

Cognitive plasticity as a moderator of functional dependency in elderly patients hospitalized for bone fractures

Introduction

As several studies have pointed out, we are experiencing the progressive aging of our population [1–3]. Social and healthcare advances extend our lifespan. This phenomenon, in turn, brings about new social and healthcare challenges. Increased life expectancy leads to more dependency and deterioration in the population: in many cases, the additional years are not accompanied by a good quality of life.

One of the most frequent healthcare problems in older adults has to do with bone fractures, which are generally caused by falls, osteoporosis etc. [4]. Bone fractures account for a quarter of hospitalizations, whereby the length of hospital stay varies as a function of several variables [5]. As these authors indicate, traumatology problems and particularly broken hips have increased hospital admissions of seniors over the age of 65 years by 25% in Spain in recent years. In this context, one phenomenon particularly significant to gerontology research is loss of functionality, characterized by a loss of independence and increased cognitive decline, which is sometimes associated with the lack of mobility brought on by a bone fracture (be it a hip [4] or another part of the anatomy [6, 7]).

A hip fracture, besides producing loss of mobility and the corresponding functionality, requires hospitalization in every case [8, 9]. This is a costly circumstance, not only in familial and financial terms, but also in terms of the poten-

tial decrease quality of life, increased dependency, functional or cognitive decline and depression that this may be associated with. In fact, some studies indicate that the most vulnerable patients and those most susceptible to cognitive decline associated with greater functional dependency, are patients over the age of 65 years, who were admitted for various fractures resulting from falls, osteoporosis and bone decalcification [10]. Therefore, studies have shown a real trend toward chronicity and disability in hospitalized older patients, regardless of the cause of hospitalization. The importance of the period immediately following hospital release as a risk factor for disability and dependency was recognized by the World Health Organization as early as 1974 [11].

Among patients hospitalized following a hip fracture, some authors indicate a death rate that is 12 to 20% higher than in older people who have not experienced this fracture. Furthermore, half of the patients who survive a hip fracture are unable to recover the same level of prefracture activity [12, 13].

Proper treatment in the acute phase of a hip fracture consumes a large share of healthcare resources [14] and influences the patient's recovery. However, there is much variability between hospitals, both in terms of how they treat this health problem and in terms of results. This variability manifests in the use of different healthcare procedures and the length of hospital stay (varying from 7 to 28 days in different publications), as well as in functional

recovery (the proportion of patients able to return home 1 month after fracture varies from 20 to 70% among the different healthcare centers) [15].

The therapeutic objective of the acute phase is to minimize the impact of the fracture on the clinical, physical, mental and social spheres of the patient. Several healthcare professionals must act in a coordinated fashion to intervene in this process—traumatologists, anesthetists, rehabilitation specialists, nurses, physiotherapists, occupational therapists, social workers etc.—and different levels of personal, health and social care are frequently involved, with nursing care proving particularly important.

With this scenario as a reference, there is no doubt that one of the current challenges in gerontology nursing is the promotion of autonomy in older patients suffering a hip fracture, where autonomy is understood as functional independence and perceived control on the part of the patient. This is one of the most important goals for nursing personnel to meet; both during hospitalization and the period immediately following discharge [16]. Toward this end, analyzing the variables involved in patient recovery or decline constitutes a very relevant research objective.

In the studies that have analyzed variables related to cognitive and functional decline associated with hospitalization and recovery thereafter, several authors have found a greater functional decrease to be associated with variables such as age [17, 18], prolonged rest [19], decubitus [8],

Tab. 1 Contingency table based on the Barthel Index (BI) classification upon hospitalization and at home and the Auditory Verbal Learning Test of Learning Potential (AVLT-LP) classification

AVLT-LP	BI upon hospital admittance			BI at home		
	Independent	Moderately dependent	Highly dependent	Independent	Moderately dependent	Highly dependent
High LP	26	23	48	74	2	0
Low LP	20	21	27	57	21	9
χ -squared =5.765; p=0.056; χ -squared with Fisher's exact test =91.745; p =0.0001						
LP learning potential						

pain caused by the surgery [20], the presence of other illnesses [21] and the number of hospitalization days prior to surgery [22]. Other authors associate functional loss with prior deterioration [23, 24] and a low level of social activity [25] or indicate the importance of development of programs such as the Functional Training Program Post Hip Fracture (FTPPHF) for the recovery of elderly patients [26].

Other studies described the psychosocial state—specifically self-efficacy expectations and outcome expectations related to exercise, mood, fear of falling, pain and health status—of older people in relation to functional recovery [27, 28]. However, results have not been linked to the level of cognitive plasticity in the elderly. This is despite the fact that previous studies have established cognitive plasticity—defined as the capacity for learning or improved performance under conditions of training or performance optimization—to be an important moderating variable in the cognitive evolution of older adults. Cognitive plasticity is considered to be the behavioral manifestation of brain reserve [29] and is a construct distinct from cognitive status in older adults, because it is related to the potential for recovery and not to cognitive performance in a given time. Some studies show that this variable can predict later cognitive decline in healthy older adults and/or those with slight cognitive decline [30–33], or can predict response to cognitive training [34]. The degree of plasticity has been associated with the cognitive state of older adults and recent studies show how adults with normal or optimal aging benefit from high levels of cognitive plasticity [35, 36]. Elsewhere, plasticity has been associated with an active life style [35], as well as with a high level of independence in activities of dai-

ly life (ADL) and with a better quality of life [37, 38].

Given that the above studies point to the importance of cognitive plasticity in old age and that its involvement in the functional recovery of older adults with bone fractures has not been analyzed to date, we have carried out an investigation to do so. The main objective of this study is to analyze to what extent cognitive plasticity (operationalized as learning potential, LP, in a word memory test) is a moderating variable in the functional recovery of older adults hospitalized for bone fracture and subjected to surgical intervention. The starting hypothesis is that there will be a significant association between cognitive plasticity and functional and cognitive recovery, both at the time of hospital release, as well as in the mid-term (3 months later).

Participants

A total of 165 older adults from the province of Jaen (southern Spain) participated in the study. To be included in the study, patients had to be over 65 years of age and hospitalized for bone fractures. The mean age was 78.55 years (standard deviation, SD =8.55; range 65–108 years). As for gender, 78% were female and 22% were male. Level of education was distributed as follows: 56.3% had no schooling, 35.4% had primary education, 5.7% secondary education and 2.5% university education. As for their living situation, 13.3% of the sample lived in the home of a family member (usually their child), 80.4% in their own home and 6.3% in a nursing home. For the whole sample, the mean Barthel Index (BI) score upon admission to hospital was 36.45 (SD =24.73); at discharge, the mean score was 67.97 (SD =226.12). The mean Auditory Verbal Learning Test of Learn-

ing Potential (AVLT-LP) score gain was 3.26 (SD =1.96).

Instruments

Semistructured interview: patient data sheet created for this study in which information on personal health, biological and social variables was recorded.

Tests for assessing the level of dependency

The BI [39, 40]: this test is composed of ten items that assess the ability to perform certain basic activities of daily life (ADL) without help, specifically: the ability to eat, get up and down from the chair or bed, personal grooming, using the toilet, bathing, moving about, going up and down stairs, dressing, intestinal and urinary control. Scores ranges from 1 to 100, with 1 being completely dependent and 100 completely independent. The internal consistency assessed with Cronbach's α is between 0.86 and 0.92 for the original version and interobserver agreement expressed using the κ index is between 0.84 and 0.97. Regarding validity, it has been observed the initial BI is a good predictor of mortality. Empirical evidence has shown that the BI is able to detect progression or decline in certain levels of the individual's functional state [41].

Lawton and Brody's Scale [42], adapted to Spanish by Cid and Damián [43]: this questionnaire measures the elderly person's ability to perform, without help, instrumental activities of daily life (IADL) that are typical for a nonhospital environment and necessary for independent living. This scale is one of the most frequently used measures of IADL internationally and the one most frequently used in Spanish geriatric units. The scale is composed of eight items that measure the ability to use the telephone, shop, prepare food, take care of the home, do laundry, use transportation and be responsible for medication and personal finances. The final score may fall anywhere between 0 (maximum dependency) and 8 (total independence). However, there are three items that generally pertain to women in Western society (food, housekeeping, laundry) and the authors of the scale suggest that these ac-

tivities not be counted in the assessment. The test's psychometric data show that it has a high inter- and intraobserver reliability coefficient (0.94). A low score obtained in this test is predictive of deterioration of basic activities during hospitalization, proposed by some authors to be an indicator of frailty [44].

Test for assessing cognitive plasticity

The AVLT-LP [45, 46]: This is a version of the classic test by Rey [47]. The traditional version consists of presentation of 15 common words which the participant must repeat immediately after hearing them. The list is presented a total of five times and on each occasion, the remembered words are recorded. In the LP version, the wordlist is presented six times. The first two repetitions are a pretest following the standard format; the next two are for training and include feedback on execution, motivation, reinforcement and repetition of words not remembered and the final two repetitions are a posttest, again following the standard format. Applying the test in this fashion provides different markers. In this study we have worked with direct scores obtained in each test trial and the AVLT-LP score gain (posttest minus pretest). This gain score indicates the degree of improvement after the training phase and several studies have established this to be a measure of learning ability or cognitive plasticity in healthy older adults and older adults with cognitive decline [48–50, 38], as well as in other populations such as persons with schizophrenia or dementia [51]. Although plasticity is a continuous variable, some authors have used typological classification criteria based on the clinical significance of the change observed from pre- to posttest, classifying participants into two main groups: people with significant improvement (high LP) and people with nonsignificant improvement (low LP). This classification has shown diagnostic and prognostic usefulness [35, 45, 52]. Among the various classification criteria, using an improvement in gain score of 1.5 SD from pretest as the cutoff has proved valid [53].

The test has also been validated by several authors with Spanish populations

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Cognitive plasticity as a moderator of functional dependency in elderly patients hospitalized for bone fractures

Abstract

Introduction. Bone fractures in older adults involve hospitalization and surgical intervention, aspects that have been related to loss of autonomy and independence. Several variables have been studied as moderators of how these patients recover. However, the implications of cognitive plasticity for functional recovery have not been studied to date.

Objective. The present study analyzes the relationship between cognitive plasticity—defined as the capacity for learning or improved performance under conditions of training or performance optimization—and functional recovery in older adults hospitalized following a bone fracture.

Patients and methods. The study comprised 165 older adults who underwent surgery for bone fractures at a hospital in southern Spain. Participants were evaluated at different time points thereafter, with instruments that measure activities of daily life (ADL), namely the Barthel Index (BI) and the Lawton Index, as well as with a learning poten-

tial (cognitive plasticity) assessment test (Auditory Verbal Learning Test of Learning Potential, AVLT-LP).

Results. Results show that most of the participants have improved their level of independence 3 months after the intervention. However, some patients continue to have medium to high levels of dependency and this dependency is related to cognitive plasticity.

Conclusion. The results of this study reveal the importance of the cognitive plasticity variable for evaluating older adults hospitalized for a fracture. They indicate a possible benefit to be obtained by implementing programs that reduce the degree of long-term dependency or decrease the likelihood of it arising.

Keywords

Gerontology · Bartel Index · Quality of life · Activities of daily life · Instrumental activities of daily life

Kognitive Plastizität als Einflussfaktor funktioneller Abhängigkeit bei Älteren mit Knochenbrüchen im Krankenhaus

Zusammenfassung

Einführung. Knochenbrüche bei älteren Menschen bedeuten einen Krankenhausaufenthalt und chirurgische Intervention. Das sind Faktoren, die mit dem Verlust der Autonomie und der Unabhängigkeit in Zusammenhang stehen. Bisher wurden verschiedene Variablen als Einflussfaktoren auf die Heilung untersucht. Bisher nicht untersucht wurden Auswirkungen der kognitiven Plastizität auf die funktionelle Genesung.

Ziel. Die vorliegende Studie analysiert die Beziehung zwischen kognitiver Plastizität, definiert als Lernfähigkeit oder als Leistungssteigerung bei Training- oder Leistungssteigerung, und funktioneller Genesung bei älteren Menschen im Krankenhaus nach Knochenfraktur.

Patienten und Methoden. In diese Studie wurden 165 ältere Patienten mit Knochenbrüchen eingeschlossen, die sich in einem Krankenhaus in Süds Spanien einer Operation unterzogen. Anschließend wurden zu verschiedenen Zeitpunkten tägliche Aktivitäten (ADL) mit dem Barthel-Index und dem Lawton-Index gemessen und ein Test zur Beur-

teilung der kognitiven Plastizität (Auditory Verbal Learning Test of Learning Potential, AVLT-LP) durchgeführt.

Ergebnisse. Die Ergebnisse zeigen, dass 3 Monate nach dem Eingriff eine Verbesserung der Unabhängigkeit bei den meisten Teilnehmern eintrat. Bei einigen jedoch bestand auch nach dieser Zeit weiterhin eine mittlere bis hohe Abhängigkeit, was im Zusammenhang mit der kognitiven Plastizität der Teilnehmer zu werten ist.

Schlussfolgerung. Die Ergebnisse dieser Studie zeigen die Bedeutung der Variable kognitive Plastizität für die Bewertung älterer Menschen, die mit einem Knochenbruch im Krankenhaus sind. Des Weiteren deuten sie auf einen möglichen Nutzen von Programmen hin, die den Grad einer langfristigen Abhängigkeit bzw. die Wahrscheinlichkeit, dass diese entsteht, verringern.

Schlüsselwörter

Gerontologie · Bartel Index · Lebensqualität · Aktivitäten im Alltag · Instrumentelle Aktivitäten im Alltag

Tab. 2 Barthel Index (BI) upon hospital admittance and at home (3 months later), taking into account the Auditory Verbal Learning Test of Learning Potential (AVLT-LP) score gain groupings

		Barthel Index hospital		Barthel Index home		F _(1,160)	P-value	η^2_p
		M	SD	M	SD			
AVLT-LP gain	Low LP	37.33	24.79	67.57	24.89	119.96	0.0001	0.70
score group	High LP	47.12	24.50	84.51	17.80	259.43	0.0001	0.79

M mean, SD standard deviation, LP leaning potential.

Tab. 3 Lawton Index upon hospital admittance and at home (3 months later), taking into account the Auditory Verbal Learning Test of Learning Potential (AVLT-LP) score gain groupings

		Lawton index hospital		Lawton index home		F _(1,160)	P-value	η^2_p
		M	SD	M	SD			
AVLT-LP gain	Low LP	4.67	2.87	6.29	2.24	71.21	0.0001	0.31
score group	High LP	3.38	2.95	5.29	2.54	1.12	0.291	0.007

M mean, SD standard deviation, LP leaning potential.

similar to that participating in this study [48, 49, 54].

Procedure

The research was carried out in a hospital in Jaen (southern Spain). Once the project was explained to and approved by the hospital ethics committee, the principal investigator checked on a daily basis for patients over 65 years of age who had been admitted with a hip fracture diagnosis. Patients who met the study inclusion criteria were visited personally by the researchers, who explained to them the objective of the study and requested their signed informed consent (Helsinki declaration, 2004). Once the participant had given consent, the relevant medical history was collected and the semistructured interview cited in the instruments section was conducted that same day. Six days after hospital admittance, the patient was visited again and a second assessment lasting approximately 45 min to 1 h was carried out. During the hospital stay, the patient's socio-cultural and healthcare data were collected and the tests described above were administered, with the exception of the AVLT-LP which was applied between 60 and 90 days after discharge from hospital. The patients' condition does not allow application of the AVLT-LP in the hospital, since this is a longer test that requires concentration and other studies indicate that this

test is stable for periods of over 6 months, such that results will not change over a short period of time [48].

During this visit, other sociodemographic data were collected and new functional and cognitive assessments were carried out using all the tests described in the instruments section.

As a function of the scores obtained on the BI at home, older adults were classified as highly dependent (scores from 0 to 30), moderately dependent (scores between 31 and 59) or independent (scores higher than 60). As a function of the AVLT-LP gain score, participants were classified as having "meaningful plasticity or high LP" (gain score ≥ 3 points) or "nonmeaningful plasticity or low LP" (gain score < 3 points).

Design and statistical analysis

A quasi-experimental design with repeated measures was used. The statistical analyses consisted of contingency tables, χ -square analyses, Pearson correlations, analyses of variance (ANOVAs) and analyses of covariance (ANCOVAs).

Results

In order to analyze the relationship between cognitive plasticity and dependency, we performed Pearson correlations between AVLT-LP gain scores and BI scores

collected on admission, hospital discharge and at home. The results showed an increase in the association of these two tests as time progressed, being nonsignificant upon admission ($r_{xy} = 0.148$), but significant at discharge ($r_{xy} = 0.195$, $p < 0.05$) and at home ($r_{xy} = 0.335$, $p < 0.0001$).

We proceeded to analyze the distribution of the participants as a function of their degree of dependency (highly dependent, moderately dependent and independent), taking into account their BI score upon hospital admittance and at the home follow-up visit, as well as the level of cognitive plasticity (high or low LP) as a function of the AVLT-LP gain score. As shown in **Tab. 1**, according to the BI assessment upon hospital admittance, the distribution of dependent and independent older adults is significantly different between the two LP groups

$$(\chi^2_2 = 19.64, p < 0.001).$$

A greater percentage of low LP patients are observed in the high-dependency group upon hospital admittance. By contrast, results from the home visit 3 months after discharge show that the number of independent persons increases: only 9 out of the 48 patients who were initially assessed (upon admittance) as highly dependent maintain this status, and all of these 9 had low plasticity (LP) scores. As the results show

$$(\chi^2_2 = 91.74, p < 0.0001),$$

the distribution of the two groups is not homogeneous.

In order to verify whether there were differences between high and low LP with regard to progression or improvement in functional status based on the BI, we carried out a comparison of the mean values (M). The outcomes confirmed the existence of significant differences between the two groups ($t_{(1,164)} = -2.143$, $p < 0.034$; $d = 0.338$), in the sense that older adults with meaningful plasticity (LP) experience a greater functional recovery at home (M = 22.50, SD = 15.55), in comparison to the group with no meaningful plasticity (M = 17.62, SD = 13.24).

Moreover, a mixed factorial ANOVA was carried out with registered AVLT-LP

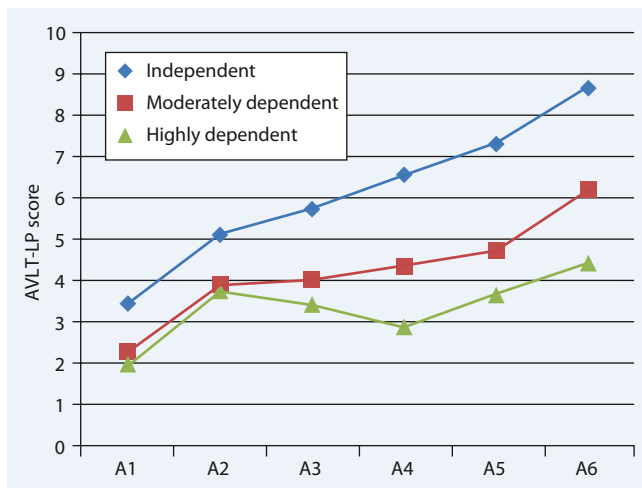


Fig. 1 ◀ Learning curve showing the scores in the six Auditory Verbal Learning Test of Learning Potential (AVLT-LP) trials (A1 to A6) for the three groups of participants classified as a function of Barthel Index (BI) score at home

scores. The three groups (independent, moderately dependent and highly dependent) defined by BI score at the home visit were used as the interparticipant factor and the six AVLT-LP trials as the intraparticipant variable.

The results of this analysis showed a significant intrasubject effect: $F_{(2,160)}=53.875$, $p<0.0001$, $\eta^2=0.252$, as well as an interaction between the two factors of $F_{(1,160)}=12.540$, $p<0.0001$,

$$\eta_p^2 = 0.136$$

There was also a significant effect on the interparticipant factor $F_{(2,160)}=15.328$, $p<0.0001$,

$$\eta_p^2 = 0.161.$$

As shown in **Fig. 1**, the participants who are dependent in the follow-up assessment have a fairly flat learning curve compared to the independent participants. In five of the six AVLT-LP trials, the analysis of the interaction showed a significant difference between the independent patients and the other two groups (between which there were no significant differences). Therefore, beginning from a rather similar situation in the first trial (A1), the distances between the groups become progressively wider **Fig. 1**. Specifically, post-hoc tests show no significant differences for A1, while there are significant differences for A2: $F_{(2,159)}=3.55$, $p<0.031$; A3: $F_{(2,159)}=3.114$, $p<0.047$; A4: $F_{(2,159)}=3.88$, $p<0.023$; A5: $F_{(2,159)}=4.44$, $p<0.013$ and A6: $F_{(2,159)}=3.52$, $p<0.023$, i.e.

after the training, with gains. These data reveal a significant difference in cognitive plasticity (LP) between those participants that managed to become independent after 3 months of recovery and those that did not.

Finally, an ANCOVA was carried out with the repeated measures of BI and the Lawton Index (upon hospitalization and later at home), taking into account the participants' LP status (low/high) and using gender as a covariate in order to control the influence of this variable. The results of these analyses showed gender differences in both measures ($F_{(1,159)}=4.79$, $p<0.03$,

$$\eta_p^2 = 0.029$$

in BI and $F_{(1,159)}=8.80$, $p<0.003$,

$$\eta_p^2 = 0.05$$

in Lawton Index), whereas no significant effect of interactions in which the covariate was engaged was observed ($F_{(1,59)}=0.065$, $p<0.80$ for the BI and $F_{(1,159)}=1.35$, $p<0.25$ in the case of the Lawton Index). Moreover, these analyses show significant differences between the assessment conducted upon hospitalization and at home, both in terms of the ADL dependency score on measured by the BI, $F_{(1,159)}=38.46$, $p<0.000$,

$$\eta_p^2 = 0.20$$

and in terms of the IADL dependency score measured by the Lawton Index, $F_{(1,159)}=7.52$, $p<0.007$,

$$\eta_p^2 = 0.04$$

for the entire group of participants, with scores in both tests indicative of greater independence at home.

As shown in **Tab. 2** and **Tab. 3**, when these differences in scores on the two tests are related to the AVLT-LP score gain, the differences between scores upon hospitalization and at home continue to be significant in the case of the BI, but lose significance in the case of the Lawton Index for subjects in the high LP group. This indicates that, although participants as a whole are much more independent in terms of basic ADL and IADL 3 months after surgery, the differences that relate to their high or low LP status are those associated with basic ADL (BI) and not with IADL (Lawton Index).

Discussion

We designed a study to analyze the extent to which cognitive plasticity relates to the functional recovery of older adults who were hospitalized for hip fractures and subsequently underwent surgery. Our hypothesis was that cognitive plasticity would be significantly related to the functional recovery of older adults, both at the time of hospital discharge and in the mid-term (3 months after surgery).

Our results allow us to draw the following conclusions:

- Firstly, although there was no significant relationship between plasticity status (assessed by the AVLT-LP) and degree of dependency (BI) in older adults with bone fractures at the time of hospital admittance, a relationship does appear 3 months after release from hospital, at which point almost all subjects who continue to have dependent status belong to the low LP group. Subjects classified as having high LP according to the AVTL-LP gain score show the most functional recovery.
- Secondly, we verified that there are significant differences between the three groups of older adults (grouped

as a function of their level of dependency at home), in terms of the learning curve constructed from the AVLT-LP scores. The independent adults show a greater capacity for verbal learning in a memory task, since they showed the greatest improvement in execution of the test after the training phase, thus producing gain scores (indicative of cognitive plasticity) that were significantly higher than those of dependent participants.

Thirdly, the results show that, for the entire group of participants, scores on the dependency scales indicate significant improvement in levels of independence at home, both for basic ADL and IADL. Accordingly, we observe that most of the participants have significantly increased independence 3 months after their surgery, an improvement that interacts with the gain or LP score on the AVLT-LP test. Results also show that the basic ADL (BI) scores are significantly associated with cognitive plasticity status. This result is in line with previous studies on the relationship between plasticity and independence in daily life [37, 38]. The relationship between plasticity and IADL (Lawton Index) is not significant.

These results demonstrate that a large majority of older adults recover their level of independence a few months after hospital release, even if this applies to basic ADL to a greater extent than to IADL. Nonetheless, one group of participants continues to show slight or substantial levels of dependency. Results from this study show that cognitive plasticity, understood to be capacity for learning as measured on a verbal memory task, is one variable that relates to the recovery of older adults after surgery: low LP is associated with greater dependency. This result is particularly relevant, firstly for its novelty—this is the first study analyzing the relationship between this variable and the functional recovery of older adults with bone fractures—and secondly, because it seems to indicate that the capacity for learning is related to how old people cope with a dependency situation and can help them to overcome it in a short time. Older adults

with a high LP are able to become independent again, particularly in terms of control over basic ADL, a certain time after the fracture and surgery. Moreover, as other studies have shown that the cognitive plasticity variable is not only seen in association with the cognitive status of elderly people [30, 33, 34, 55], but is also associated with their functional activity and quality of life [37, 38]. We also consider these results to be valuable in terms of prognosis and prevention, since they could help to avoid a serious impact on the patient's activity level, brought on by a hip fracture [12, 13]. It seems very relevant to the field of nursing and to the initial interventions to take into account the cognitive plasticity of the patient—his/her potential to recover—in order to achieve full functional recovery.

We would propose that older adults who initially obtain low scores on techniques that assess cognitive plasticity should be included in nursing intervention programs designed to increase their level of independence, rather than just simply waiting to see how well they recover on their own. As we have seen, such unaided recovery is likely to be less for low LP elderly patients than for those who show high cognitive plasticity when assessed.

As for the limitations of this study, we note that the study was performed in a single hospital in the south of Spain and the results should be replicated in other hospitals with other samples. In this regard, one characteristic of the older adults in this geographic area is their low level of education, which may be a moderating variable of interest.

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Compliance with ethical guidelines

Conflict of interest. M.J. Calero-García, M.D. Calero, E. Navarro and A.R. Ortega state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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