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COGNITIVE PLASTICITY IN ALZHEIMER'S DISEASE PATIENTS RECEIVING COGNITIVE STIMULATION PROGRAMMES

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The main objective of the present work is to examine whether cognitive plasticity increases after cognitive training in Alzheimer's disease patients. Twenty-six patients participated in the study, all of them diagnosed with mild Alzheimer's disease. Seventeen received a six-month cognitive training programme and the other 9 were assigned to the control group. Assignment to the experimental or control condition was in accordance with clinical criteria. In order to assess cognitive plasticity, all patients were assessed, before and after treatment, by means of three subtests from the Battery for the Assessment of Learning Potential in Dementias (Bateria de Evaluación de Potencial de Aprendizaje en Demencias, BEPAD). After treatment, Alzheimer's disease patients improved their performance in all the tasks assessing cognitive plasticity: viso-spatial memory, audio-verbal memory and verbal fluency. However, control group patients' cognitive plasticity scores fell. In conclusion, this study showed that cognitive stimulation programmes can improve mild dementia patients' cognitive functioning, while that of untreated patients may worsen.
***Keywords**: Cognitive plasticity, cognitive stimulation, viso-spacial memory, audio-verbal memory, verbal fluency.*

El objetivo de este estudio es el de investigar potenciales cambios en plasticidad cognitiva tras entrenamientos de psicoestimulación en enfermos de Alzheimer en fase leve. Participaron en el estudio 26 pacientes diagnosticados de enfermedad de Alzheimer en fase leve, 17 de los cuales seguían un programa de estimulación cognitiva durante 6 meses y los otros 9 fueron asignados al grupo control. Con el objetivo de evaluar la plasticidad cognitiva, todos los participantes fueron evaluados antes y después del tratamiento con tres subtests de la Batería de Evaluación del Potencial de Aprendizaje (BEPAD). Los sujetos tratados incrementaron su rendimiento en todas las pruebas de evaluación de potencial de aprendizaje con respecto al nivel previo al entrenamiento: memoria viso-espacial, audio-verbal y fluidez verbal. Sin embargo, los pacientes del grupo control disminuyeron su rendimiento en todas las pruebas. Los resultados de este estudio ponen de manifiesto que el entrenamiento cognitivo realizado puede eficazmente incrementar la plasticidad cognitiva, en pacientes con enfermedad de Alzheimer en fase leve, en tareas de memoria viso-espacial, audio-verbal y en fluidez verbal, y que los pacientes que no son tratados declinan en su plasticidad cognitiva.
***Palabras clave**: Plasticidad cognitiva, estimulación cognitiva, memoria viso-espacial, memoria audio-verbal, fluidez verbal.*

Alzheimer's disease (AD) presents in its early stages, as its principal manifestation, a marked deterioration of mnesic functions (both viso-spatial and audio-verbal memory), as well as reduced capacity for synthesis, evocation, deduction or reasoning.

Until a few years ago it was thought that people with AD suffered an essential loss of learning capacity, so that any attempt at cognitive intervention would presumably have only very slight effects, or indeed, no effect at all. However, in recent years it has been shown that elderly people, and even those diagnosed with mild- or moderate-stage Alzheimer's disease, are also –albeit to a limited extent– capable of learning (Calero, 2000; Fernández-Ballesteros, Zamarrón, Tárraga, Moya & Iñiguez, 2003; Junqué, 1994). The biological bases of this learning capacity emerge from the substantial empirical evidence on the capacity of damaged neurons to regenerate themselves and establish new connections (Goldman, 1995). This plasticity of the nervous system, or neuroplasticity, exists in the older brain, even in people in the mild or moderate phases of dementia, though this is not the case in severe phases of the illness, given the great loss of neurons and the lack of synaptic connections (Carr, 1993; Kass, 1995; Goldman, 1997). From a methodological point of view, studies on cognitive plasticity revolve around experimental designs with test-training-retest format. This type of assessment is known as "dynamic assessment", "learning potential

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tests", "interactive assessment", "mediated assessment" or "testing the limits". Such methodology consists in the presentation of a cognitive task in a standard situation (permitting researchers to set a baseline for functioning in that task), training in the same type of task, and finally, further assessment in the standard conditions. The objective of research using this type of methodology has been to measure not merely respondents' performance, but also their learning potential or possibility of taking advantage of different cognitive psychostimulation programmes (Calero, 2004). Likewise, learning potential has been used as a sensitive diagnostic instrument for differentiating between normal and pathological cognitive ageing (Baltes, 1992); moreover, it has even shown satisfactory sensitivity for distinguishing between individuals with mild cognitive impairment (MCI) and those with mild-stage dementia and controls (Fernández-Ballesteros et al., 2003). This is a particularly problematic area in view of the considerable overlap of symptoms between these groups (Multe, Sánchez-Casas, Arrufat, Figuera, Labad & Rosich, 2005).

In sum, research on cognitive plasticity in elderly people has demonstrated that its assessment results, as well as serving as diagnostic indicators for detecting early cognitive impairment, are also useful in estimating the rehabilitation potential of elderly people, with or without the cognitive impairment associated with a process of dementia.

Such advances have now led to a change in therapeutic approaches and attitudes to Alzheimer's disease. Thus, the optimum treatment type for such patients is considered to be that of a comprehensive bio-psycho-social nature (Arroyo-Anilló, 2003) –that is, involving the combined application of pharmacological and non-pharmacological treatment. Pharmacological treatment consists, basically, in the administration of drugs for the inhibition of acetylcholinesterase, which work to compensate the cholinergic dysfunction and maintain effective levels of acetylcholine, resulting in an improvement in the patient's cognitive abilities (Boada, 2003). Such drugs have demonstrated their efficacy in restraining or slowing down the course of the illness for a period.

As far as so-called "soft" or "non-pharmacological" therapies are concerned – which include stimulation of cognitive capacities, memory training, behavioural interventions for the maintenance of daily life skills, psychosocial interventions, and so on–, considerable efforts are being made to promote their use. Such therapies have the effect of slowing down cognitive impairment at the same time as boosting the effect of the drugs (for a review, see Tárraga, 1994, 1998, 2001). As we remarked above, such therapies are based on the notion of "plasticity of the nervous system" or "neuroplasticity" as '*the response given by the brain to adapt to new situations and re-establish the balance altered after a lesion'* (Geschwind, 1985). Cognitive stimulation increases cognitive reserve, given that training works to restore intellectual capacities so that deterioration can slow down and the effects on the patient's daily life functioning can be retarded. The efficacy of some cognitive training programmes has been shown in various studies in which participants with dementia who are treated improve significantly with respect to the control group (Ermini-Fünschilling, 1998; Herlitz, 1991; De Vreese, 1999; Tárraga 1994; Tárraga et al., 2006).

The chief objective of our study was to determine whether the application of a cognitive psychostimulation treatment is capable of improving the reserve capacity, cognitive plasticity or learning potential of individuals diagnosed with mild-stage Alzheimer's disease. Or put another way, whether people diagnosed with mild-stage AD improve their performance in a battery of learning potential tests after a programme of cognitive psychostimulation treatment.

METHOD

Participants

Twenty-six patients (mean age: 75.3 years; SD= 6.4) diagnosed by the Diagnostic Unit at the *Fundació ACE* (*Institut Català de Neurociències Aplicades*, Catalonian Institute of Applied Neurosciences, Barcelona) with mild-stage Alzheimer's disease, 19 of whom were women (mean age: 72.01 years; SD= 6.5) and 7 men (mean age: 76.7; SD= 6.06). As regards educational level of the participants, 7.7% had no formal education, 65.4% had Primary Education, 3.8% had Secondary Education and 23.1% had Higher/University Education. In accordance with the requirements of the clinical unit, 17 patients (14 women and 3 men) participated in a cognitive stimulation programme (*Programa de Psicoestimulación Cognitiva*, PPI; see Tarraga, 2001), whilst the remaining nine (5 women and 4 men), who did not take part in any psychosocial programme, made up the control group. All the patients (experimental and control groups) had been on stable treatment regimes for more than four months, with acetylcholinesterase inhibitors, before beginning the study, and continued with the same treatment throughout the experimental

process.

Procedure

We used a quasi-experimental design with non-equivalent control group. Assignment of participants to the experimental or the control group was according to clinical criteria. All participants were assessed both immediately before the treatment and immediately after it (6 months later), with the MMSE and the BEPAD (see Instruments section)

Statistical analysis

The data were analyzed with the Student t test for related samples (in order to study the inter-group differences of the variables measured at baseline and at 6 months for the treated sample and the controls separately) and a two-factor analysis of variance (ANOVA) with repeated measures in one factor (in order to study the effect of the between-group factor [treatment/control) in each of the within-group factors [at baseline and at 6 months]). The scores used for the comparisons of the BEPAD subtest measures were those corresponding to the gains on each of the subtests. Such scores result from subtracting the baseline (standard) score from the final score (after the training). In the case of the MMSE we used the total raw scores in our analyses. For all the comparisons a difference with $p<0.05$ was considered significant.

The program used for the statistical analyses was the SPSS.14.

Instruments

For assessing participants' mental state we used the *Mini-Mental State Examination* (MMSE, Folstein et al., 1975), given its widespread use as a screening test in both clinical and research contexts. Moreover, it is the most extensively used instrument for assessing the effects of interventions in patients with dementia, as well as for measuring the progression of cognitive impairment (Lezac, 2004; Pino, Guilera, Gómez, Rojo, Vallejo & Purdon, 2006). The MMSE assesses cognitive capacities such as temporal-spatial orientation, short-term memory, language, and ideatory and constructive praxias.

Assessment of cognitive plasticity was carried out by means of the Battery for the Assessment of Learning Potential in Dementias (*Batería para la Evaluation del Learning potential en Demencias*, BEPAD; Fernández-Ballesteros et al., 2003), which has shown high capacity for discrimination between different groups of individuals with and without cognitive impairment (Fernández-Ballesteros, Zamarrón & Tárraga, 2005). The BEPAD contains four subtests, three of which were selected for this study because they measure the areas or functions which, according to experts, best discriminate cognitive impairment: 1) *Viso-spatial memory*. "Learning potential Positions Test" (adapted from Rey, 1964), in which the participant is required to reproduce the crosses shown in a square over 6 trials: pre-test, post-test and 4 intermediate trials in which the participant is trained; 2) *Audio-verbal memory.* "Learning potential Verbal Learning Test", adapted from Rey, 1964; Lezak, 1983; and Calero and Lozano, 1994. Fifteen common words are presented over 7 trials, the first and sixth trials being those of pre- and post-test. In order to assess the interference effect or delayed recall, the seventh trial is administered after the Hanoi Tower test; 3) *Verbal fluency.* "Learning potential Verbal Fluency Test" (adapted from Fernández-Ballesteros, 1968). Participants are asked to say all the words they can in 1 minute, after which they are provided with strategies for resolving the task; finally, their performance is recorded. In accordance with the criteria related to learning potential tests, different learning procedures were developed in the resolution of the different tasks: practice (present in all the tests), feedback (present in all the tests), reinforcement (positions, verbal learning and verbal fluency), visualization (positions and verbal fluency), and verbal encoding (positions).

For the cognitive training we used the Comprehensive Psychostimulation Programme (*Programa de Psicoestimulación Integral*, PPI), which has demonstrated its efficacy in patients with cognitive impairment in dementias (Tárraga, 1994, 2001). Its aim is to maximize higher cognitive capacities, with exercises suited to the degree of impairment, and therefore to the residual capacities of the individual in question. In the present study, the PPI was administered to experimental participants in daily 90-minute group sessions over a period of 6 months. The abilities targeted are as follows: 1) Reasoning, attention and concentration; 2) Verbal and written language; 3) Praxias; 4) Gnosias; 5) Arithmetic and calculation; and 6) Association-ordering. A more detailed description of the programme and its efficacy levels can be found in Tárraga (1994, 1998, 2001).

RESULTS

First of all, it should be stressed that all controls differed from experimental participants in all the scores obtained before the treatment. Experimental participants presented poorer mental state, as well as greater

impairment of viso-spatial memory, audio-verbal memory and verbal fluency. This was due to the assignment of participants to the experimental condition according to clinical criteria. It should also be highlighted, with regard to these differences favouring the control group, that any biasing effect of them would work against our change-related hypotheses.

MMSE

As can be seen in Figure 1, both groups present a lower MMSE score in the post-test than at baseline. However, and although the differences are not significant, the control group's score decreases to a greater extent than that of the experimental group (1.7 points vs. 1.2 points, respectively).

Learning potential Positions Test

Figure 2 shows in graphic form how experimental participants' learning potential score in the Positions Test improves, whilst that of the controls falls. In other words, those who have received cognitive training improve their cognitive plasticity scores (being able to benefit from the training sessions), whilst the performance of those who have not received cognitive intervention not only fails to improve, but indeed worsens. However, these differences, though graphically and descriptively apparent, do not reach significance.

Learning potential Verbal Learning Test

Figure 3 shows the results for gain scores on this test obtained by those who received cognitive training and by controls. The treatment group significantly (t= -4.243; p<0.001) improved their mean score on the test over the period (6 months) in which they were receiving treatment (from 1.47 to 2 words recalled); on the other hand, the control group not only failed to increase the number of words –after being trained to perform the test task– but actually got significantly worse (t= 2.530; p<0.035) over the same period (from 2.78 words recalled at baseline to 2.33 words recalled at 6 months). Likewise, the ANOVA with two factors and repeated-

Figure 1
MMSE score at baseline and after 6 months' cognitive training of treated patients and of controls

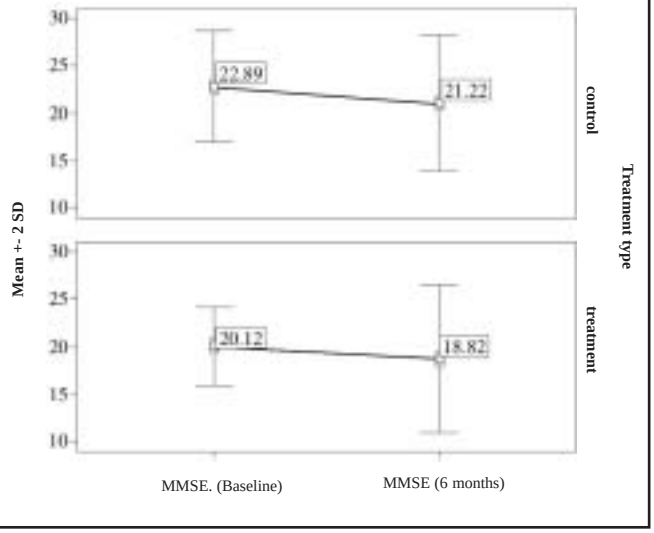


Figure 2
Gain scores in the Learning Potential Positions Test before and after the cognitive training of treated patients and controls

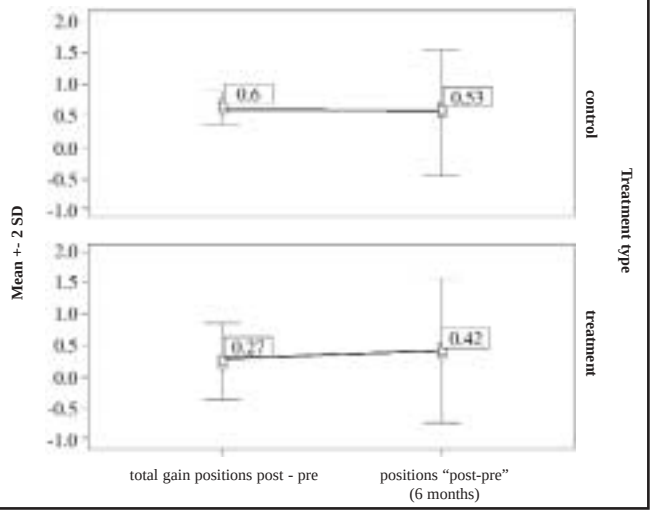
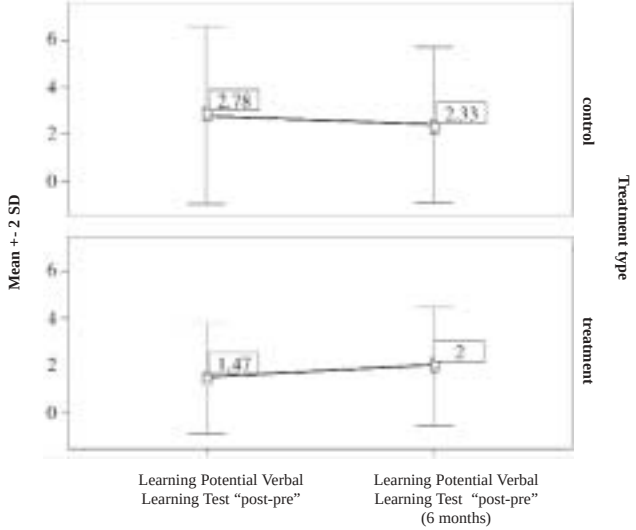


Figure 3
Gain scores in the Learning Potential Verbal Learning Test before and after the cognitive training of treated patients and controls



measures in one factor permitted us to confirm the existence of significant differences between the two groups (treatment and control) in this variable (F= 20,742; p>0.000).

As regards delayed recall score for this verbal learning test –that is, the score corresponding to the number of words recalled after introducing an interference phenomenon in the recall process–, Figure 4 shows in graphic fashion how, after cognitive training, there is less effect of this interference phenomenon: the control group score falls by 0.11 words, while the score for the group that received psychostimulation treatment increases by 0.2 words. However, the differences found are not significant at either the within-group (score at baseline and at 6 months) or the between-group (treatment and control group) level.

Learning potential Verbal Fluency Test

Figure 5 shows the results for gain scores (improvement in number of words at post-test) obtained in this verbal fluency test across the two measurement points and by the two groups (treatment and control). The group that received cognitive training benefited from it, since there are significant differences (t= -3.782; p<0.002) between the mean scores obtained by this group at baseline and those obtained after 6 months of treatment. These participants improved their performance by a mean of 1.6 words, whilst controls' performance worsened (by 0.89 words) over the same time interval. Furthermore, the differences between the two groups are significant (F= 12,667; p<0.002).

DISCUSSION AND CONCLUSIONS

The main objective of our research was to observe whether cognitive training for a 6-month period can increase cognitive plasticity or learning potential in people with mild Alzheimer's disease –that is, whether cognitive programmes can improve the learning capacity of these patients with cognitive impairment. It should be stressed that this is a first experiment carried out with a small number of participants assigned to experimental and control conditions for clinical reasons. This is clearly apparent in the baseline differences between the two groups, the control group scores being higher and reflecting their better cognitive functioning than that of the experimental participants; this is a fact whose effect, if there were any, would work against our assumptions.

First of all, it should be pointed out that the cognitive training programme chosen (the PPI) did not improve mental state as measured by the MMSE, though it did produce slight changes (not significant) in the deterioration gradient of the experimental group by comparison with that of the control group. In other words, in either group, over the 6 months between baseline and post-test there is a decrease in scores (indicating more impairment), but this decrease is smaller (1.2 points) in the treatment group than in the control group (1.8 points). These results do not concur with those obtained in previous work which found, after the application of similar programmes to the one used

Figure 4
Total delayed gain score in the Learning Potential Verbal Learning Test before and after the cognitive training of treated patients and controls

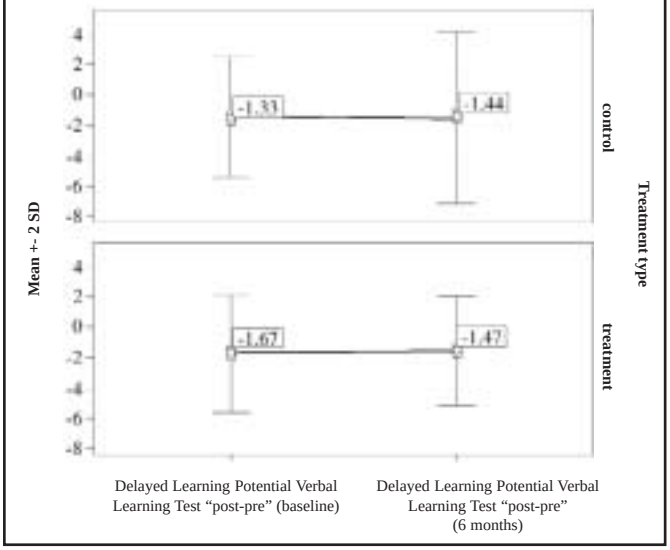
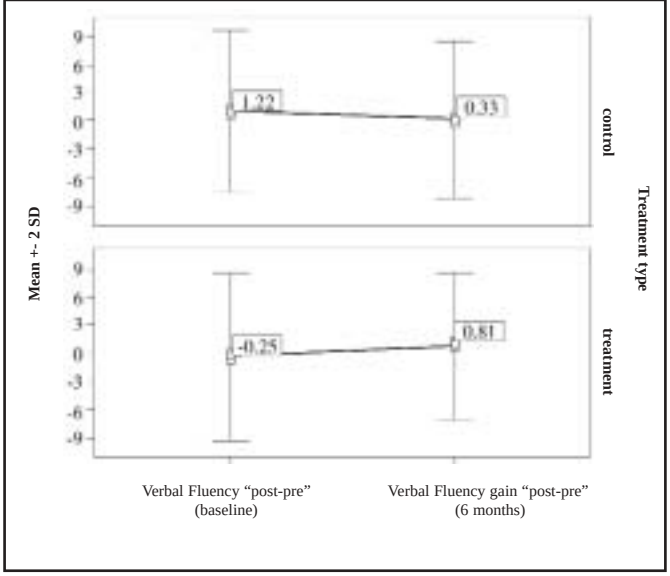


Figure 5
Gain score in the Learning Potential Verbal Fluency Test before and after the cognitive training of treated patients and controls



here, that patients with dementia improved their mental state (Tárraga, 2001) or it remained constant (Ermini-Fünschilling, 1998). If we consider the annual rate of cognitive deterioration measured by the MMSE to be 2-4 points (Haxbi, 1992; Katman, 1988; Salmon, 1990), the two groups (experimental and control) in the present study would have presented differences in their MMSE scores at 6 months that fell within the expected range (1-2 points).

As regards our central objective, that is, to observe a positive change in cognitive plasticity or learning potential in patients with mild Alzheimer's disease who received training, the results obtained in the BEPAD tests were as follows:

After six months of treatment, patients diagnosed with mild AD significantly improved their learning capacity in immediate verbal recall, as well as in that of verbal fluency, and showed a trend towards improvement (non-significant) in viso-spatial memory and delayed verbal recall. For their part, the control group showed a reduction in their viso-spatial learning capacity and those of immediate and delayed verbal recall and verbal fluency after the same six-month period. In brief, while the treated patients improve in all our learning potential measures, the controls get worse in all of them.

We cannot conclude that our participants experienced a global improvement in their cognitive functions as a result of the application of the psychostimulation programme. However, what we can say is that they improved their learning potential in immediate and delayed recall, as well as in that of verbal fluency, with respect to the control group. Through the psychostimulation programme, they developed the capacity for learning; in other words, they "learned to learn".

The conclusions of our study are in support of the assumptions of all those authors who consider cognitive training as a palliative measure in the treatment of Alzheimer's disease and similar disorders (Kizmiller, 2002; McKitrick, Camp & Black, 1992); moreover, we have seen how a psychostimulation programme enabled the experimental patients to develop their learning capacity, or to learn to learn. Thus, we can state that it is possible to increase cognitive reserve or learning potential in patients with this type of neurological lesion (Calero & Navarro, 2006; Stern, 2002, 2003).

In any case, the most notable result, which indeed concerns not only the scientific dimension but also the ethical one, is that the performance of the non-treated patients –even though they present better functioning at baseline than the treated patients– worsens because they do not receive the cognitive training programme.

Among the limitations of the present work are the small sample size and the lack of equivalence between the two groups. Such limitations are to some extent characteristic of this type of study (McKitrick, 1992; Camp, 1996; Kizmiller, 2002; Clare, 2000), given the difficulty of obtaining patients with comparable characteristics who can be assigned to experimental and control conditions. Future research will attempt to overcome limitations of this nature.

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