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ABSTRACT

Knee osteoarthritis (KOA) is a chronic condition strongly associated with pain, in which central sensitization plays a key role. Yet, its neurobiological mechanisms remain poorly understood. Quantitative resting-state EEG offers a non-invasive approach to investigate these processes. This longitudinal study examined EEG changes before and after rehabilitation in patients with chronic KOA. Resting-state EEG and WOMAC pain and function scores were assessed pre- and post-rehabilitation. Relative power in delta, theta, alpha, and beta bands was analyzed across frontal, central, and parieto-occipital regions. Subgroup analyses explored the influence of baseline characteristics and clinical response. Fifty-nine patients (median age 67.6 years; pain duration 3 months–41 years) completed the study, with 80.7% showing clinical improvement. Although no statistically significant EEG changes were observed, trends suggested increased beta and decreased alpha power following rehabilitation. Subgroup analyses revealed higher left frontal beta power in patients without pain relief, while those with pain lasting ≥10 years showed reduced right frontal beta power. This first real-world investigation indicates that EEG may capture maladaptive or compensatory mechanisms in KOA and holds promise as a biomarker, warranting confirmation in future research.

Keywords: Osteoarthritis, Knee; Chronic Pain; Central Nervous System Sensitization; Electroencephalography; Neuronal Plasticity, Biomarkers

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INTRODUCTION

Osteoarthritis is a chronic, complex and multifactorial disease with an important impact on global public health as shown by findings in the Global Burden of Disease Study (GBS) [1]. The lifetime risk of knee osteoarthritis (KOA) is estimated to be approximately 44.7% [2]. Projections from the GBS estimate a 74.9% increase in knee osteoarthritis cases by the year 2050 [3]. KOA is, therefore, a condition with a significant impact on both patients and health systems. Unfortunately, there does not appear to be a universally applicable strategy for managing this disease. Clinical practice guidelines recommend a combination of various treatments that generally show small to moderate effect sizes [4].

Pain is the main symptom of KOA. In addition to peripheral mechanisms, central sensitization associated with chronic pain also plays a significant role in these patients [5]. The prevalence of central sensitization-related pain in the context of knee ostheoarthritis has been reported to range between 10% and 15% [6]. This central component may also explain why, among patients undergoing surgical treatment involving total knee replacement, a procedure considered a definitive treatment for the disease, up to 44% report persistent post-surgical pain [7].

Although central sensitization is recognized as a significant factor in various chronic pain conditions, its precise biological mechanisms remain incompletely understood. Reliable biomarkers for the associated neurophysiological changes have yet to be established. One possible method to investigate these changes is the quantitative electroencephalography (qEEG), owing to its non-invasive nature and ability to measure brain activity in real time [8].

A scoping review published in 2023, which examined evidence of functional and structural brain changes in individuals with knee osteoarthritis, did not identify any studies that investigated the use of EEG in this population [9]. In contrast, a systematic review from 2022 included two studies that employed EEG to assess neuroplasticity in this population [10]. These studies did not utilize resting-state EEG; instead, they focused on evoked potentials following painful stimuli.

An exploratory study assessed 10 patients with KOA before and after a rehabilitation program, suggesting potential parameters for future investigation, described as relative

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increase of density measures [11]. However, again this study did not include resting-state EEG which records spontaneous brain activity, is less prone to artifacts, and measures the EEG present during the patients' real-life, day-to-day functional status.

The association between the various waves measured in the EEG and the clinical changes in patients with OA was investigated cross-sectionally in this study's sample, using patient data collected before the start of the rehabilitation protocol (baseline). Based on a multivariate regression, Simis and colleagues (2022) reported an increase in high-beta wave power in the fronto-central region and a reduction in central theta power, both positively correlated with pain intensity [12]. These findings suggest that resting-state EEG may serve as a valuable tool in the search for rehabilitation biomarkers.

Based on the above, we can conclude that there is limited evidence regarding the use of EEG for cerebral assessment in this specific population. To our knowledge, the use of resting-state EEG specifically for the assessment of patients with osteoarthritis of the knee who go through a rehabilitation program has not yet been investigated [9,10,13]. The available studies of EEG for knee osteoarthritis and chronic pain are heterogeneous in terms of the EEG variables measured (e.g., evoked potentials, resting-state activity, relative power, location of electrodes), as well as the study design in which the EEG assessments were conducted (e.g. longitudinal with intervention or cross-sectional).

The aim of the study was to investigate the difference in resting-state quantitative EEG measurements before and after rehabilitation in a cohort of patients with chronic knee osteoarthritis to explore its potential as a biomarker in this disease. Secondary analysis consisted of investigating whether there were differences in these EEG measurements depending on demographic or clinical variables.

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METHODS

We conducted a longitudinal analysis of EEG assessments in patients with knee osteoarthritis (KOA) enrolled in the cohort study titled "Deficit of Inhibition as a Marker of Neuroplasticity (DEFINE study) in Rehabilitation," for which the protocol has been published previously [14]. The DEFINE study was approved by the Research and Ethical Committee of the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (HC FMUSP) (registration number: 86832518.7.0000.0068). All the procedures and methods in this study are in accordance with Brazilian research ethics regulations and the Declaration of Helsinki.

Participants

Patients were recruited between October 2018 and December 2019 at the Instituto de Medicina Fisica e Reabilitacao (IMREA) of the HC FMUSP in Brazil. Patients enrolled in the conventional outpatient rehabilitation program were invited to participate in this study. Those who expressed interest were screened, and if found eligible, were invited to sign the informed consent form. Informed consent was obtained from all participants. Data collection and follow-up were completed in January 2020.

Eligibility criteria were as follows: age over 50 years, clinical or radiological diagnosis of knee osteoarthritis, absence of active OA in any joint other than the knee, and no clinical and/or social condition that could hinder participation in the conventional rehabilitation program, such as communicable infectious diseases, clinical instability, lack of family support, inability to attend the institute during the research period, among others.

Demographic and clinical assessments

At baseline, demographic variables such as age, gender, education level, skin color, BMI, duration of pain, and current medications use were collected. Clinical assessments included radiological evaluation of both knees, as well as pain and physical function using the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index [15]. The WOMAC pain and physical function subscales were the primary clinical outcome

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measures and were assessed both before and after completion of the ambulatory rehabilitation program executed in a hospital context. The pain subscale evaluates pain in five specific situations. Patients report their pain level in each situation on a scale from 0 (none) to 4 (extreme). The physical function subscale assesses difficulty performing 17 daily activities, using the same 0 to 4 scale. Scores from individual items are summed, resulting in a total pain score ranging from 0 to 20, and a physical function score ranging from 0 to 68.

Rehabilitation protocol

The rehabilitation program consisted of one to two weekly sessions and included focal shock waves, radial pressure waves, paravertebral block with lidocaine, and electrical neuromuscular stimulation according to the patient's needs. It is important to emphasize that the objective of this study was not to evaluate the efficacy of the interventions. Therefore, patients underwent individualized rehabilitation protocols tailored to their specific needs. Therefore the exact number of sessions, total duration of interventions, individual treatment goals, among others vary between individual patients.

Resting-state electroencephalography

Patients underwent two EEG assessments, before and after the rehabilitation program. EEG recordings were performed using the 128-channel EGI system (Electrical Geodesics, Inc) (EGI, Eugene, USA). EEG was recorded in a resting state for four minutes with eyes closed. The original data were pre-processed to correct any biological or nonbiological artifact that compromised the analyses, using EEGLab [16] in MATLAB (MATLAB R2014b, The MathWorks Inc. Natick, MA, 2000). Thus, using the Darbeliai EEGLAB plugin, we performed Makoto's preprocessing pipeline [17]: (i) Band Pass of 1 Hz (high-pass) and 50 Hz (low-pass); (ii) downsampling from 1000 Hz to 250 Hz; (iii) channels were re-referenced by the average of the electrodes; (iv) 60-Hz powerline noise correction (Brazilian frequency). Next, using the Clean_rawdata EEGLAB plugin (v2.2) we excluded the channels that were flat for more than 3 s; presented high frequency noise greater than

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2 standard deviations; and had correlation with nearby channels lower than 0.8. Before proceeding to perform the Independent Component Analysis (ICA), a visual inspection and rejection of periods with artifacts was performed which was also validated by a neurophysiologist. The remaining channels were again submitted to the Darbeliai plugin for the Infomax ICA calculation. This analysis is effective in identifying artifacts [16,18] and is significantly related to other techniques, showing greater efficiency in identifying components [16]. Components related to eye movement, blinking, heart rate and muscle noise were excluded.

The final measure and main variable included in the analysis was relative power, defined as the power within a specific frequency band divided by the total power across all bands. Relative power was calculated for the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz), in three regions of interest: frontal, central, and parieto-occipital areas of each hemisphere. The electrodes included in the different regions and their placement are presented in Supplementary Table S1 and Supplementary Figure S1 online, respectively.

Statistical analysis

The KOA cohort of the DEFINE study consisted of a convenience sample, given the exploratory nature of this analysis. The sample size was originally determined based on the objectives of the DEFINE study, as described in the published protocol [14].

Baseline characteristics were summarized accordingly. Continuous variables were reported as mean ± standard deviation (SD) or as median and interquartile range (IQR), depending on their distribution. Categorical and dichotomous variables were presented as frequencies and percentages. Histograms and the Shapiro–Wilk test were used to assess the normality of data distributions. For continuous variables measured before and after rehabilitation, comparisons were made using the paired t-test when data followed a normal distribution; otherwise, the Wilcoxon signed-rank test was applied.

To investigate potential differences in EEG measurements between groups, the cohort was stratified based on the median values of the following variables: age and interval

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between EEGs. For the body mass index (BMI), patients were classified as having a BMI lower than 30 or not [19]. For the variable "duration of pain," the following grouping was applied: 3 months to 1 year, more than 1 year to 5 years, more than 5 years to 10 years, and more than 10 years. For the Pain Catastrophizing Scale (PCS), measured using the validated Brazilian version [20], which consists of 9 items rated on a Likert scale from 0 to 5, a cut-off score of 9 was pragmatically chosen to divide the sample. Patients' medication use was classified as either 'yes' or 'no', with 'yes' indicating the use of at least one of the following substances: antidepressants, analgesics, muscle relaxants, antipsychotics, benzodiazepines, or antiepileptic drugs.

Statistical analyses were conducted using Stata Statistical Software, version 17 (StataCorp LLC). As this was an exploratory study, no correction was applied for multiple comparisons.

RESULTS

Sample Characteristics

In total, 113 patients were enrolled in the cohort, of which ultimately 59 completed the final assessment and were included in the analysis. For further details we refer to the flow diagram (Figure 1). Below we report the demographic and clinical variables of the 59 patients who had validated and complete resting-state EEG data before and after rehabilitation. The characteristics of the patients who did not have complete EEG data or who discontinued study participation are available in the Supplementary Tables S2 to S5 online.

Insert Figure 1 here

The median age of the sample included in this analysis was 67.6 years, ranging from 53.1 to 99.9 years and 91.5% were female. The BMI ranged from 21 to 42.9 kg/m^2 with a median of 30.9 kg/m^2. The median pain duration was 72 months, ranging from 3 months to 41 years, with nearly half of the individuals (49.2%) experiencing pain for up to five years (Table 2).

Insert table 1 here

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Regarding the education level of the patients, the majority of the sample had completed primary education (37.3%) and the groups with secondary and higher education were of equal size (Table 2). With respect to skin color, the majority of participants self-identified as white (66.1%).

Insert table 2 here

The majority of patients (59.3%) had bilateral radiographic OA according to the Kellgren-Lawrence (KL) scale. However, thirteen patients (22%) showed no evidence of radiographic OA in either knee (Table 3). As measured by the VAS, knee pain was present bilaterally in 57/59 (96.6%) patients with 44.1% of patients experiencing bilaterally severe pain (VAS of 7.5 or higher – see Supplementary Table S6 online). The sample can therefore be considered to have bilateral osteoarthritis. At baseline, the mean WOMAC pain score was 10.8 (SD 3.8) and physical function score was 35.2 (SD 14.4).

Insert table 3 here

The median duration of rehabilitation was 31 days (IQR 13 to 68 days) and the median time between the two EEG assessments was 45 days (IQR 28 to 79 days). For further information regarding the content of the individualized rehabilitation program we refer to the corresponding article [21].

Comparison of pain, physical function, and EEG measurements before and after rehabilitation

Table 4 shows the statistically significant difference in pain and physical function scores, as measured by the WOMAC, between the assessments conducted before and after rehabilitation in this cohort. Changes in the WOMAC pain subscale ranged from a 3-point increase (indicating worsening) to a 16-point decrease, with a mean reduction of 3.4 points. For the physical function subscale, scores ranged from an 18-point increase to a 41-point decrease, with a mean reduction of 9.5 points. Overall, 80.7% of patients showed improvement in both pain and physical function based on the WOMAC scores.

Insert table 4 here

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There were no statistically significant differences in EEG measurements before and after rehabilitation (Table 5). When examining the range of mean differences between pre- and post-rehabilitation, as well as the percentage of participants who showed either an increase or decrease in power, we observed that across all wave types and brain regions, some individuals exhibited increases while others showed decreases in EEG power (Table 6). On average, beta power increased and alpha power decreased across all regions whereas for theta and delta waves, the pattern was less consistent.

Insert table 5 here

Insert table 6 here

Subgroup analysis based on clinical improvement

A subgroup analysis based on clinical improvement in the WOMAC pain and physical function subscales revealed no statistically significant differences in EEG measurements before and after rehabilitation, with two exceptions: an increase in right parieto-occipital delta wave power in the group that showed improvement, both for WOMAC pain and physical function, and an increase in left frontal beta wave power in the group without improvement in WOMAC pain. Full details of this analysis are provided in Supplementary Table S7 online.

Subgroup analysis based on demographic variables

When examining the differences in changes in EEG wave power between groups based on demographic and baseline variables, there was a statistically significant increase in theta power in the parieto-occipital and frontal regions among individuals experiencing pain for a duration of three months to one year. Those with chronic pain lasting for ten years or more exhibited a decrease in beta power in the parieto-occipital region and the right frontal region. Additionally, participants who reported higher levels of pain catastrophizing showed a reduction in alpha power across the frontal and parieto-occipital regions. For a comprehensive presentation of the data, please refer to Supplementary Tables S8 to S10 online.

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DISCUSSION

This publication is the first to report changes in quantitative resting-state EEG across different brain regions in patients with KOA undergoing a real-life rehabilitation program that led to improvements in pain and function. Additionally, subgroups were thoroughly analyzed to explore potential associations between EEG changes and demographic or clinical factors—an area that remains underexplored in the current literature. We did not find a statistically significant difference in the relative power of delta, theta, alpha, and beta EEG waves before and after rehabilitation in the 59 patients who showed improvement in pain and physical function.

Similar results were reported by Zebhauser and colleagues (2023) in a systematic review on the use of resting-state EEG in patients with chronic pain, in which no clear associations were observed between pain reduction and electrocortical measures in longitudinal studies [13]. However, it is important to interpret our findings with caution, considering that the limited sample size, inherent to the exploratory nature of the investigation, reduced the available statistical power. In fact, the post-hoc analysis of our data indicated that the statistical power to safely conclude the absence of significant differences was not achieved. The lack of formal sample size calculations in studies investigating EEG in chronic pain had already been highlighted by the review by Zebhauser et al.

Despite the fact that there was no statistically significant difference, several findings and trends reported in this study are noteworthy and merit discussion, as they may provide a foundation for future research.

Across all regions, a general trend was observed in the analyzed sample: the mean relative beta power increased, while relative alpha power decreased. However, it is important to note that for alpha and beta power—as well as for theta and delta—the number of patients showing an increase in power was roughly balanced with those showing a decrease. The most notable deviation from this pattern was found in central alpha waves (left and right), where 61% of patients showed an increase in relative power, compared to 39% who showed a decrease. We hypothesize that this variability is due to considerable heterogeneity within the sample, particularly with respect to demographic

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characteristics such as older age (25% of the sample being older than 76 years), as well as clinical factors including pain duration (ranging from 3 months to 41 years), the time interval between EEG assessments (ranging from 28 to 79 days), and the applied interventions, which were individualized for each patient. In future analyses investigating EEG in similar populations, these variables should therefore be carefully considered.

Previously published baseline data of this cohort reported an association in a multivariate regression model between increased frontocentral beta power and higher scores on the WOMAC pain subscale [12]. The replication of the multivariate regression model reported by Simis et al. after the rehabilitation protocol was not possible due to the fact that there was no significant change in EEG measured power but can be further explored in future studies. The higher beta power with pain found by Simis et al [12] has been confirmed by a systematic review, although in a broader chronic pain population compared to healthy controls, and only in cross-sectional studies without specifying the location of the increased power [13]. In our sample, pain intensity—as measured by the WOMAC—decreased following rehabilitation. However, we also observed a general trend toward increased beta power across all assessed brain regions, although this change did not reach statistical significance. This finding appears to contrast with evidence that linked increased beta power with greater pain intensity. The lack of a corresponding reduction in beta power in previous longitudinal studies [13] as well as in this study with patients who experience clinical improvement raises important considerations. One possible explanation is the methodological limitations of those longitudinal studies. However, it may also suggest the need to examine whether different subgroups of patients who improve clinically exhibit distinct patterns of EEG changes, reflecting different cerebral mechanisms in those subgroups.

To further explore the reported pattern, we analyzed EEG power changes stratified by WOMAC pain and physical function improvement. Interestingly, in the group that did not show clinical improvement, beta power increased over all regions, with a statistically significant raise ($p = 0.02$) in the left frontal region (Supplementary Table S7 online). In contrast, the group that showed improvement in pain exhibited a trend toward a reduction in beta power in the frontal and parieto-occipital regions. This trend might be another indication that beta power should be further investigated as a possible biomarker

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associated with pain. This interpretation should be viewed with caution. Additional longitudinal studies with larger sample sizes and different therapeutic interventions are needed to determine whether beta activity can be established as a biomarker and whether neuromodulation strategies could represent therapeutic alternatives in cases refractory to conventional treatments.

In addition to changes in beta wave activity, the subgroup analysis based on clinical improvement revealed a statistically significant increase in delta wave power in the right parieto-occipital region. Unlike the changes observed in relative beta wave power, his change was observed in participants with both pain relief and functional improvement, as assessed by the WOMAC. These results suggest that delta wave power warrants further investigation as a potential biomarker of rehabilitation-associated clinical improvement, particularly given that this frequency band remains underexplored in the existing literature.

A notable finding regarding beta power reduction emerged from the subgroup analysis based on demographic and clinical variables. Specifically, we observed a mean decrease in beta power among patients who had experienced pain for more than 10 years, compared to a mean decrease in other subgroups. This reduction was statistically significant in the right parieto-occipital and in the bilateral frontal regions, suggesting that beta power decreases alongside clinical improvement following rehabilitation in the subgroup that can be expected to have more pronounced maladaptive compensatory mechanisms and central sensitization at baseline due to the long-standing nature of their pain. Furthermore, those long-standing pain patients also seem to improve in parallel, showing the benefits of rehabilitation for this subgroup. In this study, patients with chronic pain, as defined by the IASP [22], were included, which resulted in heterogeneity in pain duration. We hypothesize that the criterion of a minimum of three months of pain may not be the most appropriate for studies aiming to identify maladaptive compensatory mechanisms in patients with knee osteoarthritis. Although individuals may present a predisposition to central sensitization regardless of pain duration [23] that is, even patients with recent pain may develop maladaptive brain changes—it is plausible that patients with longer pain duration exhibit this condition more frequently and/or more intensely.

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Other subgroup findings based on age and BMI did not reveal any consistent patterns, except for a further increase in beta power in all brain regions, along with a reduction in alpha power in the left frontal region ($p = 0.039$), in the group with higher levels of pain catastrophizing. Catastrophization of pain is often associated with the chronic aspect of the condition [24]. These findings may suggest that in this group, reducing beta power—and potentially addressing maladaptive compensatory mechanisms—may be more challenging due to the catastrophizing component of the clinical profile. Additionally, we observed a reduction in beta power in the group with a longer interval between EEG measurements. This may indicate the value of long-term treatment plans and suggest that more time is required for central adaptations to occur —an idea that aligns with the chronic nature of the symptoms.

When interpreting the findings of this study, several limitations should be considered. Firstly, there are several considerations related to the analyzed sample. As reported, the study experienced a significant amount of participants with incomplete EEG data or with dropout. The final sample showed potentially relevant heterogeneity, and its size was insufficient to provide adequate statistical power to detect subtle but potentially meaningful effects. Future studies should address these limitations to enhance the validity and applicability of their findings. Secondly, there are inherent limitations associated with EEG, such as its limited spatial resolution and susceptibility to various factors during assessment — for example, participant drowsiness or subtle movements. While these issues remain challenging, we anticipate that future technological advancements will help address them. Currently, EEG is a highly sensitive tool, but its specificity remains limited, a fact which has been illustrated by heterogeneous and inconsistent results in published literature. Future research should aim to improve the spatial resolution of EEG and further explore the clinical relevance of localized changes in cerebral EEG power. This analysis studied the most complex structure in the human body, involving biological processes occurring at microscopic scale that cannot be fully captured by EEG alone. Therefore, the value of EEG may lie not in its use as a standalone diagnostic tool, but rather in its integration with clinical signs and symptoms, as well as with other neurophysiological methods offering greater spatial and temporal resolution.

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Future research should focus on more specific patient groups based on clinical variables known to influence EEG signals. This would allow for greater sample homogeneity and thus enhance investigations into the use of EEG in KOA by adressing potential confounding variables. A three-month duration of chronic pain, as defined by the IASP [22], may not be an appropriate criterion for studying maladaptive compensatory mechanisms in KOA patients. Instead, emphasis should be placed on individuals with a longer history of pain, typically spanning several years. It should, however, be acknowledged that it is highly probable that the state of the EEG depends on a wide array of factors, many of which remain unknown.

In the present analysis, resting-state EEG was assessed. Given EEG's high temporal resolution, future studies could also explore EEG responses to specific stimuli, as previously analyzed in this cohort [25,26] and reported in a systematic review [10]. Additionally, EEG assessments should be integrated with standardized and controlled interventions within a defined timeframe. This approach would help evaluate EEG's practical value in clinical settings. Such study designs are considered the most effective for evaluating diagnostic strategies [27], and although not mentioned in this publication, they may also provide valuable frameworks for identifying prognostic and predictive biomarkers, as well as surrogate outcomes—key objectives of the DEFINE project.

Based on previously reported analyses showing the association between frontocentral beta waves [12] and findings reported here, it is suggested that further investigation of the potential of EEG as an assessment tool for patients with chronic KOA should focus on those with longer pain duration, and those undergoing a longer duration of rehabiliation time between EEG assessments. Current evidence regarding EEG for KOA and chronic pain is heterogeneous with regard to the methodology of EEG measurement, as well as reported findings [13]. While EEG cannot yet be confirmed as a reliable tool for KOA, nor for chronic pain in general, it would be premature to dismiss its potential, particularly given its biological plausibility and ongoing technological advancements that may substantially improve its diagnostic utility. However, due to current uncertainties regarding its effectiveness, EEG should be limited to research settings for the time being. At present, there are no validated clinical applications of EEG for the assessment of

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patients with knee osteoarthritis. It should however definitively be subject of future research.

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Authors Contributions

Data collection was performed by MI. SVC and FT performed statistical analyses. All authors participated in the analysis and interpretation of the data, the writing of the paper, and approval of its final version.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Additional Information

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Competing Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Figure legends

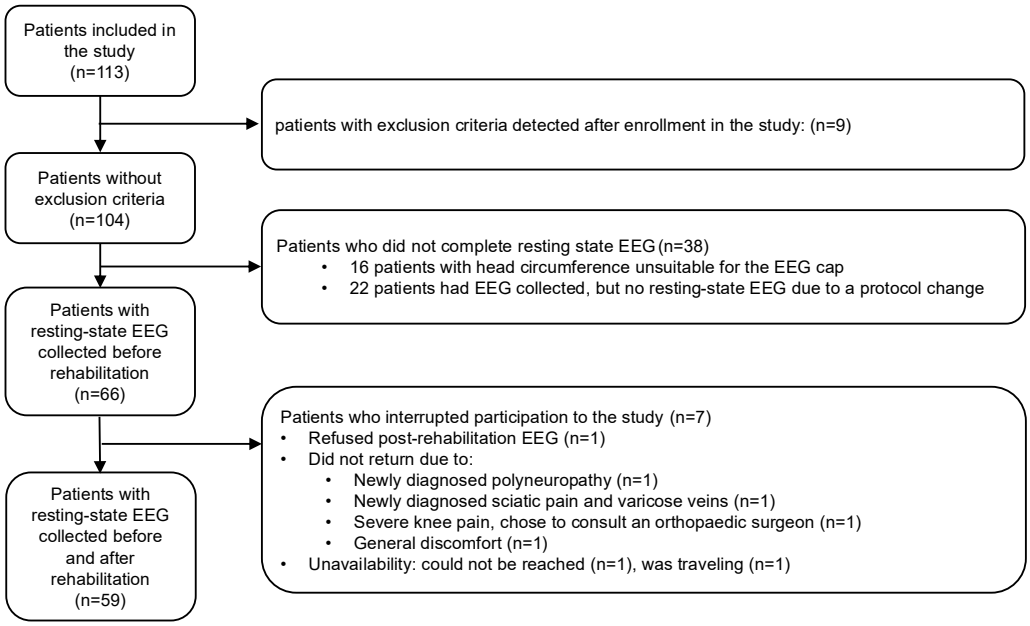


Figure 1 – Flow chart of the individuals at each stage of the study

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Tables and Figures

Table 1 – Continuous demographic and clinical variables

	N	Median	IQR
Age (years)	59	67.6	61.9 - 76.3
BMI (kg/m^2)	59	30.9	28.1 – 35.2
Duration of pain (months)	59	72	36 – 120
Duration of rehabilitation (days)	59	31	13 – 68
Duration between EEG assessments (days)	59	45	28 – 79
Pain Catastrophizing Scale	58	9	4 – 21

BMI, Body Mass Index; EEG, electroencephalography; IQR, interquartile range.

Table 2 – Categorical and dichotomous demographic and clinical variables

Sex	n = 59	Male Female	5 (8.5%) 54 (91.5%)
Skin color	n = 59	White Brown Black Yellow	39 (66.1%) 11 (18.6%) 5 (8.5%) 4 (6.8%)
Education level	n = 59	Illiterate Primary education Secondary education Higher education	1 (1.7%) 22 (37.3%) 18 (30.5%) 18 (30.5%)
Duration of pain	n = 59	3 months to less than 1 year One year to less than 5 years Five years to less than 10 years Ten years or more	7 (11.9%) 22 (37.3%) 18 (30.5%) 12 (20.3%)
BMI	n = 59	<30 kg/m^2 ≥30 kg/m^2	28 (47.5%) 31 (52.5%)
Pain Catastrophizing Scale	n = 58	≤9 >9	32 (55.2%) 26 (44.8%)
Medication consumption	n = 59	No Yes*	38 (64.4%) 21 (35.6%)

BMI, Body Mass Index.

** Use of any of the following: antidepressant, analgesics, muscle relaxants, antipsychotics, benzodiazepines, and antiepileptic drugs*

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539 Table 3 – Radiological osteoarthritis measured by the Kellgren-Lawrence (KL)
540 classification (N=56)*.

Contralateral KL	Grade 1	Grade 2	Grade 3	Grade 4
Grade 1	13 (22%)	2 (3.4%)	- (0%)	- (0%)
Grade 2	3 (5.1%)	9 (15.3%)	3 (5.1%)	- (0%)
Grade 3	2 (3.4%)	4 (6.8%)	3 (5.1%)	- (0%)
Grade 4	1 (1.7%)	- (0%)	1 (1.7%)	15 (25.4%)

541 * The 3 participants (5.1%) are not included in this table due to unilateral knee arthroplasty; in hese, the contralateral
542 knee KL grade was 3..

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543 Table 4 – Evolution of patients measured by the WOMAC pain and physical function subscales who went through rehabilitation and
544 completed resting-state EEG assesments (n=57).

	Pre rehabilitation	Post rehabilitation		Improvement (patients with lower score)	No improvement (patients with higher or equal score)
	Mean (SD) *95% CI* *Range*		p-value	*Frequency (percentage)*	
WOMAC pain	10.8 (3.8) 9.8 – 11.8 1 – 18	7.4 (4.2) 6.3-8.5 0 - 18	<0.0001†	46 (80.7%)	11 (19.3%)
WOMAC physical function	35.2 (14.4) 31.4 – 39 8-61	25.6 (14.1) 21.9 - 29.4 2-57	<0.0001†	46 (80.7%)	11 (19.3%)

545 EEG, electroencephalography; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Arthritis Index; 95% CI, 95% confidence interval.
546 † Paired t-test

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Table 5 – Comparison of relative power of resting-state EEG before and after rehabilitation (n = 59).

Relative power			Pre rehabilitation			Post rehabilitaiton			*P-value*
			Median	*IQR*		*Median*	*IQR*		
Delta	**Frontal**	Right	0.1454	0.0967	0.2149	0.1493	0.0944	0.2176	0.3819†
		Left	0.1532	0.0982	0.2096	0.1482	0.0975	0.2150	0.3578†
	Central	Right	0.1306	0.1013	0.1879	0.1293	0.0987	0.1901	0.5765†
		Left	0.1343	0.1008	0.1823	0.1271	0.1043	0.1933	0.8018†
	Parieto-occipital	Right	0.1160	0.0789	0.1976	0.1195	0.0940	0.1939	0.0524†
		Left	0.1231	0.0728	0.1873	0.1199	0.0783	0.2017	0.5362†
Theta	**Frontal**	Right	0.1759	0.1311	0.2389	0.1944	0.1464	0.2313	0.4375†
		Left	0.1805	0.1328	0.2410	0.1915	0.1405	0.2328	0.4738†
	Central	Right	0.1736	0.1512	0.2340	0.1857	0.1444	0.2242	0.2982†
		Left	0.1677	0.1391	0.2212	0.1774	0.1356	0.2239	0.7332†
	Parieto-occipital	Right	0.1618	0.1189	0.2395	0.1695	0.1371	0.2283	0.3738†
		Left	0.1596	0.1258	0.2272	0.1729	0.1282	0.2281	0.2677†
Alpha	**Frontal**	Right	0.3769	0.2382	0.5253	0.3789	0.2544	0.4844	0.2720‡
		Left	0.3766	0.2517	0.5265	0.3672	0.2664	0.4775	0.2271‡
	Central	Right	0.3644	0.2180	0.4785	0.3457	0.2623	0.4575	0.2989‡
		Left	0.3564	0.2274	0.4580	0.3557	0.2475	0.4590	0.6193‡
	Parieto-occipital	Right	0.4425	0.2576	0.5418	0.4167	0.2868	0.5115	0.1889‡
		Left	0.4063	0.2499	0.5343	0.3879	0.2681	0.5063	0.2821‡
Beta	**Frontal**	Right	0.2203	0.1606	0.2957	0.2244	0.1609	0.2941	0.7388†
		Left	0.2125	0.1366	0.2907	0.2105	0.1629	0.2809	0.6557†
	Central	Right	0.2538	0.1892	0.3268	0.2653	0.1950	0.3293	0.3731‡
		Left	0.2628	0.1739	0.3469	0.2672	0.1877	0.3303	0.2240‡
	Parieto-occipital	Right	0.2174	0.1561	0.2938	0.2152	0.1610	0.2864	0.8632‡
		Left	0.2480	0.1587	0.3071	0.2469	0.1689	0.3045	0.9671†

EEG, electroencephalography; IQR, interquartile range.

†Wilcoxon matched-paired signed-rank test; ‡Paired t-test.

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Table 6 – Mean difference of EEG measurements, direction of difference and percentage of patients with increased or decreased power (n=59).

			Mean difference	*Standard deviation*	*Lower range*	*Higher range*	*Patients with decreased power*	*Patients with increased power*
Delta	**Frontal**	Right	0.0019	0.0697	-0.2258	0.1365	44.07%	55.93%
		Left	0.0074	0.0612	-0.1836	0.1415	45.76%	54.24%
	Central	Right	-0.0053	0.0611	-0.2960	0.1065	54.24%	45.76%
		Left	-0.0043	0.0593	-0.2143	0.0893	50.85%	49.15%
	Parieto-occipital	Right	0.0085	0.0572	-0.2341	0.1094	38.09%	61.91%
		Left	0.001	0.0726	-0.2114	0.256	44.07%	55.93%
Theta	**Frontal**	Right	0.0061	0.0592	-0.1733	0.1661	44.07%	55.93%
		Left	0.0017	0.0562	-0.1705	0.1036	44.07%	55.93%
	Central	Right	0.0064	0.0530	-0.1377	0.1389	44.07%	55.93%
		Left	-0.0018	0.0473	-0.1531	0.1302	50.85%	49.15%
	Parieto-occipital	Right	0.0036	0.0619	-0.2061	0.1334	49.15%	50.85%
		Left	0.0061	0.0605	-0.1617	0.1606	44.07%	55.93%
Alpha	**Frontal**	Right	-0.0134	0.0932	-0.2684	0.3811	55.93%	44.07%
		Left	-0.0154	0.0967	-0.2369	0.3434	59.32%	40.68%
	Central	Right	-0.0107	0.0786	-0.2536	0.2592	61.02%	38.98%
		Left	-0.0054	0.0829	-0.2223	0.3262	61.02%	38.98%
	Parieto-occipital	Right	-0.015	0.0864	-0.2669	0.2065	59.32%	40.68%
		Left	-0.0123	0.0869	-0.259	0.2211	54.24%	45.76%
Beta	**Frontal**	Right	0.0034	0.0558	-0.1285	0.177	50.85%	49.15%
		Left	0.0044	0.0538	-0.1071	0.1638	47.46%	52.54%
	Central	Right	0.008	0.0688	-0.1365	0.2661	54.24%	45.76%
		Left	0.0102	0.0635	-0.0986	0.1712	45.76%	54.24%
	Parieto-occipital	Right	0.0013	0.0590	-0.1121	0.1899	57.63%	42.37%
		Left	0.0033	0.0564	-0.1335	0.1658	54.24%	45.76%

EEG; electroencephalography

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