Cognition and Perception Deficits in Fibromyalgia and Rheumatoid Arthritis

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Introduction: Cognitive disturbance in patients with fibromyalgia and rheumatoid arthritis is today a topic of a great clinical interest, largely due to the fact that these persons often complain about cognitive problems.

Objective: This study is aimed to assess the visuospatial memory, attention, and perceptive capacities in chronic pain patients.

Material and methods: Groups were constituted by fibromyalgia patients and rheumatoid arthritis patients, as well as a control group. All the subjects completed a battery of visual and spatial memory, speed of processing, working memory, attention, orientation, and visuoperceptive abilities. A cognitive reserve measurement was obtained.

Results: Results show that chronic pain patients displayed worse cognitive performance than controls. Moreover, arthritis patients execute poorly when compared to the group of fibromyalgia in tasks that demand visuoperceptive integration and visuomotor processing. Patients suffering fibromyalgia obtained worse punctuations than those with arthritis in spatial memory and spatial orientation tasks.

Conclusions: Both groups developed important cognitive deficits, which cannot be explained by the collateral effects of such pathologies, because cognitive profiles are not similar and appear from the beginning of the disease.


Déficit mnésicos y perceptivos en la fibromialgia y la artritis reumatoide

Introducción: El deterioro cognitivo en los pacientes con dolor crónico es hoy día un tema de gran interés clínico, debido a que estas personas con frecuencia se quejan de problemas cognitivos.

Objetivo: Investigar las capacidades de atención, perceptivas y de memoria visuoespacial en los pacientes con dolor crónico en comparación con un grupo control y evaluar si entre estos pacientes hay diferencias, teniendo en cuenta las características de la propia enfermedad y la capacidad de reserva cognitiva.

Material y métodos: Se seleccionó a 2 grupos de pacientes, enfermos de fibromialgia y artritis reumatoide con corta duración de la enfermedad, y se los comparó con un grupo control. Todos los sujetos completaron un protocolo de exploración de memoria visual y espacial, velocidad de procesamiento, memoria de trabajo, visuopercepción, atención y orientación. Para todos ellos se obtuvo una medida de reserva cognitiva.

Resultados: Los pacientes con dolor crónico presentan una peor ejecución cognitiva que los controles. Además, los pacientes con artritis ejecutan la tarea peor que los de fibromialgia cuando requieren mayor velocidad de procesamiento visuomotor y un déficit en la integración en tareas visuoperceptivas. Los enfermos de fibromialgia obtuvieron peores puntuaciones en las tareas de memoria espacial y orientación.

Conclusiones: Los pacientes aquejados de fibromialgia y artritis tienen déficit aun cuando la cronicidad de la enfermedad sea breve. Dicho déficit parece no explicarse por efectos colaterales de dichas afecciones, ya que los perfiles cognitivos no son similares y aparecen desde el inicio de la enfermedad.


Introduction

In the past decades, illnesses that present with chronic pain have revealed themselves to be a important health
problem in our society. In the year 2001, results of the EPISER 2001 project were unveiled, showing that rheumatic diseases are the most frequent chronic diseases in Spain, affecting 22.6% of the population. Fibromyalgia (FM) and rheumatoid arthritis (RA), together with osteoarthritis, are the diseases that most affect the functional capacity of patients. According to the EPISER study, FM is a very common disorder that affects around 2% and 4% of the Spanish population. This means, in our country, more than 11 million persons older than 18 years, the majority of which are women (90%). RA, on its part, affects 200 000-400 000 Spaniards, mostly women between 45 and 55 years.

The exploration of potential cognitive deficits of patients affected by diseases that implicate chronic pain constitutes today a barely explored field, but of enormous clinical interest. Persons affected by these illnesses inform of problems related to attention, memory, or concentration and, in fact, they perform worse in certain cognitive tasks. For this motive, in the past few years, attention has been called to the role that the central nervous system could be playing, next to factors such as pain and stiffness, as determinants of the deficits found in patients with rheumatic disease. Dick et al in 2002 compared subjects with fibromyalgia, rheumatoid arthritis, and patients with rheumatic pain in subjects without illness nor chronic pain, and found an attention deficit, especially selective and sustained attention, and problems with work memory. Bartolini et al in 2002 employed a sample constituted only by RA patients exposed to neuroimaging techniques and neuropsychological evaluations and presented visuospatial alterations in a sample constituted only by RA patients who had been exposed to neuroimaging techniques and a neuropsychologic evaluation and had alterations in visuospatial processes, motor planning and mental flexibility, which correlated with alterations in the frontal lobe and the parietal lobe.

Park et al, in 1 of their studies, analyzed memory deficits and found between patients with FM, a control group of the same age and another group with older subjects. These patients had a worse in work memory and free memories than a control group of the same age. On the other hand, some authors like Shur recognize the existence of memory problems in these patients, though they are attributed to secondary effects of fatigue, depression and pain.

One of the possible variables that could explain these results is cognitive reserve, a theory that has gained strength during the past decades and was originally introduced as an attempt to explain the relation between the degree of cerebral affection and its clinical expression. The active model of cognitive reserve states that a more efficient synaptic processing of the cerebral connections exists or that an alternative use of these when faced with progression of the disease. In this manner, both in healthy persons as in patients with cerebral damage, cognitive reserve (CR) can be defined as the ability of an individual to deal with the advance of a cerebral lesion to minimize the symptoms. This can be mediated by a group of abilities or repertoire, or inherent abilities such as education, intellectual quotient, or occupational status.

Our study, therefore, attempts to relate the results of cognitive deterioration found in previous studies and the capacity of reserve of these patients. For that, in first place we will evaluate the presence of attention problems and visuospatial memory in patients with RA and FM. In second place, we will try to establish if there are any differences in the cognitive deterioration in relation to the concrete alteration in pain that we are treating and, lastly, we will try to prove if CR could explain the differences in the abilities. This project is part of a larger study still under development, in which the efficacy of alternative treatment and the relationship with cognitive variables are combined; in it we are implementing virtual tasks of spatial memory in this population that allow the specific measure of the possible deficit.

Patients and Method

This study had a sample of 45 participants, all of them women, divided in 3 groups: 15 patients with FM, 15 patients with RA, and 15 controls. All gave verbal informed consent before participating in the study, which was carried out following the ethical principles for medical research of the Helsinki declaration.

All of the participants spoke Spanish as their original language and had a normal sense of hearing and eyesight, or they had been corrected to normality. The exclusion criteria for all patients included a history of neurological problems, brain damage, medical conditions that could affect cognition, or a history of psychiatric illness. The inclusion criteria consisted in complying with the diagnostic criteria for RA or FM, being less than 60 years old, and a duration of illness between 0 and 5 years, so chronicity would not be so long.

Participants were recruited by telephone and verbally. The sample of patients was selected from among the rheumatology database and the associations, and federations of patients affected by this diseases. Once the patients had shown interest in participating in the study, they would undergo an interview by the specialist, who had to select those that complied the inclusion criteria and had alterations in visuospatial processes, motor planning and mental flexibility, which correlated with alterations in the frontal lobe and the parietal lobe. The study had a sample of 45 participants, all of them women, divided in 3 groups: 15 patients with FM, 15 patients with RA, and 15 controls. All gave verbal informed consent before participating in the study, which was carried out following the ethical principles for medical research of the Helsinki declaration.

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Neuropsychological Evaluation

Based on the symptoms described by previous studies for this disease, the neuropsychological evaluation consisted in a series of tests that could be sensitive for the measurement of the difficulties mentioned. Individual tests were grouped by functional domains. The attention tests employed were the Stroop test (ST), the digit test (DI) of WAIS (Wechsler Adult Intelligence Scale 3), and the number key test (NK) of WAIS. Stroops' was designed to evaluate the effects of interference in the subject. Scaled scores are employed. Interference is considered high from 10 onward. The DI test is a subtest of WAIS in its Spanish adaptation; the task for the subject is to repeat chains of digits of growing length in direct and inverse order with respect to the examiner. The normality criterion for this group is between 3 and 7 digits (inverse and direct, respectively). The NK is a WAIS subtest that examines visuomotor processing and its range of normality is between 9 and 12.

Visual memory was evaluated with the reproduction and copy test of the complex figure of Rey (ROFCT), the 10/36 Spatial Recall Test (10/36 SRT), and the visual reproduction test (VR) I and II WMS-3 (Wechsler Memory Scale 3). The copy trial of the ROFCT evaluates the capacity of organization and planning of strategies for the resolution of problems, as well as the visuoconstructive capacity. Afterwards, 2 recall trials are carried out, with the objective of evaluating the capacity for learning and non-verbal material recall. Each 1 of the tries is scored on a validated scale that oscillates from a minimum 0 to a maximum 36 points. The scores are considered within normality from a percentile of 50. The 10/36 SRT is a test designed to evaluate the curve of spatial learning and its recall in the long term. A progressive acquisition of the material must be produced, reaching 10 positions by the third try. The VR test is used to measure immediate and long-term visual memory, with a normality range of 9 and 12 in the scale. The visuospatial, visuoperceptive, and visuoconstructive function measures were a copy of the complex figure of Rey, the shape recognition test of Benton (BVFRT), and the line orientation test of Benton (BJLT).

Both tests, designed by L. Benton, consist of a perceptive trial, in the first case of shape recognition and in the second one, angles. The range of normality for the first one is between 28 and 32, and for the second one, 29 and 30. Finally, spatial orientation was measured with the Road Map Test, in which a number of turns are counted (a total of 32) when indicated correctly (to the left or to the right) in one plane. In the case of tests 10/36 SRT, VR I and II, direct and inverse digits and Road Map, were obtained and direct scores were employed; in the rest (Stroop, CN, Rey figure), typical or scaled punctuations were employed.

Cerebral Reserve Data

To measure CR, instructions for the previously done studies were obtained. The mean of the WAIS vocabulary subtest was used along with the years of education received, and divided the subjects in high or low reserve.

Procedure

The participants in this study were evaluated between September 2005 and June 2006, in 2 sessions carried out with a maximum separation of 1 week between. The evaluations were carried out in the university, under open conditions, and similar schedules. In each evaluation session approximately 90 min were employed, although this time could vary in relation to the capacities of each participant specifically. The order of the tests was maintained for all participants. Taking into account the planned objectives and to respond to them, diverse data analysis were carried out, the first one referring to the study sample. The next studies, on the contrary, on 1 side the cognitive function measures in the different illnesses and, on the other hand, the effect of CR in this execution. The description of the subjects, the neuropsychological execution data, the CR, and all of the analysis were carried out on SPSS software (version 12).

Results

Sample Characteristics

In Table 1 the most important demographic data of the sample is shown next to the clinical data on duration of illness and the pharmacologic treatment received by patients of both groups (Table 2) for the relevant variables. In this case, a variance analysis (ANOVA), the results of which demonstrated statistically significant differences and, therefore, samples were similar with regard to sociodemographic and clinical variables. Nevertheless, there were significant differences regarding distribution of the groups in the manual dominance variable, with a larger number of purely right handed persons in the FM group.

Neuropsychologic Performance

As has been pointed out, an analysis of variance (ANOVA) of 1 factor took place first to prove if significant differences existed between the groups in each 1 of the measures of the neuropsychologic battery of tests. In Table 2, means, variances and statistical F values together with the associated probability to each 1 of the variables. Differences
in the SRT 10/36 tests can be observed (trial 2, F=5.82; P=.007; trial 3, F=6.33; P=.005; long-term trial, F=3.90; P=.03). They are also seen in the number key test (F=8.47; P=.001), copying of the figure of Rey (F=5.46; P=.009), BVFR (F=8.14; P=.001), and the Road Map (F=11.92; P=.01).

The post hoc analysis (Figure) done through the MSD test (minimal significant difference) reveals that patients with FM obtain lower mean scores in the trials of the SRT 10/36 test. In the learning trials, differences between the control group and those with RA or FM can be observed (trial 2, SRT controls vs FM, P=.004; controls vs RA, P=.016; trial 3, controls vs FM, P=.002; controls vs RA, P=.015). In the long term, worse scores can be seen in FM patients than controls (P=.011).

Something similar occurs in BVFR (FM vs controls, P=.00; RA vs controls, P=.019). In this last case, in spite of differences, the mean values of the 3 groups are found in normal ranges. In the case of the Road Map, the FM group obtained worse scores and, therefore, more errors in execution than in the control group (P=.003). The RA patients obtain lower mean scores in the number key test of the WAIS (RA vs controls, P=.002; RA vs FM, P=.01) and in the copying the complex figure of Rey test, in which scores were significantly lower than in controls and those of the FM group (RA vs controls, P=.00; RA vs FM, P=.01).

**Influence of the Cognitive Reserve**

The last analysis attempted to show the influence of the CR in the neuropsychological tests. Using a mean contrast through the F statistic, there are no observed significant differences in the neuropsychologic means applied in low and high reserve. The analysis through variable correlation techniques showed a weak correlation between the vocabulary tests and the number key test of the WAIS (Pearson=0.46) with the figure recognition test of Benton (Pearson=0.328), and RV LP (Pearson=0.43). The reserve variable, nonetheless, it is only significantly correlated with long-term recall of RV, though it is a weak correlation (Pearson=0.373).

**Discussion**

In the past few years, a group of studies has evidenced the possible cognitive alterations that patients with FM and other rheumatic diseases. The results of the present study point to the fact that patients FM and RA present a deficit in short-term memory, spatial orientation, and figure perception. In addition, RA patients present alterations in visuoperceptive practices and the speed in visuomotor processing. In the case of FM patients, a long-term visual memory deficit was observed. These results were obtained by selecting patients whose disease after diagnosis did not surpass a duration of 4 years at the moment of evaluation; those patients with secondary affections were also excluded (cardiac, etc) and sociodemographic variables, and the premorbid education level were controlled. The gender variable was equaled.

If we evaluate and contrast previous literature regarding cognitive findings, it is difficult to establish a comparative analysis, mainly due to the fact that there are very few studies that have centered their attention on the study of memory in these populations, more concretely in visual memory, spatial orientation, and visuospatial integration. In addition, the majority of cases have centered almost exclusively in patients with FM.

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**TABLE 1. Clinical Variable Description in the Experimental Groups***

<table>
<thead>
<tr>
<th></th>
<th>Fibromyalgia (n=15)</th>
<th>Arthritis (n=15)</th>
<th>Control (n=15)</th>
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<td>Tramadol 20%</td>
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<td></td>
<td>Ansylotics 50%</td>
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*SD indicates standard deviation; TNF, tumor necrosis factor; WAIS, Wechsler Adult Intelligence Scale 3.
†Statistically significant.
‡Expressed in years since diagnosis of disease.
§Percentage of patients; only the ones with the greater frequency are reflected.

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Nonetheless, in relation to the deficit found in patients with FM, the similarity to our results with those of the Grisart (2002) group must be emphasized, showing that with a short-term and a long-term task, alterations in FM patients with respect to localized chronic pain patients is seen. In this case the task was verbal.

One of the first studies done on this type of population manifested alterations in general quotients of memory, relating them to the severity of pain and aspects of anxiety in those patients. More controversial are the conclusions obtained in the area of attention and FM. In regard to a recent study published by Leavitt et al. in 2006, the results

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*SD indicates standard deviation; LT, long term; SRT, spatial recall test.*

TABLE 2. Descriptive Values, Contrast, and Statistical Significance for Each One of the Neuropsychological Tests Employed

Nonetheless, in relation to the deficit found in patients with FM, the similarity to our results with those of the Grisart (2002) group must be emphasized, showing that with a short-term and a long-term task, alterations in FM patients with respect to localized chronic pain patients is seen. In this case the task was verbal.
of the present research indicate that there are no alterations in tests that measure interference, as the ones they obtain, nor in working memory, though it is true that the sample of patients employed in each one of the studies differ significantly both in disease duration as in the inclusion of RA patients into the sample in our case. Results similar to ours, in the case of tasks of attention, were obtained by Dick et al. (2002) some years ago with samples similar to the ones in the present study, though with a larger chronicity. In the case of the study of visual memory, a
previous study by Sephton et al\(^1\) (2003) manifested the relationship between endocrine alterations in FM and immediate and long-term visual. That study had no control group, making it impossible to compare the results. In any case, they manifested the independence of these alterations with the depressive state of the patients, which has also been manifested before.\(^4,6\)

This conclusion is not unanimous either; data from the work by Shur \(^2\) (2003) manifested that memory alterations and those in the speed of visuomotor processing disappeared once fatigue, pain, and depression had been controlled.

Results obtained in the present study with patients with RA are consonant with those obtained by Bartolini et al\(^3\) (2006) with regard to the visuocostructive deficit that they found. In its case, also, no relation to duration of illness was found. What’s more, the neuroimaging studies in that group point to a possible disconnection in the subcortical white cortex between the frontal and parietal lobe. These results could well explain the visuomotor slowness obtained in our study.

Perhaps one of the problem at the moment of extracting results and conclusions in this type of studies is heterogeneity of the variables that affect this type of disease and greatly influence and characteristics associated to them (pharmacology, chronicity, alterations in mood, secondary clinical complications).

With respect to the role of the cognitive reserve and contrary to conclusions of most of the studies in different affections,\(^4,5,20,21\) the results of this study indicate that, a priori, the absence of effect of the reserve in the execution by the subjects. The reasons can be several, among them having selected a sample with a very similar reserve capacity (keep in mind that the reserve variable is constructed from, among other things, a score in the vocabulary test, in which little difference can be observed among subjects) or even the size of the sample, reduced to carry out contrasts between groups and different reserve levels. Maybe the reserve measure is not the ideal one for the Spanish population. In any case, these are still methodological problems. Maybe no differences appear because they do not exist in this aspect and with this type of test (perceptive, orientation, etc). What seems unquestionable is the existence of such a capacity, reserve, demonstrated in a large number of articles in the past 2 decades (for a review see Stern 2002, 2003, 2006).

In summary, the results from the present study manifest 2 important findings: the first is that both diseases, in spite of sharing the characteristic of chronic pain and shared aspects (depressed mood, fatigue, etc), do not present the same neuropsychological profile. Second, if this is so, clearly, in some aspect the cognitive alterations are not owed to some secondary effect of these affections, but are related to the illness itself, from the beginning.

The existing literature on the role of drugs in the genesis of the cognitive deficit has found a possible relationship between the cognitive deficit and drugs in the case of FM. Pregabalin (Lyrica\(^8\)) produces adverse reactions in the cognitive area: alterations in attention, psychomotor excitement, memory alterations, mental confusion, difficulties for oral expression, etc. Nonetheless, its effects on cognitive functions are minimal and less notable than the ones observed with benzodiazepines.\(^22,26\) In addition, visuospatial functions in concrete, do not seem affected. With respect to trazodone (Deprax\(^8\)), the analysis of cognitive function did not produce statistically significant results. A great variety of adverse effects were registered (mainly in attention), without a significant difference between trazodone and placebo. What’s more, results have proven that the active metabolite of trazodone (Mcpp) produces no significant change in cognitive execution.\(^27-33\) Antidepressants such as citalopram (Cipralex\(^8\), Eserti\(^\text{a}\) or Prisdal\(^8\), Seropram\(^8\)) do not produce a significant cognitive decline, at least up until 9 months of use. Treatments for depression with this medication in populations of middle-aged women have shown an improvement in mood and cognitive efficacy in complex attention, short and long term recall and cognitive flexibility. Low doses of citalopram are useful for the treatment of memory deficits and alterations in conscience.\(^34-39\)

This same effect is seen with tramadol (Adolonta\(^8\), Dolodol\(^8\), Zytram\(^8\), Zaldiar\(^8\), Pontalsic\(^8\), Dolpar\(^8\)).\(^40-42\)

Within the group of ansiolytics, 1 of the most commonly employed is bromazepam (Lexatin\(^8\)), with unapparent effects on cognitive processes. In this group of drugs, the results on cognitive function are more contradictory, but in chronic doses, in the majority of cases, they produce alterations in the formation of memory and sleep.\(^43-58\)

In the case of arthritis there is an absence in the relationship between cognitive defects and drugs, except when using tramadol, ansiolytics, and/or antidepressants. Although the findings do not speak of a specific relationship between pharmacologic treatment and visuospatial and visuo perceptual deficit and spatial orientation, it is important to take into account the type of medication and its chronic use for future studies.

From a neuropsychologic point of view, explaining the cause, the mechanism or the origin of the cognitive deficit is still complicated. The possibility that the alterations in mood could explain the findings of memory and attention alterations has been shuffled, but it would be very anomalous to explain the current results in the visuospatial and visuo perceptual areas. What’s more, why do patients with minimal time since onset of disease also have this deficit, why is the pattern different between FM and RA patients, if in both cases we are referring to patients with fatigue and depression?

The relationship with post-traumatic stress is also shuffled, though in this case there is no clear pattern. Studies have
centered on working memory and results do not seem to be compatible with those found in these patients up until now. Improvements in our study, as is the increase in the number of subjects, the evaluation of the pain and depression scales, and the development of more efficient and discriminating memory evaluation techniques, will possibly contribute to developing a line of study: that of perceptive processes and visuospatial orientation, that together with the group of data obtained up to date have shown a central nervous system dysfunction in these chronic diseases.

As a conclusion and in light of the results obtained in the different studies, it seems that there is not a specific and clear pattern of the cognitive alterations that accompany these affections. Though it is true, also, that all studies reveal at least one deficit related to different memory processes. In the case of attention, the results are more controversial. The studies with RA patients are few, though our data and that in previous studies show certain similarities in visuoconstructive deficits.

References


