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Altered associative learning and emotional decision making in fibromyalgia☆

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Abstract

Objective: The present study examines the possibility that a chronic pain condition, such as fibromyalgia, was associated with deficits in decision making and associative learning. **Methods:** Fifteen patients with fibromyalgia (aged 42–59 years) and 15 healthy controls (aged 39–61 years) participated in the experiment. Subjects completed anxiety (STAI) and depression (BDI) questionnaires, as well as standardized neuropsychological tests (Stroop and WAIS subscales). In addition, an emotional decision-making task (Iowa Gambling Task) and a conditional associative learning task (CALT) were administered to all participants. **Results:** Results indicated that fibromyalgia had a poorer performance than healthy controls in both tasks, showing more perseveration errors in the learning task, and more disadvantageous decisions, as well as a more random behavior in the gambling task. Moreover, we observed that poor performance on the associative learning task was mediated by depression, whereas performance on the gambling task was not influenced by depression. No group differences were found on the standardized neuropsychological tests. **Conclusion:** These findings indicate that pain and depressive symptoms in fibromyalgia might lead to significant deficits in emotionally charged cognitive tasks. Furthermore, it suggests that chronic pain might impose a high cost on executive control, undermining mainly affective processes involved in learning, memory, attention, and decision-making.

Keywords: Fibromyalgia; Emotional decision making; Chronic pain; Perseveration

Introduction

Although the pathophysiology of pain in fibromyalgia syndrome still remains unclear, recent functional neuroimaging studies have shown significant alterations in sensory [1–5] and affective brain processing of body information [6,7]. Several studies have also emphasized the role of emotions and psychological stressors in fibromyalgia, suggesting that these patients might be particularly vulnerable to the effects of negative mood [6–9].

Moreover, structural neuroimaging data demonstrated that fibromyalgia might be associated with gray matter dysfunction in brain regions such as parahippocampal gyrus, insular, and medial prefrontal cortices [10–14], although it has also been noted that these abnormalities seem to be associated with depressive symptoms in these patients [15]. Functional neuroimaging data have further suggested that fibromyalgia patients may suffer a dysfunction of the medial pain matrix, characterized by different patterns of temporal activation in the prefrontal cortex, anterior cingulate cortex, and insula when compared to healthy controls [1,16–17]. All

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these findings seem to be of particular interest since those brain regions are implicated not only in sensory and affective pain processing, but also in other cognitive processes, like decision making and associative learning [18–22].

Impaired cognitive functioning is one of the most salient subjective complaints in fibromyalgia [23–28]. However, inconsistent results have been obtained using standardized neuropsychological tests, suggesting that cognitive impairments in fibromyalgia might be too subtle to be detected by standardized neuropsychological test batteries [23–25,27]. Thus, for example, memory deficits are usually found in these patients, although it has also been noted that fibromyalgia patients do not perform worse on memory tests than patients with depression [26] or healthy controls when depression was statistically controlled for [28]. In addition to memory impairments, some authors have pointed out that executive functions are also impaired in fibromyalgia conditions [29], since the same neural substrate is related to both executive processes and chronic pain conditions (as shown above). However, little is known about the influence of pain on executive functions necessary to deal with novel tasks, set new goals and plans, or choose between alternative sequences of behavior. In this line, some previous research has found that patients suffering from fibromyalgia show a poor performance in some executive functions [29,30], as evidenced by concentration and working memory deficits when compared with age-matched healthy controls [28], a diminished ability to inhibit irrelevant information [27], a reduced ability to deal with parallel processes related to their limited processing resources that focus on their chronic pain [25,31], as well as a low cognitive flexibility and poor decision making [30]. This would be in accordance with data signaling prefrontal dysfunctions in fibromyalgia, as shown by functional neuroimaging studies [1].

Contrasting with studies of selective attention and memory deficits in chronic pain patients and fibromyalgia, little is known about the influence of pain on executive functions necessary to deal with novel tasks, set new goals and plans, or choose between alternative sequences of behavior. In this sense, it has been argued that chronic pain would act as a controlled process [31], consuming an important portion of the limited attentional resources and, consequently, reducing their availability for other parallel processes. According to this hypothesis, it has been observed that fibromyalgia patients have reduced attentional resources for processing of other information than pain [31], as well as a diminished ability to inhibit irrelevant information [27]. Recent research has further revealed that fibromyalgia patients showed a poor performance on executive functioning, such as cognitive flexibility or emotion-based decision making, as measured by the Wisconsin Sorting Card Test and the Iowa Gambling Task (IGT), respectively [30].

In the present study, we used a conditional associative learning task (CALT), in addition to the IGT, to examine the cost that chronic pain may impose on executive control among patients with fibromyalgia. Thus, considering the relevant involvement of frontal cortices and executive functioning in these tasks, we were interested in assessing to what extent the exacerbated negative mood and pain experience observed in patients with fibromyalgia would influence different measures of cognitive functioning.

Methods

Participants

Fifteen patients with diagnosis of fibromyalgia for at least 6 months (mean age 50.4 years, S.D.=4.6) and 15 healthy volunteers (mean age 49.0 years, S.D.=6.7) participated in the study. Participants had no history of head trauma or drug abuse. All fibromyalgia patients were regularly taking some pain medication in low doses at the time of the examination, including analgesics, muscular relaxants, NSAIDs, antidepressants, or anxiolytic drugs (Table 1).

During the recruitment, patients were verbally informed about the details of the study. A specifically designed patient information leaflet was also given, and after agreeing to participate, each patient provided written consent. The study was in accordance with the Declaration of Helsinki (1991) and was approved by the local ethics board.

Procedure

Clinical and standardized neuropsychological assessment

All participants underwent an extensive medical and psychological interview, including assessment of clinical characteristics through self-report questionnaires and a standardized neuropsychological test battery. The Spanish versions of the Beck Depression Inventory (BDI) [32] and the State-Trait Anxiety Inventory (STAI) [33] were completed as measures of mood, since altered emotional states such as depression and anxiety might influence cognitive processing. In addition, subjective ratings of current pain, worst, and average pain intensity in the last week were also obtained for fibromyalgia patients.

A standardized neuropsychological test battery including the Stroop Interference test and six WAIS subscales was applied individually to all participants. The Golden [34] version of the Stroop Color-Word Interference Test was used to assess cognitive flexibility and resistance to interference in patients with fibromyalgia and healthy volunteers. The test consists of a Word Page with 100 color words (red, blue, green) printed in black ink; a Color Page with 100 Xs printed in either blue, red, or green ink; and a Color–Word Page with 100 words from the first page printed in colors from the second page (no match between colors and words). Participants are asked to read the words (Word Page) or to name the ink color (Color and Color–Word Page) as quickly as possible with a time limit of 45 s. The test yields three scores corresponding to the number of items completed on

Table 1
Demographic and clinical characteristics of fibromyalgia patients and healthy volunteers

		Healthy controls (n=15)	Fibromyalgia patients (n=15)	Statistics
Age (years)				
	Mean (S.D.)	49.0 (6.7)	50.4 (4.6)	
	Range	39–61	42–59	
Education (%)				
	<8 years	7%	33%	
	8–12 years	66%	60%	
	>12 years	27%	7%	
Medication (%)				
	Antidepressants	0%	87%	$\chi^2(1)=9.29$*
	Analgesics/ muscular relaxants/ NSAIDs	0%	87%	$\chi^2(1)=22.94$**
	Anxiolytics	0%	60%	$\chi^2(1)=9.60$*
Current pain intensity (VAS, 0–10 cm)				
	Mean (S.D.)	–	4.5 (1.5)	
	Range	–	1.3–9.0	
Average pain intensity last week (VAS)				
	Mean (S.D.)	–	6.5 (1.8)	
	Range	–	2.1–9.4	
Worst pain intensity last week (VAS)				
	Mean (S.D.)	–	8.9 (0.9)	
	Range	–	5.6–10.0	
State-Trait Anxiety Inventory (raw score)				
	Mean (S.D.)	11.6 (6.5)	32.1 (12.0)	$t(28)=6.10$*
	Range	2–25	12–53	
Beck Depression Inventory (raw score)				
	Mean (S.D.)	4.3 (3.0)	23.1 (11.6)	$t(28)=5.82$*
	Range	0–10	7–43	
Stroop Interference test (age corrected)				
	Mean (S.D.)	51.8 (6.7)	47.5 (8.2)	$t(28)=-1.56$
	Range	40–60	35–63	
WAIS (raw scores)				
Vocabulary	Mean (S.D.)	9.0 (2.2)	9.4 (2.4)	$t(28)=0.40$
	Range	5–13	7–12	
Similarities	Mean (S.D.)	9.1 (3.2)	10.4 (1.4)	$t(28)=1.48$
	Range	4–15	8–12	
Comprehension	Mean (S.D.)	8.2 (1.4)	8.1 (2.3)	$t(28)=1.54$
	Range	7–11	4–13	
Digit span	Mean (S.D.)	10.9 (2.2)	11.1 (2.1)	$t(28)=0.17$
	Range	7–16	8–15	
Block design	Mean (S.D.)	9.5 (3.0)	11.1 (2.5)	$t(28)=-0.20$
	Range	5–16	6–17	
Picture completion	Mean (S.D.)	9.1 (2.5)	7.7 (2.6)	$t(28)=-1.60$
	Range	4–13	4–12	

Significant group differences were found in the number of participants taking medication and in levels of depression and anxiety. Significant level for group differences: *P<.05, **P<.01.

each page. An interference score is also derived by computing the Color–Word score minus the age-adjusted Word and Color scores, which reflect the baseline reading and color naming. A higher score indicates less interference.

Six Wechsler Adult Intelligence Scale (WAIS, 1976) subscales were used to examine general cognitive functioning. The "vocabulary" subscale is a measure of expressive word knowledge and correlates very highly with the full-scale IQ score. The "similarities" subscale is a measure of concept formation, in which subjects are asked to explain how two seemingly dissimilar items might in fact be similar. The "comprehension" subscale comprises several questions which focus on issues of social awareness. The "digit span" subscale is a test of immediate auditory recall (subjects are given sets of digits to repeat initially forwards then backwards). The "block design" subscale involves putting sets of blocks together to match patterns on cards. The "picture completion" subscale is a visual attention test (subjects are asked to detect relevant detail missing in small pictures).

Emotional and associative learning tasks

Two experimental learning tasks were administered to examine differences in executive functioning between fibromyalgia patients and healthy volunteers: a CALT and a gambling task. A CALT was designed to assess the acquisition of arbitrary associations between targets and colors [35]. This task was based on the visual CALT originally devised by Petrides et al. [36] and assesses the ability to discriminate between past correct and incorrect responses and use this information to guide response selection. During the task, subjects were instructed to keep trying different target-color associations until the correct one was found through the feedback delivered by the examiner (trial-and-error training). Once the first stimuli were correctly paired, the next color was presented and the whole process started again. The matching process restated until the six colors were correctly associated with their corresponding targets. Subjects were told to remember these associations in order to complete four consecutive blocks of trials containing the same target stimuli, but rearranged in a different order. Two runs of four blocks each were presented using either abstract words ("soul," "essence," "opinion," "fun," "liberty," "truth") or nonverbal targets (visual patterns) in a counterbalanced order across the subjects. The number of perseveration errors, after having received prior feedback, during the last three blocks of each run (verbal or nonverbal target) was computed.

The IGT [37] was used to examine cognitive functioning in emotional decision-making. The game consisted of 100 card choices from four decks and was programmed to award different amounts of play money (rewards) after each card selection and to deliver monetary losses of different amounts (punishments) in specified trials. High amounts of monetary gains and losses were associated with two decks (disadvantageous decks), whereas low amounts of monetary gains and losses were associated with the other two (advantageous decks). Participants were told that the goal of the task was to gain and to avoid losing as much money as possible. Behavioral performance on the IGT was analyzed by calculating the number of choices for the two types of decks (advantageous vs. disadvantageous) within each block of 20 trials. Net scores were obtained by subtracting

the number of disadvantageous from the number of advantageous choices for each block according to the standardized method described by Bechara et al. [37]. In order to further examine group differences on the IGT, we compared the net scores of the two first blocks (Trials 1 to 40) (learning phase) with the last three blocks (Trials 41 to 100) (performance phase) [38]. A persistence index was also obtained by computing the total number of trials in which the participant chose cards from the same deck. Finally, time series of card choices were further analyzed using autocorrelation analyses to compare the performance of fibromyalgia patients and healthy controls.

The order of administration of both tasks was counterbalanced across the subjects. The time for the complete testing session was about 90 min with a break of 15 min.

Statistical analyses

Group differences in scores on the standardized neuropsychological instruments and sociodemographic variables were analyzed using *t* tests for independent samples. Repeated-measures analyses of variance with the between-subject factor "group" (fibromyalgia vs. healthy volunteers) were performed to test group differences on the two domains of the associative learning task, as well as on the net scores of the emotional decision-making task.

Results

Clinical and neuropsychological assessment

Table 1 displays the clinical characteristics of fibromyalgia patients and healthy volunteers, as well as the mean scores in the standardized neuropsychological tests. Fibromyalgia patients and healthy controls were comparable in age [$t(28)=0.67$, NS] and education ($\chi^2=4.52$, NS). Nevertheless, patients showed more depression (BDI) and anxiety (STAI) than healthy controls, and they were taking more analgesics, antidepressants, and anxiolytics than healthy controls (see Table 1). No significant group differences were found in the Stroop Interference test or in the WAIS subscale scores (all *P*'s>.1).

Conditional associative learning task

The average numbers of perseveration errors during the verbal and nonverbal CALT are displayed in Fig. 1. Repeated-measures analyses of variance (ANOVA) with the within-subjects factor "blocks" (three levels) and the between-subjects factor "group" (fibromyalgia vs. healthy controls) were computed using the type of task (verbal vs. nonverbal) as a repeated measures. Univariate analyses revealed that patients with fibromyalgia displayed more perseveration errors than healthy volunteers in the verbal task [$F(1,28)=4.12$, $P=.050$, $\eta^2=.128$], whereas no significant group effects were observed in the nonverbal task [$F(1,28)=1.45$, NS]. Moreover, perseveration errors diminished over the blocks in the nonverbal task [$F(2,56)=8.04$, $P=.003$, $\eta^2=.223$], but not in the verbal task [$F(2,56)=.41$, NS].

A significant positive correlation was also found between depression and the total number of perseveration errors in the verbal [$r(30)=.40$, $P=.028$], but not in the nonverbal task [$r(30)=.21$, NS]. In addition, no significant correlations were found between anxiety and perseveration errors [verbal task: $r(30)=.20$, NS; nonverbal task: $r(30)=.23$, NS]. In order to control for the effects of depression and anxiety on perseveration errors, further repeated-measures ANOVAs were carried out using them as covariates. Results indicated that group differences in the verbal [$F(1,26)=1.00$, NS] and the nonverbal task [$F(1,26)=.15$, NS] were not significant after controlling for mood variables.

Iowa Gambling Task

The average net gain across the 100 trials showed that patients with fibromyalgia and healthy controls displayed a great variability and that both groups began to differ from Trial 30 (Fig. 2). Net scores obtained by subtracting the number of disadvantageous from the number of advantageous choices for each block of 20 trials showed that healthy controls gradually shifted their preference toward the

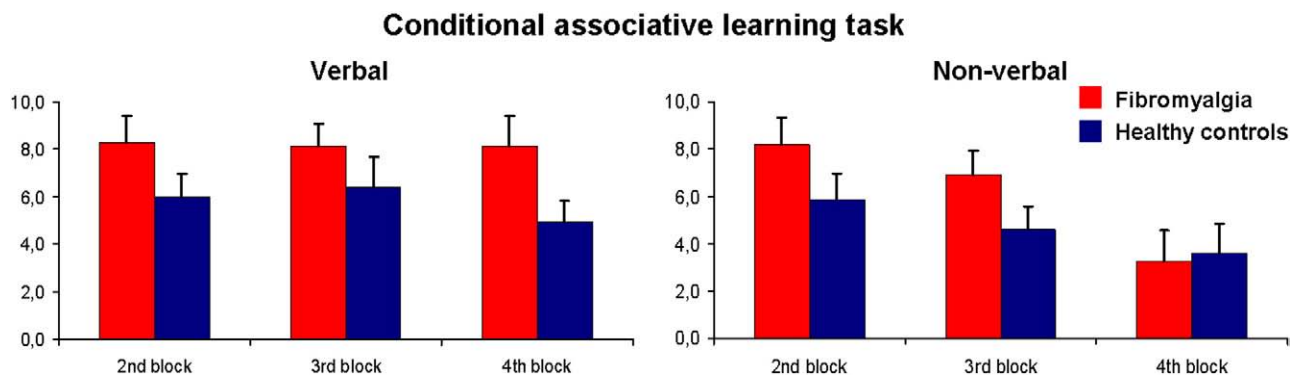

Fig. 1. Number of perseveration errors in the second, third, and fourth blocks during the verbal and nonverbal parts of the conditional associative learning task.

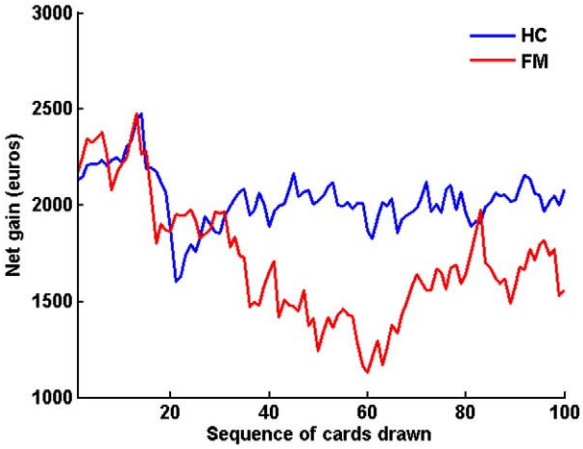

Fig. 2. Net gain obtained by fibromyalgia patients and healthy volunteers in the Iowa Gambling Task across the 100 trials.

advantageous decks, whereas fibromyalgia patients showed a persistent trend toward the disadvantageous decks (Fig. 3).

A repeated-measures ANOVA with the within-subjects factor "phase" (learning vs. performance phase) and the between-subjects factor "group" (fibromyalgia vs. healthy controls) was computed. Significant "group" [$F(1,28)=8.76$, $P=.006$, $\eta^2=.238$] and "Group×Phase" [$F(1,28)=7.48$, $P=.011$, $\eta^2=.211$] effects were found, indicating that healthy controls selected more advantageous decks during the performance phase than during the learning phase ($P=.007$), whereas no differences were found between the two phases in fibromyalgia patients. Moreover, significant differences appeared between fibromyalgia patients and healthy controls in the performance phase ($P=.005$) and in the learning phase ($P=.044$).

Finally, a significant negative correlation was found between depression and net score in the performance phase of the gambling task [$r(30)=-.40$, $P=.029$], but not in the learning phase [$r(30)=-.17$, NS]. In order to control for the effects of depression and anxiety on net scores of the gambling task, a further repeated-measures ANOVA was computed using them as covariates. Results showed that differences between fibromyalgia patients and healthy controls were still significant after controlling for those mood variables [$F(1,26)=6.13$, $P=.020$, $\eta^2=.191$]. Nevertheless, the interaction effect of Group×Phase was not significant after controlling for depression and anxiety [$F(1,25)=1.38$, NS].

Examination of individual performances on the gambling task revealed that there were interindividual differences in the sequences of cards drawn from the four decks. In order to further assess the level of persistence, the average number of consecutive cards selected from the same deck was calculated for each subject. Results indicated that patients with fibromyalgia showed a less marked tendency to draw consecutive cards from the same deck (mean=20.7, S.D.=17.8) than did healthy controls (mean=40.6, S.D.=20.4) [$t(28)=2.84$, $P=.008$].

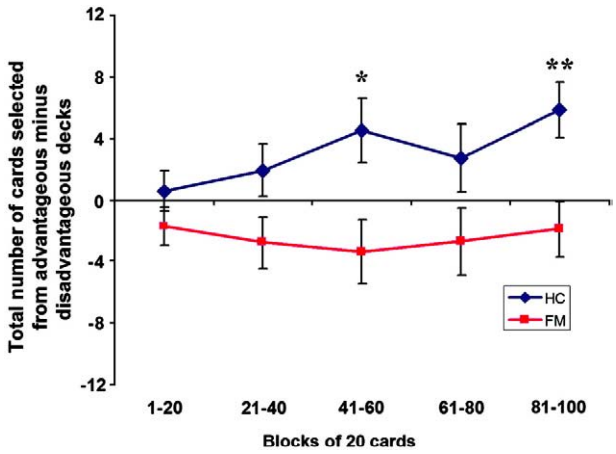

Fig. 3. Behavioral performance on the IGT. Net scores were obtained by subtracting the number of disadvantageous from the number of advantageous choices for each block of 20 trials.

Discussion

The present study revealed a significant impairment of executive functioning among patients with fibromyalgia, who displayed more perseveration errors in a CALT, as well as more disadvantageous decisions and a less persistent behavior in an emotion-based decision-making task than healthy participants. Interestingly, fibromyalgia patients and healthy volunteers showed significant differences in the performance of the gambling task, even when depression was controlled for. Moreover, fibromyalgia patients and healthy volunteers were not different in standardized measures of cognitive functioning, such as the Golden version of the Stroop Interference test or several WAIS subscales. Our results therefore are not explained by a general deficit of patients with fibromyalgia in cognitive functioning as assessed by those tests, such as attention, concentration, or immediate memory. Furthermore, higher depression scores were associated with a poorer performance in the associative learning and the performance phase of the gambling task. These findings confirm our assumption that fibromyalgia patients display specific cognitive impairments, which might be related to the processing of affective information and difficult to be detected by standardized neuropsychological test batteries.

In CALTs, subjects are required to form an association between arbitrary stimuli (i.e., to choose put an "X" if stimulus A is shown or "Y" if stimulus B is shown) through a process of trial and error. It has been suggested that good performance on such conditional tasks might be related to the ability to discriminate between past correct and incorrect responses and to use that information in guiding response selection [36,39–41]. Previous research has further shown that the necessary skills for executive or controlled processing are basically facilitated by intact frontal functioning and that patients with frontal brain

damage are significantly impaired in these tasks [40]. Moreover, neuroimaging data has consistently demonstrated a critical dependence of conditional associative learning on prefrontal structures [40,41]. In a similar way, frontal lobe regions such as the medial prefrontal and insular cortices, as well as the parahippocampal gyrus have been identified as key regions involved in the sensory and affective components of pain in fibromyalgia and other chronic pain conditions [1,3]. It is possible therefore that the poor performance pattern of patients with fibromyalgia in conditional learning tasks could be related to possible deficits in frontal lobe functioning.

Given that conditional associative learning appears to be impaired in fibromyalgia only for verbal (abstract words), but not for nonverbal targets (visual patterns), we may further speculate that altered executive functioning in these patients was not attributable to primary deficits in the ability to acquire conditional associations, but to specific deficits in those strategic control processes that facilitate conditional associative learning under conditions of minimal external cuing and that require internally derived strategic processing for successful task completion. Thus, we reason that chronic pain imposes a high cost on executive control, undermining mainly affective-based learning, but leaving intact perceptual processes, such as those involved in Stroop-like tasks or in the nonverbal part of the present CALT. In this sense, our findings are also in agreement with previous research suggesting that chronic pain might reduce the availability of the limited attentional resources for parallel processing of other information than pain [27,31]. Nevertheless, these findings should be considered with caution due to the modulatory effect of affective mood variables, such as depression, on the differences between fibromyalgia patients and healthy controls.

Our finding that fibromyalgia patients were unable to develop an advantageous strategy in the IGT was also in agreement with recent data on fibromyalgia [30] and low back pain [42]. Additionally, we found that fibromyalgia patients were less persistent in their choices, switching more often between competing responses and thus exhibiting a more random behavior than healthy controls. All these results might be interpreted according to the somatic marker hypothesis proposed by Damasio [43], which suggests that bodily signals might help in guiding decision making by the association between each response option with the somatic responses provoked by its consequences in previous similar situations. In this context, it seems plausible that an abnormal processing of somatosensory information and emotional disturbances as it occurs in chronic pain syndromes [30,42], as well as in depressed patients [44], might be interfering with somatic markers necessary for adaptive decision-making. This interpretation seems to be in line with the idea that emotional processes, such as negative affect, chronic pain, or even continuous stress, could be modulating patients' performance on CALTs and other executive tasks which require parallel processing. This could also explain the relationship observed in the present study between depression and poor performance on the gambling and the associative learning tasks.

There were some shortcomings that must be borne in mind when interpreting our findings. The samples were relatively small, and although they were large enough to detect large effect sizes, smaller effect sizes may have been obscured. Nonetheless, the sample sizes here were comparable to others reported in previous reports on neuropsychological deficits (range between 12 and 40 patients). Healthy control subjects are, however, difficult to compare with clinical groups because they cannot be matched according to illness-related factors such as pain history, medication, and treatment. In the case of medication, it should be further noted that many patients with fibromyalgia in the present study were taking centrally acting pain and antidepressant medication, whereas healthy controls were not. In this sense, it has been suggested that many of the potential pharmacological interventions that relieve pain can also have a negative impact on cognition [45]. There appears, however, to be no clear-cut evidence about the effects of drugs prescribed for chronic pain [46–48] and depression [49,50] on sensory processing and cognitive functioning.

In summary, we found that persistence of pain and negative mood (depression), as it occurs in patients with fibromyalgia, led to significant performance impairments on emotionally charged cognitive tasks. The fact that fibromyalgia patients and healthy controls did not differ in standardized measures of executive functioning further indicates that a more pronounced attention or working memory deficit could not be responsible for our results. Although strong tests of attention and working memory were not used, it is possible that a poor performance of patients with fibromyalgia in emotional decision-making and CALTs seems to be due to some kind of abnormal processing of emotional cues, rather than to a general cognitive deficit. Thus, our findings suggest that chronic pain might impose a high cost on cognitive processing, undermining mainly affective processes involved in learning, memory, attention, and decision-making. In this sense, it should be borne in mind that group differences between fibromyalgia and healthy controls in the gambling task were still present when depression was controlled for. To further explore whether bad performance of fibromyalgia patients in cognitive tasks is due to an anomalous processing of affective signals and not to general cognitive deficits, it would be interesting to apply tasks in which the processing of emotional stimuli (i.e., through affective picture presentation) may interfere with cognitive tasks (i.e., lexical decision) or tasks in which the emotional context (i.e., emotional "framing") differentially influences decision making in these patients. The measure of somatic markers, i.e., autonomic responses to anticipation of choices, in decision making tasks could also bring important data on the contribution of bodily reactions to decision making in fibromyalgia patients and healthy controls. Since heightened

pain experience and increased negative mood, in particular depression, influence the performance of some specific cognitive tasks, future research should also explore whether quantitative (mood state and/or pain experience) or qualitative (i.e., depression, anxiety) aspects of negative mood influence cognitive functioning either in fibromyalgia patients alone or in comparison with other patients.

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