust to risk in a gambling context, by pressing a key repeatedly to inflate a virtual balloon as much as possible and stop just before it exploded. If they stopped before the explosion, they received a virtual monetary gain proportional to the volume of air pumped (*win* condition); however, they received nothing if the balloon exploded (*loss* condition). The task involved 28 game iterations, each leading to a potential win/loss. Every game comprehended up to 11 inflations, each remaining on the screen until a response was provided, and followed by an inter-inflation interval ranging between 1.5-2.5 sec. Win/loss feedbacks lasted 2.5 sec and were followed by an interval ranging between 2-4 sec. The task never exceeded 15 minutes.
3. *Social Harm Avoidance Monitoring Experiment (SHAME)*[24]. We implemented an error-monitoring task involving similar stakes to clinical decision making, where one's errors

may cause harm to another person (the patient). The nurse inside the scanner took turns with a colleague outside (another nurse from the experimental group) in performing a dot-counting task. Overall, there were 98 trials, organized in 14 blocks (7 per player) of 7 trials each. Every erroneous response had a 50% probability to cause a painful stimulation to the arm of the nurse outside the scanner, and was signalled with an *ad hoc* feedback for 5 sec, followed by an interval ranging between 2-9 sec. The overall amount of correct/erroneous trials depended on participants' proficiency in the counting task, whose difficulty was adjusted on-line to avoid ceiling/floor effects. The critical condition was when the nurse in the scanner caused pain to the one outside (one's painful errors). This was compared with a condition in which the same harmful outcome was caused by the nurse outside to him/herself (others' painful errors). The task lasted 12 minutes.

Data Analysis

In the behavioural survey, we first assessed the dependency between the three pain management measures through Pearson's correlation coefficient. Subsequently, we assessed how each of these three measures was related with age, gender, years of experience and *anxiety for uncertainty*. Results are reported as significant under an $\alpha = 0.003$ (Bonferroni-corrected for 15 tests). Uncorrected effects ($\alpha = 0.05$) associated with *anxiety for uncertainty* scores are also reported, as one of the aims of the study was to investigate specifically how error/uncertainty processing might affect different stages of pain management.

For the neuroimaging investigation, we first preprocessed functional data of each nurse using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/) to account for head movements,

geometric distortions by the magnetic field, and anatomical differences between subjects. The preprocessed images were then fed to first-level General Linear Models (GLMs) testing, in each task, for increased activity in the main condition of interest, and for the tailored control (see previous studies[15,21–24] and supplements for details). The activity maps estimated in each individual GLM were then used for group-level analyses testing whether the condition of interest in each task: (*a*) exhibited increased activity with respect to the control; (*b*) was linearly modulated by nurses' professional behaviour. Activations were reported if surviving correction for multiple comparisons for the whole brain or for regions-of-interest masks. These masks were obtained by reanalysing, under the same parameters used here, previous datasets obtained by running the same three paradigms on lay individuals[15,23,24] (see Supplements and Tables S1-3 for more details).

In addition, we used Least Absolute Shrinkage and Selection Operator (LASSO)[25–28] and Random Forest (RF) regression[29] to identify distributed patterns of activity that could predict nurses' professional behaviour. In particular, this analysis involved: (1) extracting the activity associated with each event of interest from *a priori* masks (the same used for the univariate analysis). (2) Feeding the extracted signal to the two algorithms for multivariate modelling. (3) Testing the generalizability of the estimated models through cross-validation techniques: i.e., assessing whether a model tailored on a portion of subjects could predict the clinical behaviour of the remaining (independent) subjects. (4) Obtaining an overall mean squared error (*MSE*) as measure of prediction proficiency, which was then validated statistically through permutation techniques (see Supplements).

Results

70 ED nurses responded to the survey, 33 of which agreed to take part to a subsequent neuroimaging investigation (see Table 1 for details). Two nurses asked to discontinue the neuroimaging session prematurely: hence, BART was completed by 32 participants, and SHAME by 31.

Behavioural survey

When assessing the nurse-led analgesia protocol data, we found a large inter-individual variability in Treatment Application (Figure 1B). This variability was related to both individual Documentation Rate and CI rate: nurses that applied analgesia more frequently were more inclined to document patients' pain (r = 0.36, p = 0.002), and less likely to report contraindications (r = -0.54, p < 0.001) (Figure 1C). None of these indexes were associated with nurses' age, years of experience ($|r| \leq 0.17$, *n.s.*) or gender ($|t| \leq 0.99$; except for potentially larger Documentation Rate in males nurses $t_{(30.31)} = 2.15$, p = 0.039, uncorrected). Interestingly, nurses with higher scores on the *anxiety from uncertainty* scale showed higher CI rates (r = 0.29, p = 0.017 uncorrected; for the other indexes $|r| \leq 0.18$, *n.s.*).

Neural responses to Others' Pain

Subsequently, we engaged a subgroup of nurses in a fMRI task where they witnessed pictures of injured hands. This task recruited a brain network classically associated with pain-processing and empathy[15,16,21], involving the posterior insula, postcentral gyrus, and midline cortical areas (Figure 2A). No activation was observed in the anterior insula and middle cingulate cortex, which are known to respond to others' pain in lay individuals, but not in professional healthcare providers[30,31].

We then tested whether these neural responses to others' pain could predict nurses' clinical behaviour. First, by using a univariate linear regression, we found a significant relationship between the activity the right postcentral cortex and Documentation Rate, with stronger neural response to injured hands in those who reported most frequently patients' pain in their daily work. We then tested whether clinical behaviour could be predicted from distributed patterns of brain activity (rather than isolated regions) during this task. For this purpose, we extracted the neural activity evoked by viewing injured hands from a predefined network (see Methods), and fed it to two machine learning algorithms (LASSO and RF) to predict clinical behaviour. Both algorithms revealed that empathy-related activity was a good predictor of the documentation rate of individual nurses (Figure 2B). No significant effects (neither univariate nor multivariate) were associated with the other two measures.

Neural responses to Negative Outcomes

We performed similar analyses for brain activity evoked when observing self-caused errors and negative outcomes. When confronted with monetary losses (*vs*. gains) in the BART[22,23], nurses exhibited widespread activations in the middle cingulate cortex, anterior insula, and thalamus (Figure 3A), a network often associated with the detection of errors[17,18], and other salient outcomes[32,33]. Univariate linear regression showed that the activity of several regions within this network, including the insula and cingulate areas, were related to the documentation of contraindications to analgesia. In addition, multivariate regression with LASSO and RF revealed that distributed patterns of activity related to money loss was a reliable predictor of nurses' CI rate (Figure 3B).

Similarly, when observing harmful consequences of their own (vs. someone else) errors in the SHAME[24], nurses activated the anterior portion of the middle cingulate cortex. Moreover, regression analysis showed that activity related to one's painful errors was linearly coupled with CI rate in both the middle cingulate cortex and left middle frontal gyrus. Thus, as found for the BART, these areas were more strongly activated in those individuals who were more likely to spot contraindications to analgesia. Finally, LASSO and RF regression confirmed that activity patterns in the network activated by harmful errors were a reliable predictor of CI Rate (Figure 4). Data from neither BART nor SHAME were significantly associated with the other two clinical measures.

Discussion

Healthcare providers appraise and treat pain very differently from one another[3–7], resulting in patients being more or less likely to receive analgesia according to the person who is in charge of them. The demographic characteristics of healthcare providers explain only partially this variability[3], suggesting that other factors are at play. By using a battery of well-established questionnaires[20] and experimental paradigms from neuroscience[15,21–24], we shed new light on the mechanisms underlying these inter-individual differences. First, the likelihood of reporting contraindications to analgesia in clinical practice can be explained by personal anxiety towards uncertain outcomes (from the behavioural survey), as well as differences in brain responses to negative feedbacks (neuroimaging investigation). Second, the frequency of documenting patients' pain can be explained by differences in brain patterns evoked by witnessing others' injuries. Overall, our study underscores the role played by two main processes which exert

opposite, but concurrent influences on the decision leading to the prescription of analgesia in clinical practice.

Ideally, choices such as documenting a symptom, reporting contraindications or prescribing treatment should be motivated exclusively by the clinical characteristics of patients. Hence, no variability should be observed between ED nurses, as long as they all handle a similar mix of cases, matched in aetiology and severity. Surprisingly however, nurses behave quite differently from one another, ranging from those who prescribe analgesia to ~5% up to 20% of patients (Figure 1B; see also[3–7]). Considering that patients' assignment was independent of the nurses' identity, and that the clinical variables of interest were obtained by collapsing data from all cases handled by each operator in 15 months (see Methods), it is unlikely that the observed variability was influenced by the severity of patients examined. Instead, it is more plausible that each nurse is characterized by a personal disposition/attitude towards pain management. Previous studies have already categorized healthcare providers according to their attitudes (more *vs*. less attentive to case severity[5], more *vs*. less reliant on patients' self-reports[11]), without however shedding light on the processes that might contribute to this categorization. Our study extends previous findings, not only by providing a working model according to which pain management is driven by two clear dimensions, but also by associating these processes with distinct brain networks.

Brain responses evoked by observing others' pain have been thoroughly investigated in neuroscience research, pointing to a major role of the insula, middle cingulate cortex, and postcentral gyrus[16]. The most popular interpretation of these activations is that they reflect the engagement of circuits implicated in first-hand nociception, which are then re-enacted

"empathetically" when pain is not felt on oneself but observed in others[15,16]. Critically, however, these regions are not homogeneous in their function, but can be broadly classified into two functionally-segregated networks, coding different aspects of the painful experience. In particular, brain patterns in the anterior insula and middle cingulate cortex might not be pain-specific, but generalize also to other aversive experiences such as arousing pictures[15], disgusting tastes, or monetary losses[34]. Hence, these regions could serve a domain-general purpose involved in detecting events of high relevance for one's survival[32], including errors[17,18] and risky decisions[22,23], with painful or financial consequences for oneself and others[33]. In contrast, the posterior insula and postcentral somatosensory cortex appear to process pain in a more specific fashion, with little generalization to other forms of affect[15,35]. This might underlie a sensory-specific component of the painful experience, which is re-enacted when witnessing also others' sufferance[15,16]. In our study, these functionally segregated networks were associated with independent components of pain management, with the postcentral gyrus predicting the frequency with which healthcare providers documented pain in patients, and the middle cingulate cortex predicting the frequency with which they noted potential contraindications.

Overall, our study offers a comprehensive model of pain management decisions in which healthcare providers hold at least two distinct representations of their patient's state. First, there is the patient's *current* pain, which is estimated through evaluation of diagnostic signs as well as self-reports, but also influenced by doctors and nurses' empathic skills. Second, there is the patient's *prospective* state, which is estimated by predicting the potential consequences of analgesia and thus taps into one's ability to make decisions under uncertainty

and to learn from previous errors. Critically, although healthcare providers are deontologically bound to relieve patients' current pain with analgesia, they are equally bound to prevent potential side-effects by withholding analgesia, a conflict which is resolved differently in each individual, based on specific characteristics of the case, but also personal traits of empathy, dispositions towards errors/uncertainty, etc. Training techniques already exist to modulate empathy and compassion[36], but also to help individuals reduce anxiety about potential errors[37]. These could serve as a basis for future educational programs for doctors and nurses, to promote a more efficient pain treatment and a more coherent level of care.

In this study, we exploited the rare opportunity to monitor pain management behaviours of professional healthcare providers for 15 months, and relate them to brain activity patterns in well-known tasks. The drawback of this approach lies in the difficulty of obtaining independent cohorts (e.g., for assessing power or replicating effects), as other hospitals usually do not record the same behavioural indexes. The application of rigorous cross-validation techniques insured generalizability within the sample tested. However only future implementations of the same pain management protocol in other EDs will allow extend our findings to different countries and healthcare systems.

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Authors' contribution

C.C.D.: Study design, Data collection, Data analysis, Interpretation of Results, Manuscript drafting.
M.F.: Study design, Subjects recruitment, Manuscript critical revision.
G.S.: Data collection, Manuscript critical revision.
L.T.: Data Analysis, Manuscript critical revision.
E.F.: Subjects recruitment, Manuscript critical revision.
Y.F.: Study design, Manuscript critical revision.
P.V.: Study design, Interpretation of Results, Manuscript critical revision.
O.H.: Study design, Interpretation of Results, Manuscript critical revision.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work (thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved).

Declaration of Interest

None Declared.

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Appendix

De-identified data files and scripts for the multivariate analyses are available at Open Science Framework: https://osf.io/2bved/.

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Figure Legends

Figure 1. (**A**) Flowchart subsuming the key steps of the nurse-led protocol implemented in the Emergency Department. Nurses were expected to follow and document this procedure for each patient under their care. Data collected for each nurse over 15 months following the protocol implementation were used to estimate three different scalars indexing their pain management behaviour (Pain Documentation Rate, CI Rate, and Treatment Application). Each measure was computed as the percentage among patients who passed a specific protocol step, as noted in the flowchart. Full details in methods section. **(B)** Bar-graphs displaying between-nurse variability in pain management behaviour. Each subplot represents one of the three scalars of interest, whereas each bar represents one isolated nurse. Nurses' identity is here coded with a number ranging from 1 to 70 according to their percentage of Treatment Application value. **(C)** Scatter plots describing the linear relation between the three measures. **(D)** Scatter plots describing the linear relation between the Anxiety due to Uncertainty score and each of the three behavioural measures of interest. Each plot shows a linear regression line (with a grey area describing the 95% confidence interval), plus the Pearson correlation coefficient. The significance of the correlation is highlighted as follows: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

Figure 2. Empathy for Pain **(A)** Whole brain map depicting regions implicated in processing pictures of injured hands (Painful – Control Images). **(B)** Linear regression of Documentation Rate. Surface rendering of a human brain highlighting suprathreshold coordinates in which neural responses to Painful Images explained nurses' Documentation rate in univariate linear regression. Three subplots are also displayed. The left-low subplot describes the linear relation

between Documentation Rate and the average parameter extracted by the right Postcentral Gyrus (grey area refers to the 95% confidence interval). The remaining two subplots refer to data from Multivariate Pattern Analysis (color-coded according to the machine-learning algorithm used). On top, the overall proficiency of LASSO and RF classifiers for prediction of the three clinical measures of interest is displayed. White circles refer to mean square error (MSE) associated with out-of-subject predictions, superimposed with violin-plots of the permutation-based null distribution of MSE. The right-low subplot describes the linear regression between nurses' Documentation rate and the value predicted by each of the two classifiers. PostC: Postcentral Gyrus. PreC: Precentral Gyrus. SMG: Supramarginal Gyrus. IFG: Inferior Frontal Gyrus. Ins: Insula. *r*: Pearson correlation coefficient. ***$p < 0.001$, *$p < 0.05$ associated with standard parametric analysis (for linear regressions) and permutation-based analysis (for MVPA).

Figure 3. BART **(A)** Whole brain map depicting regions implicated in Money Loss (Loss – Win). **(B)** Linear regression of CI Rate. Surface rendering of a human brain highlighting suprathreshold coordinates in which neural responses to Money Loss explained nurses' CI rate in univariate linear regression. Three subplots are also displayed. The left-low subplot describes the linear relation between CI Rate and the average parameter extracted by the Middle Cingulate Cortex (grey area refers to the 95% confidence interval). The remaining two subplots refer to data from Multivariate Pattern Analysis (color-coded according to the machine-learning algorithm used). On top, the overall proficiency of LASSO and RF classifiers for prediction of the three clinical measures of interest. White circles refer to mean square error (MSE) associated with out-of-subject predictions, superimposed with violin-plots of the permutation-based null

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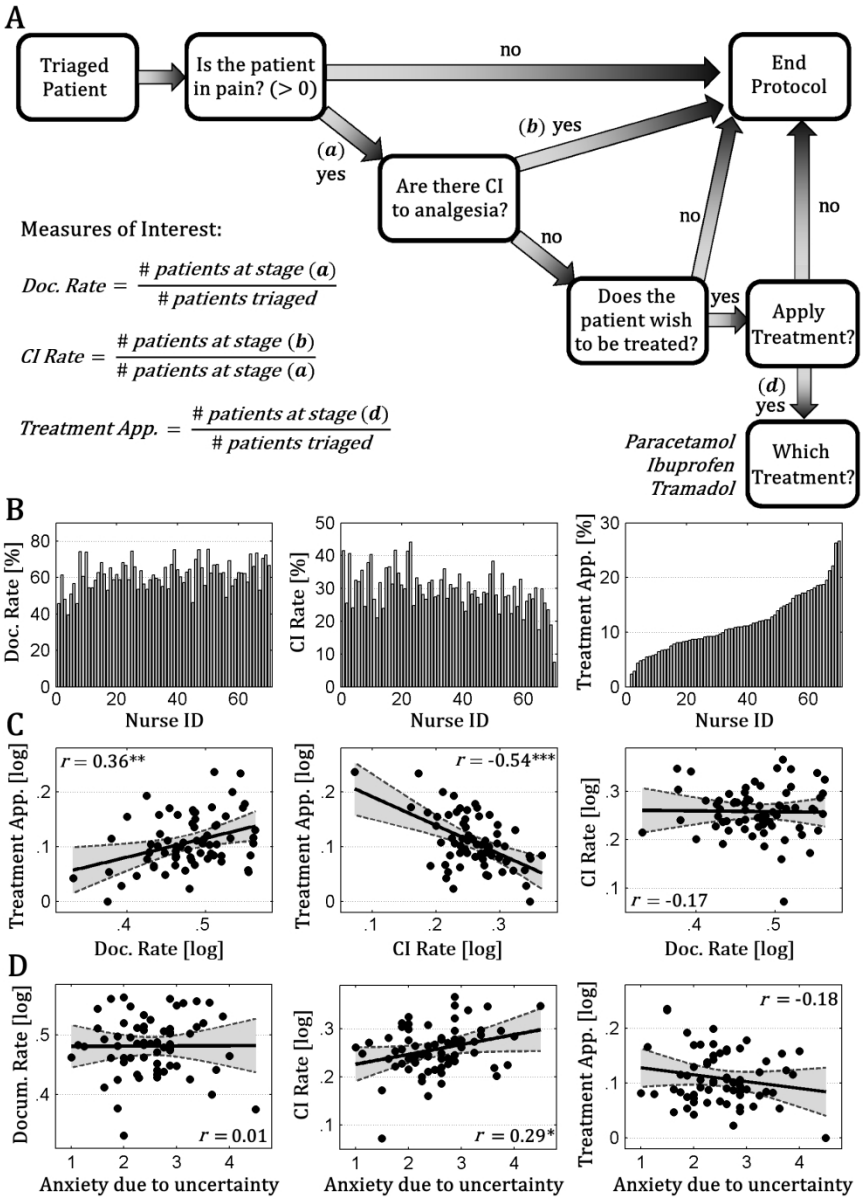
Figure 4. SHAME **(A)** Whole brain map depicting regions implicated in painful outcomes of one's errors (One's – Others' Painful Errors). **(B)** Linear regression of CI Rate. Surface rendering of a human brain highlighting suprathreshold coordinates in which neural responses to One's Painful errors explained nurses' CI rate in univariate linear regression. Three subplots are also displayed. The left-low subplot describes the linear relation between CI Rate and the average parameter extracted by the anterior Middle Cingulate Cortex (grey area refers to the 95% confidence interval). The remaining two subplots refer to data from Multivariate Pattern Analysis (color-coded according to the machine-learning algorithm used). On the top the overall proficiency of LASSO and RF classifiers for prediction of the three clinical measures of interest. White circles refer to mean square error (MSE) associated with out-of-subject predictions, superimposed with violin-plots of the permutation-based null distribution of MSE. The right-low subplot describes the linear regression between nurses' CI rate and the value predicted by each of the two classifiers. aMCC: anterior Middle Cingulate Cortex. MFG: Middle Frontal Gyrus. ***p < 0.001, *p < 0.05 associated with standard parametric analysis (for linear regressions) and permutation-based analysis (for MVPA).

Tables

Table 1

Demographic information. Eligible ED nurses responding to the survey, and subsequently subdivided into those who took part to the neuroimaging investigation, and those who did not. Each of the three groups is described in terms of overall size, number of women (including percentage value to the overall size), and median age, experience in ED and number of triages per nurse in a time window of 15 months (bracket values refer to inter-quartile range). For each of measures reported, the subgroup taking part to the neuroimaging investigation discloses similar values to the group who did not.

	Survey	***Neuroimaging Participants***	***Other Participants***
Population Size	70	33	37
Females	51 (73%)	22 (67%)	29 (78%)
Age [years]	33 [31, 38]	34 [31, 39]	33 [30, 37]
ED Experience [years]	6 [4, 9]	9 [4, 13]	6 [4, 8]
Triages per nurse	452 [273, 694]	480 [405, 694]	445 [210, 692]



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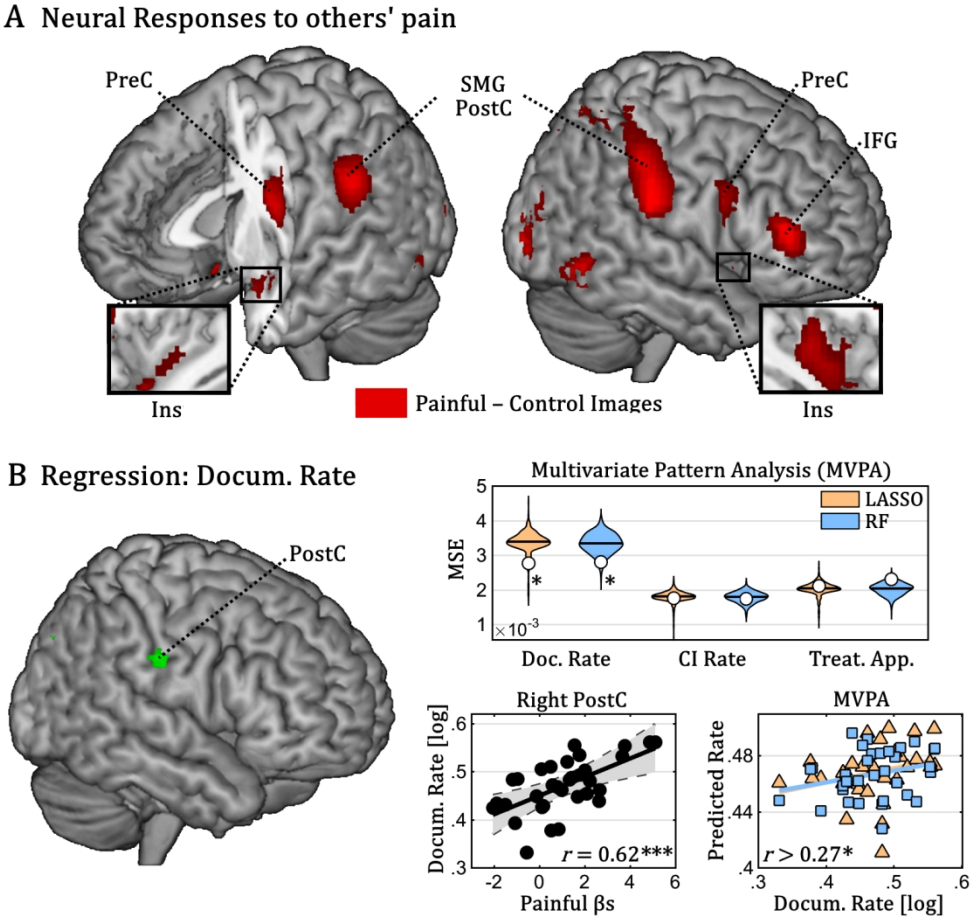

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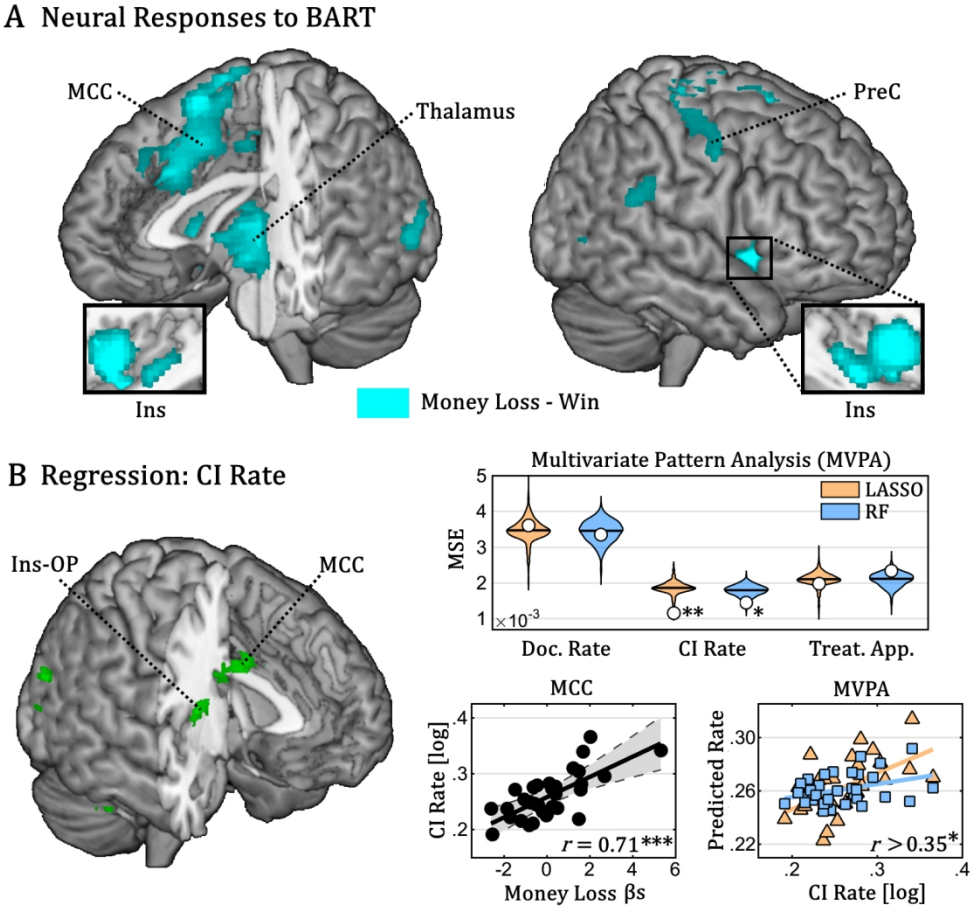

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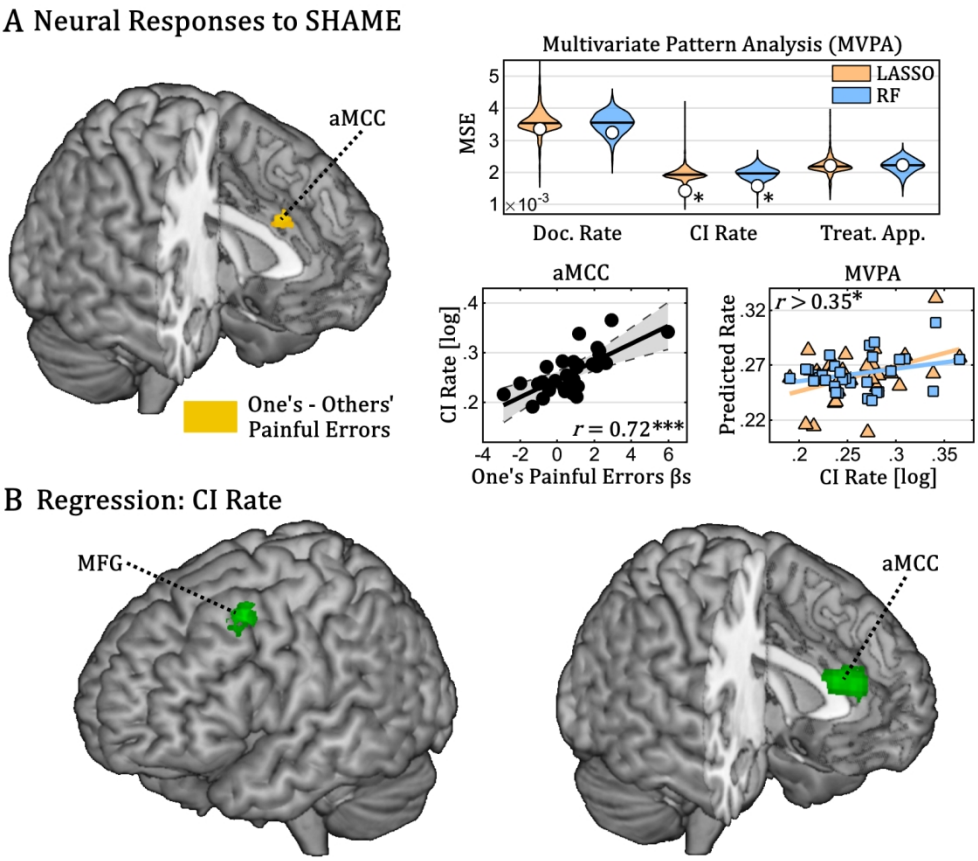

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