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Neuropsychological Alterations in Narcolepsy with Cataplexy and the Expression of Cognitive Deficits

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Abstract

Objective: The objective of our study was to assess attention processes and executive function in patients with narcolepsy with cataplexy (NT1). To do so, we compared the results with those of a control group from the general population using an extensive neuropsychological test battery. **Method:** We studied 28 patients with NT1 and 28 healthy control participants matched for age, gender, and educational level. They all completed questionnaires on sleepiness, anxiety, and depression symptoms. In addition, they underwent neuropsychological tests. The ability to maintain attention was assessed using three computer tasks with different levels of complexity. **Results:** Patients had significantly more daytime sleepiness than controls. A significant negative correlation between depression and disease duration was found in NT1 patients. The results of the anxiety questionnaire correlated with the presence of sleep paralysis. There were significant differences in information processing speed subtasks. Patients made significantly more omissions and generally reacted slower and more variably than controls in computerized tasks. As for executive function, patients performed worse in phonologic fluency tasks than controls. However, when the influence of processing speed on fluency tasks was statistically controlled, part of this significant difference disappeared. **Conclusions:** Our results indicate that the negative correlation between depression and disease duration probably reflects progressive adaptation to the functional burden of the disease. Information processing speed plays a fundamental role in the expression of cognitive deficits. We emphasized the need to control the influence of processing speed and sustained attention in the neuropsychological assessment of NT1 patients.

Keywords: Attention, Cognition, Depression, Executive function, Narcolepsy, Neuropsychological test

INTRODUCTION

Narcolepsy with cataplexy, or narcolepsy type 1 (NT1), is a chronic central hypersomnia with an estimated prevalence of 25–50/100,000 people (.025–.05%) (Longstreth, Koepsell, Ton, Hendrickson, & van Belle, 2007). NT1 is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and disrupted nocturnal sleep (American Academy of Sleep Medicine, 2014). The criteria for NT1 are cataplexy plus either of the following: (1) two sleep-onset rapid eye movement periods (SOREMPs) in the multiple sleep latency test (MSLT) or a SOREMP in the nocturnal polysomnogram plus one SOREMP in the MSLT; (2) a cerebrospinal hypocretin-1 concentration ≤110 pg/ml or <1/3 of mean values obtained in healthy individuals using the same standardized assay in addition to the excessive daytime sleepiness (American Academy of Sleep Medicine, 2014). The selective loss of hypocretin neurons located in the lateral hypothalamus is an etiologic factor in NT1 (De Lecea et al., 1998; Nishino, Ripley, Overeem, Lammers, & Mignot, 2000; Peyron et al., 1998). The mechanism underlying loss of neuronal hypocretin suggests an autoimmune process based on the association with the human leukocyte antigen (HLA) marker DQB1*06:02, which is an almost but not quite a risk factor for NT1 (Mahlios, De la Herrán-Arita, & Mignot, 2013; Mignot et al., 1992). Despite the many potential links between NT1 and autoimmunity, only a few genetic risk factors have been characterized to date. Together, these findings suggest that NT1 is a T cell-mediated autoimmune disease, with involvement of influenza-A as a critical trigger (Luo et al., 2018). The

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projections of the hypocretin system are widespread throughout the central nervous system and are involved in many behavioral functions (Nevárez & de Lecea, 2018). One study in mice suggests that the loss of hypocretin is associated with visuospatial working memory deficits (Dang et al., 2018). Since this finding has not been replicated in neuropsychological studies, only one study to date has reported poor performance in the Corsi block tapping test (Yoon, Joo, Kim, Hwang, & Hong, 2013). Other studies have pointed out the relationship between hypocretin and arousal and attentional processing (Fadel & Burk, 2010).

Several studies have shown that almost half of NT1 patients report learning and memory difficulties (Broughton et al., 1981). Nevertheless, subjective complaints are not always supported by the results of objective neuropsychological evaluations (Bayard, Croisier Langenier, Cochen De Cock, Scholz, & Dauvilliers, 2012; Zamarian et al., 2015). Subjective complaints are probably part of depressive symptoms, which are more frequent in NT1 patients than in the general population (Vandeputte & Weerd, 2003), as are anxiety symptoms (Ohayon, 2013). No precise neuropsychological profile of NT1 patients has been published to date. The two main cognitive processes affected in NT1 appear to be attention and executive function. Poor performance has been reported in tasks which assess sustained, selective, and divided attention (Naumann, Bellebaum, & Daum, 2006; Rieger, Mayer, & Gauggel, 2003; Zamarian et al., 2015). Specifically, findings for poor performance in long tasks related to sustained attention are consistent in the literature (Medrano-Martínez, Ramos-Platón, & Peraita-Adrados, 2018). Recent research has pointed to a deficit in the alerting network (Filardi et al., 2017), which could be related to limitations in cognitive processing resources (Naumann et al., 2006). As for executive function, NT1 patients have shown consistently poor performance in the inhibition of automatic responses, verbal fluency tasks, and decision-making according to their results in the Iowa Gambling Task (Delazer et al., 2011; Naumann et al., 2006; Zamarian et al., 2015).

The study of attention deficit in NT1 is usually based on two extended theoretical models (Posner & Petersen, 1990; Sohlberg & Mateer, 1987). Sohlberg and Mateer propose that attention is not a unitary concept but that it can be divided into different hierarchically organized subprocesses. Therefore, an alteration in "basic levels," such as sustained attention, could influence performance in other tasks. In the case of executive function, the factorial model developed by Miyake et al. (2000) identifies three executive components: (1) inhibition of prepotent response; (2) information updating and monitoring; and (3) set shifting. Other factors associated with this initial model include fluency (Fisk & Sharp, 2004) and behavior planning (Tirapu-Ustárroz, Cordero-Andrés, Luna-Lario, & Hernáez-Goñi, 2017).

In the present study, we hypothesized that processing speed may partially explain some of the performance differences described in executive function tasks. The aims of this study were as follows: (1) to assess changes in attention and executive function during task performance in NT1 patients and to compare the results with those of a control group; (2) to verify how information processing speed influences performance in other statistically controlled tasks; (3) to investigate changes in accuracy and response time in long tasks with different levels of complexity; (4) to assess the correlation between anxiety and depression symptoms and NT1 symptoms; and (5) to assess the correlation between anxiety and depression symptoms and cognitive deficits in NT1 patients.

METHODS

Patients

The study population comprised 30 Caucasian patients with NT1 (13 females; mean age, 40.9 ± 12.4 years; age range, 19–64 years) and different educational levels: high school education ($n = 11$; 39.3%); professional training ($n = 9$; 32.1%); and higher education ($n = 8$; 28.6%). The patients were recruited from the outpatient Sleep and Epilepsy Unit, Clinical Neurophysiology Service, University General Hospital Gregorio Marañón (University Complutense of Madrid), Madrid, Spain. NT1 patients were diagnosed using the criteria of the International Classification of Sleep Disorders, third edition (American Academy of Sleep Medicine, 2014). Mean age at diagnosis was 22.3 ± 9.5 years, and disease duration was 18 ± 2.2 years. All patients had sleep and cataplexy attacks, which were assessed based on sleep diaries. With respect to ancillary symptoms, 13 patients (46.6%) reported sleep paralysis and 6 patients (21.4%) had hypnagogic hallucinations in the 2 weeks preceding the assessment. Two patients were excluded because they had been diagnosed with a psychiatric disorder (eating disorder and post-traumatic stress disorder). A Beck Depression Inventory (BDI-II) score ≥ 17 was an exclusion criterion. Positive HLA DQB1*06:02 results were recorded in 26 patients, and negative results were recorded in two cases of familial hypocretin deficiency with a myelin oligodendrocyte glycoprotein mutation (Hor et al., 2011). Three out of twenty-eight NT1 patients had comorbid obstructive sleep apnea syndrome and were treated with nasal continuous positive airway pressure. Eighteen patients (64.2%) were under pharmacological treatment. Eight patients (28.6%) were treated with monotherapy (one patient was taking a stimulant, another an antidepressant, and the remaining six were taking sodium oxybate). Eight patients (28.6%) were treated with two drugs (three patients with a stimulant and an antidepressant, four patients with an antidepressant and sodium oxybate, and one patient with a stimulant and sodium oxybate). Finally, two patients (7.1%) were treated with polytherapy (stimulant, antidepressant, and sodium oxybate). The remaining 10 patients (35.7%) did not receive any pharmacological treatment 1 month before the assessment, although they took a nap after lunch and followed regular daily schedules for meals and night sleep. Patients decided to stop the medication temporarily for different reasons, such as change in their quality of life (e.g., holidays, better management of the non-pharmacological treatment, a less demanding job and more flexible schedule).

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Control Group

The control group consisted of 28 healthy Caucasian subjects (12 females; mean age, 40.9 ± 12.5 years; age range, 20–65 years) recruited from the general population and with different educational levels: high school ($n = 8$; 28.6%); professional training ($n = 9$; 32.1%); and higher education ($n = 11$; 39.3%). The control subjects were matched with the patients by age, gender, and educational level. The exclusion criteria were a BDI-II score ≥ 17 and an Epworth Sleepiness Scale score ≥ 10.

The Ethics and Clinical Research Committee of Gregorio Marañón University General Hospital approved the study. All participants signed an informed consent document, and the research was completed in accordance with the Declaration of Helsinki.

Procedure

Neuropsychological testing was performed in the morning between 10 am and 1 pm, and the approximate duration was 90 min. Lunchtime in Spain is around 2 pm. All participants completed the Epworth Sleepiness Scale questionnaire at the beginning of the assessment. Anxiety and depression questionnaires were only administered at the end. The presentation order of the neuropsychological tests was randomized. The participants did not take a break during the assessment, and none of them napped before testing.

Assessment of Excessive Daytime Sleepiness

The Epworth Sleepiness Scale assesses the possibility of falling asleep in different situations (Johns, 1991), and the maximum score is 24. According to the validated Spanish version, a score < 10 is considered normal (Izquierdo-Vicario, Ramos-Platón, Conesa-Peraleja, Lozano-Parra, & Espinar-Sierra, 1997).

Assessment of Anxiety and Depressive Symptoms

The BDI-II was used to assess depressive symptoms (Sanz & Vazquez, 2011). According to the manual, a cut-off score ≤ 17 is recommended for clinical research (Beck, Steer, & Brown, 1996). The State-Trait Anxiety Inventory (STAI) was administered to estimate the level of anxiety (Spielberger, Gorsuch, & Lushene, 1970). The STAI consists of two subscales, state (STAI-S) and trait (STAI-T): STAI-S assesses the level of anxiety during the evaluation, whereas STAI-T assesses predisposition to being in a state of anxiety (Buela-Casal, Guillén-Riquelme, & Seisdedos Cubero, 2011).

Neuropsychological Evaluation

Trail making test

The Trail Making Test (TMT) consists of two parts (AIBT, 1944). TMT-A was used to assess speed processing and visuoperceptual abilities, and TMT-B was used to assess working memory and alternating attention (TMT-B). Additionally, in this study, the difference between TMT-B and TMT-A was calculated to eliminate the influence of processing speed and working memory (Sánchez-Cubillo et al., 2009; Strauss, Sherman, & Spreen, 2006).

Stroop word and color test

In this test, the subject must read the three parts of the Stroop test as fast as possible, that is, (a) monochromatic words (StroopW); (b) colors (StroopC); and (c) the color of the ink in which the name of the color is printed (StroopWC). In the third part, the subject must inhibit an automatic response, whereas StroopW and StroopC can be used to estimate processing speed (Ríos-Lago et al., 2008). The interference index (Golden, 2007) was used to assess the automatic response inhibition process proposed elsewhere (Friedman & Miyake, 2004).

Digit and arithmetic test

The digit and arithmetic tests (fourth edition of the Wechsler Adult Intelligence Scale) were administered according to the standard protocol (Wechsler, 2012). The digit tests were used to assess verbal working memory.

Verbal fluency

The subject must utter as many words as possible within a certain category in 1 min. Phonologic fluency was evaluated using the FAS test (Benton, Hamsher, & Sivan, 1994). For the assessment of semantic fluency, the category was "animals".

Zoo map test

The Zoo Map Test from the Behavioral Assessment of the Dysexecutive Syndrome battery assesses planning ability (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). In this study, the time to complete the first part of the test was recorded owing to its relationship with processing speed (Oosterman, Wijers, & Kessels, 2013).

Computerized assessment of maintenance of attention

Three computer tasks, each of which had a different level of complexity (Medrano-Martínez, 2019), were conducted to assess changes in performance and reaction time in long tasks. The duration of each task was 5 min, and hits, omissions, false positives, and reaction time were recorded. In the first task, a simple response time task, a circle formed by other smaller circles appeared on the screen. One of these smaller circles advanced one position at a time. The subject had to press a button when the circle advanced two positions instead of one. The circle advanced one position per second. In the second task, the multiple response time task, the subject

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Table 1. Questionnaire scores

	NT1 ($n = 28$) (Mean ± SD)	Controls ($n = 28$) (Mean ± SD)	p-Value	d
ESS	16.3 ± 4.3	6.1 ± 2.7	<.001[a]	2.8
BDI-II	8.7 ± 5. 3	4.4 ± 3.7	.001[a]	.954
STAI-S	15.0 ± 8.7	7.2 ± 7.5	.001[a]	.963
STAI-T	23.5 ± 8.5	11.1 ± 7.2	<.001[a]	1.5

ESS, Epworth Sleepiness Scale; BDI-II, Beck Depression Inventory (2nd ed.); STAI-S, State-Trait Anxiety Inventory: State; STAI-T, State-Trait Anxiety Inventory: Trait.
[a] $p < .05$

had to press a different button depending on where the stimulus (asterisk) appeared on the screen. There were four different positions for the appearance of random stimuli. The stimulus remained on the screen for 250 ms, with a delay between stimuli of 1 s. In the third task, the complex response time task, a three-digit number appeared on the screen. The subject had to press a button only if all digits within this number were even or odd. The stimulus remained on the screen for 250 ms, and the subject had 1 s to decide and respond.

Statistical Analysis

Quantitative variables are expressed as mean ± SD or median and interquartile range. Qualitative variables are expressed as frequency and percentage. The t test or the Mann–Whitney test was used for numerical variables depending on the normality of the distribution. The association between qualitative variables was studied using the chi-squared test and Fisher's exact test. An ANCOVA was performed with StroopW as a covariable to evaluate the performance of fluency tasks. The results for the influence of pharmacological treatment on cognition and the influence of the duration of NT1 on the patient's group were analyzed using nonparametric statistics. Correlation analyses (Pearson r or Spearman ρ) were carried out to assess the influence of anxiety and depression. Cohen's d was reported as a measure of effect size, with values of .41, 1.15, and 2.70 suggesting, respectively, a minimum, moderate, and strong effect size (Ferguson, 2009). Differences were considered statistically significant if $p < .05$. The analyses were performed using SPSS Statistics for Windows, Version 17.0.

RESULTS

Table 1 summarizes the questionnaire scores for perceived sleepiness, depression symptoms, and anxiety. The mean Epworth Sleepiness Scale score was 16.3 ± 4.3 in patients and 6.1 ± 2.7 in the control group; perceived daytime sleepiness was significantly higher in the NT1 group. As for depression symptoms, significant differences were found between groups in the BDI-II scores. Although the NT1 group reported more depressive symptoms, the mean score was below the cut-off for standardized values. BDI-II scores did not correlate with performance in the neuropsychological tests. In the STAI, patients showed higher anxiety levels in both subscales than controls. With respect to the relationship between anxiety levels and performance in neuropsychological tests, STAI-S scores only correlated with the digit sequencing subtest performance ($r = -.50$; $p = .001$). Another correlation analysis between the STAI-S score and narcolepsy symptoms revealed the only significant relationship to be for the presence of sleep paralysis ($\rho = .45$; $p = .015$).

We analyzed the correlation between disease duration, narcolepsy symptoms, and anxiety and depression symptoms. There was a significant negative correlation between the BDI-II score and disease duration ($\rho = -.44$, $p = .018$). Patients were treated with sodium oxybate and with doses of antidepressant that were significantly lower than those administered to depressive patients. To ensure that this correlation was not due to the duration of treatment, we verified that it was the same regardless of whether disease duration was intermediate or long. No significant correlation was found between years of disease duration and narcolepsy symptoms.

Neuropsychological Test Battery

Table 2 summarizes the scores achieved in the neuropsychological tests.

Attention and Information Processing Speed

Information processing speed

There was a significant difference in performance in StroopC, in that the patient group named fewer colors than the control group. Performance in StroopW and TMT-A was similar in both groups.

Sustained attention

The scores obtained in the computer tasks are shown in Table 3. In the simple response time task, patients reacted significantly slower than the control group; however, the total number of hits was similar. Both groups also differed significantly in the number of omissions and false positives. The patient group performed worse than the control group in the multiple response time task. They made more omissions and reacted slower than the control group. The complex response time task was the most demanding task of the three. Again, the patient group performed worse than the control group and had more omissions. However, the reaction time was similar in both groups.

To summarize, the number of omissions was different between groups in all tasks. The NT1 group achieved fewer hits than the control group in the multiple and complex response time tasks. Concerning reaction time, the NT1 group reacted slower than the control group in the simple and multiple response time tasks.

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Table 2. Results of the neuropsychological assessment

	NT1 ($n = 28$) (Mean ± SD)	Controls ($n = 28$) (Mean ± SD)	*p*-Value	*d*
Trail Making Test				
TMT-A	27.6 ± 8.3	26.9 ± 8.0	.74	.087
TMT-B	63.9 ± 20.1	62.2 ± 15.9	.83	.090
TMT B-A	36.3 ± 18.5	35.4 ± 13.4	.83	.057
Stroop Test				
Stroop W	108.2 ± 16.4	116.2 ± 16.7	.076	−.484
Stroop C	72.9 ± 13.3	81.0 ± 11.6	.019[a]	−.644
Stroop WC	47.3 ± 8.9	52.9 ± 7.8	.014[a]	−.679
Stroop Interference	3.9 ± 4.9	5.4 ± 7.0	.35	−.248
Digit Test				
Forward	9.8 ± 2.5	9.7 ± 1.6	.88	.034
Backward	8.4 ± 2.7	8.7 ± 1.6	.63	−.127
Sequencing	7.8 ± 2.1	8.9 ± 1.7	.050	−.534
Arithmetic	13.5 ± 2.3	14.7 ± 2.2	.050	−.536
Verbal fluency tasks				
F/min	12.9 ± 3.3	14.9 ± 4.1	.007[a]	−.747
A/min	12.7 ± 3.6	15.5 ± 4.9	.018[a]	−.650
S/min	14.3 ± 3.4	17.3 ± 5.4	.019[a]	−.648
Total score	39.2 ± 7.7	47.8 ± 12.8	.004[a]	−.808
Semantic	23.7 ± 6.5	26.1 ± 4.9	.13	−.408
Zoo Map Test				
Total score[b]	14.5 (11.0–16.0)	15.5 (12.0–16.0)	.42	−.232
Time	146.5 ± 78.5	111.39 ± 58.52	.06	.501

TMT-A, Trail Making Test – Part A; TMT-B, Trail Making Test – Part B; B-A, difference between TMT-B and TMT-A.
[a] $p < .05$.
[b] Median, interquartile ranges and Mann–Whitney test.

Table 3. Results of computerized assessment of attention maintenance

	NT1 ($n = 28$) (Mean ± SD)	Controls ($n = 28$) (Mean ± SD)	*p*-Value	*d*
STRT				
Hits	27.7 ± 5.7	29.9 ± 4.2	.10	−.441
Omissions[a]	1.0 (.0–2.7)	.0 (.0–1.0)	.041[b]	.656
FP[a]	2.0 (1.0–4.0)	1.0 (.0–1.7)	.008[b]	.276
RT-Hits	724.4 ± 81.4	683.8 ± 48.8	.034[b]	.878
MTRT				
Hits[a]	220 (192.3–225.0)	229 (216.2–223.0)	.003[b]	−.716
Omissions[a]	5.0 (3.0–23.5)	1.0 (.0–4.7)	.001[b]	.547
FP[a]	11.50 (7.0–21.7)	8.0 (5.0–14.7)	.15	.429
RT-Hits	566.2 ± 108.7	483.7 ± 76.1	.002[b]	.878
CTRT				
Hits	9.3 ± 5.8	14.5 ± 6.5	.002[b]	−.851
Omissions	16.6 ± 6.9	12.2 ± 6.5	.017[b]	.655
FP[a]	14.0 (8.2–26.5)	13.5 (10.0–22.0)	.94	.136
RT-Hits	777.3 ± 205.3	780.4 ± 149.6	.95	−.017

STRT, simple response time task; FP, false positives; RT, response time; MTRT, multiple response time tasks; CTRT, complex response time tasks.
[a] Median, interquartile ranges and Mann–Whitney test.
[b] $p < .05$

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Selective attention and alternating attention

The NT1 group performed worse than the control group in StroopWC. In the case of alternating attention, no differences were found between groups in TMT-B or in the difference between TMT-B and TMT-A.

Working Memory

The NT1 group showed similar performance in the forward digit subtest and in the backward digit subtest. The groups achieved different results in the digit sequencing subtest and in the arithmetic test. The patient group remembered one digit less than the control group.

Executive Function

Automatic response inhibition

The groups showed similar performance in the interference index score, despite the significant differences found in StroopC and Stroop WC.

Verbal fluency

Performance in the semantic fluency task was similar in both groups. However, there were significant differences in all the phonologic fluency subtasks and in the total score. The patient group named three words fewer per minute than the control group, regardless of the initial letter. An ANCOVA was carried out to validate these results. Significant differences were maintained in the first subtest ($p = .028$) and in the total score ($p = .019$). The differences for the second subtest (A) and third subtest (S) were not significant. The model in which the "total score" was the dependent variable explained 25% of the variance.

Planning ability

There were no significant differences in the results of the Zoo Map Test between the groups.

Comparison Between Patients Receiving Medication and Patients not Receiving Medication

There were no significant differences in the main neuropsychological tasks. The arithmetic test score was significantly higher in medication-free patients than in patients receiving medication (median = 15.5, interquartile range (IQR) = 14.00–16.00 *vs.* median = 13, IQR = 10.00–14.25) ($p = .001$). Medication-free patients obtained a lower score for TMT-B and TMT-A than patients receiving medication (median = 29.5, IQR = 19.50–34.00 *vs.* median = 35, IQR = 25.5–50.00) ($p = .027$).

DISCUSSION

The results of the questionnaires administered in this study indicate that the BDI-II score was significantly higher in NT1 patients; this finding is similar to findings reported elsewhere (Vandeputte & Weerd, 2003). Some authors argue that the high prevalence of depression symptoms could be related to the pathophysiology of NT1 (Pizza, Magnani, Indrio, & Plazzi, 2014), although the importance of psychosocial and environmental factors in the development and maintenance of depressive symptoms should not be ignored (Kales et al., 1982). Additionally, and in contrast to Vignatelli, Plazzi, Peschechera, Delaj, and Alessandro (2011), disease duration was related to the reduced frequency of depressive symptoms in our NT1 sample, probably because patients had developed coping strategies to manage the functional burden of the disease (De Zambotti et al., 2014). This would have a positive effect on mood, as reflected by the correlation described. It would be interesting to study this relationship in greater depth in order to identify coping strategies that could mediate this process and to quantify impact on quality of life. The doses of antidepressant drugs administered for control of cataplexy are significantly lower than in patients with depression. NT1 patients rated their anxiety levels relatively high during the assessment, although this had a limited influence on cognitive performance. Moreover, the STAI score was related to a higher presence of sleep paralysis in the 2 weeks before the evaluation. One recent systematic review reported a similar association between stress or anxiety symptoms and sleep paralysis in studies carried out in the general population (Denis, French, & Gregory, 2018).

The contradictory results in the processing speed subtests might be explained by the differences between automatic and controlled processing (Schneider & Shiffrin, 1977). Automatic processing requires less effort and is quite resistant to the decrease in performance associated with sustained attention, whereas controlled processing requires active attention and, therefore, demands more effort (Fisk & Schneider, 1981; Schneider & Chein, 2003). For this reason, performance in TMT-A and StroopW, which is related to automatic processing of information, was similar between groups, in contrast with performance in StroopC, which is related to controlled processing. The fact that these tasks require less effort could be a fundamental characteristic that explains the absence of differences.

As described in a previous study (Naumann et al., 2006) and replicated in our sample, NT1 patients were able to compensate for a slower reaction and achieved similar results to those of the control group in simple and monotonous tasks. When the complexity of the task was increased, the patient could not compensate for the slowness and consequently achieved a lower number of hits and more omissions. These findings are in line with those of other studies, that is, NT1 patients showed reduced capacity to maintain attention for longer periods. Furthermore, the difficulties increased when the effort required to complete the tasks increased. The above-mentioned observations suggest a

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limitation of cognitive resources and corroborate findings from previous studies (Bayard et al., 2012; Naumann et al., 2006). Taken together, the duration and cognitive demand of the tasks could account for much of the decrease in performance, regardless of the type of task. Any cognitive process other than sustained attention could be assessed with a short-term test (≤3 min). Such a procedure would prevent misinterpretations of the results.

The most interesting results for executive function are those related to verbal fluency. The NT1 group performed poorly in the phonological fluency tasks, which are considered more difficult than the semantic ones (Lezak, Howieson, Bigler, & Tranel, 2012; Schmidt et al., 2017). Therefore, successful performance of complex tasks requires more cognitive resources, and the lack of these resources may be a determining factor in the decreased performance. Other cognitive processes are involved in the performance of these tasks (i.e., language, working memory, shifting, and processing speed) (Schmidt et al., 2017; Whiteside et al., 2016). As far as we know, ours is the first study to statistically control the potential influence of processing speed on performance of verbal fluency tasks, although this hypothesis has been put forward elsewhere (Naumann et al., 2006). According to our results, the differences found in the second and third subtests are better explained by a slowdown in processing speed. Therefore, when the influence of processing speed on fluency tasks was statistically controlled, some of these significant differences disappeared. In contrast to previous studies (Bayard et al., 2012; Delazer et al., 2011; Yoon et al., 2013; Zamarian et al., 2015), we found no significant differences in the inhibition of automatic responses. The interference index is assumed to be independent of the influence of processing speed, in contrast to commonly used tasks, where the relationship between reaction time and performance is clear (Ríos-Lago et al., 2008). Additionally, we emphasize the tendency toward the significant findings for time spent to complete the first part of the Zoo Map Test, which some studies have related to processing speed (Oosterman et al., 2013). Once again, the decrease in performance in neuropsychological tests in patients with NT1 seems to be mediated by processing speed.

This study has several limitations. First, our NT1 sample consists of patients who were medicated and patients who were not. The patients were not randomized to medication-free status, and there may be unknown confounds between medication status and other variables, such as symptomatology severity. However, regarding cognitive deficits, we only found significant differences in the arithmetic test and in the difference between TMT-B and TMT-A. Interestingly, the medication-free group performed better than the medicated patients. In all the other tests, as well as in the computer tasks, performance was similar between treated and untreated NT1 patients. Our results are similar to those reported elsewhere (Delazer et al., 2011; Naumann et al., 2006; Zamarian et al., 2015); therefore, there is little evidence of the positive influence of stimulants and sodium oxybate on cognitive processing (Medrano-Martinez & Peraita-Adrados, 2017; Saletu et al., 2009; van Schie et al., 2016). Second, our methodology only enabled us to hypothesize about the neurobiological correlates of task performance in NT1; further studies are required to explore the neurobiological correlates of neuropsychological performance in NT1. Third, our study design was cross-sectional; the relationship between the duration of the disease and the symptoms of depression warrants further investigation.

In conclusion, to our knowledge, this is the first study to provide a statistical comparison of the relationship between processing speed and executive function in the performance of verbal fluency tasks in NT1 patients and a control group. If our results are taken together with those of other studies (Filardi et al., 2017), we see that attention and processing speed play a fundamental role in the manifestation of cognitive abnormalities in NT1 patients. This could partially explain the poorer performance of NT1 patients in tests of executive function compared with healthy controls. Consequently, a fresh perspective is necessary when considering the design of new research protocols and interpreting literature data. The negative correlation between the duration of the disease and the BDI-II score suggests that patients develop coping strategies to manage the functional burden of the disease. More accurate strategies should be identified, and these should consolidate the development of more efficacious psychological therapy in the future. This therapy should be applied in the cognitive rehabilitation of these patients.

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CONFLICT OF INTEREST

The authors report that they have no conflicts or disclosures regarding this manuscript.

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