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MASTER´S THESIS

Organizational strategies in verbal fluency as a potential screening tool for Cognitive Impairment in individuals diagnosed with Multiple Sclerosis

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With gratitude,

DECLARATION OF ORIGINALITY

The undersigned DECLARES to be the author of the Master´s Thesis presented as the culmination of his graduate studies at the Faculty of Psychology of the University of Granada and the University of Padova. The thesis will be evaluated by the corresponding Evaluation Committee, and the undersigned wishes to state the following:

1. The work is original and unpublished and is the product of the author´s intellectual contribution, under the guidance of one or more professors from his Faculty.

2. The figures, tables and illustrations accompanying the work faithfully represent the reported facts and have not been digitally altered.

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To certify the aforementioned, this declaration is signed in Granada, June 28th, 2024.

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ABSTRACT

Multiple sclerosis (MS) is the most common chronic disease of the central nervous system and one of the most frequent causes of non-traumatic neurological disability in young adults. Between 50-65% of patients with MS will develop cognitive impairment (CI), with verbal fluency (VF) tasks being one of the most sensitive measures for its detection. It is estimated that 40-64% of the population shows impaired performance. However, only a limited number of studies have investigated the underlying cognitive processes of these tasks, considering variables such as organisational strategies (switching and clustering) and execution time. The present study aims to analyse the efficacy of phonological verbal fluency (pVF) and semantic verbal fluency (sVF) tasks as a screening tool for CI in MS. It is an exploratory case-control study with 16 patients diagnosed with MS, 5 with CI and 11 without CI, following the STROBE checklist. The results reveal differences between groups for both VF tasks, especially in those with semantic restriction, in total word recall and in the use of organisational strategies. Additionally, greater sensitivity to CI is suggested during the first time interval (0-30sec) independently of the group. Process analysis revealed the relationship between total words evoked of pVF with language, and sVF with language and EF. In both tasks, the first time interval correlated with memory, language and EF. In organisational strategies of sVF, total clusters were related to EF, total switchings to attention, and clustering during the first time interval to memory and EF. No cognitive process predicted strategies in pVF.

Keywords: Verbal fluency, clustering, switching, Multiple Sclerosis, Cognitive Impairment, Bayesian approach.

1. INTRODUCTION

Multiple sclerosis (MS) is the most common chronic disease of the central nervous system, being one of the most frequent causes of non-traumatic neurological disability in young adults (Ghiasian et al., 2024; Piacentini et al., 2023). It is an autoimmune inflammatory pathology, attributed to the deterioration of the neuronal tissue membrane, myelin and oligodendrocytes (Jellinger, 2024; Tafti et al., 2024). In other words, this condition is characterised by transient or permanent demyelination, axonal damage, and neurodegeneration of grey and white matter cells in the brain and spinal cord (Cavaco et al., 2022).

The random nature of the lesions indicates that the broader tracts of white matter are more often the target of the disease, particularly in paraventricular, juxtacortical and infratentorial frontal regions. No other condition produces irregular or asymmetric lesions with such a degree of selectivity in the destruction of neuronal tissue, making their identification possible through neuroimaging techniques, specifically magnetic resonance imaging (MRI) (Filippi et al., 2018).

Taking the data provided by the Spanish Association of Multiple Sclerosis and the International Federation of Multiple Sclerosis as a reference, approximately 2.9 million people worldwide had MS in 2024 (Multiple Sclerosis International Federation, n.d.). In Spain, the estimated prevalence is 120 cases per 100,000 inhabitants, approximately 55,000 diagnosed cases in our country (García López et al., 2022; Multiple Sclerosis International Federation, n.d.). The most frequent age of diagnosis is between 20 and 40 years old, although onset may be earlier, being the main cause of disability in young people (García López et al., 2022; Habbestad et al., 2024).

1.1. Aetiology and prognosis

Its aetiology is unknown (Tafti et al., 2024). Epidemiological studies suggest a multifactorial model where combined genetic and environmental components increase the risk of developing the disease (Tafti et al., 2024).

The genetic predisposition highlights miscegenation as a crucial factor in the spread and occurrence of MS across different continents (Villa-Rodriguez et al., 2017). The prevalence of MS in family history is 13% for all phenotypes. Various studies have described the relationship of this disease with different alleles (i.e., phenotypic alternatives of a gene) that appear to be associated with milder forms or benign manifestations of MS. Among the identified alleles, DRB1*1501 stands out (Tafti et al., 2024). Additionally, these manifestations seem to be associated with gender, as MS is up to three times more likely in women than in men (Tafti et al., 2024; Villa-Rodriguez et al., 2017). Regarding environmental theories, there is higher presence of MS as we move away from the equator (the highest prevalence rates are observed in

Caucasians, mostly from Scandinavian countries, while the lowest are observed in Asians) (Tafti et al., 2024).

The evolution of the disease is unpredictable. There is significant variability in the manifestations of MS, reflected in affected individuals. In some cases patients suffer 2 or 3 relapses without developing any degree of disability (Cavaco et al., 2022). Conversely, there are other examples where a single flare-up significantly affects daily activities, and in extreme cases, it can lead to death within a few months (Benedict et al., 2020; Cavaco et al., 2022; Meca-Lallana et al., 2021). Notably, in 2016, around 70% of MS patients were diagnosed during early adulthood, typically at the onset of their working lives. Of these, 43% would have left their jobs in subsequent years, increasing to 70% after 10 years with the disease (Vázquez-Marrufo et al., 2018). The presence of cognitive impairment (CI) at the time of MS diagnosis is considered one of the worst prognostic markers of the disease (Meca-Lallana et al., 2021).

Once the prognostic variability in individuals with MS is known, how is the presence or absence of this pathology currently determined?

The existing classification system is based on the McDonald diagnostic criteria, first introduced in 2001 (McDonald et al., 2001) and later modified in 2005 (Polman et al., 2005) due to the incorporation of evidence from MRI (Hawkes & Giovannoni, 2010) (See **Appendix 1**). Three different categories are established: 1) Definite MS: all criteria are met and there is no better explanation for the clinical presentation, 2) Possible MS: the criteria are not fully met, but the presentation is suspicious, and 3) Not MS: another diagnosis better explains the clinical manifestations (Villa-Rodriguez et al., 2017). However, the mentioned diagnostic system does not allow us to observe the prognostic variability that normally characterizes individuals with the disease, as it makes it difficult to determine their most frequent symptomatic symptoms.

1.2. Clinical manifestations

The most common symptoms in MS are limb weakness or numbness, vision loss, diplopia, weakness, ataxia, nystagmus, anxiety, depression, and cognitive dysfunction (Tafti et al., 2024). About 25% of people with the disease start with optic neuritis due to demyelination of the optic nerve, which can cause blurred vision, eye pain, or even blindness (DiGiuseppe et al., 2018; Rosca & Simu, 2020). Regarding cognitive symptoms, it is notable that between 50-65% of patients will develop neuropsychological alterations (Kania et al., 2024; Meca-Lallana et al., 2021), with the degree of impairment varying among patients.

Considering the degree of disease progression and the relapse pattern experienced by patients, the classification of the phenotypic variants of MS has been created (current Lublin classification 2014) (Villa-Rodríguez et al., 2017). Two main forms are established: relapsing-remitting and progressive (Jellinger, 2024). The current classification is detailed in **Figure 1**.

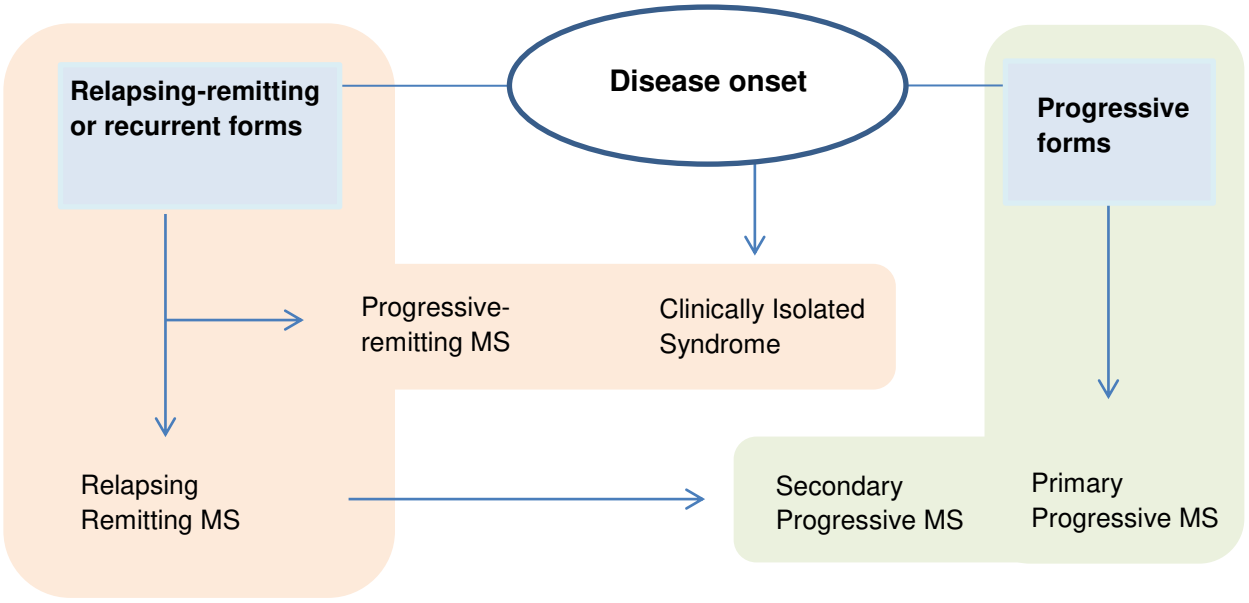

Figure 1.

Phenotypic manifestations of MS.

The most common manifestation is the relapsing-remitting form (RRMS), diagnosed in up to 85% of patients (Jellinger, 2024; Wu et al., 2024). It is characterized by acute episodes of neurological dysfunction, followed by periods of complete recovery. The disease course remains stable without progression of dysfunction between acute episodes (Wu et al., 2024). However, around 50% of diagnosed individuals will develop secondary progressive MS (SPMS) (**Figure 1**) after approximately 10 years from the diagnosis. The latter is characterized by a gradual worsening, more severe relapses, and a significant number of residual sequelae (Villa-Rodríguez et al., 2018). This progression can also be observed in patients who develop cognitive deficits at early ages (Rosca & Simu, 2020).

On the other hand, there is primary progressive MS (PPMS), affecting 15% of patients, and progressive-relapsing MS (PRMS), observed in 5% of them (Jellinger, 2024; Tafti et al., 2024). PPMS is characterized by the progression of neurological deficits from the onset of the disease without relapses, whereas PRMS involves gradual deterioration with occasional relapses (Tafti et al., 2024).

In addition, the relapsing-remitting or recurrent forms currently include the clinically isolated syndrome (CIS), according to various authors. CIS refers to cases where the affected person presents a single manifestation of symptoms with lesions visible on MRI and no relapses or disease progression (Dong et al., 2022; Tafti et al., 2024; Vázquez-Marrufo et al., 2018). It could be considered that this syndrome, rather than an independent diagnostic entity from the described phenotypic forms, refers to

subclinical phases that may or may not develop into the forms described in the current classification (Cavaco et al., 2022).

1.3. Neuropsychological alterations

Until recently, cognitive functioning and its impairments received little attention. It was in the 1990s when Jean Martin Charcot made one of the first approaches to cognitive function in MS patients (Lugosi et al., 2024; Piacentini et al., 2023). In 1929, the first research on the prevalence of CI in MS was published by Ombredane (Villa-Rodríguez et al., 2017). The study evaluated various cognitive domains, including memory, reasoning, comprehension, arithmetics, and learning, aiming to obtain data on the prevalence of impairment in this population. The authors concluded that 76% of the assessed patients showed cognitive dysfunction, known at that time as 'intellectual deterioration' (Villa-Rodríguez et al., 2017).

Currently, CI is considered one of the main determinants of quality of life in MS patients (Jellinger, 2024). The increased interest in studying CI provides several advantages: knowledge of the premorbid conditions of the affected patients, information on potential cognitive changes during the course of the disease and prognostic relevant parameters that can guide the selection of treatments capable of modifying the course of the disease (Meca-Lallana et al., 2021). These efforts provide relevant data to patients and their families regarding cognitive status, aiming to facilitate personal, social and family adaptation. Additionally, the cognitive approach allows for early and individualized work planning to each person´s needs (Meca-Lallana et al., 2021).

Cognitive performance is typically classified into two categories: impaired or preserved (Mistri et al., 2024). Hancock et al. (2023) established the presence of an impaired cognitive domain when at least two related test scores are below 1.5 standard deviations from their normative group. As for the diagnosis of mild or major CI, the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are used, emphazising the presence of impairment in at least two cognitive domains and additional impact on daily living activities in cases of moderate impairment (Mistri et al., 2024). Similarly, Fischer et al. (2014) suggested that CI in MS can be defined as 1.5 or 2 standard deviations below the normative group in at least 20-30% of the tests administered, and performance below 1.5 or 2 standard deviations in two cognitive domains (Meca-Lallana et al., 2021). The domains to be assessed are: learning and memory, complex attention, EF, language, perceptual-motor function and social cognition (Mistri et al., 2024).

The study of cognitive alterations in people with MS has significantly advanced our understanding of the disease and the development of therapeutic approaches. However, is there a specific neuropsychological profile associated with individuals who have this pathology?

Although the neuropsychological profile of patients with MS varies among individuals, certain alterations are more commonly observed (Piacentini et al., 2023).

VF and verbal memory deficits are prominent in the early stages of the disease (Mistri et al., 2024). These alterations are followed by processing speed (PS), complex attention systems, concentration, and viuospatial skills (Kania et al., 2024; Mistri et al., 2024; Piacentini et al., 2023). The latter may reflect difficulties in planning and organization, related to the EF of frontal systems, occurring in 43-70% of individuals at both early and late disease stages (Lisak & Trkanjec, 2021; Meca-Lallana et al., 2021). Additionally, recent research has described additional deficits, including alterations in social cognition, moral judgments and decision-making (Piacentini et al., 2023).

Language skills, semantic memory and attentional span are typically preserved in individuals with MS (Mistri et al., 2024). It is unlikely to encounter complications such as agnosia, apraxia or aphasia (Benedict et al., 2020; Neuhaus et al., 2018; Villa-Rodríguez et al., 2017).

Due to the diverse patterns of neuropsychological impairment in affected individuals, the way these deficits interfere with their daily lives also varies. Several factors influence this variability in cognitive symptoms: lesion location, severity of damage, disease duration, and the individual´s educational level (Vázquez-Marrufo et al., 2018).

Additionally, considering the different clinical phenotypes that patients present (CIS, RRMS, SPMS, PPMS and PRMS) is essential, as they can lead to differences in the development of cognitive alterations (Jellinger, 2024; Rosca & Simu, 2020). Cognitive dysfunction occurs across all types of MS, affecting 20-25% of CIS patients, 30-35% of RRMS patients and 75% of those diagnosed with SPMS (Piacentini et al., 2023). A progressive cognitive decline is observed from CIS to RRMS, PPMS and SPMS (Jellinger, 2024). Specifically, dysexecutive syndromes are more predominant in progressive forms of MS (Meca-Lallana et al., 2021). Researchers such as Jellinger (2024), Rosca & Simu (2020), and Vazquez-Marrufo et al. (2018) conducted reviews of studies, identifying differences in the cognitive profiles among the main MS manifestations. **Table 1** provides details on the profiles concluded by these various studies.

Table 1.

Neuropsychological profiles of cognitive alterations regarding the clinical manifestation of MS

Phenotypic manifestations			
CIS	**Relapsing-Remitting**	**Progressives**	
	RRMS	**PPMS**	**SPMS**
PS	PS	PS	PS
Atention	Atention	Atention	

Memory (visuospatial, verbal episodic)	Working memory	Episodic memory	Verbal episodic memory
VF		VF	VF
			Visuoconstruction
EF	**EF**	EF	EF

Note. **PS**: Processing Speed; VF: Verbal fluency; **EF**: Executive Functions; **RRMS**: Relapsing-Remitting Multiple Sclerosis; **PPMS**: Primary Progressive Multiple Sclerosis; **SPMS**: Secondary Progressive Multiple Sclerosis; **EF**: Executive Functions; **CIS**: Clinically Isolated Syndrome

Although there are some similarities in the cognitive performance across different phenotypic manifestations of MS, such as deficits in PS and episodic memory, certain differences have also been established. Visuospatial memory deficits appear early and follow a slow progression, while deficits in memory and executive functions (EF) tend to emerge as the disease progresses (Rosca & Simu, 2020). Notably, the pattern of VF impairment is altered in both the CIS and progressive forms (see **Table 1**).

As observed, cognitive alterations can occur in all phenotypic manifestations of MS, characterized by significant variability among affected individuals. However, these findings reinforce the idea that neurocognitive deficits may serve as an initial manifestation of the disease (Benedict et al., 2020).

1.5. Neuropsychological assessment of cognitive alterations

Early detection of cognitive impairments in young individuals has become possible due to the development of specific, highly sensitive tests (Villa-Rodríguez et al., 2017).

Given the difficulty of detecting cognitive deficits through simple interviews or routine screening tests, a proper neuropsychological evaluation is essential (Meca-Lallana et al., 2021; Vázquez-Marrufo et al., 2018). This approach is widely recognized as a valid, cost-effective, and time-efficient technique complementary to neuroimaging methods (Corfield & Langdon, 2018). However, neuropsychologists have shifted away from using large cognitive batteries for MS patients, opting for more sensitive tests(Benedict et al., 2020). Early neuropsychological assessment in the disease has proven utility not only for identifying individuals with cognitive dysfunction but also for determining the expected course of the pathology, including its alterations and limitations (Rosca & Simu, 2020). Recommendations for neurocognitive follow-ups include positive screening test results or negative results accompanied by subjective cognitive complaints from both patients and their families (Meca-Lallana et al., 2021). Additionally, any negative impact on work and social life should be considered (Meca-Lallana et al., 2021).

Regarding assessment instruments, there are currently a limited number of scales with high sensitivity to MS-related cognitive decline (Corfield & Langdon, 2018). Elwick et al. (2021) conducted a systematic review of commonly used tests for cognitive evaluation in MS, analysing data from 1526 studies. These instruments largely align with the recommendations of Meca-Lallana et al. (2021) and the viability criteria established by Villa-Rodríguez et al. (2017) for MS. Below, the most frequently used tests in the field are detailed, grouped by the cognitive dimension they assess:

Table 2.

Classification of the most frequently used neuropsychological tests in MS according to the cognitive dimension they assess:

Cognitive domain	Neuropsychological tests
Memory	CVLT, forward and backward digit span and symbol digit test (WAIS)
Attention	Symbol digit and CPT, TMT A and B.
Executive Functioning	WCST, VF, STROOP
Processing speed	PASAT, SDMT
Visuoperception and visuoconstruction	Visual retention of Benton and ROCF

Note. CPT: Continuos Performance Test; **CVLT**: California Verbal Learning Test; **WCST**: Wisconsin Card Sorting Test; **VF**: Verbal fluency; **PASAT**: Paced Auditory Serial Addition Test; **SDMT**: Simbol Digit Modified Test; **TMT**: Trail Making Test; **ROCF**: Rey-Osterreich Complex Figure; **WAIS**: Weschler Adult Intelligent Scale.

1.5.1. Verbal fluency

VF is considered a fundamental language ability, involving the capacity to produce fluent speech (Lezak et al., 2004). Specifically assess the ability to generate lists of words within certain constraints, either semantic or phonological, within a specified time frame (Barois et al., 2021; Lezak et al., 2004).

Both phonological verbal fluency (pVF) and semantic verbal fluency (sVF) share a multifactorial nature, involving sustained attention, word selection, inhibition of competing words, working memory, language production, planning, response organization, monitoring, and PS (Barois et al., 2021; Pitteri et al., 2023). Especially, detailed studies have linked memory processes to sVF and EF to pVF(Delgado-Álvarez et al., 2021; Pitteri et al., 2023). Given that the most affected cognitive domains in MS are episodic memory and PS, it is expected that VF tasks would be of great interest for this population (Pitteri et al., 2023). Actually, a quantitative review of 35 studies by Henry & Beatty (2006) concluded that VF tasks are more sensitive to CI in MS than many other neuropsychological measures. Specifically, 40-64% of affected individuals show impairment in these tasks (Estrada-López et al., 2021). Even in early stages

before the appearance of neuropsychological deficits, VF has been associated with subjective complaints in MS patients (Matotek et al., 2001).

The VF test offers several advantages over other measures. It is a short and simple test, requiring no specialized equipment or training for professionals (Barois et al., 2021). Additionally, VF performance is minimally affected by motor and visual deficits, which are common symptoms in MS patients (Pitteri et al., 2023). The VF task remains reliable even in severe manifestations of the disease, demonstrating sensitivity and specificity of 80.6% and 97.2%, respectively, as an indicator of cerebral impairment (Barois et al., 2021). The necessary cognitive processes for efficient VF performance seem to reflect the skills involved in daily functioning(Messinis et al., 2013).

Regarding result analysis in VF tasks, the method of correction used can also impact interpretation. Traditionally, correction has been based on the number of correctly recalled words within the total task time (Pitteri et al., 2023). Recently, additional qualitative and quantitative analysis alternatives have emerged.

Based on the work of Thurstone & Thurstone (1962, as cited in Lezak et al., 2004), numerous versions of the VF test have been developed to assess the more executive aspects of behavior, allowing for analysis of how individuals organize their thoughts (Lezak et al., 2004). In this regard, one approach is the component analysis proposed by Troyer et al. (1997), which captures the organizational strategies employed by the individual during the task. Two types of VF strategies are described: clustering and switching. Clustering occurs when two or more consecutively recalled words share similar characteristics, such as phonological similarity (e.g., sharing the same initial sound) or semantic similarity (e.g., subcategories like domestic animals, birds). When a cluster is exhausted, the person must efficiently change to a new category, which is identified as a switch (Lezak et al., 2004; Troyer et al., 1997). Efficient performance largely depends on the organizational capacity of the output produced by the person evaluated (Lezak et al., 2004).

On the other hand, analyzing task performance during specific time intervals has been proposed. Crowe (1998) suggested analyzing performance every 15 seconds during the task, observing a reduction in word production over time. Similarly, Fernaeus & Almkvist (1998) conducted an analysis at two different time points, following their dynamic two-factor model. According to this model, the initial phase of VF execution (first 15/20 sec) involves lexical access and retrieval of frequently used words. This process operates semi-automatically with minimal cognitive effort due to high accessibility. Regarding the second factor of the model, the late execution phase (from 15/20 sec to 60 sec) requires more effort and the use of strategies to search for new words, as the accessible word group becomes exhausted (Pitteri et al., 2023). In other words, there is greater involvement of EF.

Regarding the predictors of performance in VF tasks, the emergence of organizational strategy analyses and the division into performance intervals makes it difficult to determine which cognitive processes are involved in pVF and sVF tasks (Delgado-Álvarez et al., 2021). Additionally, age, sex, education level, and ethnicity have shown to be influential variables (Estrada-López et al., 2021; Lezak et al., 2004).

Henry & Beatty (2006) and Messinis et al. (2013) include to this list the type of MS, disease duration, and Expanded Disability Status Scale (EDSS) scores.

With the aim of analysing the existing literature on VF in MS, with or without organizational strategy analysis, a search was conducted using PubMed and Web of Science. The search equation was “verbal fluency (title/abstract) AND multiple sclerosis (title/abstract),” without filter for publication years. From a total of 205 and 298 publications in PubMed and Web of Science, respectively, 11 experimental design articles were selected based on title and abstract reading. The inclusion criteria were MS patients, administration of pVF and sVF tasks in this population, and performance analysis in terms of correct word recall or organizational strategies. Below, I describe their characteristics in ascending order of publication:

Table 3.

Review of studies analyzing different VF variables in patients with MS.

Authors	Objective	Sample	Instruments	Variables	Results
(Altun et al., 2024)	To compare VF in RRMS HC	N= 48 (24 RRMS, 24 HC)	MMSE VF EDSS	Total CR Clusters mean Switchings	Total CR and switchings differences between groups.
(Pitteri et al., 2023)	Analyze the role of EF in VF due to the PS alterations in MS	N= 75 (43 patients with MS and 32 HC)	SDMT sVF (colors, animals y fruits) pVF (FAS)	Total words (0-15sec) Total words (15-60sec)	Globally, MS patients produce less words than HC in pVF but not in Svf. Especially during the second time interval. It is related with EF involvement.
(Farazi et al., 2021)	Study the differences in VF between RRMS, PPMS and SPMS	N= 72 (persian population) (24 RRMS, 24 PPMS y 24 SPMS)	MMSE sVF (animals, meals and drinks) pVF (FAS)	Total pVF Total sVF *Switchings (not mentioned in methodology)	Only variables for RRMS and PPMS found differences. No differences between switchings were found.
(Barois et al., 2021)	To compare the execution between MS and HC including errors	N=101 (68 MS patients, 33 HC)	pVF (letter P) sVF (animals)	-Total words and errors -Time from the first word -Curve change corresponding to the cognitive process swift -Word producing speed before a swift -Maximum time between words	Total words, time from first word and time from swift were relevant for both pVF and sVF in MS.
(Delgado-Álvarez et al., 2021)	To assess cognitive processes underlying VF	N= 200 patients with MS	Exhausted neuropsychological baterry pVF (letter P) y sVF (animals)	Total CR Repetitions Intrusions Total clusters Total swiftchings Clusters mean size Correct words percent in clusters	Tests related to attention and EF, memory and language were the strongest predictors of differences in VF. Memory was more relevant for sVF and clustering, EF in pVF and switchings. EF obtuvieron más relevancia en PVF y

Note. **VF**: Verbal Fluency; **pVF**: phonological Verbal Fluency; **sVF**: semantic Verbal Fluency; **PS**: Processing Speed; **EDSS**: Expanded Disability Status Scale; **MMSE**: Mini-Mental Status Scale; **RRMS**: Relapsing-Remitting Multiple Sclerosis; **HS**: Healthy controls; **CR**: Correct responses; **CS**: Cluster size; **PPMS**: Primary Progressive Multiple Sclerosis; **SPMS**: Secondary Progressive Multiple Sclerosis; **EF**: Executive Functions; **CIS**: Clinically Isolated Syndrome; **CI**: Cognitive Impairment.

Table 3 (Continued).

Review of studies analyzing different VF variables in patients with MS.

Authors	Objective	Sample	Instruments	Variables	Results
(Lebkuecher et al., 2021)	Assess the contribution of the language ability, oral speed, PF and EF in VF	N= 74 MS patients.	pVF (FAS) pVF (animals and names for boy) Neuropsychological tests of PS, EF and language.	Total words.	Both vocabulary and PS predicted pVF but only vocabulary sVF. Authors suggest that VF deficits may reflect language and PS impairment.
(Velázquez-Cardoso et al., 2014)	Compare the execution in organizational strategies in VF between MS patients and HC	N= 79 (46 MS patients, 33 HC)	sVF (animals) pVF (PMR) CI and depression screening tools	Total words Switchings Clusters Clusters mean size	Total words in pVF wound differences between groups. Higher nº of switchings in MS
(Messinis et al., 2013)	Explore possible differences in VF strategies (clustering and switching) in patients with RRMS versus patients with SPMS.	N= 148 (74 MS patients, 60 RRMS y 14 SPMS; 74 HC).	Greek pVF (chi, sigma and alpha) sVF (animals, fruits and objects)	Total words Total clusters Total switchings	No differences were found between MS groups (RRMS and SPMS), for total words and clusters. Total switchings showed evidence in pVF between SPMS and RRMS
(Viterbo et al., 2013)	Study the predictive capacity of VF deficits on CI in CIS MS.	N= 100 (CIS MS patients).	BRB pVF (FAS) sVF (fruits and vegetables)	Total words	Fewer than 28 words reached a sensibility of 82% and specificity of 66% in discriminating CI patients
(Connick et al., 2012)	Analyze the usefulness of pVF and sVF as screening tools for CI in progressive MS.	N= 175 (88 MS patients: 60 SPMS y 28 PPMS and 87 HC)	pVF (letter P) sVF (animals)	Total words	A sensitivity of 84.6% and specificity of 85.5% in fewer than 10 words for pVF. A sensitivity of 93% and specificity of 61% for fewer than 20 words in sVF
(Beatty, 2002)	Analyze the efficacy of a category of sVF that includes a wide variety of phonological beginnings to substitute and resolve the limitations of pVF dependent on native language	N= 290 (203 MS patients, 87 HC)	pVF (FAS) sVF (animals and body parts)	Total words	The three tasks of VF (FAS, animals and body parts) found similar sensitivity and specificity when discriminating between MS and HC.

Note. **VF**: Verbal Fluency; **pVF**: phonological Verbal Fluency; **sVF**: semantic Verbal Fluency; **PS**: Processing Speed; **EDSS**: Expanded Disability Status Scale; **MMSE**: Mini-Mental Status Scale; **RRMS**: Relapsing-Remitting Multiple Sclerosis; **HS**: Healthy controls; **CR**: Correct responses; **CS**: Cluster size; **PPMS**: Primary Progressive Multiple Sclerosis; **SPMS**: Secondary Progressive Multiple Sclerosis; **EF**: Executive Functions; **CIS**: Clinically Isolated Syndrome; **CI**: Cognitive Impairment.

All included investigations analysed some type of VF variable in the MS population. Despite the large number of VF investigations, few studies specifically addressed organizational strategies in MS patients during these tasks. Only 2 studies (Messinis et al., 2013; Velázquez-Cardoso et al., 2014) explicitly stated the purpose of organizational strategy analysis, and 5 studies covered these variables in their results. Regarding the Fernaeus & Almkvist (1998) model, only Pitteri et al. (2023) divided the task into two time intervals as moderators of the results (0-15 sec and 16-60 sec).

Every analysed study included pVF and sVF tasks. Categories varied among “animals,” “fruits and vegetables,” and “colors,” while letters used “F,” “A,” and “S” or “P,” “M,” and “R.”

Finally, only Delgado-Álvarez et al. (2021) and Pitteri et al. (2023) conducted analyses to determine the cognitive processes involved in VF task execution. Both authors highlight the existing controversy due to the inclusion of organizational strategies and the division of VF tasks into execution intervals.

In conclusion, to date, a limited number of studies have investigated the cognitive processes underlying VF, analysed all organizational strategies (switches, clusters, and mean cluster size) in Spanish individuals diagnosed with MS, and considered execution time. Additionally, given the controversy in the results reported by previous VF studies, it is interesting to contribute new findings using diverse statistical methodologies.

Among the current recommendations for working with individuals diagnosed with MS, several objectives are proposed. In the context of this study, the identification and validation of standardized neuropsychological instruments sensitive enough to detect CI in early stages of the disease are crucial (Elwick et al., 2021). Early and effective detection of CI allows for faster initiation of treatments which are associated with better prognoses, reduced relapse rates, disability, and cerebral atrophy (Uher et al., 2023). Additionally, it can mitigate the high unemployment rate and improve quality of life after the disease (Piacentini et al., 2023). Therefore, the following main objectives are proposed:

- Evaluate the efficacy of pVF (letter P) and SVF (animals) tasks in the early detection of CI in MS, by studying the total number of words recalled and the use of organizational strategies (switches and clusters).
- Analyse differences between MS groups with CI (MSCI) and without CI (MSnoCI) in terms of the number of correct recalled words and the use of organizational strategies (switches and clusters) during sVF (animals) and pVF (letter P) tasks at different execution times (0-30sec, 30-60sec) (Pitteri et al., 2023).
- Conduct a cognitive process analysis of pVF (letter P) and sVF (animals) tasks based on total performance and execution time (0-30sec, 30-60sec) (Pitteri et al., 2023) in MS patients.
- Perform a cognitive process analysis of organizational strategies (switches and clusters) in pVF (letter P) and sVF (animals) tasks based on total performance and execution time (0-30sec, 30-60sec) in MS patients.

Regarding the proposed hypotheses:

- First objective. Given the existence of differences in performance in pVF and sVF between healthy individuals and MS patients in terms of total words recalled (Henry y Beatty, 2006), it is expected that:
    - H1: Patients diagnosed with MSCI will show substantial evidence of differences in the total number of words recalled during PVF and SVF tasks compared to those with MSnoCI.
    - Ho: Patients diagnosed with MSCI will not show evidence of differences in the total number of words recalled during PVF and SVF tasks compared to those with MSnoCI.
    - H2: Patients diagnosed with MS-noCI will exhibit better organizational strategies (more clusters and fewer switches) than those with MSCI.
    - Ho: Patients diagnosed with MSnoCI will not show evidence of differences in organizational strategies (number of clusters and number of switches) compared to those with MS-CI.
- Second objective:
    - H1: Individuals diagnosed with MSCI will recall fewer words during the second execution time (30-60 sec) than those with MSnoCI, consistent with the findings of Pitteri et al. (2023) regarding total words recalled in MS patients compared to healthy subjects.
    - Ho: Both MSCI and MSnoCI groups will not show evidence of differences in the total number of correctly recalled words based on execution time (0-30 sec and 30-60 sec).
    - H2: Individuals diagnosed with MSCI will exhibit fewer clusters and more switches during the second execution time (30-60 sec) than patients with MSnoCI.
    - Ho: Both MSCI and MSnoCI groups will not obtain differences regarding the organizational strategies (number of switches and clusters) base don execution time (0-30sec y 30-60sec).
- Third objective:
    - H1: The total number of words with letter P will show evidence of correlation with EF, attention, and language, while the total number of animals will show evidence of correlation with memory, attention, and language domains (Delgado-Álvarez et al., 2021) in MS patients.
    - Ho: There will be no substantial evidence of relationship between the total number of words in pVF and sVF and the indices of EF, language, attention, and memory.
    - H2: The EF index will show substantial evidence of correlation with the variable words recalled 30-60 sec in pVF and sVF, consistent with the previous results of Pitteri et al. (2021) in MS patients .
    - Ho: The EF index will not show evidence of correlation with the words recalled 30-60sec in pVF and sVF.
- Fourth objective:
    - H1: The total number of clusters in pVF and sVF will show more evidence of correlation with the memory domain, while the total number of switches in both tasks will correlate with EF, according to Delgado-Álvarez et al. (2021) in MS patients.

- Ho: No relation will be obtained between pVF and sVF tasks regarding memory and EF domains.
- H2: The number of clusters and switches in pVF and sVF during the 30-60 sec time interval will show substantial evidence of correlation with EF in MS patients.
- Ho: There will be no evidence of correlation between EF and organizational strategies in pVF and sVF during the 30-60 sec Interval.

2. METHODOLOGY

2.1. Participants

The present study is composed of 16 participants who constitute the pilot of the project "Adaptation of the computerized neuropsychological evaluation battery COGNITO in a Spanish sample of patients with Multiple Sclerosis and its relationship with daily life activities", still in progress. Of the total, 7 were women and 5 men, with an average age of 41 years. They were divided into 2 groups based on the CI diagnosis defined by a clinical neuropsychologist blinded to the evaluation, as carried out by Ozkul et al. (2020). For the diagnosis, the final results obtained in the two diagnostic tests (BNB and COGNITO) were assessed, taking as a criterion the presence of at least two altered cognitive domains (the diagnostic process and classification are specified in section 1.3.). All participants were selected incidentally through a convenience screening after attending the "Asociación Granadina de Esclerosis Múltiple (AGDEM)" in Armilla, Granada (Spain).

The total number of participants that constitute the study will be the one that allows obtaining substantial evidence of stability in Bayesian statistical analyses. For this, the following recruitment interruption criterion is established: 20 consecutive participants for whom the Bayes factor (BF10) does not drop below 3 in all the dependent variables previously considered in the hypotheses. This BF10 is established because it can be interpreted as moderate to strong evidence in favor of the alternative hypothesis, which justifies its use to determine the sample size (van Doorn et al., 2021).

The inclusion criteria were: being Spanish speakers, preserving reading and writing skills, being between 18 and 64 years old, meeting the MS diagnosis according to the McDonald criteria (**Appendix 1**) and having an evolution time between the last relapse and the evaluation moment of more than one month. The exclusion criteria were: a) visual disorders that impede the correct visualization of the administered tests, b) sensory-motor alterations that hinder the administration of the COGNITO battery, c) suffering from any neurological or psychiatric alteration that explains the cognitive symptomatology and d) taking antiepileptic, antipsychotic, narcotic opioid and cholinesterase inhibitor pharmacological treatment.

The following sociodemographic and clinical variables were collected for all participants: sex, age, handedness, years of schooling, employment status, type of phenotypic manifestation and years of disease progression.

2.2. Instruments and variables

All participants underwent an extensive neuropsychological evaluation. Sociodemographic and clinical data were collected through a semi-structured interview (see **Appendix 2**). The cognitive tests administered were as follows:

- Brief Neuropsychological Battery (BNB) (Duque, 2012): This is a screening instrument to detect CI in patients with MS. The tests that compose the BNB include:
    - Free and Cued Selective Recall Test (FCSRT). A memory and learning task. Participants acquire 12 words through reading and semantic reinforcement. Subsequently, learning is evaluated through free recall and semantic cues both immediately and after a delay (Duque, 2012).
    - Symbol Digit Modalities Test (SDMT). Assesses PS, sustained attention, working memory, visuospatial function, and constructive praxis. Participants write the numbers associated with each symbol in the template as quickly as possible during 90 seconds (Lezak et al., 2004).
    - Lexico-Semantic Categorical Recall: This is a VF test that assesses amnestic recall, inhibitory capacity, and planning (Duque, 2012). It includes various tasks:
        - Words without the letter “E”: Participants produce as many words as possible that do not contain the letter “E” within 1 minute (Lezak et al., 2004).
        - pVF: Evaluates the subject’s ability to generate words under specific rules or restrictions. Participants are asked to recall all words starting with the letter “P” within 1 minute, avoiding proper nouns, city names, or derivatives (Lezak et al., 2004).
        - sVF: The subject must evoke all the words they can within a certain category for 1 minute. In this case, the category “animals” was requested (Lezak et al., 2004).

      In each of the categories, the words will be recorded in two time intervals, that is, every 30 seconds according to the model of Fernaeus & Almkvist (1998).
    - Paced Auditory Serial Addition Test (PASAT). Assesses complex attention, working memory, PS, and inhibition. Patients are read sequential numbers, and they must continuously add the last two numbers read by the evaluator. Both the result of each sum and the execution time every two rows of the task are written (Duque, 2012).

- Computerized Information Processing Assessment Battery (COGNITO) This is the validation in a Spanish sample of the original battery developed by Ritchie et al. (2014). The first prototype, called ECO (from French, “Examen Cognitif par Ordinateur”), was used as the main measure in a longitudinal study on cognitive aging (Ritchie et al., 1993). It is a computerized cognitive examination based on frequently known cognitive tests. This battery has been used for various purposes, such as detecting changes caused by depression after undergoing anaesthesia due to anticholinergic drugs and for establishing

diagnostic criteria for mild cognitive impairment. COGNITO evaluates the following cognitive processes: verbal and visuospatial memory, working memory, reaction times, learning, language (VF, naming, and comprehension), categorization, reasoning, focused and divided attention, and crystallized intelligence. All instructions and responses are provided through a touchscreen that records both correct answers and response latency.

The tests that constitute the battery are indicated below, however, in table 5 they will be classified according to the domains they evaluate: Reaction time, reading and comprehension of syntax, auditory attention, visual attention, working memory, Stroop test, immediate verbal recall, visuospatial registration, recognition of geometric figures, comprehension of words, recognition of objects and their functions, progressive matrices, delayed verbal recall, recognition of faces, learning of name-face associations, verbal fluency, text recall, vocabulary, implicit memory, reproduction of designs and complex figures.

Once the evaluation was completed, a qualitative analysis of the VF tests was carried out. For this purpose, the letter “P” and the category “animals” were selected, as they are tasks included in the BNB and according to the review carried out (see **table 3**), they appear most frequently in previous studies with a Spanish population.

Two types of organizational strategies were collected: clusters and switches. Clusters occur when two or more successive words share similar characteristics. In pVF tasks, clusters can share the same initial phonetic sound (e.g., in Spanish “salvaje” and “salud”), be homonymous words (i.e., spelled the same but with different meanings, e.g., in Spanish, “rosa”), or have similar assonance or consonance (e.g., in spanish “poza” and “rosa”). In sVF tasks, clusters involve words with related meanings (e.g., in spanish “azúcar” and “sal”). When tasks require words within a specific category (e.g., “animals”), subcategorization strategies can be considered clusters (e.g., in spanish “cebra,” “león,” and “jirafa” as animals from the savanna). When a cluster is exhausted, efficient change to a new category is necessary, described as “switchings” (Lezak et al., 2004; Troyer et al., 1997). The analysis, similar to Velazquez-Cardoso et al. (2014), followed the guidelines for qualitative VF analysis in Spanish sample by Villodre et al. (2006), based on the work of Troyer et al. (1997). See **Appendix 3** for an example of VF organization strategy analysis.

The **table 4**, ncludes variables obtained from similar research after analyzing organizational strategies in FV (Ledoux et al., 2014), which are relevant for addressing the first two objectives of our study.

Table 4.

Variables obtained through the qualitative analysis of VF tasks.

Neuropsychological test	Variables
pVF (letter P) and sVF (animals)	Total evoked words
	Evoked words 0-30sec
	Evoked words 30-60sec
	Total clusters
	Clusters 0-30sec

	Clusters 30-60sec Total switchings Switchings 0-30sec Switchings 30-60sec

Note. pVF: Phonological Verbal Fluency; **sVF**: semantic Verbal Fluency.

Regarding the cognitive indices necessary for the process analysis of the third and fourth objectives, the tests that compose these domains are specified in **Table 5**.

Table 5.

Variables and neuropsychological tests administered according to cognitive dimensions of the COGNITO test.

Cognitive domain	Tests and selected variables
Attention	Reaction time Auditory attention Visual attention Auditory and visual attention Stroop test
Language	Reading and syntactic comprehension Phonemic comprehension Naming pVF and sVF Vocabulary
Memory	Articulation and immediate recall Visuospatial span Delayed recall of names Name-face association Narrative and descriptive recall Implicit memory
EF	Stroop test (Interference) Auditory and visual attention PASAT (corrects) Generation of words without “E”

Note. **EF**: Executive Functions; **pVF**: phonological Verbal Fluency; **sVF**: semantic Verbal Fluency.

2.3. Procedure

The evaluations were conducted at the "Asociación Granadina de Esclerosis Múltiple" (AGDEM) by the researchers/collaborators in neuropsychology of the project. Interested participants were provided with information about the research project’s objectives, inclusion criteria, and compensation for their participation through a blinded clinical report.

A quiet space with the necessary materials was available for accurate and quick assessment without environmental distractions. The evaluations were conducted individually, without companions, lasting 45-60 minutes each, split into two sessions on different days to manage participant fatigue.

Following the assessments, a brief interview was conduct to collect sociodemographic and clinical data from the patients. Participants were informed about the evaluation process, procedures, and task instructions. Neuropsychological tests were administered in a predetermined order to avoid possible interference biases. 4 weeks after completing both evaluation sessions, participants were scheduled for result feedback and report explanation.

2.4. Design

The study proposes a quasi-experimental observational case-control design with a mixed-methods analysis (combining qualitative and quantitative information). To appropriately present the results, the recommendations indicated in the Guidelines for reporting observational studies in observational studies (STROBE) (von Elm et al., 2014) were taken as a reference. The detailed checklist is provided in **Appendix 4**. The recruitment protocol is represented in the flowchart (**Figure 2**).

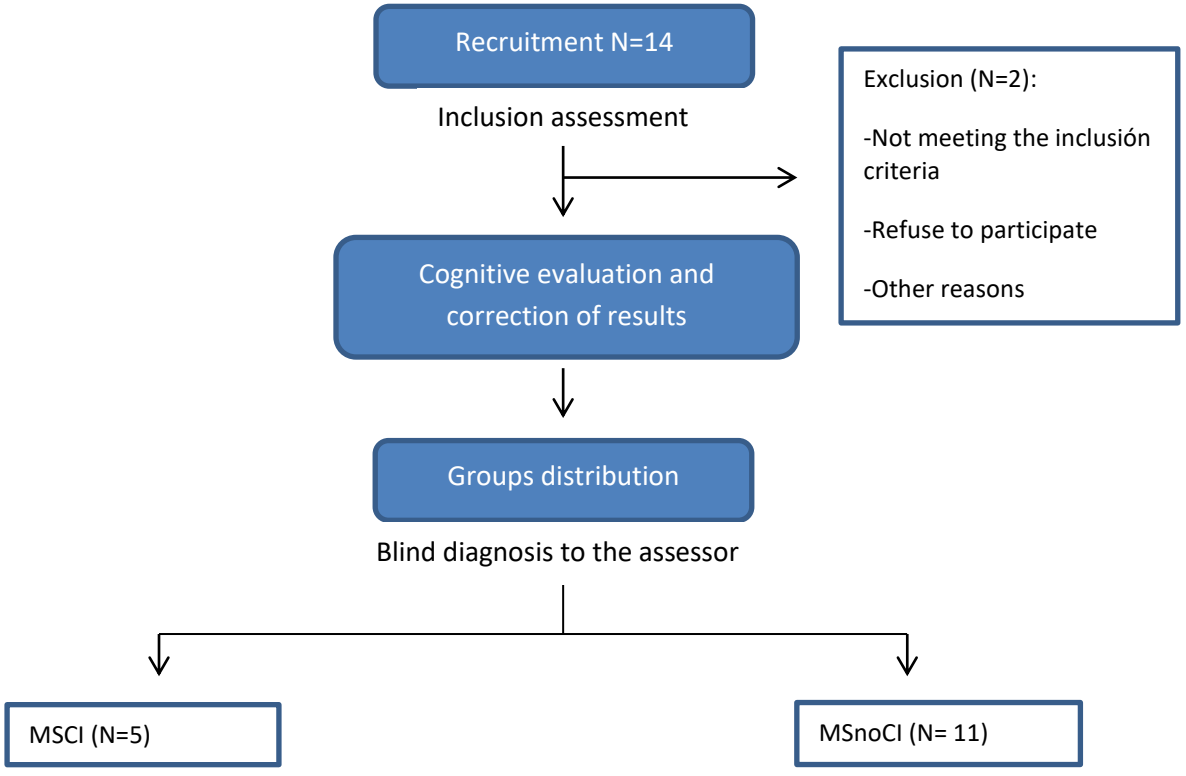

Figure 2.

STROBE flowchart. Recruitment and group assignment protocol.

The independent variable (IV) was the CI diagnosis (IV1). The dependent variables (DV) were “total correct words P” (DV1), “correct words P 0-30sec” (DV2),

"correct words P 30-60sec" (DV3), "total clusters P" (DV4), "clusters 0-30sec P" (DV5), "clusters 30-60sec P" (DV6), "total switchings P" (DV7), "switchings P 0-30sec" (DV8), "switchings P 30-60sec" (DV9). In addition, "total correct words animals" (DV10), "correct words animals 0-30sec" (DV11), "correct words animals 30-60sec" (DV12), "total clusters animals" (DV13), "clusters 0-30sec animals" (DV14), "clusters 30-60sec animals" (DV15), "total switchings animals" (DV16), "switchings animals 0-30sec" (DV17), "switchings animals 30-60sec" (DV18).

2.5. Data analysis

The data collected were analyzed using the free access statistical software JASP, version 16.4.0. The analysis was carried out using a Bayesian approach, which allows the incorporation of prior information and a probabilistic interpretation of the results(Kelter, 2020). In other words, it considers relative evidence rather than absolute evidence. While this method compensates for the small recruited sample and facilitates updating the estimation as new data are incorporated, parametric frequentist statistics would be unreliable due to the lack of sample robustness and statistical power, leading to a high risk of false negatives (Kelter, 2020). Therefore, in this work, we assume a normal distribution and conduct Bayesian independent samples t-tests for all proposed hypotheses. However, the final decision on results will be based on the outcome of the normality test once a sufficient sample size is available.

Specifically, the Bayes Factor (BF10), expressed as a ratio, refers to the relative changes in beliefs about the alternative hypothesis with respect to the null hypothesis (Kelter, 2020). Given a series of prior assumptions, the BF10 expresses the degree to which we should change our belief in one hypothesis versus the other, according to the accumulated evidence. The classification of the evidence obtained by the BF10 analyses is established according to Jeffreys' scale as: 1-3=Anecdotal in favor of H1; 3-10= moderate in favor of H1; 10-30= strong in favor of H1; 30-100= Very strong in favor of H1; >100= Extreme in favor of H1; <1-0.33= Anecdotal in favor of Ho; <0.33-0.01= Moderate in favor of Ho; <0.01-0.03= Strong in favor of Ho; <0.03-0.01= Very strong in favor of Ho; <0.01= Extreme in favor of Ho (Kelter, 2020).

First, an exploratory descriptive analysis of the sample was conducted, considering sociodemographic and clinical variables. The following variables and their categories were examined: "sample size" and "sex" (female/male), "age," "handedness" (right-handed/left-handed), "years of schooling," "employment status" (active/inactive), "phenotypic manifestation" (RRMS/PPMS/SPMS), and "years of disease evolution." Means, standard deviations, and subgroup frequencies were obtained. Additionally, mean comparisons between both groups were performed to assess evidence of differences related to influential variables described in the literature (age, educational level, and disease duration). Bayesian independent samples t-tests were conducted, and only variables with BF > 3 showed substantial evidence of differences between the groups.

Regarding the first objective of the study, the aim was to analyze the differences in the total number of words evoked and the number of organizational strategies

according to the CI diagnosis, and for the second objective the same differences were studied including the temporal moment in which the dependent variables were collected (0-30 or 30-60 sec). The Bayesian T-student test for independent samples was used. Only those variables with a BF10>1 showed evidence in favor of the alternative hypothesis and only those with a BF10>3 substantial evidence to reject the null hypothesis.

For the third objective of the study, the possible existence of relationships between the cognitive domains constructed with the number of words evoked and the organizational strategies of pVF and sVF was analyzed, while for the fourth and last objective of the study the possible existence of the same relationships according to the temporal moment was analyzed. A Bayesian Pearson correlation analysis was carried out. Obtaining a BF10>1 indicates the existence of a relationship between the analyzed variables, however, only the BF10>10 allows obtaining substantial support due to the simultaneous performance of multiple correlation analyses. Again, the evidence of the relationships is classified according to Jeffreys' scale. The results relative to the magnitude of the relationship were interpreted according to Rowntree (1984), being 0= Null; 0.0-0.4 = weak; 0.4-0.6 = Moderate; 0.6-0.8= High; 0.8-1 = Very high; 1=Perfect..

2.6. Ethical considerations

The Ethics Committee for Research in the province of Jaén (Spain) approved and registered the research project "Adaptation of the computerized neuropsychological evaluation battery COGNITO in a Spanish sample of patients with Multiple Sclerosis and its relationship with daily life activities" from the University of Granada on January 30, 2020, of which this work is part. See Appendix 5.

The study was conducted in accordance with the ethical principles established in the Declaration of Helsinki (World Medical Association [WMA], 2013). All patients were adequately informed about the voluntary nature of participation in the study and their right to withdraw at any time. Data administration and collection occurred only after obtaining informed consent (Appendix 6). Anonymity and preservation of data were compiled in accordance with Organic Law 7/2021, of May 26th, on the protection of personal data processed for the purposes of prevention, detection, investigation and prosecution (Government of Spain, 2021). Alphanumeric codes with five digits were used for this purpose.

Given the quasi-experimental observational nature of the research, no potential risk to the participants was identified. In addition, once their collaboration was completed, each of the participants received a neuropsychological report with their performance on the neuropsychological tests. The presence and degree of cognitive impairment were also detailed according to standardized scales in the Spanish population.

3. RESULTS

First of all, sociodemographic and clinical characteristics were analysed in the MSCI and MSnoCI groups (see **Table 6**).

Table 6.

Sociodemographic and clinical characteristics of the subjects based on the presence of CI.

	MSCI	**MSnoCI**	**Total**
N	5	11	16
Sex (Males/Females)	1/4	9/2	10/6
Age	43,80 (5,675) [34-48]	43,18 (10,796) [27-57]	43,38 (9,294) [27-57]
Handedness (Right-handed/Left-handed)	4/1	9/2	13/3
Years of schooling	14,60 (3,847)	15,82 (3,188)	15,44 (3,326)
Employment status (Active/Inactive)	1/4	5/6	6/10
Phenotypic manifestation (RRMS/PPMS/SPMS)	4/1/0	9/1/1	13/2/1
Years of disease evolution	14 (11,203) [1-26]	6,64 (5,870) [1-20]	8,94 (8,298) [1-26]

RRMS: Relapsing-Remitting Multiple Sclerosis; **PPMS**: Primary Progressive Multiple Sclerosis; **SPMS**: Secondary Progressive Multiple Sclerosis; **MSCI:** Multiple Sclerosis Cognitive Impairment; **MSnoCI**: Multiple Sclerosis no Cognitive Impairment. **Note**. Means, standard deviations (), minimum-maximum range [], and frequencies by subcategories are shown.

The sample was characterized by a predominance of women with an average age of 43 years, university education, and inactive employment status. Clinically, most participants had RRMS, although three patients with progressive forms of the disease were included.

Regarding the demographic and clinical variables described in the literature as influential for VF tasks, there was no substantial evidence of differences (BF10 > 3) between the two groups (MSnoCI, MSCI) concerning age (BF10 = 0.451), years of schooling (BF10 = 0.518), and disease duration (BF10 = 1.152).

3.1. Differences in the number of correct words evoked and organizational strategies used in the presence or absence of CI.

To analyze the utility of pVF and sVF tasks in the early detection of CI based on the total number of recalled words and the use of organizational strategies (switchings and clusters), descriptive characteristics and bidirectional evidence (BF10) were obtained for each of the included variables using Bayesian independent samples t-tests. **Table 7** shows the accumulated evidence for the existence or absence of differences between the MSnoCI and MSCI groups.

Table 7.

Differences between the presence or absence of CI in the dependent variables collected for the objective 1.

		N	M (dt)	Difference of means	BF10	Median	CI 95%	
							Inferior	Superior
Total correct words "P"	MSnoCI	11	16,27 (2,05)	3,273	1.680	0.764	-0.166	1.930
	MSCI	5	13 (4,30)					
Total correct words "animals"	MSnoCI	11	21 (2,86)	5,200	2.913	0.979	-0.039	2.213
	MSCI	5	15,80 (5,40)					
Total clusters P	MSnoCI	11	2.63 (1.80)	-0.17	0.452	-0.048	-0.908	0.783
	MSCI	5	2.80 (2.28)					
Total switchings P	MSnoCI	11	13.09 (3.30)	2.89	1.028	0.564	-0.299	1.651
	MSCI	5	10.20 (3.19)					
Total clusters animals	MSnoCI	11	6.09 (1.30)	1.69	1.742	0.779	-0.157	1.949
	MSCI	5	4.40 (1.82)					
Total switchings animals	MSnoCI	11	11.27 (3.07)	2.87	1.399	0.691	-0.213	1.829
	MSCI	5	8.40 (1.67)					

Note. Data are means (M) of raw scores. Standard deviations (SD) are shown in parentheses. N: sample size. Credibility interval (**CI**): lower-upper bounds. **BF10**: Bayes Factor (for continuous variables); **MSCI**: Multiple Sclerosis Cognitive Impairment; **MSnoCI**: Multiple Sclerosis no Cognitive Impairment.

For the first hypothesis, the total number of words recalled starting with the letter P and the total number of words recalled related to animals were analysed in both groups. Anecdotal evidence of differences was found for both variables (see Figure 3). The total number of words recalled in pVF had a BF10 score of 1.680, with the MSnoCI group having a mean of 16.27 (±2.05) and the MSCI group having a mean of 13

(±4.30). In the total number of words recalled in sVF, a BF10 of 2.913 was obtained, with the MSnoCI group having a mean of 21 (±2.86) and the MSCI group having a mean of 15.80 (±5.40) (see **Table 7**).

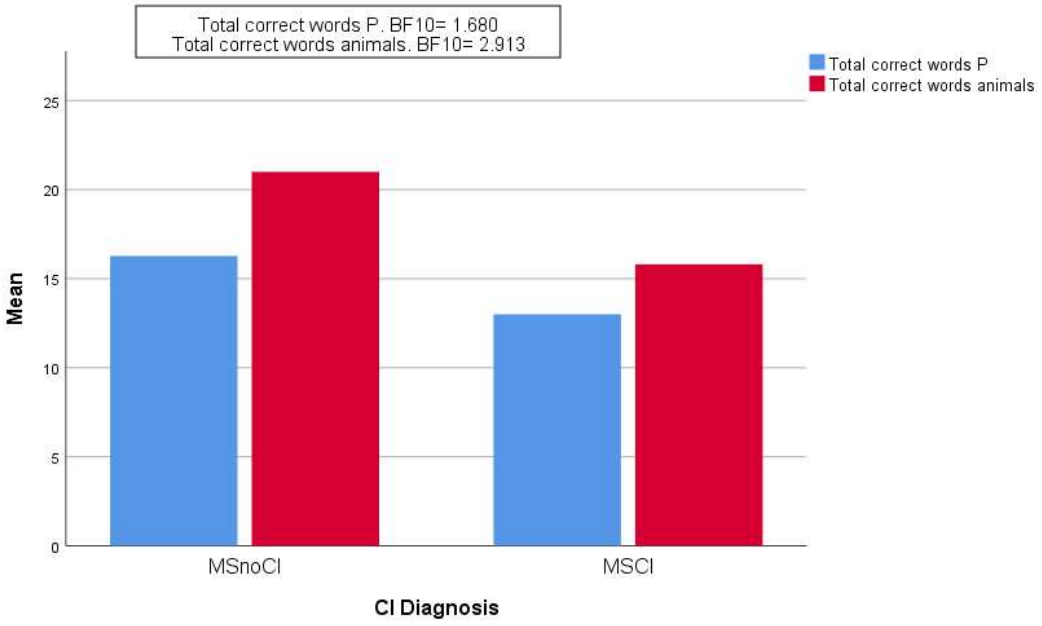

Figure 3.

Compared mean scores for MSCI and MSnoCI groups in "total number of correctly recalled words with P" and "total number of correctly recalled animal words." The BF10 for each variable is also shown. MSCI: Multiple Sclerosis Cognitive Impairment**; MSnoCI:** Multiple Sclerosis no Cognitive Impairment**.**

Additionally, sequential data analysis was requested to observe the evolution of accumulated evidence (BF10) as more information is obtained. As an example, **Figure 4** is described below. For the total number of correct words evoked with P, the data show a fluctuating trend towards the alternative hypothesis although with anecdotal evidence. The remaining sequential analyses are provided in **Appendix 7**.

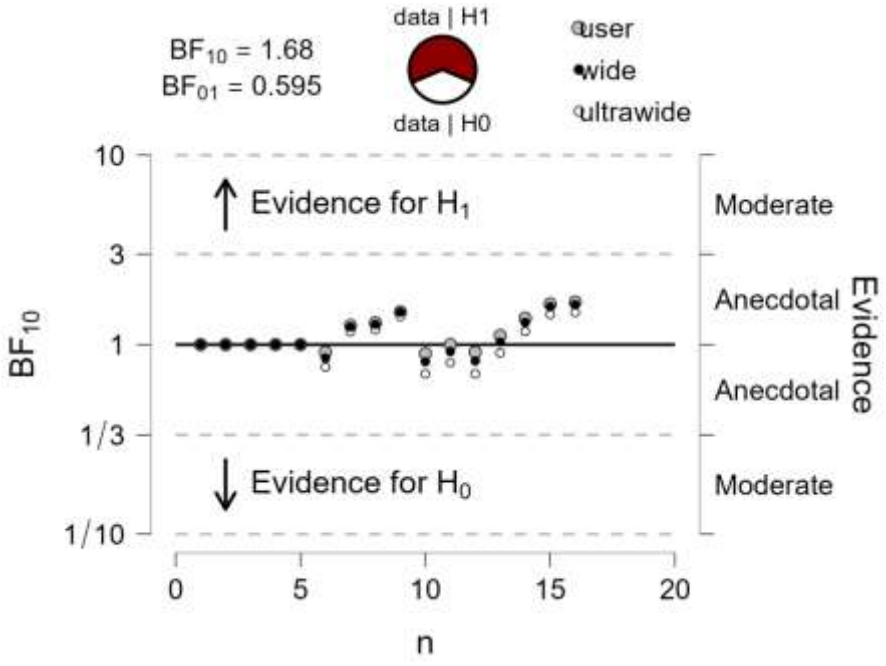

Figure 4.

Sequential analysis for the variable "total number of correctly recalled words with P".

For the second hypothesis, differences in the total number of organizational strategies (clusters and switchings) were analyzed for both pVF and sVF tasks in both groups. Specifically, in pVF, only the total number of switchings showed anecdotal evidence of discrepancies (BF10 = 1.028) between MSnoCI and MSCI, with means of 13.09 (±3.30) and 10.20 (±3.19), respectively. In sVF, both strategies showed anecdotal evidence of differences between the groups. The total number of clusters had a BF10 = 1.742, with the MSnoCI group having a mean of 13.09 (±3.30) and the MSCI group having a mean of 4.40 (±1.82). The total number of switchings (BF10 = 1.399) had a mean of 11.27 (±3.07) in the MSnoCI group and 8.40 (±1.67) in the MSCI group (see **Figure 5**). Similar to the previous hypothesis, sequential evidence accumulation was performed for each dependent variable analyzed in both pVF and sVF (see **Figure 9** in **Appendix 7)**.

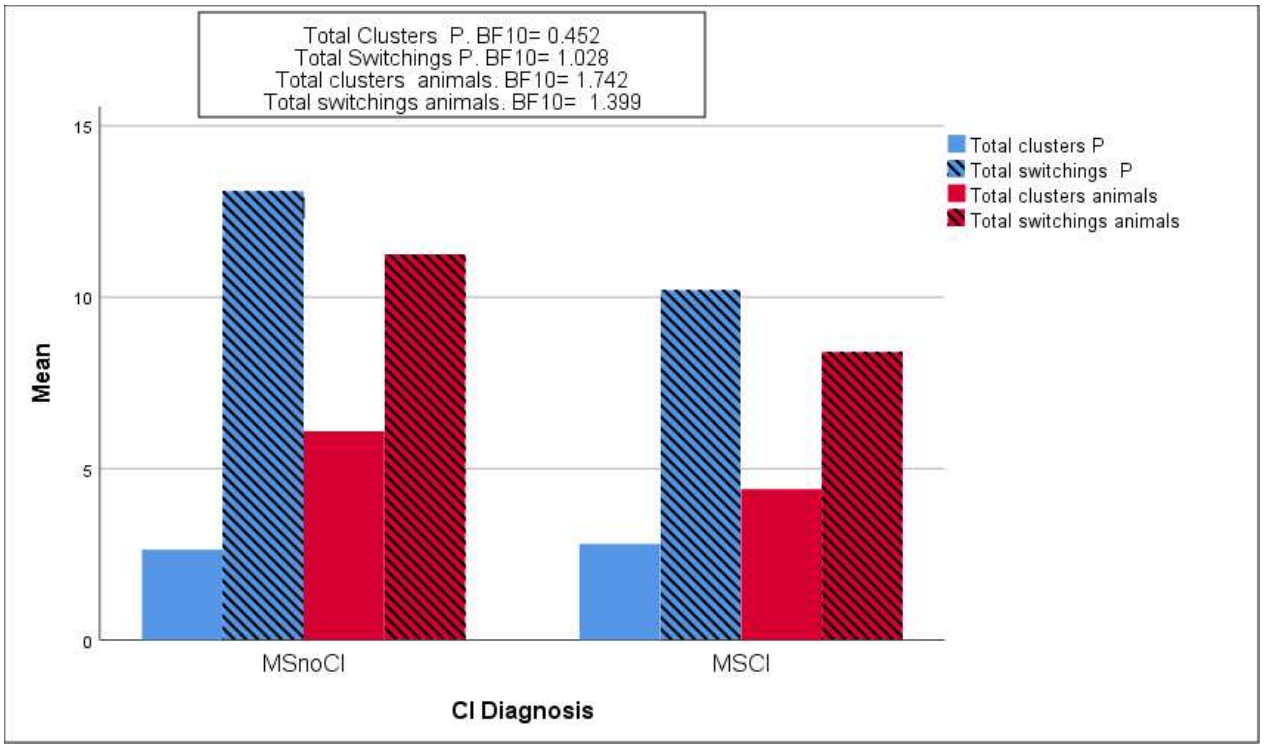

Figure 5.

Compared mean scores for MSCI and MSnoCI in "total number of clusters and switches starting with P" and "total number of clusters and switches related to animals." The BF10 for each variable is also shown. MSCI: Multiple Sclerosis Cognitive Impairment**; MSnoCI:** Multiple Sclerosis no Cognitive Impairment.

3.2. Differences in the number of organizational strategies used based on temporal intervals in the presence or absence of CI.

For the second objective, we aimed to analyse the same differences studied in the previous objective but considering the temporal moment when the dependent variables were collected (0-30 or 30-60 sec). Bayesian independent samples t-tests were conducted (see **Table 8**).

Table 8.

Differences between the presence or absence of CI in the dependent variables collected for objective 2.

	N	M (dt)	Difference of means	BF10	Median	CI 95%	
						Inferior	Superior

Correct words “P” 0-30´	MSnoCI	11	10.36 (1.57)	2.16	1.658	0.759	-0.170	1.923
	MSCI	5	8.20 (2.59)					
Correct words “P” 30-60sec	MSnoCI	11	6 (1.67)	1.2	0.767	0.433	-0.397	1.462
	MSCI	5	4.80 (1.79)					
Correct words “animals” 0-30sec	MSnoCI	11	13.63 (3.17)	4.43	3.436*	1.043	-0.003	2.295
	MSCI	5	9.20 (2.78)					
Correct words “animals” 30-60sec	MSnoCI	11	7.36 (2.20)	0.76	0.499	0.180	-0.631	1.092
	MSCI	5	6.60 (3.05)					
Clusters “P” 0-30sec	MSnoCI	11	1.81 (1.66)	0.01	0.448	0.007	-0.836	0.853
	MSCI	5	1.80 (1.48)					
Clusters “P” 30-60sec	MSnoCI	11	0.82 (0.60)	-0.18	0.480	-0.143	-1.039	0.672
	MSCI	5	1 (1)					
Switchings “P” 0-30sec	MSnoCI	11	8.09 (2.17)	1.89	1.008	0.555	-0.305	1.639
	MSCI	5	6.20 (2.17)					
Switchings “P” 30-60sec	MSnoCI	11	4.18 (1.89)	0.98	0.636	0.340	-0.476	1.325
	MSCI	5	3.20 (1.30)					
Clusters animals 0-30sec	MSnoCI	11	4.45 (1.29)	1.65	2.615	0.938	-0.063	2.159
	MSCI	5	2.80 (1.10)					
Clusters animals 30-60sec	MSnoCI	11	1.64 (0.92)	0.04	0.449	0.023	-0.815	0.874
	MSCI	5	1.60 (0.89)					
Switchings animals 0-30sec	MSnoCI	11	7.82 (2.56)	1.62	0.788	0.446	-0.387	1.481
	MSCI	5	6.20 (1.10)					

Switchings animals 30-60sec	MSnoCI	11	3.09 (1.45)	1.29	1.092	0.589	-0.281	1.687
	MSCI	5	1.80 (1.30)					

Note. Data are means (M) of raw scores. Standard deviations (SD) are shown in parentheses. N: sample size. Credibility interval (**CI**): lower-upper bounds. BF10: Bayes Factor (for continuous variables); **MSCI**: Multiple Sclerosis Cognitive Impairment; **MSnoCI**: Multiple Sclerosis no Cognitive Impairment. An asterisk "*" indicates substantial evidence in favor of a specific hypothesis.

For the first hypothesis, we aimed to analyze differences in the number of words recalled during the first time interval (0-30 sec) and the second interval (30-60 sec) for sVF and pVF in the MSCI and MSnoCI groups. Both tasks showed discrepancies between groups during the first temporal moment. For words recalled with the letter P, the evidence was anecdotal (BF10 = 1.685), with a mean of 10.36 (±1.56) in the MSnoCI group and 8.20 (±2.58) in the MSCI group. Regarding words recalled related to animals, substantial evidence was found (BF10 = 3.436), with the MSnoCI group having a mean of 13.63 (±3.17) and the MSCI group of 9.20 (±2.77) (see **Figure 6**). The sequential analysis of accumulated evidence for the analyzed variables is shown in **Figures 10 and 11** in **Appendix 7**.

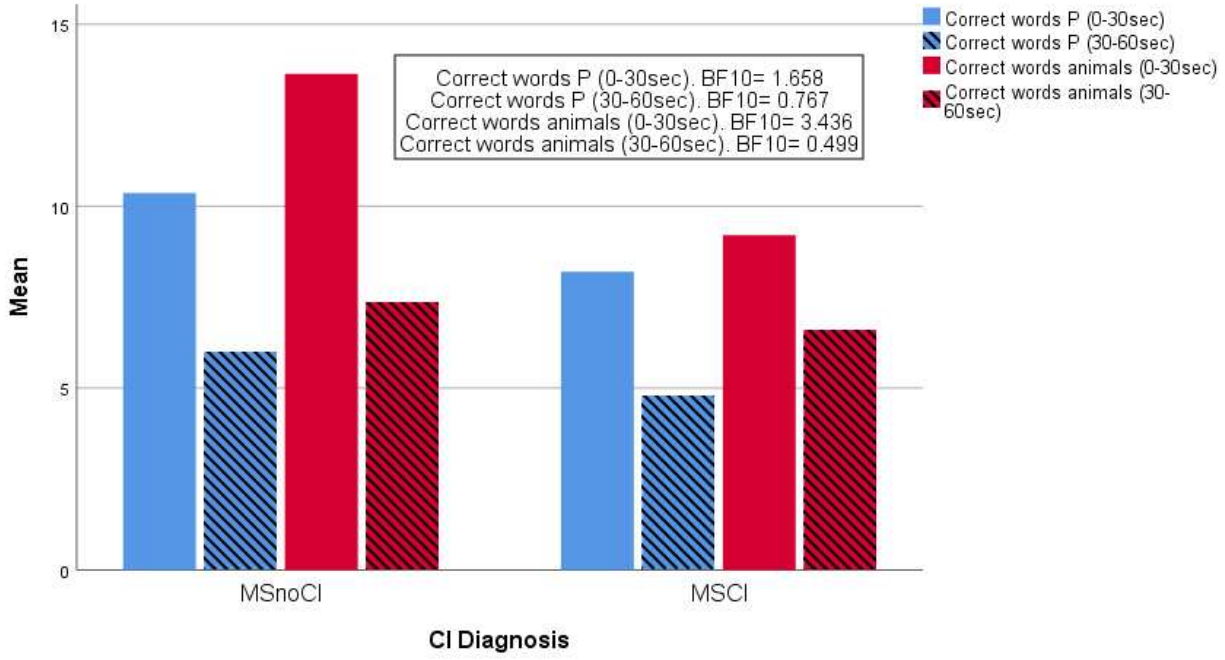

Figure 6.

Compared mean scores for "correct recalled words with P" and "correct recalled animal words" in 0-30 sec and 30-60 sec based on MSCI or MSnoCI diagnosis. MSCI: Multiple Sclerosis Cognitive Impairment**; MSnoCI:** Multiple Sclerosis no Cognitive Impairment**.**

For the second hypothesis, we analyzed the organizational strategies (switchings and clusters) in pVF and sVF based on the temporal moment of recall (0-30 sec, 30-60 sec) in the MSnoCI and MSCI groups. Regarding pVF, no differences were found in the number of clusters. The number of switches during the first temporal interval showed anecdotal evidence (BF10 = 1.008), with the MSnoCI group having a mean of 8.09 (±2.17) and the MSCI group of 6.20 (±2.17) (see **Figure 7**). In sVF, the number of clusters during the first interval showed differences (BF10 = 2.615), with the MSnoCI group having a mean of 4.45 (±1.29) and the MSCI group of 2.80 (±1.10). Discrepancies were found for the number of switches during the second interval (BF10 = 1.092), with the MSnoCI group having a mean of 3.09 (±1.45) and the MSCI group of 1.80 (±1.30) (see **Figure 8**). To observe the sequential analysis of accumulated evidence for the variables included in this hypothesis, refer to **Figures 11, 12, and 13** in **Appendix 7**.

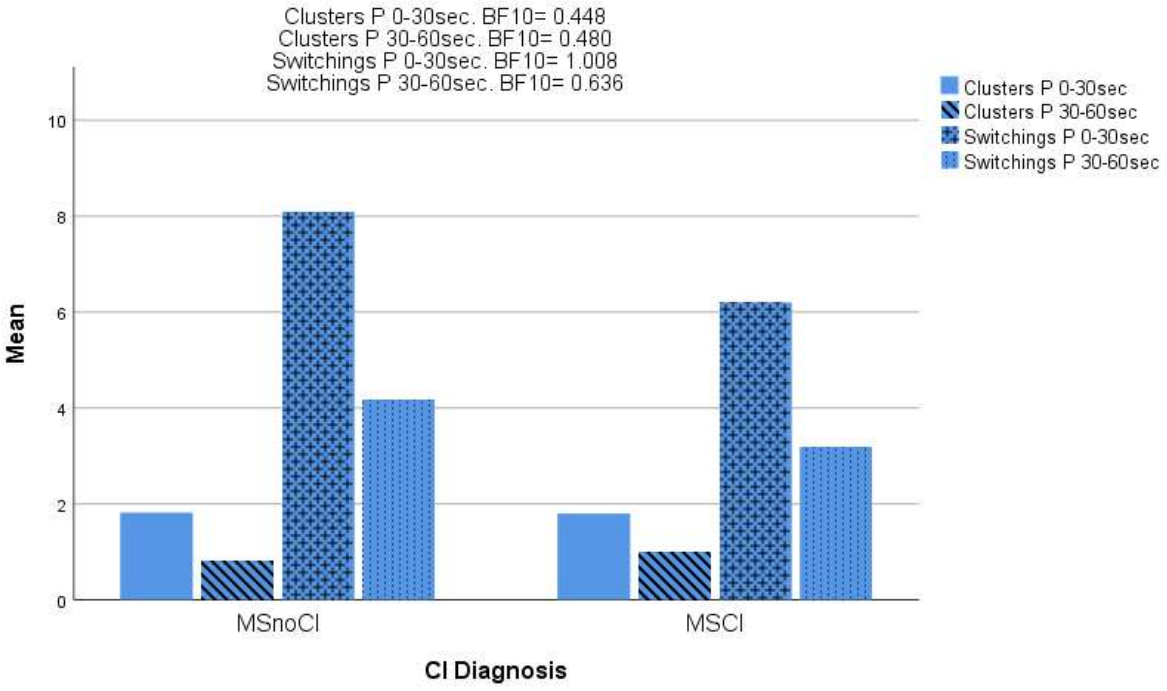

Figure 7.

Compared mean scores for "clusters and switches with P" in 0-30 sec and 30-60 sec regarding MSCI or MSnoCI diagnosis. MSCI: Multiple Sclerosis Cognitive Impairment**; MSnoCI:** Multiple Sclerosis no Cognitive Impairment.

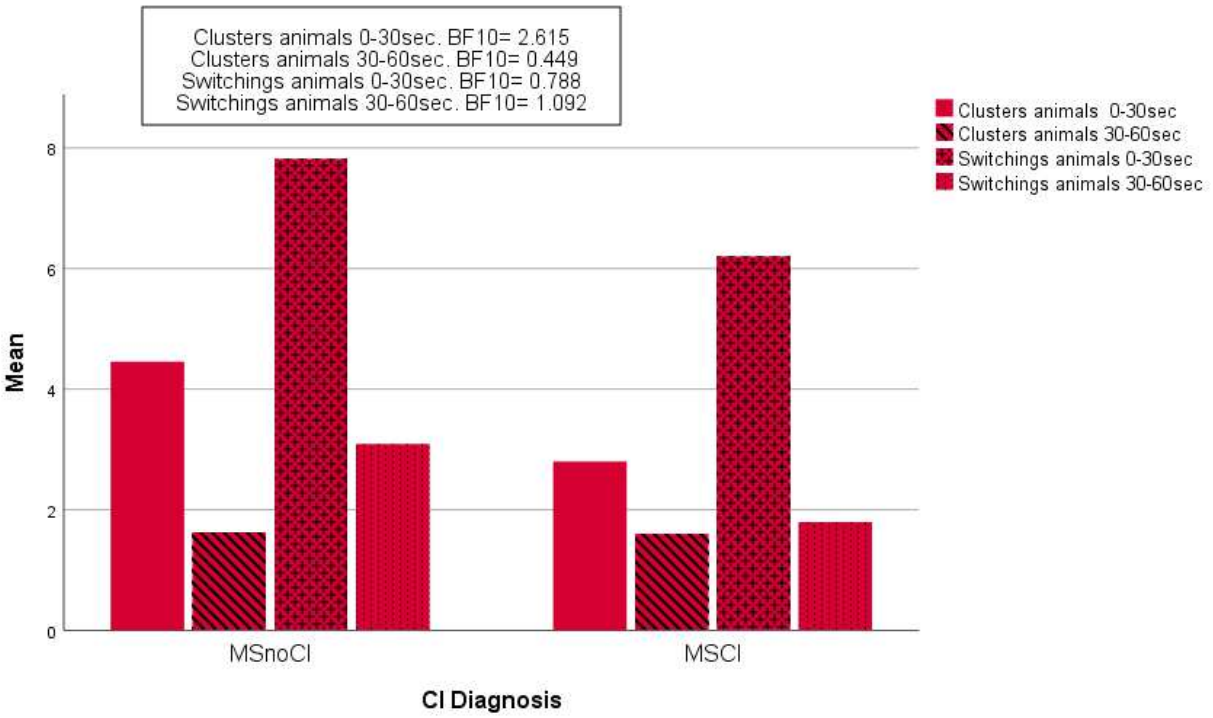

Figure 8.

Compared mean scores for "clusters and switches related to animals" in 0-30 sec and 30-60 sec regarding MSCI or MSnoCI diagnosis. MSCI: Multiple Sclerosis Cognitive Impairment; **MSnoCI**: Multiple Sclerosis no Cognitive Impairment.

3.3. Process analysis underlying VF. Study of relationships between cognitive domains and number of word recalled.

To analyse the relationships between attention, memory, language, and EF domains and performance (number of words recalled and organizational strategies) in pVF and sVF, Bayesian Pearson correlations were conducted.

Regarding the first hypothesis, a process analysis was conducted for the total number of evoked words in sVF and pVF. The number of words evoked with P showed a moderate correlation with the language domain (R=0.753; BF10=54.508), and animals with both, language (R=0.794; BF10=143.798) and EF (R=0.848; BF10=781.308), in moderate and high degrees, respectively. For the second hypothesis, the number of evoked words was analysed based on time intervals (0-30sec, 30-60sec). In pVF, there was a relationship between the number of words during the first time interval (0-30sec) and the domains of memory (R=0.680; BF10=14.413), language (R=0.773; BF10=86.455), and EF (R=0.730; BF10=34.647), all positively correlated in a moderate manner. In sVF, the number of words during the first time interval showed a relationship with memory (R=0.731; BF10=35.059), language (R=0.711; BF10=24.100), and EF (R=0.820; BF10=303.803), with all

relationships being positive and moderate except for EF, which resulted in a high magnitude. No prediction of cognitive processes was obtained for any of the variables in the second time interval (see **Table 9**).

Table 9.

Relationship, magnitude, and directionality between overall performance in FV and cognitive processes.

	Attention	Memory	Language	EF
Total correct words P				
Pearson coefficient	0.423	0.569	**0.753**	0.652
BF10	1.054	3.506	**54.508***	9.578
Correct words P 0-30sec				
Pearson coefficient	0.538	**0.680**	**0.773**	**0.730**
BF10	2.600	**14.413***	**86.455***	**34.647***
Correct words P 30-60sec				
Pearson coefficient	0.120	0.239	0.463	0.329
BF10	0.338	0.445	1.392	0.632
Total correct words animals				
Pearson coefficient	0.548	0.648	**0.794**	**0.848**
BF10	2.853	9.063	**143.798***	**781.308***
Correct words Animals 0-30sec				
Pearson coefficient	0.538	**0.731**	**0.711**	**0.820**
BF10	2.576	**35.059***	**24.100***	**303.803***
Correct words Animals 30-60sec				
Pearson coefficient	0.190	0.081	0.377	0.312
BF10	0.388	0.321	0.803	0.584

Note. *Correlation with substantial evidence for one of the hypotheses. EF: Executive Functions

3.3. Process analysis of VF. Investigating relationships between cognitive domains and organizational strategies.

Lastly, for the fourth objective, Bayesian Pearson correlations were conducted to analyse the relationship between attention, memory, language, and EF domains and the organizational strategies (switchings and clusters) used in pVF and sVF, both in total and within time intervals (0-30sec and 30-60sec).

In the first hypothesis, the total clusters and switchings strategies in pVF and sVF were examined. Evidence of correlation was found between the number of animal clusters and EF (R=0.743; BF10=44.544), as well as the total number of switchings and attention (R=0.687; BF10=16.131), both positively and in a moderate degree. However, no organizational strategy in pVF was related to the collected cognitive domains. Regarding the second hypothesis, strategies were studied within the first and second time intervals in pVF and sVF. Specifically for animals, the number of clusters during the first time interval correlated with memory (R=0.660; BF10=10.688) and EF (R=0.686; BF10=15.909). All observed relationships were positive and moderate. Once

again, no cognitive process predicted organizational strategies within time intervals in the phonological task (see **Table 10**).

Table 10.

Relationship, magnitude, and directionality between organizational strategies and cognitive domains.

	Attention	Memory	Language	EF
Total clusters P				
Pearson coefficient	-0.080	0.119	0.310	0.410
BF10	0.321	0.337	0.580	0.972
Clusters P 0-30sec				
Pearson coefficient	0.017	0.180	0.234	0.349
BF10	0.309	0.379	0.439	0.695
Clusters P 30-60sec				
Pearson coefficient	-0.247	-0.077	0.307	0.319
BF10	0.457	0.320	0.572	0.604
Total switchings P				
Pearson coefficient	0.377	0.395	0.510	0.427
BF10	0.803	0.888	2.008	1.085
Switchings P 0-30sec				
Pearson coefficient	0.386	0.482	0.567	0.500
BF10	0.842	1.601	3.451	1.849
Switchings P 30-60sec				
Pearson coefficient	0.141	0.126	0.238	0.141
BF10	0.350	0.341	0.444	0.350
Total clusters animals				
Pearson coefficient	0.431	0.581	0.643	**0.743**
BF10	1.110	4.010	8.445	**44.544***
Clusters animals 0-30sec				
Pearson coefficient	0.354	**0.660**	.618	**0.686**
BF10	0.710	**10.688***	6.127	**15.909***
Clusters animals 0-30sec				
Pearson coefficient	0.220	0.001	0.182	0.257
BF10	0.421	0.308	0.381	0.472
Total switchings animals				
Pearson coefficient	**0.687**	0.464	0.248	0.387
BF10	**16.131***	1.399	0.458	0.850
Switchings animals 0-30sec				
Pearson coefficient	0.618	0.444	0.261	0.441
BF10	6.115	1.216	0.478	1.186
Switchings animals 30-60sec				
Pearson coefficient	0.500	0.340	0.258	0.265
BF10	1.849	0.664	0.475	0.486

Note. *Correlation with substantial evidence for one of the hypotheses. EF: Executive Functions

4. DISCUSSION

Throughout this study, the relevance of neuropsychological assessment in screening for CI in patients with MS has been demonstrated. MS is one of the chronic conditions associated with a high degree of disability in young adults. Therefore, the main objective of this study was to analyse the efficacy of VF tasks as a screening tool due to their high sensitivity in MS (Henry & Beatty, 2006). Specifically, we investigated the overall performance and organizational strategies employed by participants in sVF and pVF tasks. Additionally, we observed subject performance based on temporal intervals, given the previously established influence of this variable on performance (Pitteri et al., 2023).

The study of VF in MS lacks methodological consensus. Despite its clinical relevance and interest, the most recent systematic review was conducted by Henry & Beatty in 2006. In the recent literature review conducted in this study (Table 3), the variability in the selected letter restriction for PVF tests (P, M, R, F, A, S) and the categories used for SVF tasks (animals, foods and beverages, fruits and vegetables, colours, and boys' names) stands out. Regarding performance analyses, the type of organizational strategies collected shows similarity across different studies, with a focus on clusters, average clusters size, and the number of switchings. Additionally, two approaches for assessing performance over time are proposed: one suggested by Crowe (1998), involving analysis at four temporal moments (every 15 sec), and another proposed by Fernaeus & Almkvist (1998), which defines two time intervals (0-15 sec, 15-60 sec). Only one study in MS considered temporal factors, collecting variables within two execution intervals during the task. The existing literature is limited, and as mentioned, there is considerable controversy in the results due to the lack of a standardized administration or correction protocol for these tasks.

In our research, although the number of participants is limited, the population characteristics of the pathology were adequately represented, obtaining data similar to the epidemiological studies provided by the Multiple Sclerosis International Federation (n.d.). Specifically, our sample was characterized by an average age of 43 years, with a predominance of women diagnosed with RRMS. Despite the small sample size, the advantages of the Bayesian probabilistic approach allow us to interpret and discuss the provisional results without drawing definitive conclusions (Martín et al., 2019).

Our results revealed evidence of differences between the MSCI and MSnoCI groups for both VF tasks. This discrepancy was more pronounced in the sVF task. Although research in MS has primarily focused on pVF, various authors have attempted to explain the differences found in semantic tasks. Lebkuecher et al. (2021) analysed the involvement of language and EF in both VF tasks and, contrary to expectations, identified deficits in lexical access speed and vocabulary, which are highly related to sVF tasks. Additionally, Amunts et al. (2021) highlighted that sVF, and particularly the total words evoked, can be used as a screening tool for executive dysfunction—a domain often impaired in MS. In this context, Delgado-Álvarez et al. (2021) also demonstrated an association between sVF and EF, although with lower extent than with memory processes. Regarding performance analysis, our results showed evidence of group differences both in the total words evoked and in clusters

and switching strategies. Our findings were similar to those obtained by Velázquez-Cardoso et al. (2014), who described deficient clusters strategies and, consequently, a higher number of switchings in MS patients. However, no study has previously analysed the discriminatory sensitivity level of these variables for CI. Except for Delgado-Álvarez et al. (2021), who despite investigating the predictive capacity of VF for CI and EF in these patients, they did not specified which of the variables included.

In contrast to many studies, the evidence found for pVF between MSCI and MSnoCI is weaker compared to that obtained in sVF. Some researchers did not observe differences between the two tasks in terms of their efficacy in discriminating between healthy individuals and MS patients (Messinis et al., 2013). However, previous studies indicate greater impairment in pVF because it is more strongly associated with EF and less with memory processes, unlike sVF (Delgado-Álvarez et al., 2021; Pitteri et al., 2023). Connick et al. (2012) analysed the utility of VF as a screening tool for CI in subjects with progressive forms of MS compared to healthy individuals. For pVF, an execution of fewer than 10 words achieved a more balanced sensitivity and specificity, 85% and 86%, respectively. In contrast, naming animals showed a sensitivity of 93% and specificity of 61% for an execution of fewer than 20 words. However, most studies that have analysed VF in MS have compared patients to healthy controls, which may explain the lower evidence obtained when comparing between MS groups. Additionally, Meca-Lallana et al. (2021) observed a higher prevalence of dysexecutive syndromes in progressive forms of MS, so the greater presence of RRMS in our sample could make it challenging to observe differences in this task due to clinical homogeneity.

The differences observed in pVF and sVF regarding EF may be attributed to the variability in the tests used to assess this cognitive domain (Delgado-Álvarez et al., 2021). Currently, EF is considered a broad term encompassing various processes such as inhibitory control, working memory, and cognitive flexibility, among others. Not to mention the methodological differences in each task, such as timing and materials (Greek alphabet letters, Latin alphabet, etc.). In this context, the authors suggest a greater involvement of processing speed of execution, rather than EF in general, as tasks with higher correlation include time tracking (Lebkuecher et al., 2021).

Regarding the first study objective, our results provide evidence in favour of differences between groups for the total number of correctly evoked words with P and animals, although with anecdotal evidence. Various authors have previously investigated performance in VF tasks and organizational strategies among patients with MS and healthy subjects, observing changes in VF between groups with and without CI, especially in the phonological restriction task (Altun et al., 2024; Velázquez-Cardoso et al., 2014).

Regarding the second hypothesis about organizational strategies, the results show variations in the number of clusters in animals and the number of switchings in P and animals. There are discrepancies of means between groups for all organizational strategies, except for the total number of clusters with P. These results do not agree with the existing literature. Unlike the findings of Velázquez-Cardoso et al. (2014), in our study, the MSnoCI group evoked a greater number of words both in the total number of switchings with P and in animals. This discrepancy in the number of switchings could be due to the higher number of words evoked by the MSnoCI group.

Additionally, it's worth noting that Velázquez-Cardoso et al. (2014) obtained such results by comparing MS patients with healthy controls. Regarding variations in the total number of clusters in animals, the obtained result supports the initially proposed hypothesis, the MSnoCI group performed more clusters than the MSCI group..

For the second objective, we included execution time in the comparisons for the number of evoked words and organizational strategies. First, regarding the hypothesis about the total number of words, we found substantial evidence between groups for the correct words of animals during the 0-30 sec period, with the MSnoCI group evoking a greater number. For the second time interval (30-60 sec), we did not find discrepancies between the two groups. Therefore, the results from the sVF task performance do not confirm our initial hypothesis. The MSnoCI group evoked a greater number of words only in the first time interval, unlike the findings of Pitteri et al. (2023), who highlight the second time interval (30-60 sec) as the most sensitive to CI between MS patients and healthy individuals. In fact, our results show anecdotal evidence of the absence of variations in most analysed variables for the second time interval (30-60 sec). For the pVF task, similar to animals, the correct words with P in the first time interval (0-30 sec) also show anecdotal evidence. The MSnoCI group evoked a greater number of words, confirming the proposed hypothesis.

Again, finding differences in the first interval but not the second could be because both compared groups consist of MS patients, which might homogenize clinical characteristics and reduce the possibility of differences between the groups. Additionally, Pitteri et al. (2023) emphasize the second time interval as the most sensitive due to its association with EF, which are frequently altered in MS compared to controls. Meanwhile, the first interval could be more related to lexical access speed and vocabulary, and its performance might show more differences between different MS profiles, as indicated by our results and suggested by Brandstadter et al. (2020) and Lebkuecher et al. (2021).

Regarding the second hypothesis about organizational strategies, no evidence was found for differences between the two groups in terms of the number of clusters and switchings with P. It is expected that accumulating more data may reveal differences for the number of switchings with P during the first time interval. However, for the sVF task, the results showed discrepancies in the number of clusters during the first time interval (0-30 sec) and in the number of switchings during the second interval (30-60 sec). In the first case, the obtained data coincide with the initially proposed hypothesis, where the MSnoCI group performed a greater number of groupings.

On one hand, the clusters strategies seem to support our hypotheses, based on previous results by Delgado-Álvarez et al. (2021). The group MSnoCI shows better performance in average scores (a higher number of clusters) when the analyses indicate both, differences or absence between groups. However, for the number of switchings, the MSCI group achieved scores related to a more efficient strategy than those obtained by the MSnoCI group (Delgado-Álvarez et al., 2021; Velázquez-Cardoso et al., 2014). As explained earlier, this discrepancy in the number of switchings could be due to faster lexical access in the MSnoCI group, resulting in a greater number of words and therefore more switchings.

To expand our understanding of VF tasks, we conducted a process analysis for the total evoked words and organizational strategies, as well as execution times. Various authors have proposed different cognitive domains as predictors of VF, highlighting the wide range of cognitive functions involved in these tasks. Specifically, both pVF and sVF are related to naming tasks, memory, and EF. However, sVF is more closely related to the memory domain, while pVF is associated with EF (Delgado-Alonso et al., 2021; Lebkuecher et al., 2021).

For the third objective regarding the total evoked words in different time intervals, the correlations show similar relationships of cognitive domains with pVF and sVF. However, while the total correct words with P correlate positively and significantly with language, and the total animals correlate with language and EF, the words evoked during the first time interval (0-30 sec) with both P and animals show substantial evidence of a relationship with memory, language, and EF domains. Notably, in this case, contrary to what Delgado-Álvarez et al. (2021) and Lebkuecher et al. (2021) describe, sVF exhibits a stronger relationship with the EF domain. Despite the magnitude of the correlation, the initial hypothesis would be confirmed based on the obtained results. In fact, these results support previous evidence of greater differences in sVF between groups, both in total performance and organizational strategies, given its stronger association with EF tasks.

Finally, regarding the fourth study objective concerning organizational strategies employed, substantial evidence of relationship was found only for the sVF task during the first time interval (0-30 sec) between clusters and memory, overall performance and EF, as well as the total number of switchings and attention. In this case, despite providing evidence in favour of a relationship, the results do not agree with our initial hypotheses. Delgado-Álvarez et al. (2021) previously indicated that regardless of the task type, the total number of switchings showed a significant relationship with EF, and the total number of clusters was related to memory. As mentioned at the beginning of this section, differences in the role of EF in VF tasks across studies could be due to the inclusion of different tests and the heterogeneity of the construct used. In this context, Delgado-Álvarez et al. (2021) suggest incorporating non-time-dependent attention-executive tasks.

The results described above have significant professional implications in the clinical and research fields. Substantial evidence of differences between groups with and without CI in patients with MS opens the door to future lines of research that analyse the diagnostic utility of VF tasks. Additionally, the administration and scoring characteristics of the test make it suitable for inclusion in settings where specialized neuropsychologists are unavailable or economic and time resources are lacking. Regarding process analysis, identifying the cognitive domains that predict patient performance on specific variables is crucial for interpreting neuropsychological assessment results.

As the main limitation of this research, the obtained results must be interpreted with caution due to the small participant sample size, as previously mentioned. However, the sociodemographic and clinical characteristics of the included subjects adequately represent the population with the disease in Spain in terms of educational level and phenotypic manifestation frequency.

Regarding future research, it's important to note that the only systematic review found about impairment in VF task in MS patients was conducted in 2006 (Henry & Beatty, 2006). However, this review did not include a detailed analysis of organizational strategies or consider different phenotypic manifestations. Therefore, we intend to conduct a meta-analysis on VF task impairment in MS patients, incorporating the analysis of organizational strategies (switchings and clusters). This inclusion would allow for a more precise understanding of the impact of MS on this task and its diagnostic utility.

Furthermore, recruiting a group of healthy individuals for comparison with both MS groups, with and without CI, would help to understand the results obtained in this study. Additionally, the limited diversity of phenotypic manifestations in the current recruitment makes it challenging to compare VF tasks across different types of MS. As part of the project to which this work belongs, it is necessary to analyse whether there are differences in VF performance for various degrees of CI, considering the variables explored in this study. Various authors have previously indicated differences in the neuropsychological profile of these manifestations (Jellinger, 2024; Piacentini et al., 2023; Rosca & Simu, 2020) (see Table 1). The results would allow us to identify disease progression patterns and increase the likelihood of predicting the phenotypic manifestation that an individual will develop. Specifically, the research objective would be to determine whether there are differences in the use of organizational strategies (switchings and clusters) during pVF and sVF tasks among different disease phenotypes: RRMS, PPMS, SPMS, and PRMS.

Finally, similar to Connick et al. (2012), we aim to calculate the threshold for impairment in organizational strategies during pVF and sVF tasks for MS patients with and without CI. To achieve this, we will perform a discriminative analysis by comparing receiver-operating characteristic (ROC) curves. Through this discriminative analysis, we will obtain optimal cut-off points with higher sensitivity and specificity.

5. CONCLUTIONS

Due to the limitations of this study, none of the obtained results allow for definitive conclusions regarding the study objectives and hypotheses due to the small sample size included in this research. However, Bayesian analyses provide an initial approximation to the results:

- The existence of evidence for differences between the MSnoCI and MSCI groups would support the use of the VF task as a screening test for CI.
- Participants with and without CI showed differences particularly in their performance during the sVF task (animals), both in word recall and the use of organizational strategies (clusters and switchings).
- The MSnoCI and MSCI groups obtained differences in the first time interval (0-30 sec) for most variables, indicating greater sensitivity to CI than in the late time interval (30-60 sec).

- While words evoked with P correlate with language and, animals with language and EF, the first time interval (0-30 sec) for both VF tasks is related to memory, language, and EF.
- Organizational strategies in sVF resulted in correlations between the total number of clusters and EF, the total number of switchings and attention, and clusters during the first time interval (0-30 sec) with memory and EF. No cognitive process predicted strategies in pVF.

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7. APPENDICES

APPENDIX 1. McDonald diagnostic criteria for MS (Hawkes y Giovannoni, 2010).

Clinical presentation	Additional data for MS diagnosis
• >2 attacks • Objective clinical evidence of >2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
• > 2 attacks • Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: >1 T2 lesion in at least 2 of 4 MS typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)
• 1 attack • Objective clinical evidence of >2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack
• 1 attack • Objective clinical evidence of 1 lesion (CIS)	Dissemination in space and time, demonstrated by: Spacial dissemination: • ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial or spinal cord or Await a second clinical attacka implicating a different CNS site. Temporal dissemination: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow- up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack.
• Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: • Evidence for dissemination in space in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions • Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord. • Positive cerebrospinal fluid (isoelectric focusing evidence of oligoclonal bands and/or elevated lgG index).

CIS: Clinically Isolated Syndrome; **MS**: Multiple Sclerosis; **PPMS**: Primary Progressive Multiple Sclerosis

APPENDIX 2. Informed consent.

DOCUMENTO DE DECLARACIÓN DE CONSENTIMIENTO

ESTUDIO DE INVESTIGACIÓN: ADAPTACIÓN DE LA BATERÍA DE EVALUACIÓN NEUROPSICOLÓGICA COMPUTARIZADA 'COGNITO' EN MUESTRA ESPAÑOLA DE PACIENTES CON ESCLEROSIS MÚLTIPLE Y SU RELACIÓN CON LAS ACTIVIDADES DE LA VIDA DIARIA

Unidad de Neurología del Hospital Universitario Médico Quirúrgico del Hospital de Jaén

Universidad de Granada

Yo, (nombre del paciente)

……

Manifiesto que:

- He hablado con el equipo médico responsable de este estudio de investigación y se me ha ofrecido suficiente información acerca de su objetivo, métodos utilizados, beneficios esperables y posibles inconvenientes.
- Además de la información verbal, he leído el impreso informativo adjunto, comprendiendo todos sus puntos.
- He podido realizar preguntas sobre el estudio y mis dudas han sido suficientemente aclaradas.
- Comprendo que mi participación es voluntaria y que puedo cambiar de opinión sin que ello repercuta en mis cuidados médicos posteriores.

Presto libremente mi conformidad para participar en este estudio.

Firma del paciente: Firma del médico que informa:

Nombre: Nombre:

Fecha: Fecha:

C.N.P.:

.

Master´s Thesis, 2023-24: [Organizational strategies in VF as a potential screening tool for CI in people diagnosed with MS] [F. J. Pérez Comino].

APPENDIX 3. Semi-structured sociodemographic and clinical interview.

PLANTILLA ESPECÍFICA EM (ESCLEROSIS MÚLTIPLE)

Criterios de inclusión	Criterios de exclusión
1. Capacidad de leer y comprender el castellano. 2. Cumplir el diagnóstico de EM según los criterios de McDonald. 3. Tiempo de evolución entre el último brote y el momento de la evaluación superior a un mes. 4. Edad comprendida entre los 18 y los 64 años.	1. Mostrar alguna deficiencia sensoriomotriz que dificulte la aplicación de COGNITO. 2. Padecer algún tipo de alteración neurológica que pueda justificar la posible sintomatología cognitiva. 3. Estar recibiendo tratamiento con fármacos antiepilépticos, antipsicóticos, narcóticos opiodes e inhibidores de la colinesterasa.

Sexo: Mujer ☐ Hombre ☐ **Edad:**

Estudios: Primarios ☐ Secundarios ☐ Bachiller ☐ FP ☐ Universitarios ☐ Máster ☐ Doctorado ☐

Estatus laboral: En activo ☐ No activo ☐

Dominancia manual: Diestro ☐ Zurdo ☐

Medicación actual: No ☐ Sí ☐

Indica cuál:

Tratamiento NO Farmacológico (marque el/los que procedan):

Terapia Ocupacional ☐ Grupos de Apoyo ☐ Fisioterapia ☐
Logopedia ☐ Rehabilitación ☐ Otros (Indíquelo):

Fuma: No ☐ Sí ☐ Consumo de tabaco (nº de cigarrillos/día): Tiempo que lleva fumando:

Hipertensión Arterial (HTA): No ☐ Sí ☐

Diabetes: No ☐ Sí ☐

Colesterol: No ☐ Sí ☐

Tipo de EM (marque lo que proceda):

1. **Esclerosis múltiple con recaídas o remisiones** ☐
2. **Esclerosis múltiple progresiva secundaria** ☐
3. **Esclerosis múltiple progresiva primaria** ☐

Año en que fue diagnosticada:

Tiempo de evolución:

.
Master´s Thesis, 2023-24: [Organizational strategies in VF as a potential screening tool for CI in people diagnosed with MS] [F. J. Pérez Comino].

Tasa de brotes (nº de brotes en el último año):

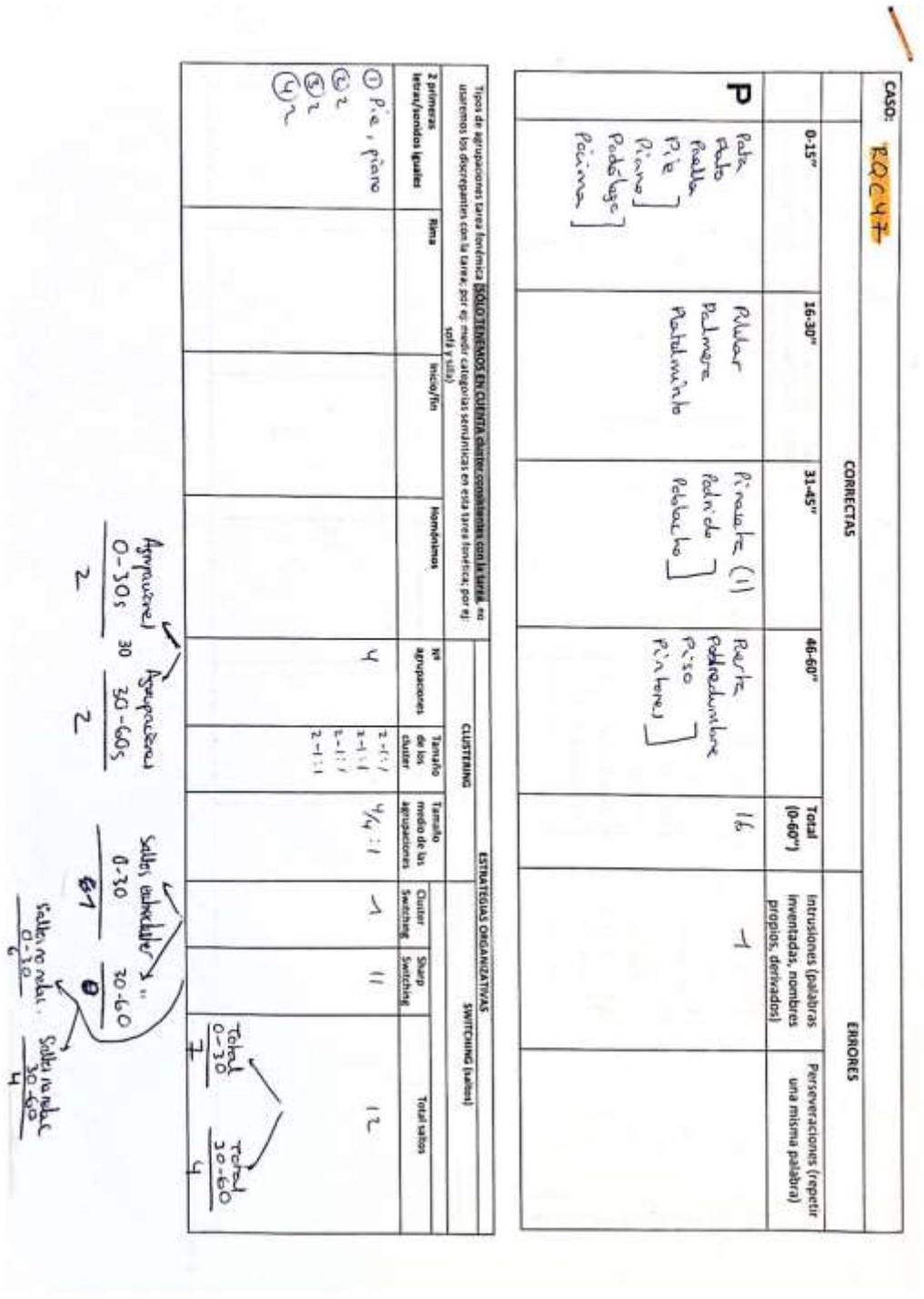
Evolución en diagnóstico de tipo de EM:

Puntuación EDSS:

Neuritis Óptica: No ☐ Sí ☐

Note. As instruments were applied in Spanish, all of them are attached in this language. Along the text, all these variables can be read can be found already translated to the english.

APPENDIX 4. Data extraction sheets for the qualitative analysis of VF



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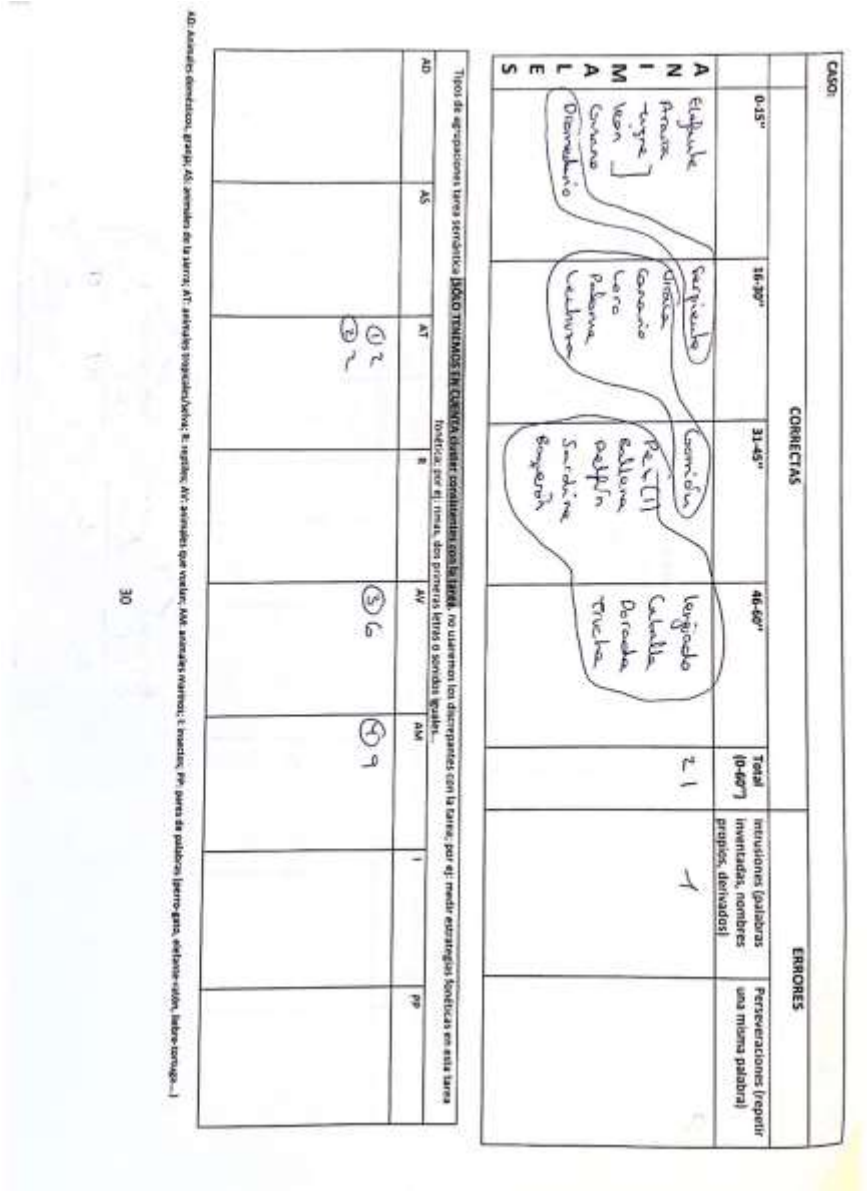
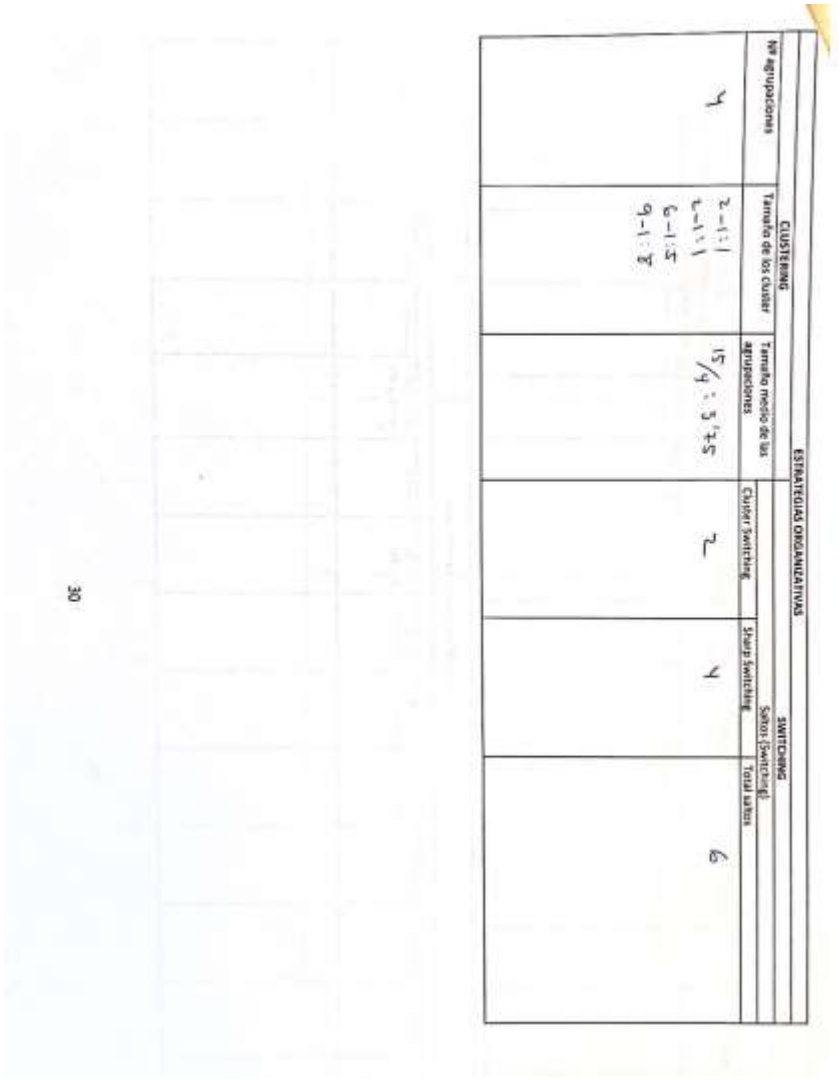
APPENDIX 4. Data extraction sheets for the qualitative analysis of VF



Note. As instruments were applied in Spanish, all of them are attached in this language. Along the text, all these variables can be read can be found already translated to the english.

APPENDIX 4. Data extraction sheets for the qualitative analysis of VF



Note. As instruments were applied in Spanish, all of them are attached in this language. Along the text, all these variables can be read can be found already translated to the English.

APPENDIX 5. STROBE checklist.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how matching of cases and controls was addressed	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	

APPENDIX 6. Project approval document of Ethics Committee

Hospital Universitario de Jaén
Servicio Andaluz de Salud
CONSEJERÍA DE SALUD Y FAMILIAS

4.1.Enero.CEI

COMITÉ DE ÉTICA DE LA INVESTIGACIÓN DE LA PROVINCIA DE JAEN

Dª. Ana Laura Ortega Granados, Secretaria del Comité de Ética de la Investigación de la Provincia de Jaén,

CERTIFICA

Que este Comité en su reunión de 30/01/2020, ha evaluado la propuesta para realizar el Estudio de Investigación titulado:

TITULO DEL ESTUDIO (TD): **"Adaptación de la batería de evaluación neuropsicológica computarizada COGNITO en muestra española de pacientes con Esclerosis Múltiple y su relación con las actividades de la vida diaria"**
INVESTIGADOR/ES PRINCIPAL/ES: **Tutora Asistencial Dª. Diana Vidal de Francisco, Tutora Académica Dª. Carmen Rosa Saez Zea, Doctoranda Dª. Mª de las Nieves Revert Alcántara.**
PROTOCOLO: COGNITO / 1264-N-19 Versión y fecha: 1 de 12/06/2019
HIP y CI: Versión: 1 de 12/06/2019

Y considera que,

- Se cumplen los requisitos necesarios de idoneidad del Protocolo y de la Hoja de Información al Paciente y Consentimiento Informado, en relación con los objetivos del estudio y se ajusta a los principios éticos, aplicables a este tipo de estudios.
- La capacidad del/a Investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Están justificados los riesgos y molestias previsibles para los participantes.
- Que los aspectos económicos involucrados en el Proyecto, no interfieren con respecto a los postulados éticos.

Por ello, el Comité de Ética de la Investigación de Jaén, tras la valoración del citado estudio, **APRUEBA** la realización del mismo.

Lo que firmo en Jaén, a 30 de enero de 2020,

CONSEJERÍA DE SALUD
SERVICIO ANDALUZ DE SALUD
COMITÉ DE ÉTICA DE LA
INVESTIGACIÓN

Fdo.: **Dª. Ana Laura Ortega Granados**
Secretaria del CEI de Jaén

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APPENDIX 7. Sequential analyses of the accumulated evidence in the dependent variables analyzed**.**

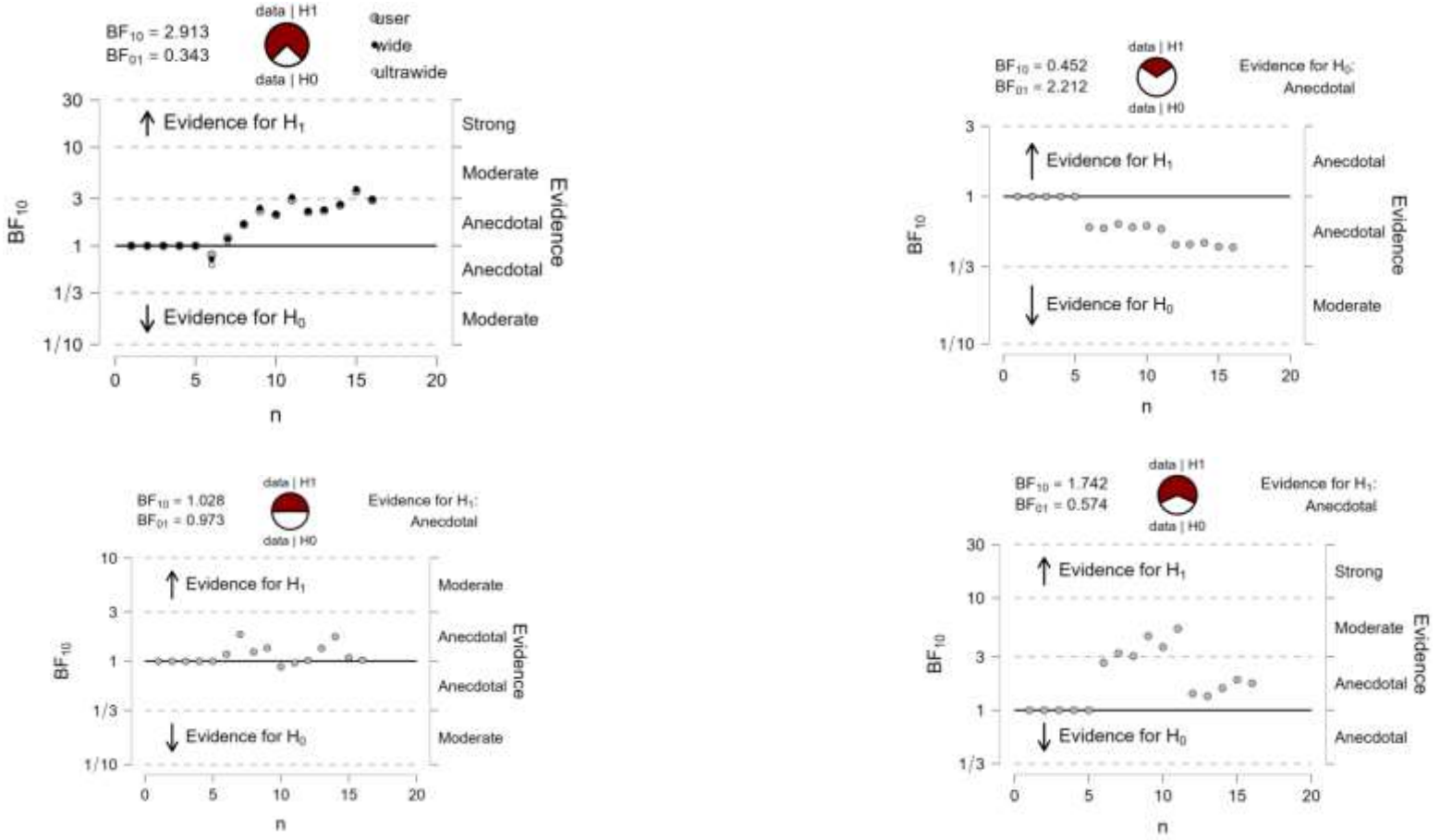

Figure 9.

From left to right and top to bottom, sequential analysis for the total correct animal words, total P clusters, total P switches, and total animal clusters

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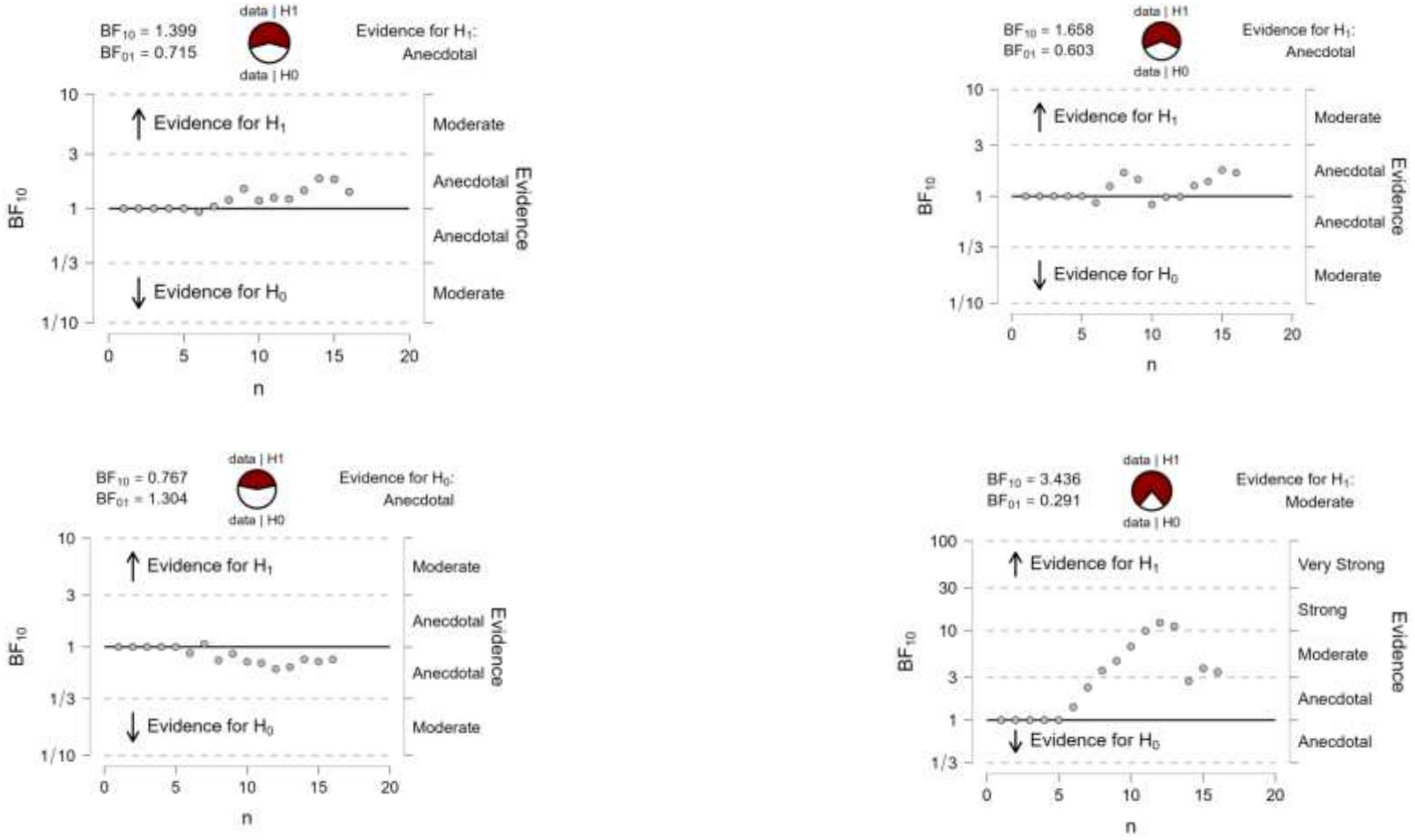

Figure 10.

From left to right and top to bottom, sequential analyses of the accumulated evidence for the number of animal switches, number of words 0-30 sec, number of words 30-60 sec, and animal words 0-30 sec.

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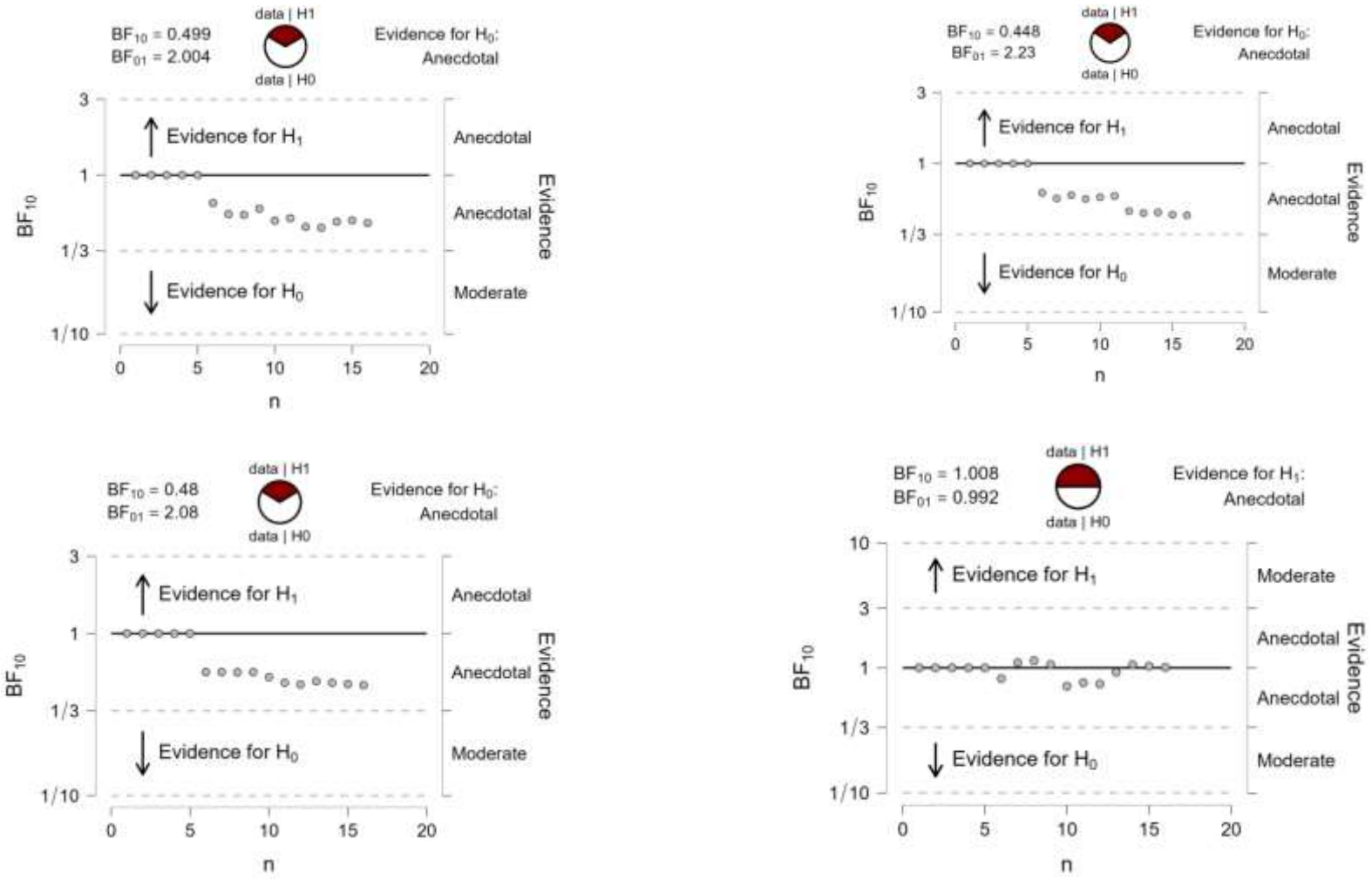

Figure 11.

From left to right and top to bottom, sequential analysis of the accumulated evidence for the total number of animal words 30-60 sec, number of P clusters 0-30 sec, number of P clusters 30-60 sec, and number of P switches 0-30 sec.

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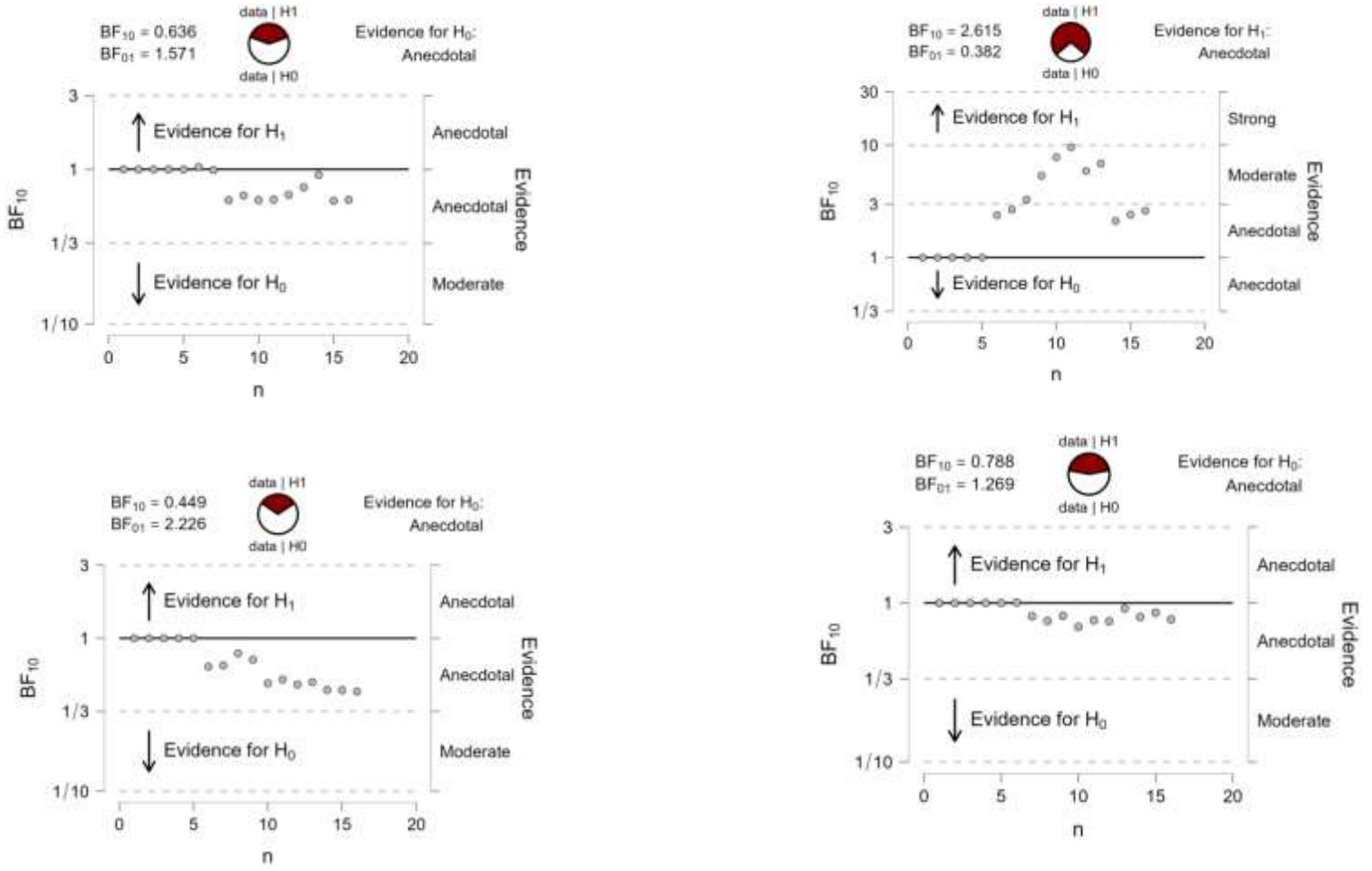

Figure 12.

From left to right and top to bottom, sequential analysis of the accumulated evidence for the number of P switches 30-60 sec, number of animal clusters 0-30 sec, number of animal clusters 30-60 sec, and number of animal switches 0-30 sec.

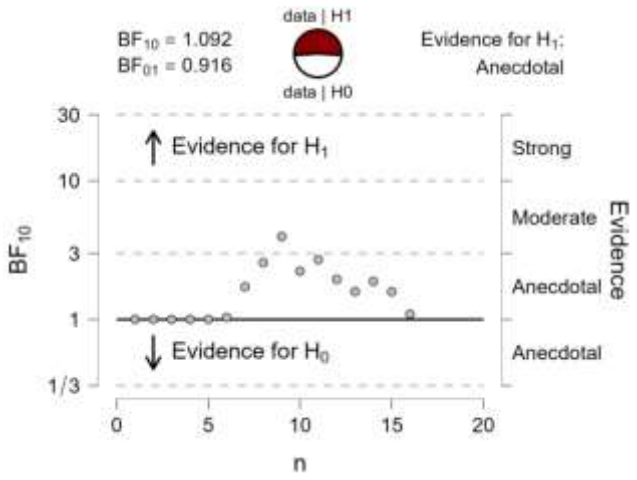

Figure 13.

Sequential analysis of the accumulated evidence for the number of animal switches 30-60 sec.