Prospective memory in patients with relapsing remitting Multiple Sclerosis*

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Resumen

La *Memoria Prospectiva* (MP) es un conjunto de habilidades cognitivas que permite recordar y realizar acciones planeadas o intenciones demoradas. El objetivo de este estudio fue investigar la MP en pacientes con *Esclerosis Múltiple Recaídas y Remisiones* (EMRR) con dos pruebas experimentales que evalúan distintos aspectos de la MP. Se evaluaron 36 pacientes con EMRR y un grupo control de 35 voluntarios sanos (GC), apareados por edad y escolaridad. Se administró una batería de tests neuropsicológicos que incluye dos técnicas que evalúan la MP: El Cóndor y el Test de Memoria Prospectiva de Tareas Múltiples (MTPM). Los pacientes obtuvieron un puntaje más bajo que el GC (en puntaje total de El Cóndor, $p = .007$, $d = 0.7$). En el MTPM, el GC obtuvo significativamente más puntos en la Fase de Formación de la intención ($p = .027$, $d = .5$). El 63% de los pacientes versus el 88.5% del GC, autoiniciaron la intención ($p = .014$). Los pacientes que obtuvieron mejor puntaje en Formación, autoiniciaron más la acción proyectada ($p = .012$). La educación, la duración de la enfermedad y la depresión correlacionaron leve y significativamente con el Cóndor y el MTPM. La discapacidad física se relacionó sólo con la capacidad de autoiniciar del MTPM. Se concluye que la MP parece estar afectada negativamente en pacientes con EMRR. Se encontró un deterioro de la planificación y la autoiniciación de la intención. La autoniciación fue influenciada por la calidad de la planificación. Los resultados destacan la necesidad de evaluar objetivamente la MP en pacientes con EMRR para poder detectar cualquier alteración en las etapas iniciales de la enfermedad y comenzar una rehabilitación apropiada.

Palabras clave: Memoria prospectiva; Esclerosis múltiple; Recaídas y remisiones; Aprendizaje.

Abstract

Prospective Memory (PM) is a set of cognitive abilities that allow us to remember to perform planned actions or delayed intentions. It requires the recall of the content of the planned task in the form of an intention to be able to execute it at the appropriate moment. Previous studies have yielded conflicting results as some show that MS patients have difficulty in remembering the content of intentions and others in the process of self-initiation of delayed intentions. Moreover, the relationship between PM and clinical variables also remains unclear. The aim of this study was to investigate PM in *Relapsing-Remitting Multiple Sclerosis* (RRMS) with two experimental tests that evaluate different aspects of the MP. Another aim of the current study was to analyse the relationship between PM and demographic variables and clinical variables. 36 outpatients with a diagnosis of RRMS attending to two centers specialized in multiple sclerosis clinics, were recruited. Thirty five healthy volunteers formed the contrast group (CG), matched for age, gender and education with the MS patients. A neuropsychological test battery that included two techniques for measuring PM was administered. The Condor Test consists of reading a text whilst simultaneously executing many actions. In the Multitask Prospective Memory (MTPM), the participant must remember to initiate a complex intention, which was previously planned. The test yields formation scores of the intention, initiation, plan retention capacity and finally two execution scores. A depression scale (Beck Depression Inventory, BDI-II) was administered and physical disability was revealed using the Expanded Disability Status Scale. In the RRMS group, the majority of patients (80.6%) had none or minimal signs of depression according to BDI-II classification criteria. Seventy five % of patients were in full- or half-time employment, 13.9% were unemployed or in occasional employment and 11.1% were house wives or retired on grounds of age. With respect to cognitive performance 47.2% of MS patients presented cognitive impairment. RRMS patients and the CG did not differ significantly on age and years of formal education. Groups showed no significant differences in distribution of Gender. Patients scored significantly lower than the CG on the Condor's total score, $p = .007$, $d = .7$. On the MTPM, the CG obtained significantly more points for intention formation than patients, $p = .027$, $d = .5$. Sixty-three percent of patients versus 88.5% of the CG self-initiated the intention, $p = .014$. Patients who obtained a higher score on Formation, self-initiated more often, $p = .012$. Education, disease progression and depression measure with the Beck Depression Inventory, significantly and mildly correlated with the Condor and the MTPM. Physical disability was only associated with the intention planning phase of MTPM.

PM appears to be impaired in patients with RRMS. A deficit was found in planning and self-initiation of planned actions. Self-initiation was influenced by planning quality. Education, disease progression and depression were shown to influence recall and execution of future intentions. Physical disability was only associated with the intention planning phase. Some previous studies have not found a significant relationship between physical disability and cognitive measures. This study suggests that PM can be affected in patients with a low level of physical impairment. Results highlight the need for objective assessment of PM in RRMS patients to be able to detect any disorder in the initial stages of the disease and start appropriate rehabilitation. Amongst the limitations of this study, the observational, non-blind design must be acknowledged, as well as the small sample size. Also, the instruments used to assess PM are relatively new and studies of their psychometric properties are lacking. Nevertheless, the use of an instrument like The Condor is notable, given that it was developed for local population.

Key words: Relapsing remitting multiple sclerosis; Learning and memory; Prospective memory; Cóndor Test; Multitask prospective memory.

Introduction

Prospective Memory (PM) can be defined as a set of processes and abilities that allow us to remember to perform intentions (Brandimonte, Einstein, & McDaniel, 1996). It re-

quires the recall of the content of the planned task in the form of an intention to be able to execute it at the appropriate moment (Ellis & Kvavilashvili, 2000; Smith, Della-Sala, Logie, & Maylor, 2000).

Electro-physiological studies (West & Krompinger, 2005) and correlational studies (Carlesimo, Casadio, & Caltagirone, 2004) support a distinction between future memory and memory that permits the recall of past events, or Retrospective Memory (RM). Also, factorial studies have demonstrated the independence of the RM construct (Gupta et al., 2010; Salthouse, Berish, & Siedlecki, 2004). Cognitive Psychology requires documented cases of double dissociation as evidence for the independence of cognitive processes. According to Burgess and Shallice (1997) only a simple dissociation is possible in this case, with RM being intact and PM impaired, because PM draws on an aspect of RM, during information retrieval. In this sense, RM is a pre-requisite of PM but not viceversa (Kliegel, Martin, Mc Daniel, & Einstein, 2002).

In research paradigms, PM and RM are differentiated. On tasks of RM, attention is explicitly directed by the examiner towards retrieval of previously stored information. In contrast, on tasks of PM, the participant needs to redirect his or her attention from the background task, the concurrent activity, to the previously formed intention without help from the examiner (Graf & Uttl, 2001).

PM is known to deteriorate in multiple neurological pathologies, such as craneoencephalic trauma and dementias (Kliegel, Jäger, Altgassen, & Shum, 2008). Clinical neuropsychological assessment of this ability is needed because of the impact the impairment has on the daily life of patients (Schmitter-Edgcombe & Wright, 2004) and their caregivers (Smith et al., 2000). In patients with HIV (Woods et al., 2011), and Multiple Sclerosis (MS) (Honan, Brown, & Batchelor, 2015), PM has been shown to be a predictor of unemployment and work difficulties.

In Argentina, a prevalence of 43.2% has been found for cognitive deterioration (CD) in patients with MS, in the RECONEM study (Cáceres, Vanotti, Rao, & the RECONEM Workgroup, 2011). CD has been linked with unemployment (Strober et al., 2012) and the completion of activities of daily living (Kalmar, Gaudino, Moore, Halper, & Deluca, 2008). Few previous studies have analysed the recall of delayed intentions in patients with MS. Bravin, Kinsella, Ong, & Vowels (2000) found that self-initiation was unimpaired but the retrospective component of PM, which consists of recalling the content of the intention, was impaired. However, they used two single-intention tasks, which raise the possibility of a ceiling effect, where most people get the highest score on a test or with little difficulty. Rendell, Jensen, and Henry (2007), Rendell and collaborators (2012) and Kardiasmenos, Clawson, Wilken, and Wallin (2008) found significant differences between patients and controls on a measure of PM called *Virtual Week* (Rendell & Henry, 2009), in which examinee simulate going through the course of a day on a circuit that resembles a board game. Players roll a virtual die to move their token through a virtual day. Along the way, players have to remember to perform several prospective memory tasks, such as taking medication or taking their dinner out of the oven at appropriate times.With this test, the authors found impairment in the capacity to self-initiate the action as well as recalling what needed to be done. However, in this paradigm the intentions were purely verbal, in that they required a verbal response rather than actions that required movements. Previous studies, have shown that there is an advantage in the recall of to-be enacted intentions than intentions for later verbal report (Eschen et al., 2007, Freeman & Ellis, 2003). Other research could relate MP performance in MS patients with deficits in executive functions (Dagenais et al., 2016) as well as the presence of pain (Miller et al., 2014). Overall, these studies provide conflicting results. Moreover, the relationship between PM and clinical variables also remains nuclear.

The aims of the study were to analyse the performance of patients with MS on PM and their relationship with clinical variables. The results will reveal the state and characteristics of PM in MS, which is necessary for adequate treatment of these patients in

clinical neuropsychological practice. Two experimental test were administered MP which aim to evaluate different aspects of MP. One of them, the Condor has been developed in Argentina, it consists in performing a number of different actions during the reading of a text, and was implemented in patients with benign forgetfulness (Taussik, 2002). The other, the Multitask Prospective Memory, was used in studies with patients with Parkinson's disease (Kliegel, Phillips, Lemke, & Kopp, 2005), head injury (Kliegel, Eschen, & Thöne-Otto, 2004) and old adults (Kliegel, Martin, Mc Daniel, Einstein, & Moor, 2007). From these tests, there are still no normative values or psychometric parameters reported. In Argentina, there are no tests of MP who have this data.

Method

Participants

Descriptive case-control correlational design. Participated in the study 36 patients diagnosed with Relapsing-Remitting MS (RRMS) and receiving outpatient care in two specialized centres where they had monitoring. All patients were under disease modifying treatment.

Inclusion criteria: confirmed diagnosis of RRMS (Polman et al., 2011), aged between 18 and 65 years, with more than 7 years of formal education.

The exclusion criterias were history of cranial trauma, alcoholism or psychotropic substance abuse, actively experiencing an episode of relapse and / or receiving treatment with corticosteroids within 4 weeks prior to the assessment, and presentation of psychiatric disorders and / or comorbidities that could cause cognitive decline.

Thirty five healthy volunteers formed the contrast group (CG), matched for age and education with the MS patients.

Informed consent was obtained from each participant. Both the research project and the informed consent format received ethical approval from the institutional Ethical Committee.

Administration

Two sheets of paper are placed in front of the participant, one with the reading text and the other with a list of instructions. The participant is told that as he or she reads the text, directives will be encountered telling him or her to read instructions from the list on the other sheet of paper to be found on his or her right. The participant is requested to memorise each instruction that he or she reads and continue reading the text, in such a way as his or her attention alternates between reading the text, reading the instructions and executing intended actions at the appropriate moment.

Participants obtain a Total Correct Score (Max. = 21) constituting the number of intended actions completed correctly at the appropriate moment. Examples of intentions are: “In exactly 5 minutes write your birthday on the story sheet”. “When you read the words ‘protected areas’ write your name on the top of the sheet”.

Instruments and procedures

Two experimental tests were administered to all participants, with the aim of assessing PM. The Condor Test was developed in Argentina (Taussik, 2002) and consists of reading a text whilst simultaneously executing planned actions.

- *Multitask Prospective Memory* (*MTPM* - Kliegel, McDaniel, & Einstein, 2000)

The instructions were presented in written form and are read aloud to the participant by the examiner. They explain that at the appropriate moment (after the participant gives his or her date of birth in answer to this question on a questionnaire that is administered later in the session) the participant should start to solve six tasks. The tasks are divided into two versions, each containing three types of task: word finding, mathematical problem resolution and figure naming. Once the tasks

have been explain ed, the rules of completion are described to the participant. When the participant has understood and memorised these rules, he or she is told that the available time (6 minutes) is not sufficient to complete all six tasks but that he or she should at least begin all of them. At this point, the participant is encouraged to form a plan that follows the rules and will allow him or her to obtain the maximum possible score. After 15 minutes the participant is asked to repeat the formulated plan and another 15 minutes later the personal information questionnaire is administered. The participant is not advised that the moment to self-initiate the tasks has arrived. The scores yielded are:

- Intention Formation, which is obtained by analysing various aspects of the participant's oral productions. Two professionals scored the transcriptions, one of whom was blind to diagnostic status.
- Percentage of Retention: which rates the recall of the plan.
- Initiation: whether or not the participant self-initiates the action after the appropriate event.

Execution includes two sub-scores:

- Percentage of Fidelity, which is the proportion of the planned tasks that were actually started, and
- Switching, which is the total number of times that the participant changed from one task to another.

- *The Brief Repeatable Battery - Neuropsychological Test* (*BRBN* - Rao, Leo, Bernardin, & Unverzagt, 1991; Cáceres et al., 2011)*:* this test was administered in order to assess cognitive performance of patients with RRMS.

- *The Beck Depression Inventory-II* (*BDI-II* - Beck, Steer, & Brown, 1996): was also administered.

- *Expanded Disability Status Scale* (*EDSS* - Kurtzke, 1983): was administered in order to study the physical disability.

Statistical analysis

The Chi-square Test, Student's *t*-test and Mann Whitney *U* Test was used to reveal differences between groups Spearman's Rho correlations were calculated to test for associations between the variables. Parametric tests were used when data showed normal distribution and non parametric tests were used when distribution was not normal.

A significance level of .05 was established. A One-way ANCOVA was conducted to determine differences on the PM test between controls and patients controlling for education.

Results

Demographic data

The RRMS and CG groups showed no significant differences in distribution of Gender [$\chi^2(1, N = 72) = 1.48$, $p = .165$], Age [$t(70) = -.99$, $p = .323$] or Education, [$t(70) = .182$, $p = .856$]. Descriptive data for the clinical variables are shown in Table 1. In the RRMS group, the majority of patients (80.6%) had none or minimal signs of depression according to BDI-II classification criteria (Beck et al., 1996). 75% of patients were in full- or half-time employment, 13.9% were unemployed or in occasional employment and 11.1% were house wives or retired on grounds of age (see Table 1).

With respect to cognitive performance 47.2% of MS patients presented cognitive impairment (2 domains under the 5th percentile of normative data of the BRBN).

Prospective Memory

On the Condor the RRMS group was found to perform significantly poorly than the CG in terms of Total Correct Score ($p = .007$).

On the MTPM, a significant difference was found between groups for Intention formation, $p = .027$, with the CG scoring higher than the RRMS group. For Initiation scores, 63.8% of patients in the RRMS group versus 88.5% of participants in the CG independently self-

initiated the act of looking for the materials to solve the 6 tasks [$\chi^2(1, N = 71) = 6.23$, $p = .014$]. Retention, Switching, and Fidelity revealed no significant differences between groups. Data is shown in Table 2.

To investigate the relationship between Intention Formation and Initiation patients with RRMS who correctly self-initiated and those who did not ,were compared. Those who self-initiated the action scored highly on Formation ($M = 10.91$, $DE = 5.57$) than those who did not self-initiate ($M = 5.77$, $DE = 5.61$), [$t(34) = 2.65$, $p = .012$]. Also, there was a significant positive correlation between Formation and Switching for the MS Group ($r = .44$, $p = .007$).

Relationship between PM and clinical and demographic variables

In the RRMS Group, the Condor Test did not correlate with age or EDSS or BDI-II, but correlated significantly with education and disease duration. The Formation score of the MTPM correlated significantly with education and BDI-II. The Switching score correlated with education, EDSS, disease duration and BDI-II. Data is shown in Table 3.

Since education can be a confounder variable, a One-way ANCOVA was conducted to determine differences on the Condor Test between controls and patients controlling for education. There was a significant effect of diagnostic status on the Condor after controlling for education [$F(1, 71) = 11.73$, $p = .001$, $\eta = .14$]. Same was found on the Formation Intention of MTPM [$F(1, 71) = 6.06$, $p = .016$, $\eta = .08$].

Discussion

The aim of this study was to investigate the performance of patients with a diagnosis of RRMS on PM using two different paradigms. Results indicate that the patients remembered fewer delayed intentions in the context of a multi-intentional task (The Condor Test) where they have to simultaneously retain multiple instructions in mind whilst completing a task of moderate complexity like reading a text. These findings are not consistent with those of Bravin and collaborators (2000), who found no initiation differences on a PM task, although their results did not assess the same complexity of PM as was assessed in the present study, in that they administered two single-intention tasks, each directed at a simply executed action.This inconsistency may indicate that patients with RRMS may have deficits in multi-intentional PM tasks, preserving the memory of isolated intentions.

On the other hand, Rendell and Henry (2009) and Kardiasmenos and collaborators (2008) found that PM was impaired when measured using the multi-intentional task the Virtual Week. However, this task requires only verbal responses, so the current study extends the previous findings in that the processing of planned actions, involving motor representation, differs from that required for verbal responses.

The Condor Test does not provide specific scores for planning and execution of a future intention. In contrast, the MTPM requires the participant to form a plan of execution, marking the fact that in daily life activity planning is continually required and detailed programming diminishes the possibility of prospective forgeting. This characteristic enriches the assessment of PM. This paradigm has been used with patients with Parkinson's disease (Kliegel, Altgassen, Hering, & Rose, 2011), craneoencephalic trauma (Kliegel et al., 2004), ADHD (Kliegel, Ropeter, & McKinlay, 2006) and normal aging (Kliegel, McDaniel, & Einstein, 2000). In the current study, the MS group formed less detailed plans than the CG. However, patients did remember the plan after a period of delay and they demonstrated no difficulties during the execution phase. Further, a smaller proportion of patients self-initiated the action at the appropriate time than did the healthy controls, and those patients who obtained a higher score on Formation self-initiated more often. This indicates that patients with MS can have a deficit in the formation of specific plans and self-initiation of intentions. Also, poor planning of intentions can affect the recall and execution of the corresponding action.

Overall, the results of this study provide evidence for the presence of disordered PM in patients with MS. This highlights the need for objective assessment of PM in such patients to be able to detect any disorder in its initial stages and start appropriate rehabilitation. Various compensatory strategies have been studied (Fish et al., 2007; Fleming, Shum, Strong, & Lightbody, 2005) from which patients with MS may benefit.

Another aim of the current study was to analyse the relationship between PM and demographic variables and clinical variables. Education, disease progression and depression were shown to influence recall and execution of future intentions. Physical disability was only associated with the intention planning phase. Some previous studies have not found a significant relationship between physical disability and cognitive measures (Smestad, Sandvik, Landrø, & Celius, 2010). This study suggests that PM can be affected in patients with a low level of physical impairment.

Amongst the limitations of this study, the observational, non-blind design must be acknowledged, as well as the small sample size. Also, the instruments used to assess PM are relatively new and studies of their psychometric properties are lacking. Nevertheless, the use of an instrument like The Condor is notable, given that it was developed in Argentina. Importing cognitive instruments from other cultures carries the risk of misinterpreting results that it generates (Ardila, 2005).

In the future it would be interesting to assess the changes in PM that are produced during disease progression and how this relates to the quality of life, employment status and activities of daily living of patients with MS. Also, variables such as fatigue and anxiety could have an impact on MP performance, so in the future it would be necessary to include in the analysis. Finally, a question that could not be responded here is if PM differences between controls and patients may be due to depression, since the variable has proven to significantly correlate to PM Test.

TABLE 1
PARTICIPANTS' DEMOGRAPHIC AND CLINICAL DATA

		MS *n* = 36	CG *n* = 35
Gender	Female	20	25
Age	*M (SD)* Range	40.19 (11.2) 18 / 62	43.03 (12.75) 21 / 61
Education in years	*M (SD)* Range	12.28 (2.77) 7 / 20	12.14 (3.44) 7 / 18
BDI-II	*M (SD)*	8.94 (6.19)	6,02 (5,13)
Disease duration in years	*M (SD)*	9.53 (7.07)	
Age at onset	*M (SD)*	30.66 (10.6)	
EDSS	Median (Range) Mode *M (SD)*	2 (0 - 7.5) 1 3.11 (2.32)	

Note:
CG: Contrast group
MS: Multiple Sclerosis
BDI-II: Beck Depression Inventory
EDSS: Expanded Disability Status Scale

TABLE 2
PROSPECTIVE MEMORY RESULTS

Neuropsychological Battery Test	MS *n* = 36 *M (SD)*	CG *n* = 35 *M (SD)*	*p*	*d*	*U*
The Condor Test					
Total correct score	13.11 (5.46)	16.37 (2.53)	.7	.7	399
MTPM					
Formation	9.06 (6.05)	12.03 (5.44)	.026	.5	437
Retention	88.38 (29.57)	96.05 (8.86)	1	.3	561
Switching	3.28 (1.78)	3.28 (1.78)	.223	0	526
Fidelity	73.51 (32.47)	79.08 (23.72)	.693	.1	436

TABLE 3
CORRELATIONS BETWEEN MP AND DEMOGRAPHIC AND CLINICAL VARIABLES

	Age	Education	EDSS	Disease duration	BDI-II
The Condor Test					
Total correct	-.17	**-.41***	-.32	**-.34***	-.20
MTPM					
Formation	-.16	**.42****	-.25	-.29	**-.42***
Formation	.17	.07	.01	-.01	-.18
Fidelity	-.10	.26	-.27	-.10	-.38
Switching	-.10	**.50****	**-.41***	**-.35***	**-.61****

*$p < .05$
** $p < .01$

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