Hyperexcitability in pain matrices in patients with fibromyalgia

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ABSTRACT

Objective. *Emerging evidence associates fibromyalgia (FM) with pain system dysfunction. In this study, using laser evoked potentials (LEPs) and paired laser stimuli, we tested excitability in the pain matrices and sought possible changes in patients with FM.*

Methods. *In 20 patients with FM and 15 healthy subjects, after recording control nociceptive system-mediated Aδ- and C-fibre-related LEPs, we measured excitability in the pain matrices by testing the Aδ-LEP conditioned by a preceding C-LEP.*

Results. *No difference was found in control LEP amplitudes for Aδ- or C-fibres between patients and healthy subjects. Conversely, the Aδ-LEP amplitude, conditioned by a preceding C-LEP, was significantly higher in patients than in healthy subjects ($p<0.001$).*

Conclusion. *Objective evidence from increased conditioned Aδ-LEP amplitudes reflecting hyperexcitability in the pain matrices in FM, provides diagnostically useful information and might help in developing new therapeutic approaches.*

Introduction

Emerging evidence showing that as well as causing widespread pain and fatigue fibromyalgia (FM) causes sleep disturbances, mood disorders, and neurocognitive impairment led some to postulate a central nervous system dysfunction including descending pain modulatory system impairment and abnormal pain matrix excitability (1, 2). The pain matrix is a controversial concept that helps to explain pain, a conscious experience, and involves several interconnected brain areas, and includes nociceptive-specific and non-nociceptive-specific perceptual regions (3, 4). The nociceptive matrix includes the posterior operculoinsular areas, and receives spinothalamic projections; the non nociceptive-specific, perceptual matrix includes the mid and anterior insula and anterior cingulate cortices and translates nociceptive system activation into pain (4).

The reference standard neurophysiological technique for assessing nociceptive system in patients with pain is laser evoked potential (LEP) recording (5). Laser stimuli activate skin mechanothermal nociceptors, thus evoking either Aδ-fibre-related or C-fibre-related LEPs (Aδ- and C-LEP) (6). The various Aδ- and C-LEP components arise in areas belonging to the pain matrix: operculoinsular, insula, and anterior cingulate cortices (7). Previous studies, using paired laser stimuli, showed that these pain matrix areas generate LEPs in a relatively refractory manner: delivering a conditioning C-LEP reduces the ensuing Aδ-LEPs, according to the *First come, first served* hypothesis (8). By objectively measuring refractoriness in the pain matrix, these paired laser stimulus procedures might help to understand possible abnormal excitability in the pain-related cortex in patients with FM. Knowing more about pain matrix excitability might explain why patients with this chronic disease experience widespread pain.

In this clinical and neurophysiological study, we sought objective information on pain matrix excitability in FM. To do so in patients with FM and healthy controls we measured pain matrix cortical excitability by delivering paired laser stimuli, and testing whether a preceding conditioning C-LEP reduced the following Aδ-LEP.

Methods

Patients

We prospectively enrolled 20 consecutive patients (19 F, 1 M; aged 27–62 years) referred to the Fibromyalgia Clinic at the Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University Rome, and 15 healthy subjects (13

F, 2 M; aged 25–54 years). Inclusion criteria were: patients aged >18 years; a medically confirmed diagnosis of FM according to the 1990 American College of Rheumatology criteria (9) and willingness to participate in all the experimental procedures. Exclusion criteria included other and additional pain sources (including pain due to arthritis) or neurological diseases. The local Institutional Review Board approved the study and all patients and healthy volunteers gave informed consent.

Clinical examination

All patients underwent clinical examination in the Rheumatology Unit. The Manual Tender Point Survey was used to rate the severity of pain elicited by palpating the 18 tender points defined by the American College of Rheumatology (10). We also collected the Fibromyalgia Impact Questionnaire (FIQ) (11), the Fibromyalgia Assessment Status (FAS) index (12), the Health Assessment Questionnaire (HAQ) (13), the Zung Self-Rating Depression (ZSDS) (14) and Anxiety Scales (ZSAS) (15). We used a visual analogue scale (VAS) to assess pain severity, at the time of examination (Table I).

After the rheumatologic examination all patients underwent LEP recording in the Department of Neurology and Psychiatry

Experiment LEP procedure

Each subject underwent three LEP conditions designed to investigate pain system functioning and pain matrix excitability. The first condition consisted of control C-LEP to adjust the best technical laser variables for eliciting C-fibre input; the second consisted of control Aδ-LEP, to obtain a reference value for the conditioning experiments. In the third (C-Aδ conditioning-test experiments) we delivered paired laser stimuli, and tested whether a preceding conditioning C-LEP reduced the ensuing Aδ-LEP.

We used two neodymium:yttrium-aluminium-perovskite laser (Nd:YAP) stimulators under fibre-optic guidance. The two laser stimulators had identical characteristics (wavelength 1.34 μm, duration 1–10 ms, maximum energy 7J). Laser stimuli variables were set to activate either small myelinated (Aδ) or unmyelinated (C) afferents in the perioral region (16).

Nd:YAP laser pulses at low intensity (38.2–44.6 mJ/mm^2), relatively long duration (20 ms) and large irradiated area (diameter ~10 mm) were used to elicit purely warmth sensations, activate C afferents and evoke scalp potentials related to the C-fibre input (C-LEP).

Pulses delivered at higher intensity (102–121 mJ/mm^2), shorter duration (5 ms), and small irradiated area (diameter ~5 mm) were used to elicit pinprick sensations, activate Aδ afferents and evoke scalp potentials related to the Aδ input (Aδ-LEP).

In the C-Aδ conditioning-test experiments, we studied changes induced by C-fibre input on the Aδ-LEP. We delivered two laser stimuli: a conditioning stimulus followed by a test stimulus. The conditioning stimulus elicited a purely warmth sensation (C-fibre input) and the ensuing test stimulus elicited a pin-prick sensation (Aδ input). The two lasers were alternated in delivering the first (conditioning) and the second (test) stimulus. Responses were recorded at stimulus intervals of 0.5 s. Because skin temperature decayed relatively slowly after the conditioning stimulus (17), to avoid peripheral effects on the test response, we fixed the two laser handles together so that they irradiated two close but different skin areas. Paired stimuli were pseudo-randomly delivered and alternated with occasional and unexpected single control stimuli (10–15 in total).

Table I. Demographic and clinical characteristics of Fibromyalgia patients.

	Patients (n=20)
Age (years), median (IQR)	44 (51-37)
Sex, F/M	19/1
Disease duration (months), median (IQR)	48 (96-12)
Tender Points, median (IQR)	15 (18-19)
pain VAS, median (IQR)	80 (100-70)
FIQ, median (IQR)	68.6 (75.59-57.923)
FAS, median (IQR)	8.450 (9.092-7.200)
HAQ, median (IQR)	0.875 (1.625-0.375)
ZSAS, median (IQR)	45 (54-42)
ZSDS, median (IQR)	48 (56-41)

IRQ: interquartile range; VAS: Visual Analogue Scale for pain; FIQ: Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Assessment Status; HAQ: Health Assessment Questionnaire; ZSAS: Zung Self-Rating Anxiety Scale; ZSDS: Zung Self-Rating Depression Scale.

Table II. Neurophysiological findings (mean ± SD).

	Patients (n=20)	Healthy controls (n=15)	*p*-value
Control C-LEP			
N2 latency (ms)	238.7 ± 21.2	244.4 ± 19.6	0.4
N2 amplitude (μV)	9.9 ± 6.0 μV	7.5 ± 3.4 μV	0.2
P2 latency (ms)	337.8 ± 21.7	339.5 ± 19.9	0.8
P2 amplitude (μV)	9.7 ± 7.6	10.9 ± 4.1	0.6
Control Aδ-LEP			
N1 latency (ms)	116.6 ± 5.5	113.5 ± 3.9	0.07
N1 amplitude (μV)	6.3 ± 2.3	7.3 ± 1.4	0.1
N2 latency (ms)	153.5 ± 8.3	158 ± 7.0	0.1
N2 amplitude (μV)	20.5 ± 11.3	18.7 ± 9.3	0.6
P2 latency (ms)	236.0 ± 17.7	245.9 ± 15.9	0.09
P2 amplitude (μV)	18.2 ± 10.4	20.5 ± 4.2	0.4
Conditioned Aδ-LEP			
N1 latency (ms)	118 ± 7.1	114.1 ± 3.9	0.06
N1 amplitude (μV)	6.7 ± 3.0	3.9 ± 2.0	0.004
N2 latency (ms)	158.8 ± 6.3	155.1 ± 7.2	0.1
N2 amplitude (μV)	17.6 ± 8.0	7.2 ± 4.5 μV	0.0001
P2 latency (ms)	257.8 ± 16.7	260.5 ± 21.5	0.7
P2 amplitude (μV)	16.1 ± 8.2	3.9 ± 4.0	0.0001

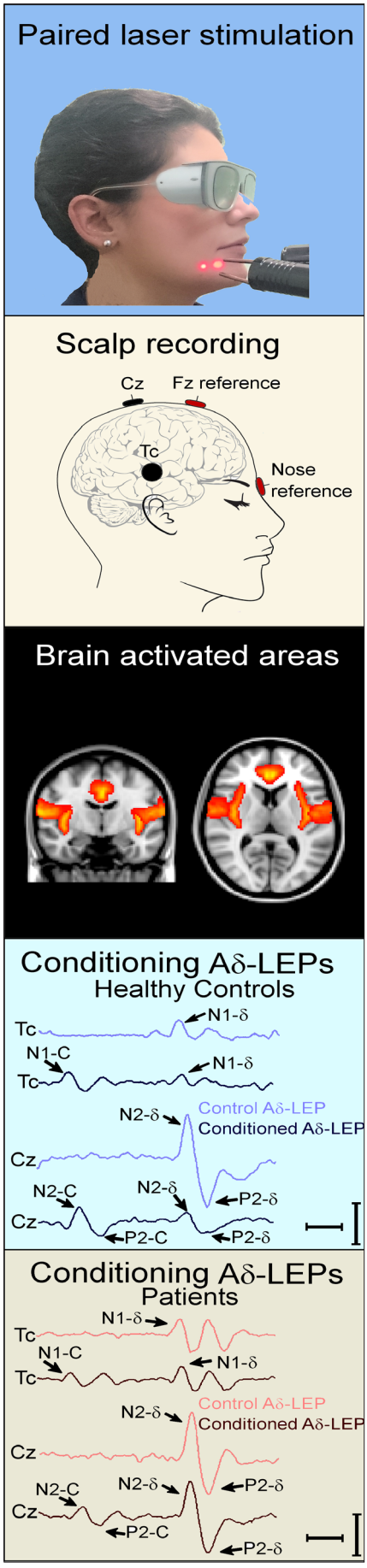

Fig. 1. (left) Summary of methods and representative neural signals.
The paired laser stimulation is delivered to the perioral region. Neural signals are recorded from the vertex (Cz-nose) and the contralateral temporal region (Tc-Fz). The laser stimulation activates opercularinsular areas, insula and anterior cingulate cortex. In healthy subjects the laser evoked potentials related to Aδ-fibres is reduced when preceded by a C-fibre input; conversely in patients with fibromyalgia the amplitude of the conditioned Aδ-LEPs is similar to the control signal. Calibration: 200ms/20μV.

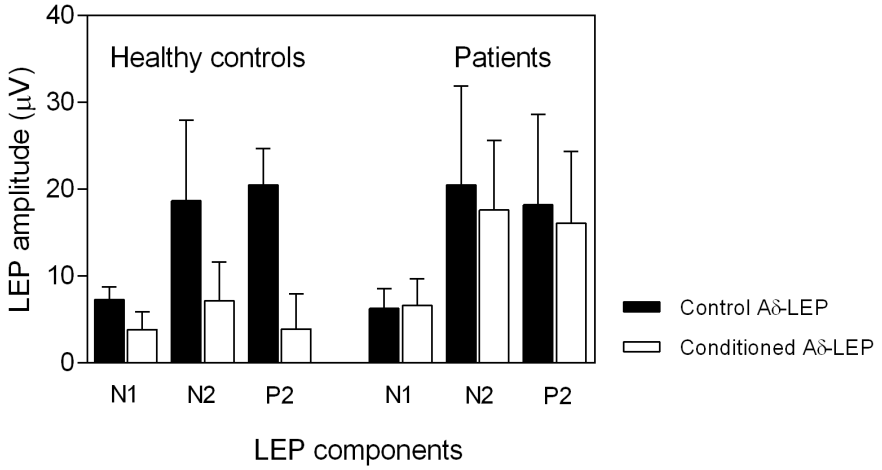

Fig. 2. Histograms representing the amplitude of control and conditioned Aδ-LEPs.
In the healthy controls the different components of conditioned Aδ-LEPs are significantly reduced by a preceding C-LEP (p<0.001); conversely in patients with fibromyalgia all Aδ-LEP components are unaffected.

Participants lay on a couch and wore protective goggles. They kept their eyes open and gazed slightly downwards. In all subjects, signals were recorded with disk electrodes from the scalp and referenced to the Fz and nose (bandwidth 0.3–50 Hz). Fifteen trials were averaged for the two control conditions (single C- and Aδ-LEP), twenty trials were recorded for the C–Aδ conditioning-test condition. The early, lateralised, N1 component of the Aδ-LEP and the main complex, N2-P2 of the C- and Aδ-LEP were recorded through disc electrodes from the temporal areas (Tc) referenced to frontal area (Fz) and vertex (Cz) referenced to the nose. Simultaneous recordings from disk electrodes, placed on the orbicularis oculi muscle at the infraorbital margin and on the lateral margin of the orbit, monitored eyeblinks and ocular movements.

In all sessions participants were asked to rate the perceived pain intensity on a 0–10 (Likert) numeric rating scale (0=no sensation, 3=pain threshold, 10=worst possible pain).

Statistical analysis

Data in the text are presented as means ± SD. Because LEP data had a Gaussian distribution (D'Agostino and Pearson omnibus normality test) paired *t*-test was used to analyse differences between control and conditioned responses within patient and healthy subject groups and unpaired *t* test for assessing LEP differences between patients and healthy subjects.

To assess differences in perceptive ratings, a non-normally distributed variable, we used Wilcoxon test for paired ranks for comparisons within patients and healthy subject groups, and Mann-Whitney test for comparisons between patients and healthy subjects.

In patients, the correlations between the conditioned Aδ-LEP (expressed as a percentage of the control (single) Aδ-LEP and clinical variables were tested using Spearman non-parametric R correlation index.

Results

No difference was found for age or the control Aδ-LEP and C-LEP variables between patients with FM and healthy controls (Table II).

In healthy controls when the C-fibre input preceded the Aδ-input the perceptive rating related to the Aδ-input remained statistically unchanged, conversely the

conditioned Aδ-LEP was attenuated (*t*-test for paired data, $p<0.001$).

In patients, a preceding conditioning C-fibre input left the perceived pain intensity rating for the Aδ-input and the tested Aδ-LEP component amplitudes unchanged ($p>0.05$, by paired *t*-test).

The conditioned Aδ-LEP components were significantly lower in healthy subjects than in patients ($p<0.005$, by unpaired *t*-test).

In patients, the conditioned Aδ-LEP amplitude (expressed as a percentage of the control Aδ-LEP) did not correlate with the clinical scores (number of TPs, pain VAS, FIQ, FAS, HAQ, ZSAS and ZSDS).

Discussion

Our clinical and neurophysiological study specifying that a preceding conditioning C-LEP leaves the following Aδ-LEP unchanged in amplitude in patients with FM indicate increased excitability in the pain matrix. This change in cortical excitability might underlie the widespread pain, patients with this chronic condition typically experience.

Although the pain associated with FM affects the limbs and torso we chose to deliver paired laser stimuli to the trigeminal territory because the facial area yields especially reliable C-fibre related LEPs (16). Equally important, applying laser stimuli to the face provided non-topographically related information on changes in cortical excitability (8).

In normal subjects the conditioning C-LEPs dampened all the Aδ-LEP components. All these components arise in different areas belonging to the pain matrix, N1 in the opercular cortex (SII area/insula), N2 in the insula, and P2 in the anterior cingulate cortex (7). Abnormal cortical excitability in patients with FM, therefore, affects both the nociceptive-specific cortical matrix, and the second-order perceptual matrix (4). This increased pain matrix excitability could underlie some FM manifestations, including spontaneous pain and the lowered pain threshold. Admittedly, increased cortical excitability in patients with FM might also be a consequence rather than a cause of chronic pain. We consider this interpretation unlikely, however, given that previous studies, using evoked potential habituation procedures, showed no changes in pain matrix excitability in patients with chronic nociceptive pain (18). Hence, we hypothesise that the abnormal cortical excitability we describe in patients with FM probably plays a direct pathophysiological role in this disease.

Why the hyperexcitability in the pain matrix our laser experiments disclosed in patients with FM did not correlate with FM severity as assessed with the clinical scores we used remains unclear. It probably failed to do because the small study sample we enrolled reduced statistical power, and thus prevented statistical significance. Alternatively, the lack of a significant relationship between cortical excitability and FM severity might imply that the clinical symptoms do not depend on the altered cortex functioning, and arise through other pathophysiological mechanisms.

Insofar as our study focuses only on abnormal excitability in brain areas belonging to the pain matrix, we cannot provide information on how FM pathophysiology involves the different central nervous system structures (including the descending modulatory system), or whether it involves peripheral nociceptive nerve fibres. A recent study using pain-related evoked potentials and skin biopsy demonstrated distally distributed peripheral nervous system damage, selectively involving nociceptive Aδ- and C-fibres (19). Conversely, in all our patients the Aδ- and C-LEP amplitudes after face stimulation came within the normal ranges, thus indicating that FM spares trigeminal peripheral nociceptive nerve fibres. Accordingly, we conjecture that FM is associated with multiple abnormalities involving both the central and peripheral nervous systems (20). Patients with chronic pain labelled as FM might also have unrecognised peripheral neuropathy (21). Further studies investigating both peripheral and central nervous systems should therefore verify whether distally distributed peripheral nervous system damage and abnormal cortical excitability coexist in the same patient.

In this clinical and neurophysiological study investigating possible pain system dysfunction in FM we provide objective neurophysiological evidence showing increased excitability in brain areas belonging to the pain matrix in patients with FM. This FM-related change in cortical excitability might be diagnostically useful and help in developing new therapeutic approaches to return hyperexcitability to normal.

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