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EULÁLIA PINHEIRO

PADRÃO ELETROENCEFALOGRÁFICO PARA DOR CRÔNICA: UMA REVISÃO SISTEMÁTICA DA LITERATURA

DISSERTAÇÃO DE MESTRADO

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PADRÃO ELETROENCEFALOGRÁFICO PARA DOR CRÔNICA: UMA REVISÃO SISTEMÁTICA DA LITERATURA

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Orientador: Prof. Dr. Abrahão Fontes Baptista

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“No momento em que o indivíduo se dá conta de sua responsabilidade, ele percebe que o mundo em que vive depende de sua vontade. Esse é um momento comovente e libertador. É comovente porque significa que o que fazemos não é trivial. É libertador porque nos dá sentido ao viver. Não lhe dá um sentido transcendente, mas um sentido imediato. As coisas que fazemos são sempre significativas, quaisquer que sejam”

Maturana

LISTA DE FIGURAS E TABELAS

LISTAS DE ABREVIATURA E SIGLAS

ACRc	American College of Rheumatology's criteria
Amp	Amplitude
AP	Absolute power
AS	Inter hemispheric asymmetry
C-	Negative correlation
C+	Positive correlation
DN4	Douleur Neuropathique 4 questionnaire
Dr.	Doutor/Doctor
EEG	Eletroencefalografia**/** Electroencephalography
EEGq/QEEG	Eletroencefalografia Quantitativa/Quantitative Electroencephalography
EP	Evoked Potential
FD	Fractal dimension
FH	Family illness history
Fig.	Figura
fMRI	Ressonância Magnética Funcional/ Functional Magnetic Resonance
GC	Gravity center
IASP	International Association for the Study of Pain
IHCS	International Headache Society's classification
MCCS	Marseille and Cambridge Classification System
MEG	Magnetoencefalografia**/** Magnetoencephalography
PC	Partial coherence
PD	Power density
PD	Pain duration
PE	Potencial Evocado
Pedro	Base de Dados de Evidência em Fisioterapia
PET	Tomografia por Emissão de Pósitrons/ Positron Emission Tomography
PF	Peak frequency
PI	Pain intensity

PMBS	Post-movement beta synchronization.
PRISMA	Transparent Reporting of Systematic Reviews and Meta-analyses
Prof.	Professor
Psycho	Psychological aspects
Pubmed	Public Medical Literature Analysis and Retrieval System Online
RP	Relative power
SCielo	Scientific Electronic Library Online
SSVEPs	Steady state visual evoked EEG-responses
TG	Sensitivity of trigger points
WHYMPi	West Haven Yale Multidimensional Pain inventory
UFBA	Universidade Federal da Bahia

SUMÁRIO

1 RESUMO

1.1 Resumo em português

O objetivo principal deste estudo foi revisar os estudos que apresentam alterações eletroencefalográficas presentes em indivíduos com dor crônica e discutir os avanços no uso da Eletroencefalografia Quantitativa (EEGq) para estudar a fisiopatologia e a reposta ao tratamento da dor. O método acompanhou as orientações do *Transparent Reporting of Systematic Reviews and Meta-analyses – PRISMA e* a coleta de dados aconteceu de fevereiro à agosto de 2014 nas bases de dados Pubmed, SCielo, Pedro. Todos os desfechos relativos à EEGq foram considerados na pesquisa. A alteração mais frequente foi a diminuição na amplitude de Potencial Evocado (PE), encontrada após estímulos sensoriais, motores e cognitivos, seguida de aumento da potência em Theta em repouso. Concluiu-se que indivíduos com dor crônica possuem uma tendência em apresentar menores amplitudes de PE durante diversos estímulos e maior potência de onda Theta em repouso. A EEGq pode ser uma ferramenta simples e objetiva de estudar os mecanismos envolvidos na dor crônica e identificar características específicas do quadro doloroso crônico, podendo ser útil como biomarcador terapêutico de terapias neuromoduladoras.

PALAVRAS CHAVES: EEGq, dor crônica, neuroplasticidade, fisioterapia, neurofisiologia.

1.2 ABSTRACT

The main objective of this work was to review and summarize electroencephalographic abnormalities present in individuals with chronic pain, and to discuss the recent advances in the use of Quantitative Electroencephalography (qEEG) to study the pathophysiology and response to pain. Data collection took place from February to August 2014 in PubMed, SciELO and PeDro databases. Cross-sectional and baseline data from clinical trials involving chronic pain participants were incorporated into the final analysis. Decrease in the amplitude of evoked potential (EP) after sensory, motor and cognitive stimulus was the most prevalent finding related to chronic pain, followed by increase in Theta power at rest. Alpha power decrease was also referred in some studies, but this finding was not

consistent. qEEG can be a simple and objective tool to study the mechanisms involved in chronic pain, as well as to identify specific characteristics of chronic pain condition, and may be useful as an outcome for therapeutic studies.

KEYWORDS:QEEG, chronic pain, neuroplasticity, electrophysiology, physiotherapy.

2 INTRODUÇÃO

Nos últimos anos, diversos dados experimentais têm sugerido que o cérebro de um indivíduo que apresenta uma síndrome dolorosa tem características e comportamento distintos ao de um sujeito aparentemente sadio. A lesão de estruturas musculoesqueléticas e a manutenção de sintomas crônicos parecem interferir na morfologia e no funcionamento do cérebro.

O diagnóstico e a fisiopatologia da dor crônica tem sido um desafio pela dificuldade em abordar sintomas e sinais subjetivos. No entanto, novas evidências apoiam a ideia que a dor crônica pode ser entendida não apenas como um estado perceptual alterado, mas também como consequência de alterações no processamento neural central.

Existem diversas maneiras de estudar os mecanismos centrais envolvidos no processo de dor crônica. A Eletroencefalografia Quantitativa (EEGq) merece destaque dentre elas, principalmente pela portabilidade, baixo custo, segurança e por se adequar facilmente às rotinas clínicas. É um método simples e que fornece inúmeros dados do funcionamento elétrico do cérebro. Além disso, a EEGq permite colher informações fisiológicas primárias da atividade elétrica neuronal, ao contrário de alguns recursos como a Ressonância Magnética Funcional (fMRI) e aTomografia por Emissão de Pósitrons (PET), que mensuram alterações metabólicas teciduais secundárias à um mecanismo adaptativo prévio.

A EEGq tem sido utilizada como biomarcador diagnóstico e terapêutico de muitas síndromes dolorosas crônicas. Apesar dos estudos mostrarem características eletroencefalográficas comuns entre os indivíduos, os dados são inconclusivos e muitas questões ainda não foram respondidas. Um conhecimento mais amplo sobre o potencial da EEGq como auxiliar no estudo dos mecanismos envolvidos na dor cônica e da sua aplicabilidade clínica pode ser útil para a reflexão sobre a doença e para discussão de novas abordagens preventivas e terapêuticas.

3 OBJETIVOS

O objetivo principal deste estudo foi revisar os trabalhos que investigaram alterações eletroencefalográficas presentes em indivíduos com dor crônica e discutir os avanços no uso da EEGq para estudar a fisiopatologia e a reposta ao tratamento de pessoas com dor. Este trabalho foi direcionado para responder as seguintes perguntas: “Existe um padrão eletroencefalográfico para dor crônica?”; “A EEGq pode auxiliar no diagnóstico e tratamento de pacientes com dor crônica? De que forma?”. Seus objetivos secundários foram revisar principais características eletroencefalográficas de populações com dor, os parâmetros/ marcadores que podem ser avaliados com EEGq e suas contribuições para o diagnóstico e tratamento de pacientes com dor.

4 RESULTADOS

4.1 ARTIGO ORIGINAL

ELECTROENCEPHALOGRAPHIC PATTERNS IN CHRONIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE

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ELECTROENCEPHALOGRAPHIC PATTERNS IN CHRONIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract

The main objective of this work was to review and summarize electroencephalographic abnormalities present in individuals with chronic pain, and to discuss the recent advances in the use of Quantitative Electroencephalography (qEEG) to study the pathophysiology and response to pain. Data collection took place from February to August 2014 in PubMed, SciELO and PeDro databases. Cross-sectional and baseline data from clinical trials involving chronic pain participants were incorporated into the final analysis. Decrease in the amplitude of evoked potential (EP) after sensory, motor and cognitive stimulus was the most prevalent finding related to chronic pain, followed by increase in Theta power at rest. Alpha power decrease was also referred in some studies, but this finding was not consistent. qEEG can be a simple and objective tool to study the mechanisms involved in chronic pain, as well as to identify specific characteristics of chronic pain condition, and may be useful as an outcome for therapeutic studies.

KEYWORDS

QEEG, chronic pain, neuroplasticity, electrophysiology, physiotherapy.

Introduction

Recent experimental data have suggested that brain functioning and behavior might be different in individuals with chronic pain as compared to healthy ones [1,2]. Musculoskeletal injuries and the maintenance of chronic symptoms over time seem to affect both brain's morphology and function [3].

Chronic pain diagnosis and pathophysiology have been a challenge for its subjective nature [4]. However, new evidence supports the idea that chronic pain can be understood not only as an altered perceptual state, but also as a consequence of changes in neural processing [5].

Among several ways to study the central mechanisms involved in chronic pain [6], quantitative Electroencephalography (qEEG) stands out as a valuable tool because of its ability and feasibility to provide relevant information about brain functioning at resting and during perception and cognition [5]. In addition, its low cost, safety and easy methodology make this technique an appropriate tool for the use in the clinical routine practice [7].

Quantitative EEG has been applied to assess people with many chronic pain syndromes [8]. However, despite those studies reveal common characteristics among individuals, data remain inconclusive, and many questions still need to be answered, such as if there is a characteristic patter of qEEG activity for chronic pain, or if qEEG can be useful for the diagnosis of patients with chronic pain. These questions have been addressed in the present work through a systematic review of studies of qEEG in patients with chronic pain.

Materials and Methods

Search strategies and selection of studies

This review followed the guidelines of the Transparent Reporting of Systematic Reviews and Meta-Analyses – PRISMA [9]. Data collection took place from February to August 2014 in PubMed, SciELO and PeDro databases, with the following criteria

for eligibility: a) Population should include people over 18 years-old, with chronic pain of any origin, lasting at least three months; b) study design should be observational studies whose primary or secondary outcomes were electroencephalographic data, or clinical trials with baseline qEEG data; c) studies should have been published from January 2005 to July 2014. All studies examining qEEG parameters in humans were considered in the survey, including absolute and relative power, coherence, and degree of symmetry, evoked potentials (EP) and peak frequency of all bands. The search descriptors in the database were "*qEEG and chronic pain OR qEEG and pain OR eeg and chronic pain OR eeg and pain OR coherence spectral and pain OR alpha power and pain OR theta power and pain OR beta power and pain OR delta power and pain OR somatosensory ERP or motor task and qEEG or electroencephalography and pain"* and their equivalents in Portuguese and Spanish. Exclusion criteria were studies involving experimentally induced pain, studies involving only healthy subjects, laboratory animals, acute pain and / or pain associated with neurological diseases such as stroke, schizophrenia, autism or brain tumors. EEG performed during sleep and other reviews were also excluded, as well as studies with no control group or those with less than four electrodes for EEG recording.

Extraction and categorization data

Initially, two independent researchers extracted data from the publications title and abstract. After a consensus about selected studies based on the presence of inclusion and exclusion criteria, full texts were extracted for analysis. The following items were manually extracted, tabulated and described in these three categories:

1) Clinical and demographic characteristics, including numbers of participants per group, sex, age, diagnosis, diagnostic criteria, intensity and duration of pain (Table 1);

2) Study design and data collection, including EEG protocols, amount and placement of electrodes, sampling modality and frequency (Table 2);

3) EEG results, including outcome variables and covariables, EEG parameters and brain locations where differences between groups were observed (Table 4).

Quality assessment and risk of bias

Risk of bias was considered through heterogeneity of diagnosis and symptoms. Analysis of exclusion criteria and patient selection, medication usage and validity of assessment instruments performed through the following parameters:

1) Did inclusion and exclusion criteria follow the recommendations of the International Association for the Study of Pain (IASP) for diagnosis and classification of chronic pain, or did the study present detailed and consistent description of inclusion and exclusion criteria for patients and controls?

2) Were standardized assessment instruments used to determine the intensity, duration and characterization of pain?

3) Did the study provide detailed information regarding the type and dose of medication and temporarily avoided drugs that could alter the electroencephalographic recordings?

Study quality was quantified by New Castle Ottawa Scale (Ottawa Hospital Research Institute)[10], which assesses the type of participant selection, sampling, use of validated instruments, evaluator blinding and consistency of statistical analysis, grading the studies up to 10 stars. Only studies scored above five stars were included in this review. Although this scale is addressed only for observational studies, data from the baseline of clinical trials were also collected, as they could represent cross-sectional information.

Results

Selected studies

According to the search strategy, 831 studies were initially found, and 33 were selected for analysis after reading the full title and the abstract. After full reading of the studies, 17 were excluded due to the presence of some of the exclusion criteria (Figure 1).

Demographic and clinical characteristics

Diagnosis

In total, eight diseases were identified between the studies, including neuropathic pain (n=5), headache (n=3), fibromyalgia (n=2), musculoskeletal pain secondary to degenerative or inflammatory disc disease (n=2), back pain (n=1), complex regional pain syndrome (n=1), abdominal pain secondary to chronic pancreatitis (n=1), and chronic pain of any origin (n=1). Most studies used standardized, validated and specific diagnostic criteria (n=13) (Table 1)

Patients' profile

In total, 290 individuals with pain and 279 controls were evaluated. The sample size of the group of patients with chronic pain ranged from 8 to 37 individuals. Women were more frequent than men (73.44%), and some studies included only females (n=5). The average age of participants was 46.05 years.

The Visual Analogue Scale (VAS) was the most frequent instrument to measure the intensity of pain. Pain intensity was above 4 in most studies (n=10) and was not reported in four studies. Only nine studies (56.25%) presented data about the duration of pain. The average duration of pain ranged between 2.87 and 20.82 years (n=9) (Table 1).

qEEG protocol

Quantitative EEG protocols varied widely among studies. Electrode placement followed the 10-20 International System for electrode placement in most of the studies (n=13). On average, 42.56 electrodes were used, and 11 out of 16 studies used more than 25 channels of EEG. Sampling frequency ranged from 167 to 1000 Hz. There were six different examination protocols: Spontaneous EEG at rest (n=7), EEG during cognitive stimulation (n=4), EEG during thermal stimulation (n=2), EEG during photic stimulation (n = 2), EEG during motor task (n=1) and EEG during somatosensory stimulation (n=1) (Table 2).

Assessment of study quality and risk of bias

The scores of the 16 included studies ranged from moderate to high quality (5-8/10) and provided detailed information about their inclusion and exclusion criteria. Categorization of chronic pain established by the IASP was used as inclusion criteria in three studies. Only one study did not provide data on the status of the medication, while the majority (n=15) described the drugs used by patients and measures taken to control the biases resulting from this use. Two studies described the use of analgesics as an exclusion criterion.

qEEG findings

Among the types of study design, cross-sectional was the most frequent (n=11), followed by clinical trials (n=3) and a longitudinal observational study (n=1). Although 11 different EEG parameters or variables were analyzed, EEG power spectra (n = 8) and the magnitude of the EP (n=7) were the most used. Significant reductions of the EP amplitude after sensory, motor and cognitive stimuli were the most frequent findings. Theta power increase was found in five out of eight studies that assessed EEG power spectra. Reductions of alpha peak frequency and power were reported by two of the studies.

Opposite findings were reported in some studies, including increased amplitude of EP (n=1), reduction of theta power (n=1) and increase of alpha power (n=1). Further results included an enhanced inter-hemispheric asymmetry in delta power spectrum (n=1), increased latency of thermal EP (n=1), and increased desynchronization of theta, alpha and beta oscillations during painful imagery (n=1). One study further analyzed nonlinear components of EEG activity, showing increased fractal dimension and entropy during viewing of pleasant images in individuals with pain.

Significant correlations between EEG activity and clinical pain characteristics were found in four studies. There was a positive correlation between duration of pain and decrease in alpha power, as well as between pain intensity and power spectra. In addition, a negative correlation was observed between EP amplitude and pain intensity. Changes in EEG activity occurred at several brain areas and more than one region in most studies (n=8), mostly at frontal (n=9) and at parieto-occipital (n=8) electrode locations.

The heterogeneity of outcome variables prevented the standardization of data, making it impossible to conduct a meta-analysis.

Discussion

Is there an EEG pattern for chronic pain?

The main objective of this review was to determine EEG patterns in the presence of chronic pain. We found a trend to increase in Theta power at rest, [11–14] which may indicate the presence of Thalamocortical Dysrhythmia (DTC) a CNS dysfunction that can be associated with many neurological disorders, and may be a marker of severe chronic neuropathic pain [15]. The possibility that the Thalamocortical Dysrhythmia detection on the scalp is controversial, and is based on the assumption that thalamus excitability changes can cause changes in the electrical frequency resonance in the region, increasing or decreasing wave power [16].

Decrease in amplitude of EP after different types of stimuli was always reported, and also seems to be a characteristic qEEG finding in people with chronic pain, suggesting that pain can modulate both cortical response to external stimuli, and internal events [17–20]. Despite reported in only two studies alpha power suppression is a very frequent finding in studies involving evoked pain [21–23]. Alpha power suppression seems to indicate increased excitability of the sensoriomotor cortex [24], reflecting a state a constant awareness of the brain, even in chronic painful conditions [25]. However, studies involving evoked pain were not evaluated in the actual study and this could explain the low frequency of those reports.

Opposite results, such as increase of the EP amplitude, decreases of theta and increase of alpha power have also been reported. Thus, for instance, decrease of theta power were observed in a experimental protocol involving the presentation of pleasant and unpleasant pictures, which could have interacted with participants' mood states to produce differential EEG patterns [26]. Another study reported an increase of the EP amplitude in migraine individuals, but without pain at the time of the evaluation. Interestingly, when subjects were tested during the migraine crisis, a decrease of the EP was clearly observed [27]. Alpha power has been also shown to

be increased in subjects with breast cancer and pain compared to patients with breast cancer without pain [28]. However, cognitive dysfunction and fatigue are frequently associated with the disease, and it might have modulated the pattern of EEG activity in a differential way in the two groups [29,30].

Changes in EEG activity associated with chronic pain have been located in different brain regions, including frontal, parietal, occipital, sensoriomotor and somatosensory electrode locations. This widespread distribution of changes in brain processing is in agreement with findings provided by neuroimaging studies including Functional Magnetic Resonance (fMRI), Positron Emission Tomography (PET), and Magnetoencephalography (MEG) in patients with pain [31–34]. Accordingly, these findings supports the idea that rather than a simple alteration of an specific 'pain center', there is multiple changes in an interconnected network of somatosensory, limbic and associative structures that receive inputs from multiple parallel nociceptive pathways [6].

Despite the heterogeneity in the type of pain and clinical characteristics of the patients´ samples discussed in this review, there is agreement on the existence of diffuse abnormalities in sensory and motor information processing in patients with chronic pain. Smaller EP amplitude (100%) and increased power of theta EEG oscillations (62.5%) are considered as the most consistent qEEG findings in people with chronic pain.

Clinical applicability of qEEG in individuals with chronic pain

Self-report of pain is the principal outcome used by health professionals assessing patients with pain [4]. However, due to its subjective nature, self-report is not enough to provide information about the mechanisms involved in chronic pain, mainly because multiple intrinsic and extrinsic factors can influence the pain experience[35]. Therefore, the study of physiological markers that can reflect underlying pain mechanisms is an important and relevant issue for clinicians. First, because it might help to obtain an accurate diagnosis of pain, based on objective parameters that reflect the involvement of the central nervous system in the genesis and maintenance of pain. Second, because it might help to improve the treatment of chronic pain by

identifying patients who may benefit from therapies aimed at changes in central mechanisms [5].

Alterations of quantitative EEG has been proposed as a biomarker in some distinct painful syndromes [6,20]. Electroencephalographic profiles of various populations with chronic pain are created with the rationale to identify the pathophysiology of pain [1] and promote the use of functional brain data as parameters of success and treatment failure [36]. The longer the exposure to pain, the greater the decrease of alpha, indicating that this oscillation frequency may indicate disease progression [5]. Changes in alpha wave also seem to predict the trend of throbbing pain in migraine [37] and disturbances in neural networks have been important to characterize pain agudization[38]. Decreased Beta synchronization after movement (SBPM) is present in pain syndromes of various origins [39–41], and seems to be related to increased cortical excitability. Its suppression could correspond to reduced inhibition of the motor cortex (disinhibition) [42]. However, our search did not identify changes in these bands as the most frequent in individuals with chronic pain, probably because they were not focused on the studies.

Interference of chronic pain on cognitive performance has also been examined by using qEEG [43]. Data suggest the possibility that qEEG associated with sensoriomotor standardized protocols can help to improve the diagnosis of those mechanisms involved in the chronification process of pain over time [5,44].

qEEG as a therapeutic biomarker

The persistence of painful stimuli can generate a maladaptive behavioral adaptation by modifying brain’s anatomy and function [2,45]. This condition is known as maladaptive plasticity [46], and recent findings have repeatedly suggested that this phenomenon is fundamental for the chronification of pain symptoms [6]. As qEEG may be used to identify some aspects of maladaptive plasticity without risks or higher costs, it may be a feasible alternative in the management of patients with chronic pain [44].

Imaging tools have helped researchers and clinicians to understand the pain phenomenon, as well as to assess treatment mechanisms and efficacy, and guide the efficacy of therapeutic approaches [47]. The recording of sensory and cognitive

EPs, for instance, has become a reliable biomarker for assessing the effects of various analgesic drugs [44,48,49]. Quantitative EEG can also document the inhibitory activity of the cortex in patients undergoing those therapies. Documentation can happen by quantifying changes in Alpha power, and EP amplitudes, as described in Transcutaneous Electrical Nerve Stimulation (TENS) [50,51] and Kinesio Taping [52] studies. Alfa and Theta peak frequencies have been recently used as markers for the therapeutic efficacy of Transcranial Stimulation Direct Current (tDCS) in individuals with neuropathic pain [53].

Advantages and disadvantages

In addition to providing a variety of data on brain electrical behavior in individuals with pain, qEEG uses a portable and low cost device compared to other techniques for the neurophysiological assessment of brain functioning. Moreover, it is possible that the simultaneous recording of EEG data and application of other techniques such as Transcanial Magnetic Stimulation (TMS) and the performance in cognitive tasks, may allow the evaluation of acute brain responses in several cortical areas with good spatial resolution [44]. Subjects do not need to lay down, and there are also no contraindications for the use of metallic implants in the body, enabling the evaluation of individuals with any kind of prosthetic devices.

Despite the advantages, qEEG faces some limitations: a) It requires long periods of training for a proper data collection and analysis; b) EEG data are extremely sensitive to external artifacts, including electromagnetic environmental factors; c) Data analysis is quite dependent on the theoretical knowledge of the evaluator; d) An examination has low power and accuracy in structural identification, in particular, deep brain structures [6].

A side from the limitations inherent to EEG discriminating power, technical and operational difficulties can be minimized through basic procedures: 1) adequacy of the environment where the examination should be performed. One should maintain an optimal temperature control, special lighting with gradual brightness adjustment or two options of brightness (strong and weak), quiet environment or soundproof room and shielding of instruments that may interfere magnetically on the record and 2) intensive team training to data acquisition and analysis.

In conclusion, low amplitudes of EP during various stimuli and increased Theta power at rest seems to be part of clinical characteristics of persons with chronic pain. Quantitative EEG can be a simple and objective tool for studying the mechanisms involved in chronic pain, identifying specific characteristics of chronic pain conditions and providing insights about appropriate therapeutic approaches.

Perspectives

Further clinical studies should be conducted to establish the clinical applicability of this instrument as an effective marker for diagnosis and to guide strategies to pain control. Systematic reviews with samples of individuals who have similar characteristics and type of pain can help determine a specific EEG pattern for each type of chronic pain.

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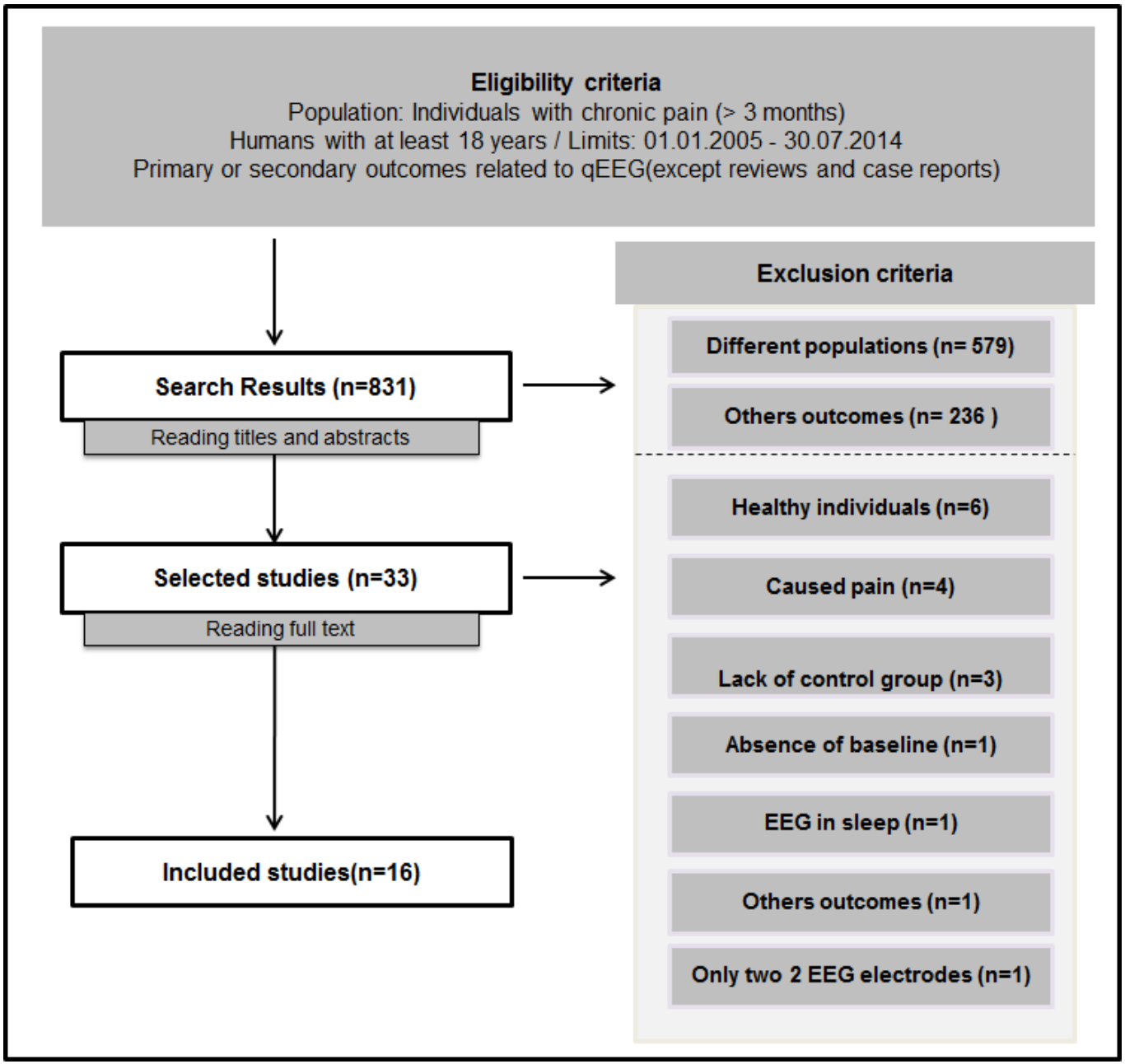
Figure Legends

Figure 1. Flow diagram of selection of the studies. **Flow diagram of selection of the studies showing the total number of articles included and excluded using the criteria of eligibility and exclusion.**

Fig 1


Eligibility criteria
Population: Individuals with chronic pain (> 3 months)
Humans with at least 18 years / Limits: 01.01.2005 - 30.07.2014
Primary or secondary outcomes related to qEEG(except reviews and case reports)
Exclusion criteria
Search Results (n=831)
Reading titles and abstracts
Different populations (n= 579)
Others outcomes (n= 236)
Selected studies (n=33)
Reading full text
Healthy individuals (n=6)
Caused pain (n=4)
Lack of control group (n=3)
Absence of baseline (n=1)
EEG in sleep (n=1)
Others outcomes (n=1)
Only two 2 EEG electrodes (n=1)
Included studies(n=16)

Supporting Information

PRISMA Check list

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Tables

Table 1

Demographic and clinical characteristics of the included studies

Source	Diagnosis	Diagnostic criteria	Patients				Controls	
			N (m,h)[g]	Age	Pain intensity (0-10)	Pain duration (anos)	N (m,h)[g]	Age
Bjork, 2009	Migraine with and without aura	Neurologist + IHSc[a]	33 (30, 3)	36.5	2.4	*	31 (28,3)	40.0
Bjork, 2011	Migraine with and without aura	Neurologist + IHSc[a]	25 (23, 2)	37.3	2.4	20.82	18 (16,2)	38.5
Broeke, 2013	Neuropathic pain	DN4[b]	8 (8,0)	52	5	*	11 (11,0)	53
Caty, 2013	Complex regional pain syndrome	Budapest Criteria	25(18,7)	40.2	*	5.1	7 (7,0)	39.6
De Vries, 2013	Chronic abdominal pain	MCCS[c]	16 (6,10)	49.5	*	5,4	16 (6,10)	48.0
Gonzalez-Roldan, 2013	Fibromyalgia	ACRc[d]	20(20,0)	53.4	6.0	18.3	20(20,0)	52.7
Mendonça de Souza, 2012	Migraine with aura	IHSc[a]	11(11,0)	19-45	*	*	7(7,0)	19-45
Montoya, 2006	Fibromyalgia	ACRc[d]	15(15,0)	49.7	7.26	13.51	15(15,0)	48.0
Reyns, 2012	Neuropathic pain	*	8(3,5)	48	8.12	2.87	9 (*)	48.5
Sarnthein, 2006	Neuropathic pain	IASP[e]	15(6, 9)	38.75	6.27	*	15(8,7)	41.7

Schmidt, 2012	Low back pain	IASP[e]	37(28,9)	50.0	4.46	*	37(28,9)	49.8
Sitges, 2007	Musculoskeletal pain	WHYMPi[f]	18(14,4)	46.39	6.25	6.37	16(15,1)	49.2
Sitges, 2010	Musculoskeletal pain	WHYMPi[f]	19(----)	48.4	5.2	6.2	21(*)	40.5
Stern, 2006	Neurogenic pain	IASP[e]	16(7,9)	63	7.06	*	16(8,8)	56
Vulkovic, 2014	Neuropathic pain	*	10(1,7)	45.2	*	*	10(2,8)	44.4
Veldhuijzen, 2006	Chronic pain of any origin	*	14(4,10)	47	4.8	9.43	30(15,15)	48
Total			**290**				**279**	

a: International Headache Society's classification, b: Douleur Neuropathique 4 questionnaire; c:Marseille and Cambridge Classification System; d: American College of Rheumatology's criteria; e: International Association for the Study of Pain; f: West Haven Yale Multidimensional Pain Inventory; g: Sample size, women / men *: not informed

Table 2

Electroencephalographic capture protocols of the studies

Source	Electrodes	Placement system	Modality	Sampling Frequency
Bjork, 2009	12	*	Spontaneous EEG at rest	*
Bjork, 2011	21	10-20	EEG during photostimulation	256
Broeke, 2013	64	10-20	Spontaneous EEG at rest	*
Caty, 2013	19	10-20	EEG during thermal stimulation	167
De Vries, 2013	26	10-20	Spontaneous EEG at rest	500
Gonzalez-Roldan, 2013	64	10-20	EEG during cognitive task	1.000
Mendonça de Souza, 2012	6	10-20	EEG before and after photostimulation	200
Montoya, 2006	32	10-20	EEG during auditory and thermal stimulation	1000
Reyns, 2012	128	10-05	EEG during motor task	512
Sarnthein, 2006	60	10-20	Spontaneous EEG at rest	*
Schmidt, 2012	60	10-20	Spontaneous EEG at rest	*
Sitges, 2007	32	10-20	EEG during cognitive task	*
Sitges, 2010	32	10-20	EEG during somatosensory task	1000
Stern, 2006	60	10-20	Spontaneous EEG at rest	250

Vulkovic, 2014	61	10-20	EEG at rest and during cognitive task (imagery)	250
Veldhuijzen, 2006	4	*	EEG during cognitive task	250

*: not informed

Table 3

Results of the quality assessment of studies and risk of bias by New Castle Ottawa Scale

Source	Selection of patients criteria	Medication status and control	Quality criteria from the New-castle Ottawa Scale			Total score (Until 10 stars)
			Sample (Until 5 stars)	Comparability between groups (Until 2 stars)	Results (Until 3 stars)	
Bjork, 2009	Inclusion/Exclusion	Yes (type)	4	2	1	7
Bjork, 2011	Inclusion/Exclusion	Yes (type)	4	2	1	7
Broeke, 2013	Inclusion/Exclusion	Yes (type)	4	1	1	6
Caty, 2013	Inclusion/Exclusion	Yes	4	1	1	6
De Vries, 2013	Inclusion/Exclusion	Yes (type)	4	1	1	6
Gonzalez-Roldan, 2013	Inclusion/Exclusion	Yes (type)	4	2	2	8
Mendonça de Souza, 2012	Inclusion/Exclusion	No	4	1	1	6
Montoya, 2006	Inclusion/Exclusion	Yes (type)	4	2	2	8
Reyns, 2012	Inclusion/Exclusion	Yes (type)	3	2	1	6

Sarnthein, 2006	IASP[a]	Yes (type)	4	2	2	8
Schmidt, 2012	IASP[a]	Yes (type)	4	1	1	6
Sitges, 2007	Inclusion/Exclusion	Yes (type)	4	2	2	8
Sitges, 2010	Inclusion/Exclusion	Yes (type)	4	2	2	8
Stern, 2006	IASP[a]	Yes (type and dose)	4	1	1	6
Vulkovic, 2014	Inclusion/Exclusion	Yes (type)	3	1	1	5
Veldhuijzen, 2006	Inclusion/Exclusion	Yes (type)	3	1	1	5

a: International Association for the Study of Pain

Table 4

Electroencephalographic abnormalities in individuals with chronic pain

Source	Studie type	Main variable	Results (Pain X Controls)					Brain areas (cortex / region)
			Absolute and Relative power	Spectral power	EP Amp	Others	Correlations	
Bjork, 2009	Cross section	AP, RP e AS	↑ Theta;	-	-	↑ AS Delta	C +(RP Delta – PI); C- (RP Delta – FH)	Parieto-occipital, fronto-central and temporal.
Bjork, 2011	Longitudinal	SSVEPs before, during and after migraine attack	-	-	↑ Before attack and ↓ During attack	-	C- (TG, photophobia,PI – SSVEPs)	Occipital
Broeke, 2013	Cross section	Alfa Amp and GC	↑ Alfa	-	-	-		----
Caty, 2013	Cross section	EP Amp and latency	-	-	↓ after thermal stimulus	↑ Latency after thermal stimulus		Somatosensory
De Vries, 2013	Cross section	Alfa Amp and PF	-	-	-	↓ PF Alfa	C+ (PD – alfa decrease)	All areas, especially occipital and parietal
Gonzalez-Roldan, 2013	Cross section	EP Amp and power waves	↑ Theta e ↓ Alfa viewing	-	↓ viewing happines s face	-		Parietal

			face of pain						
Mendonça de Souza, 2012	Cross section	PC between frontal, parietal and occipital regions	-	-	-	↑ PC			Frontal and parietal lobes in both hemispheres
Montoya, 2006	Cross section	EP Amp	-	-	↓ after auditory stimulus	-			Somatosensory
Reyns, 2012	Clinical Trial	PMBS Amp and latency	-	-	↓ after motor task	-			Contralateral Hemisphere to the painful side
Sarnthein, 2006	Clinical Trial	Spectral power	-	↑ Theta	-	-			All areas, especially occipital, frontal and parietal
Schmidt, 2012	Cross section	PD e PF	-	-	-	-	C+(DP de ondas – ID) e C+ (PF de ondas – Psico)		----
Sitges, 2007	Cross section	EP Amp	-	-	↓ after reading enjoyable descriptor ↑ after viewing pain descriptor	-			Frontal, central, centro-parietal, temporo-parietal, parietal and occipital
Sitges, 2010	Cross section	EP Amp, power entropy e FD	↓ Theta e Beta	-	↓ after visualization of pleasant images	↑ FD e entropy after viewing images not pleasurable	-		Sensoriomotor, temporal and Somatosensory

Stern, 2006	Clinical Trial	Spectral power	-	↑	Theta and Beta	-		Prefrontal and inferior parietal
Vulkovic, 2014	Cross section	PD, desynchronization and synchronization	↑	Theta	-	-	↑ Theta, Alfa and Beta desynchronization during painful imagery	Sensoriomotor, frontal and occipital
Veldhuijzen, 2006	Cross section	EP Amp e latency	-		-	-	No decrease expected EP Amp after difficult cognitive task	Fronto-central and parieto-occipital

Amp: Amplitude; AP: Absolute power; RP: Relative power; AS: Inter hemispheric asymmetry: *PF:* Peak frequency*;* ; PD: Power density; EP: Evoked potential; SSVEPs: steady state visual evoked EEG-responses; TG: Sensitivity of trigger points; FH Family illness history; C-: Negative correlation; C+: Positive correlation; PI: Pain intensity; PD: Pain duration; GC: Gravity center.; Psycho: psychological aspects: FD: Fractal dimension; PC: partial coherence; PMBS: Post-movement beta synchronization.

CARTA DE RECEBIMENTO DE SUBMISSÃO

PLOS ONE: Notification of co-authorship on manuscript [ELECTROENCEPHALOGRAPHIC PATTERNS IN CHRONIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE] - [EMID:ef53cec7e6522daa]

PLOS ONE (em@editorialmanager.com)

04/10/2014

Para: Eulália Santos Pinheiro

Dear Pos-graduate Eulália Pinheiro,

You are receiving this email because you have been listed as an author on a manuscript recently submitted to PLOS ONE and entitled "ELECTROENCEPHALOGRAPHIC PATTERNS IN CHRONIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE".

The corresponding author for the submission process is: prof Abrahão Fontes Baptista

The full author list for the submission is: Eulália Santos Pinheiro; Marion Alves Nascimento; Clara Hikari Ito; Manuela Silva; David Barros; Silvia Benevides; Pedro Montoya; José Garcia Vivas; Katia Nunes Sá; Abrahão Fontes Baptista, PhD

If you are not aware of this submission, or if you should not be listed as a co-author, then please contact the journal office at plosone@plos.org.

Kind regards,
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5 CONCLUSÃO

- Indivíduos com dor crônica possuem uma tendência em apresentar menores amplitudes de PE durante diversos estímulos e maior potência de onda Theta em repouso.
- A EEGq pode ser uma ferramenta simples e objetiva para estudar os mecanismos envolvidos na dor crônica, identificar características específicas do quadro doloroso crônico e ser útil como biomarcador terapêutico de terapias neuromoduladoras.

6 CONSIDERAÇÕES FINAIS

O trabalho aborda uma temática atual, de um instrumento útil e viável no estudo neurofisiológico de populações com dor crônica. Apresenta características que demonstram compromisso metodológico em relação aos parâmetros de qualidade para uma revisão sistemática (Prisma) e preocupação no controle de possíveis vieses dos estudos avaliados. Sua heterogeneidade de resultados impede uma metanálise contundente, que poderia confirmar ou não os dados descritivos, mas a alta frequência de alterações eletroencefalográficas (diminuição de PE e aumento potência de onda Theta) em populações com dor crônica sugere que estas possam ser, de fato, características desta população.

7 PERSPECTIVAS DE ESTUDO

Novos estudos clínicos e diagnósticos devem ser desenvolvidos para confirmar a aplicabilidade da EEGq como um marcador diagnóstico eficaz e para testá-lo como biomarcador de outras terapias. Revisões sistemáticas com amostras de indivíduos que apresentem tipologia e características homogêneas de dor podem

ajudar a determinar um padrão eletroencefalográfico específico para cada tipo de dor crônica.