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What (more) can verbal fluency tell us about multiple sclerosis?

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Abstract

Background. Clinical symptoms of multiple sclerosis (MS) are variable and may include cognitive impairment, which can be assessed with the verbal fluency test (VFT). This test is evaluated by counting words spoken during a 2-min period, which is not a functional approach.

Objective. The objectives of this observational study were to 1) determine new parameters that reflect communication and cognitive functions in persons with multiple sclerosis (PwMS) considering the evaluation of real-time word production in the VFT; 2) compare the results with those of a control group; and 3) evaluate the impact of including errors.

Methods. A phonological fluency test (“letter P”) and a semantic fluency test (“animals”) were used. The real-time word production was recorded. The main variables studied were the total number of words, first word delay, moment of inflection of the curve corresponding to the change in the cognitive process, speed of word production before inflection, and maximum delay between 2 consecutive words. These variables were studied by taking into account or not errors.

Results. We included 68 PwMS and 33 healthy controls. VFT results were impaired in PwMS. The total number of words, first word delay, speed before inflection, and maximum delay were relevant to the study of phonologic fluency. For studying semantic fluency, the total number of words, first word delay, speed before inflection, and inflection time of the curve seemed relevant. Taking into account errors was significant only for total number of words.

Conclusion. Taking into account errors in evaluating real-time word production in PwMS is of interest only for the total number of words performed but has no impact on the variables studied. These variables should be used to quantitatively evaluate verbal fluency with the objective of evaluating functionally relevant parameters (communication).

Key words. multiple sclerosis; verbal fluencies; cognitive impairment

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. Clinical symptoms of MS are variable but may often include cognitive impairment [1]. Indeed, cognitive impairment is described in 40% to 70% of persons with multiple sclerosis (PwMS) [2] in all forms and at all stages of the disease and even at a preclinical stage such as isolated clinical syndrome in which cognitive disorders can affect 12% to 80% of patients [3,4] The most affected and most-studied cognitive domains are episodic memory and information-processing speed [5]. Working memory, executive function, attention, language, and, more recently, social cognition are other affected domains that have been investigated in PwMS [5,6]. These alterations lead to negative repercussions on daily living activities [7], social life, and quality of life [8] of PwMS.

The first step in managing cognitive impairment in PwMs is its identification and quantification. Batteries of cognitive tests for PwMS exist, but they are difficult to administer in standard consultation except for the Brief International Cognitive Assessment for MS (BICAMS), which offers a feasible, cost-effective means of assessing cognition [9,10]. Among the multiple tests used for these purposes, the verbal fluency test (VFT) is of interest for several reasons. The VFT reflects multifactorial demands such as lexical and semantic stores and executive functions that control and program verbal production, activity planning,

organization of responses, elimination of previously cited responses, and access to the mental lexicon [11]. The VFT is easy and short to administer, and the clinician does not have to depend on diagnostic equipment or require special training [12]. The VFT is also reliable, even for severe forms of MS [13], and it is a sensitive indicator of brain impairment [12] that has been found effective in assessing cognitive impairment with sensitivity and specificity of 80.6% and 97.2% [14].

Phonologic (e.g., letter “p”) and semantic (e.g., “animals”) fluencies are the most common tests [15]. Phonological fluency is more closely associated with phonologic memory and requires the creation of uncommon word-recall strategies based on their lexical features and suppressing meaning-based responses. In turn, semantic fluency is more closely associated with semantic stock and the property of grouping named objects into categories [16]. Phonologic fluency seems to have a larger executive component than semantic fluency [11]. Data from functional brain imaging showed that semantic fluency tasks are temporally lobe-dependent, whereas phonologic fluency depends more on the frontal lobe [17].

To perform the VFT, participants are required to generate as many words as possible within a fixed period of time in accordance with specific instructions. Usually, the quantitative analysis of the performance in VFT is the correct number of words [18]. This parameter is useful for showing an increase in cognitive function after treatment [11], but the average improvement of 2 words in 2 min on phonologic fluency does not reflect a functional impact on PwMS. This one is reflected by communication disorders, which depends on a number of factors including cognitive skills, especially verbal function [19].

Regarding the words produced during a specified time frame, some authors have been interested in the delay of a word response. The first of these researchers was Bousfield et al. in 1944 [20]. However, the concept was actually developed by Rohrer et al. in 1995 in patients with Alzheimer disease. The authors developed 2 parameters to analyse verbal

fluencies: the number of words produced and the mean number of words produced in 5 sec [21]. They also described the decrease in words produced during the test. Crowe et al. divided the time by 15 sec [22]. The authors observed a larger production of words during the first 15 sec with a great frequency of occurrence of words. This production profile suggests that the initial responses depend on rapid access to the lexico-semantic stock, which requires little effort. For later production, lexico-semantic stock search strategies are set up, with executive function [23]. Collectively, these results suggest that in addition to the number of correct words produced during a specified period [11,14], other analyses could provide new information about cognitive impairment in PwMS.

Moreover, errors are not taken into account in the fluency assessment [18]. Different types of errors can occur when the VFT is administered, such as the rule break error (e.g., words out of category), repetitions (e.g., words already generated that are produced again), and non-item production (e.g., interjections such as “um”) [12]. These errors may be considered a lack of inhibition and an inability to resist irrelevant information [24,25].

To our knowledge, no study has explored production in real time during the VFT in PwMS. This study aimed to 1) find new parameters that reflect communication and cognitive functions in PwMS, considering the evaluation of real-time word production measured with the VFT; 2) compare the results with those of a control group; and 3) evaluate the impact of including errors in the analysis.

Methods

Study design

This observational study was conducted at the University Hospital of Besançon. This study is a part of a clinical trial designed to evaluate the impact of fampridine on the functionality of PwMS. It was approved by the French national ethics committee (no. 13/405) and by the

French Health Products Safety Agency (no. 2013-A002305-56) and was registered at ClinicalTrials.gov (NCT02849782).

Participants

A group of PwMS and healthy individuals (controls) participated in this study. All participants were recruited during their usual ambulatory consultation in the departments of Physical Medicine and Rehabilitation and Neurology of the hospital between 2014 and 2019.

The inclusion criteria for PwMs depended on the initial protocol focused on the clinical gait analysis and were 1) age 18 to 80 years, 2) MS diagnosis based on the modified McDonald criteria [26], 3) Expanded Disability Status Scale (EDSS) score 4.0 to 6.5, and 4) able to walk for at least 6 min. The exclusion criteria were 1) worsening MS symptoms during the previous 60 days, 2) immunotherapy change in the previous 60 days, 3) initiation of treatment to decrease fatigue symptoms in the previous 30 days, and 4) modification of the rehabilitation program during the study.

For controls, inclusion criteria were men and women aged 18 to 80 years and affiliated with the French social security system. The exclusion criteria were motor or neurologic deficits that could interfere with cognition. All participant underwent assessments. Written informed consent was obtained from all participants.

Evaluations

Participant characteristics

A practitioner examined all participants to check for inclusion and exclusion criteria and to collect characteristics (i.e., age, sex, height, weight, body mass index [BMI], disease duration, EDSS, and MS type).

The impact of fatigue on participants was assessed with the Fatigue Impact Scale (FIS) [27] measured in 3 domains: cognitive (10 items), physical (10 items), and psychosocial (20 items). The FIS is a self-assessment survey in which participants score the impact of fatigue in specific situations (0 = no problem, 4 = extreme problem), for a total score of 160. A high score indicates greater impact of fatigue. This is the only scale of fatigue assessment for PwMS validated in French [28]. The FIS showed a good construct validity (Cronbach $\alpha > 0.87$) [27] and reliability (intraclass correlation coefficient 0.68–0.85) [29] in PwMS.

Information-processing speed was assessed with the Symbol Digit Modalities Test (SDMT) [30,31], which consists of a legend at the top of the page with 9 symbols and 9 equivalent numbers (from 1 to 9), and several lines with these symbols are depicted in a random order. During the test, participants are required to fill in correctly, as much as possible, the lines with the correct corresponding number in 90 sec. A higher score indicates better cognitive abilities. The SDMT has sensitivity of 74% and specificity of 76% for detecting cognitive impairment in MS [32]. The SDMT is reliable and has good to excellent reproducibility [33].

Verbal fluency

Cognitive impairment was assessed with the VFT. The tests were performed in a quiet room with a voice recorder. The participants were asked to provide as many words as possible in 2 min without making mistakes and without repeating themselves (cf. posttreatment below). For methodologic considerations (e.g., good performance in healthy population), we used the letter “P” for phonologic fluency and the category “animals” for semantic fluency [18].

Afterward, SPPAS, a free software (<http://www.sppas.org/>), was used to segment the audio track in accordance with the words produced by the participants. SPPAS allows for knowing the beginning and end of the production of each word with accuracy of 1 msec

[34,35]. After this phase, we listened to all fragments to confirm, identify, and transcribe the words into a spreadsheet (Microsoft Excel).

The accounting of errors followed the criteria used by Cardebat et al. and St-Hilaire et al. [18,36]. For both phonologic and semantic fluency tests, repetition was defined as the same word produced identically one or more times and was considered an error. For phonologic fluency, the following conditions were considered errors: proper nouns; different morphologic forms of a verb, noun, or adjective (e.g., *prince*, *princesse*; *petit*, *petite*); non-words; and words that do not start with the desired letter. Anglicisms and words with the same etymologic root, explaining that they referred to distinct concepts (e.g., *tableau*, *tablette*), were accepted. For words with a similar pronunciation, the second use was considered a repetition unless the participant spontaneously explained the meaning of the word or spelled the 2 words.

For semantic fluency, the following conditions were considered errors: declension of a subcategory of animals (e.g., *caniche*, *dogue*, *teckel*), non-words, a word that does not mean an animal, and the morphologic derivations of a word (e.g., *lion*, *lionne*, *lionceau*). The name of the female or the name of the young of an animal was counted if it was expressed with a different word.

In addition to 1) the total number of words currently used to assess the cognition of PwMS, the following variables were retained for each type of fluency (Fig. 1): 2) first word delay (seconds), which corresponds to the delay between the end of the instruction and the beginning of the first word (first word delay includes the processing of the retrieval cue and the initiation of the search process [21]); 3) inflection time (seconds), which corresponds to the time of the first break in the curve determined from the interval higher than 2 standard deviations (SDs) of the intervals (inflection time corresponds to the moment when the cognitive process changes from fast access to the semantic stock to search strategies in

semantic memory, in relation to the executive functions [23]); 4) number of words produced before the inflection of the curve, which corresponds to the semantic stock [23]; 5) speed before inflection (number/seconds), which corresponds to the speed of word production before inflection of the curve; and 6) maximum delay (seconds), which corresponds to the highest interval between producing 2 consecutive words. Maximum delay gives a more precise description of the recovery process itself [21].

Procedures

The evaluation was performed in a single day at the Clinical Functional Exploration Laboratory of the Movement. First, a practitioner checked the inclusion and exclusion criteria and examined all participants to collect their characteristics. After that, participants answered the FIS and SDMT. Then, the phonologic fluency test was performed, followed by the semantic fluency test. The control group underwent the same evaluation procedure, under the same conditions as the PwMS, except for the specific tests regarding MS (i.e., disease duration, EDSS, and MS type).

Analyses

Data management and analyses involved using Statistica v10 (StatSoft, USA). The results are expressed as mean (SD). Participants' characteristics were compared, when appropriate, by independent Student *t* test or chi-square test. To compare PwMS and the control group (between-factor) and fluencies with or without errors (within-factor) for all fluency variables, 2-way ANOVA was performed. Only the main effects (i.e., the group effect and with or without fluency errors) were considered in this study. $P < 0.05$ was considered statistically significant.

Results

We included 68 PwMS and 33 healthy individuals. Table 1 presents the participants' characteristics. We found no significant difference between the groups in terms of age, sex, height, weight, or BMI. For PwMS, the mean disease duration was 14.5 (10.4) years and the mean EDSS score was 5.2 (1.1). Secondary progressive MS was the main form (48.5%) followed by the primary progressive (30.9%) and relapsing-remitting (20.6%) forms. The groups differed in FIS and SDMT scores (both $p < 0.001$).

Figure 2 shows an example of time of word production for semantic and phonologic fluency tests for a participant in each group. Verbal fluencies were variable among participants for both tests. For phonologic fluency, word production for PwMS ranged from 5 to 33 words but from 8 to 39 for controls. For semantic fluency, word production for PwMS ranged from 5 to 42 words but from 18 to 50 for controls.

Table 2 shows the mean (SD) values for all verbal fluency variables studied and comparisons between groups and considering or not the errors in word production. By comparing the results of word production for the conditions with or without error, we found a significant difference only for total number of words, lower in the “non-error” group (phonologic: $p < 0.001$; semantic $p = 0.023$).

PwMS and controls did not differ in proportion of errors as compared with total number of words. The groups differed for most of the variables studied, for both phonologic and semantic fluency. The first-word delay and the maximum delay were higher for PwMS than controls and the total number of words, inflexion time, inflexion words, and speed before inflexion were lower.

The groups differed in inflection time for semantic fluency ($p = 0.002$) but not phonologic fluency ($p = 0.061$), and values were reversed as compared with semantic fluency: inflection time was later for PwMS than controls.

The speed before inflection was slower for PwMS than controls for both semantic and phonologic fluency ($p < 0.001$).

Discussion

We aimed to find potential new variables to evaluate cognitive impairments in the VFT for PwMS and controls. We took into account other variables reflecting word pattern production as well as the impact of the errors produced during this task. The use of the new variables previously cited provides a more complete clinical interpretation of the VTF, and the development of new processing software allows for precisely knowing the time of word production.

Batteries of cognitive tests in the MS have several tests in common, but a core battery termed the Minimal Assessment of Cognitive Function in MS (MACFIMS) evaluates the most domains (attention, working memory, executive functions, verbal and spatial episodic memory, language, spatial processing of information) [37]. However, it does not include semantic fluency. It requires 90 min to complete and is not feasible to administer during a standard consultation. The Brief International Cognitive Assessment for MS (BICAMS) has been proposed as an evaluation tool for practitioners [9]. It consists of 3 tests: SDMT, the first 5 reminders of the California Verbal Memory Test-II for verbal memory, and the first 3 reminders of the Brief Visual Memory Test-R for visual-spatial episodic memory. However, the BICAMS does not include a test for evaluating executive function or language. Information-processing speed can be evaluated by the SDMT [38]. Executive functions and semantic memory can be evaluated by the VFT, which has another advantage: the absence of the use of upper-limb motricity. These 2 types of tests could be a complementary and rapid way to evaluate the cognitive function of MS patients.

Usually, the VFT analysis does not take into account errors. Taking into account errors significantly modifies only the total number of words produced and has no impact on the variables we decided to study with a pure quantitative approach. The error rate has been found to increase switching for patients with a frontal lobe lesion, which manages inhibition capabilities [39]. However, in our study, the percentage of errors was not higher for PwMS than controls and seems not a criterion to detect executive dysfunction.

We found an increase in the first word delay for PwMS as compared with controls for both semantic and phonologic fluencies. A decrease in the speed of information processing may explain this finding of a lack of initiation in the 2 types of fluencies [40]. This parameter is interesting because it is totally independent of motor processing such as dysarthria; patients have not started word production during this period. This slowness in starting a verbal activity could have a social impact by making the beginning of a conversation more difficult and can therefore decrease repartee [41]. Feenaughty et al. [42] showed a correlation between speech disorders and communication.

Another parameter highlighted is the first inflection time of the curve. The inflection of a curve suggests a cognitive process change [23], from fast access to the semantic stock to search strategies in semantic memory, in relation to executive functions. For phonologic fluency, the first inflection time did not differ between PwMS and controls ($p = 0.061$). Indeed, the moment of cognitive process change cannot be highlighted because participants may use their executive abilities from the beginning of the test, as shown by the low speed before inflection [11]. Conversely, for semantic fluency, the inflection of the curve occurs earlier for PwMS. Abad et al. [43] studied semantic networks in PwMS: during the qualitative analysis of these networks, damage occurred in connectivity between words for PwMS. As a result, the speed of word production was slower and the semantic stock depleted more quickly for PwMS.

The maximum delay between 2 consecutive words was higher for PwMS than controls only for the phonologic fluency tests. The maximum delay corresponds to the duration of the recovery process [21], which requires the use of executive functions. Because phonologic fluency depends mainly on executive functions, the maximum delay between 2 words is longer for PwMS than controls if these functions are reached.

The total number of words, first word delay, speed before inflection, and maximum delay are relevant to the study of phonologic fluency. For the study of semantic fluency, the total number of words, first word delay, speed before inflection, and inflection time of the curve could be used.

These variables, easy to collect over the consultation time, provide relevant clinical data on the executive function in PwMS and should be used to quantitatively evaluate verbal fluencies with the additional objective of evaluating functional parameters (communication). We propose adding VFT to the BICAMS, using only animals and the letter “p” (in French language) and using the analysis proposed in this paper. This addition will allow for building a more complete battery of tests, including executive function assessment and an overview of communication, while remaining within 20 min completion time, including instructions [10].

Beyond the detection of cognitive disorders, this assessment is important for cognitive rehabilitation to evaluate speech progression in a therapeutic program. However, research on therapeutics in cognition is at an early stage, but preliminary work shows promise [44]. Our approach could help detect patients who need rehabilitation.

In our study, the EDSS score was 4 to 6.5 for PwMS, which corresponds to a moderate functional disability, and most patients were at an evolutionary stage of the disease. Therefore, the PwMS included had risk of cognitive impairment, particularly executive impairments [45], as suggested by impaired PwMS results as compared with controls on the SDMT. Our variables are relevant in this population with cognitive impairment. This method

of evaluation could be studied in early MS or isolated clinical syndromes and taking into account potential confounding factors such as anxiety/depression and sleep disorders in addition to fatigue, type of MS, socio-professional status, and pharmacologic and non-pharmacologic treatments. Particular attention could be paid to the articulation, which was recently found associated with decline in information processing speed [46]. Advances in data processing and speech recognition could allow for use in clinical practice.

Limitations

We included 68 PwMS and 33 controls in this descriptive study. Although the number of participants needed was not calculated, the difference between the number of PwMS and controls gives rise to type 2 error, which could explain why the first inflection time of the curve tended to be similar between PwMS and controls. Moreover, the number of participants included did not allow us to analyse some subgroups such as MS type.

Among the potential confounding factors, dysarthria, education level, and depression were not examined. In most studies of VFT, dysarthria is not studied [13,18,22]. Future studies should include socio-professional level of patients.

However, recently, Feenaughty et al. [41] demonstrated a negative combined effect of dysarthria and cognitive impairment for communication function. Cardebat et al. [18] showed the impact of education level during the VFT: performance was better in participants with a high educational level. Depression is common in PwMS [47], and it is also a symptom with a negative effect during the VFT [48]. The FIS score was collected for all participants in our study and was greater for PwMS than controls. The impact of this psychosocial factor on cognitive function has been discussed [49]. Future studies should take these factors affecting the performance of the VFT into account in to achieve the most objective results possible.

Conclusions

For PwMS, during the VFT, taking into account errors does not affect the variables studied depending on the time of word production. However, this should be analysed as an independent variable in a qualitative approach as a marker of inhibition disorders or working memory disorders. The use of these new variables allows for better characterizing cognitive disorders and a more accurate clinical interpretation of the results of the VFT for PwMS. Further studies are needed, particularly to study the internal validity related to executive functions and communication on one hand and reproducibility of this method to use the variables in a therapeutic approach on the other hand.

Conflict of Interest. We certify that this is an original work that has not been published nor submitted to another journal, that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated, and that the French ethical committee approved this study.

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Legends

Figure 1. Word production curve illustrating variables used for verbal fluency analysis.

Figure 2. A detailed example of words time production, in verbal fluency test (VFT), for a person with multiple sclerosis (PwMS) and a control.

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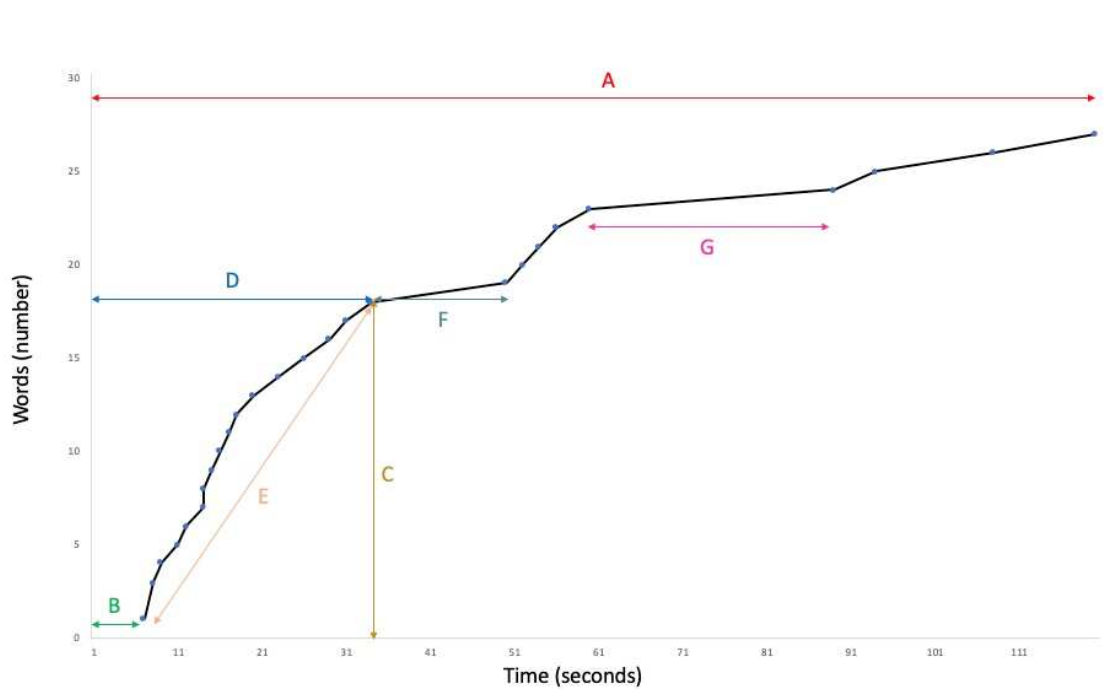
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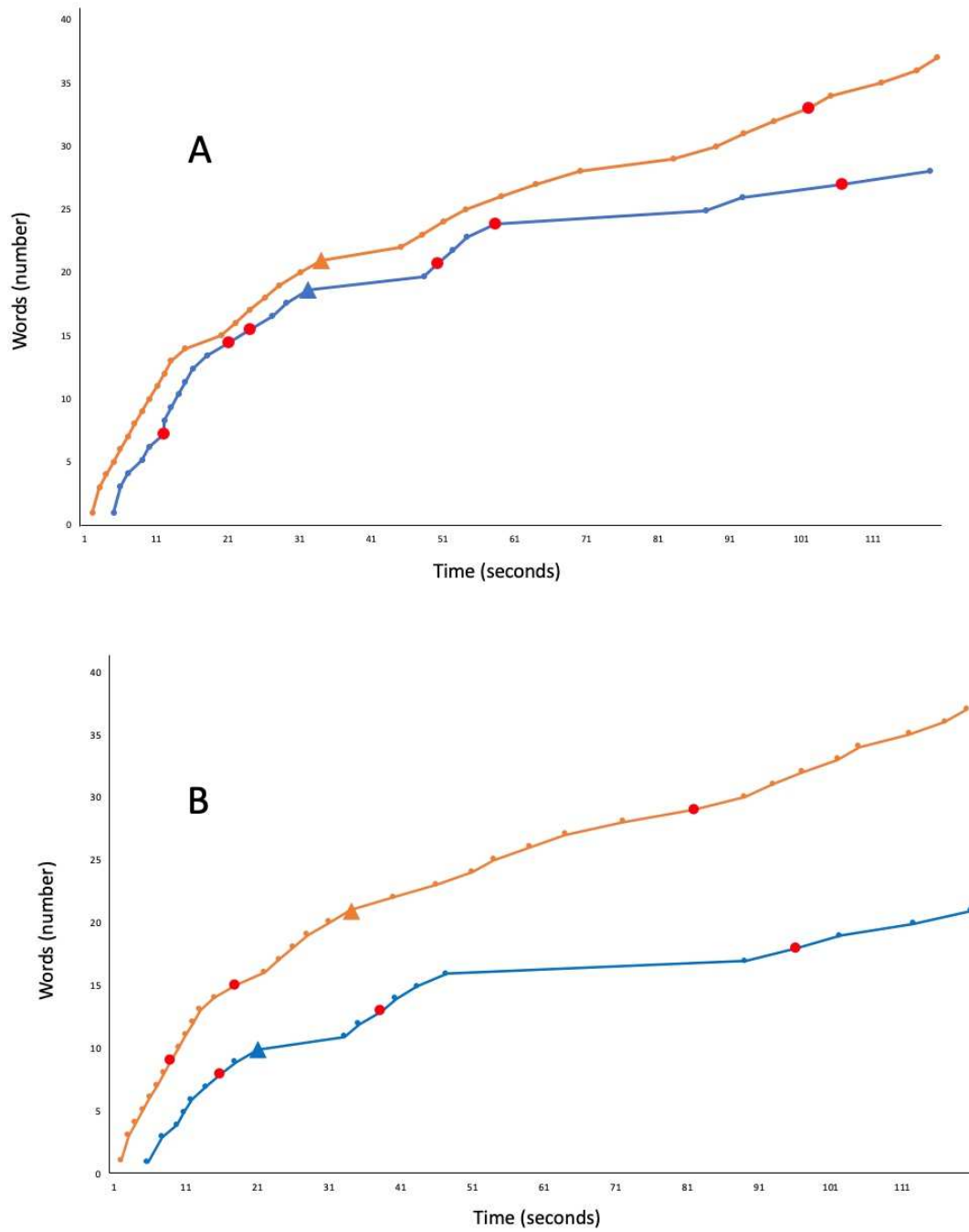
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Figure 1:



A: total number of words; B: first word delay; C: inflection time of curve; D: number of words before inflection; E: speed before inflection; F: 2 standard deviation; G: maximum delay

Figure 2:



A: phonological fluency; B: semantic fluency; / PwMS; / Controls; ● Words; ● Errors; ▲ Inflection time.

Table 1. Characteristics of persons with multiple sclerosis (PwMS) and controls.

	PwMS (n = 68)	Controls (n = 33)	<i>p-value</i>
Age (years)	52.3 (12.1)	49.4 (9.55)	0.230
Sex (male/female)*	45/23	21/12	0.801
Height (m)	1.7 (0.1)	1.7 (0.07)	0.157
Weight (kg)*	75.6 (17.7)	72.26 (13.07)	0.456
BMI (kg/m²)*	27.1 (6.3)	25.0 (3.8)	0.084
Disease duration (years)	14.5 (10.4)	NA	NA
EDSS (0-10)	5.2 (1.1)	NA	NA
MS type SP/PP/RR (%)	48.5/30.9/20.6	NA	NA
FIS (0-160)	58.2 (14.3)	37.8 (11.06)	< 0.001
SDMT (0-110)	32.9 (11.5)	52.4 (11.1)	< 0.001

Data are mean (SD).

BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SP, secondary progressive; PP, primary progressive; RR, relapsing remitting; FIS, fatigue impact scale; SDMT, Symbol Digit Modalities Test; NA, not applicable.

* Non-parametric

Table 2. Verbal fluency and comparison of the variables studied between PwMS and controls and between without and with errors conditions.

	PwMS (n = 68)		Controls (n = 33)		P value	P value
	No error	With errors	No error	With errors	PwMS vs Controls	No error vs with errors
“P”						
Errors (no.)		2.7 (1.7)		4.4 (5.5)	0.023	NA
Errors (%)		14.0 (9.4)		14.0 (11.8)	0.998	NA
Words (no.)	16.9 (5.43)	19.6 (5.9)	22.9 (6.3)	27.3 (9.4)	< 0.001	< 0.001
1 st word delay (sec)*	2.3 (4.01)	2.0 (3.6)	1.2 (1.2)	1.1 (1.1)	0.001	0.606
Inflection time (sec)	32.1 (17.1)	32.7 (18.7)	27.9 (18.1)	26.9 (16.5)	0.061	0.966
Inflection words (no.)	9.0 (4.2)	9.9 (4.5)	10.6 (5.1)	11.3 (6.2)	0.049	0.254
Speed before inflection (no./sec)	0.3 (0.1)	0.4 (0.2)	0.5 (0.2)	0.5 (0.2)	<0.001	0.302
Max delay (sec)*	26.5 (13.5)	22.6 (10.1)	21.7 (11.4)	19.6 (11.5)	0.003	0.052
“Animals”						
Errors (no.)		2.8 (2.5)		3.2 (3.7)	0.470	NA
Errors (%)		10.2 (9.0)		7.7 (6.1)	0.162	NA
Words (no)	24.6 (8.4)	27.35 (9.0)	34.9 (7.5)	38.1 (9.7)	< 0.001	0.023
1 st word delay (sec)*	1.8 (1.4)	1.75 (1.4)	0.9 (0.7)	0.9 (0.7)	< 0.001	0.814
Inflection time (sec)	30.7 (17.5)	32.8 (18.7)	41.0 (21.4)	40.1 (20.8)	0.002	0.685
Inflection words (no.)	11.7 (6.5)	12.7 (6.8)	18.2 (7.4)	19.3 (9.7)	< 0.001	0.358
Speed before inflection (no./sec)	0.4 (0.2)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	< 0.001	0.211
Max delay (sec)*	20.3 (12.5)	17.8 (8.8)	18.1 (9.0)	16.0 (7.5)	0.143	0.077

Data are mean (SD).

PwMS, persons with multiple sclerosis; NA, not applicable.

* Non-parametric test.