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Controlling the past, owning the present, and future: cholinergic modulation decreases semantic perseverations in a person with post-stroke aphasia

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ABSTRACT

Background: Perseverations in speech production tasks represent a pervasive symptom of chronic aphasia. Semantic perseverations (SPs) are defined as repetitive and unconscious production of specific linguistic forms previously produced, heard, or seen which share semantic relatedness with the target word. Neurochemically, SPs have been attributed to weakened activation of the target word due to the depletion of neurotransmitter systems (acetylcholine and dopamine) occurring in the context of activation of semantic competitors.

Aims: The present pilot study seeks to evaluate the effectiveness of a cholinergic enhancing drug combined with speech language therapy in reducing SPs and other non-perseverative semantic errors in a person with chronic post-stroke aphasia.

Methods & Procedures: Combined therapy of the cholinesterase inhibitor donepezil and conventional speech-language therapy (SLT) (2 hours/week) over 16 weeks was administered to a woman with chronic fluent post-stroke aphasia showing high rate of semantic errors. Aphasia and SPs assessments were performed at four different time-points across the study: at baseline, after donepezil 5 mg, donepezil 10 mg, and after 4-weeks of washout. The changes induced by the treatments on the occurrence of SPs and semantic paraphasias during a picture naming task were evaluated. By using a specific statistical methodology, we performed a fine-grained analysis of the frequency of SPs and their temporal course at the different time-points to dissect changes induced by the treatment.

Results: At baseline, there were significantly more SPs than expected by a random distribution, whereas a marked reduction of these errors was found in the three following evaluations. A significant reduction in aphasia severity was also found with

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high donepezil doses and this improvement maintained after a 4-week washout period. Everyday communication improved with low doses of donepezil.
Conclusion: Our findings suggest that decreased activity of the cholinergic system may exert a permissive role for the production of SPs and highlight the importance of combining cholinergic agents with speech-language therapy to reduce SPs in aphasia at the time that other language deficits are also improved.

1. Introduction

Verbal perseverations (VPs) are defined as the reproduction of particular linguistic forms that the person has previously spoken, heard, or seen when it is no longer required (Basso, 2004; Cohen & Dehaene, 1998; Dell, Burger et al., 1997; Sandson & Albert, 1984). These are frequently observed in aphasia (ranging from 50% to 93%), imposing an important limitation on the ability to accurately communicate (Basso, 2004; Helm-Estabrooks et al., 1998). However, only some aphasic subjects present high frequencies of VPs (Gotts et al., 2002; Hirsh, 1998; Lhermitte & Beauvois, 1973). Amongst VPs, semantic perseverations (SPs) refer to the intrusion of words semantically related to the names they replace. Besides their spontaneous occurrence, SPs may also be elicited in healthy subjects (Dell, Schwartz et al., 1997; Moses et al., 2004) and in people with aphasia using demanding experimental tasks (e.g., blocked-cyclic picture naming tasks) (Hsiao et al., 2009; Schnur et al., 2006).

Several dysfunctional mechanisms have been proposed to account for VPs (Stark, 2018), but two of them have survived as the most plausible ones (Nozari, 2019). First, the *activation deficit mechanism*, which proposes that VPs occur when the activation of the target name is weak and the gap is filled with the most accessible previous response (Cohen & Dehaene, 1998; Dell, Schwartz et al., 1997). Second, the *inhibition deficit mechanism*, which states that VPs are the consequence of a failure of inhibitory mechanisms, making the previous output more likely to be produced again (e.g., Nozari & Hepner, 2019). These mechanisms have been elaborated integrating information from cognitive neuropsychological models (Dell, Schwartz et al., 1997; Martin & Dell, 2004), connectionist implementations of language processing (Gotts & Plaut, 2004) and studies on the role of neurotransmitters depletion (acetylcholine and dopamine) in the pathogenesis and response to treatment (McNamara & Albert, 2004; Sandson & Albert, 1984). In spite of these valuable contributions to the understanding of VPs, most studies performed up to now are cross-sectional, whereas intervention approaches are scant and mostly based on behavioural treatments (*see* Basso, 2004; Corbett et al., 2008; Helm-Estabrooks et al., 1987; Muñoz, 2011; Stark, 2018).

A complementary strategy to behavioural approaches for reducing VPs is modulating the activity of the cholinergic and dopaminergic systems with drugs (McNamara & Albert, 2004; Tanaka et al., 2006, 1997). This suggestion is supported by the knowledge derived from cognitive, neurochemical, and anatomical studies in healthy subjects, and from the response to cholinergic manipulation in neurodegenerative diseases and stroke. Blocking the central cholinergic system in healthy subjects with the anticholinergic agent

scopolamine was associated with the production of intrusions and perseverations (Aarsland et al., 1994; Drachman & Leavitt, 1974). Post-mortem findings in persons that suffered from Alzheimer's disease disclosed that perseverations were correlated with low choline acetyltransferase levels (ChAT) (Fuld et al., 1982). In this same line, two acetylcholinesterase inhibitors (AChEIs), donepezil (Asp et al., 2006) and galantamine (Rockwood et al., 2007) attenuated reiterative speech in Alzheimer's disease. The speech-language area is innervated by the lateral cholinergic pathway (Selden et al., 1998), emanating from the nucleus subputaminalis in the basal forebrain (Ayala, 1915; Šimić et al., 1999). Recent neuropathological data from Alzheimer´s disease-related primary progressive aphasia demonstrated a marked loss of cholinergic neurons in the nucleus subputaminalis, which causes bilateral cortical denervation, mostly in speech-related regions of the left hemisphere (Hamodat et al., 2019; Mesulam et al., 2019). In support, the activity of ChAT is greater in the left temporal lobe, implicated in auditory processing, compared with the right one (Amaducci et al., 1981). Moreover, anterior language areas (Brodmann's area 45) in the left hemisphere also contain AChE-rich neurons (García et al., 2004) and a higher cholinergic receptor density than its homologous in the right hemisphere (Amunts et al., 2010).

Altogether, this information warrants the use of cholinergic drugs to treat VPs including SPs. It has been suggested that cholinergic agents may reduce SPs by increasing the sensitivity of neurons to bottom-up sensory signals, decreasing responses to ongoing stimuli that do not require immediate action (Gotts et al., 2002; Picciotto et al., 2012). Up to now, only one study has examined the response of VPs to drug treatment in people with aphasia and focal brain lesions. Tanaka and colleagues (Tanaka et al., 2006) treated three groups of people with non-fluent aphasia of mild-to-moderate severity who had VPs using three different pharmacologic agents; one group received a drug targeting the cholinergic system (donepezil), whereas the second group was treated with the dopaminergic agent bromocriptine. The third group of participants received the calcium channel blocker nilvadipine. Donepezil and bromocriptine, but not nilvadipine, reduced the number of perseverations alongside improvement in aphasia severity, word naming, and semantic fluency (animals). Limitations of Tanaka's study (Tanaka et al., 2006) include no counts of error types and lack of assessment of decay rates (*see* Buckingham & Buckingham, 2011).

During the past decades, AChEIs have been investigated in different clinical trials for the treatment of post-stroke aphasia (Berthier et al., 2011; Saxena & Hillis, 2017; Zhang et al., 2018). Agents used include donepezil (Berthier et al., 2006, 2003; Chen et al., 2010; Woodhead et al., 2017; Yoon et al., 2015), galantamine (Hong et al., 2012), and rivastigmine (Nitrini et al., 2019). In one such trial completed in our unit (Berthier et al., 2006) it was noticed that one participant produced numerous semantic errors in picture naming. Thereby, in the present study we profited from access to this subject (IMC) to perform a fine-grained longitudinal analysis of changes in semantic errors, especially in perseverative errors, induced by cholinergic modulation with donepezil and speech-language therapy (SLT), and to analyse the time-course of their occurrence. Therefore, the present study seeks to retrospectively evaluate the effectiveness of a cholinergic enhancing drug in reducing SPs and other semantic errors, opening new therapeutic alternatives for their treatment, and offering new insights into the mechanisms responsible for the occurrence of VPs in aphasia.

2. Material and methods

2.1. Ethical approval

The study was performed according to the Declaration of Helsinki and the protocol was approved by the Local Community Ethics Committee for Clinical Trials and by the Spanish Agency for Medicine and Health Products (AEMPS). Written informed consent was obtained from subject IMC and her husband. The study protocol was filed with the clinical trial registry (ClinicalTrials.gov Identifier: NCT00196690).

2.2. Participant

Subject IMC was a 34-year-old, right-handed woman with elementary education who developed a severe global aphasia, a right homonymous hemianopia, and a dense right hemiparesis after suffering a cardio-embolic stroke due to a cardiac myxoma. A complete excision of the cardiac tumour was performed without immediate postsurgical complications. After surgery, subject IMC suffered several epileptic seizures that were well controlled with pharmacotherapy. She was referred to our unit 20 months after stroke-onset for evaluation and treatment of aphasia. After screening for inclusion criteria, she was enrolled in a clinical trial (Berthier et al., 2006). At baseline, IMC´s profile of language impairment, according to the WAB taxonomical classification, was compatible with anomic aphasia (Kertesz, 1982); however, she presented additional features indicative of a transcortical sensory aphasia, such as better scores on repetition than in other language domains (fluency: 5; comprehension: 7.1; repetition; 7.4, naming: 6.8) and several instances of automatic and mitigated echolalia for word and short phrases she failed to understand (Berthier, Dávila et al., 2018; Berthier, Torres-Prioris et al., 2017). Relevantly, word retrieval was impaired, and she presented numerous semantic errors in picture naming tasks in the form of paraphasias and perseverations. At baseline, paraphasias were mainly related with musical instruments, tools, and food. She did not point out any personal interests or greater familiarity with these categories that could explain her bias. Semantic paraphasias mostly occurred in medium and low-frequency words. A structural magnetic resonance imaging (MRI) of the brain showed a large left frontal-temporal-parietal ischaemic infarction with subcortical extension into basal ganglia and white matter due to a proximal occlusion of the middle cerebral artery (Figure 1).

2.3. Study design

Subject IMC participated in a 16-week randomised, double-blind, placebo-controlled, parallel-group study of donepezil and distributed speech-language therapy (SLT) (two hours per week) (Berthier et al., 2006). The case of subject IMC was selected from the total sample of persons with aphasia included in the trial (n = 26) based on the high prevalence of semantic errors, especially SPs. At baseline evaluation, subject IMC committed a high number of SPs as well as other non-perseverative errors (i.e., semantic paraphasias) on the Naming x Frequency subtest of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA 54) (Kay et al., 1992; Valle & Cuetos, 1995). SPs in this task were observed only in one participant other than IMC, yet the frequency of occurrence was

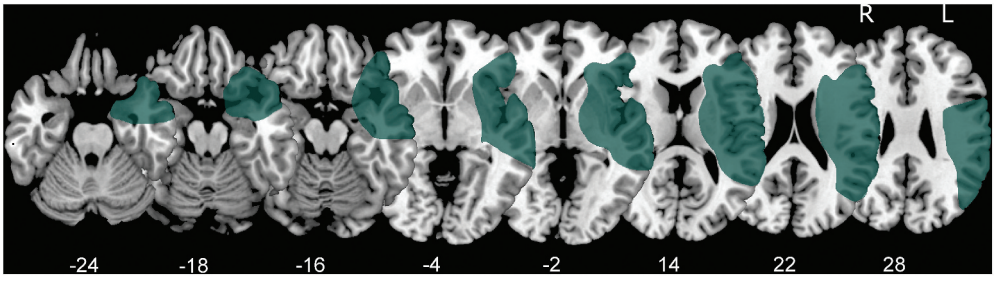

Figure 1. Axial slices of IMC´s lesion mask shown in standard space over a MNI template. The image shows a large left fronto-temporo-parietal lesion secondary to a middle cerebral artery infarction. The lesion involves the perisylvian frontal and temporoparietal region and the insular cortex with extension into the orbitofrontal cortex and the temporal pole. The basal ganglia (putamen), internal capsule and, corona radiata are also affected.

low (three instances in the Naming x Frequency subtest of the PALPA 54). Thus, given the rare occurrence of SP in the remaining aphasic subjects, only IMC was included in the present study.

Initially, subject IMC was randomly assigned to the donepezil group. The study design was as follows: after a baseline evaluation, she received donepezil (5 mg/day) during a 4-week titration phase (endpoint 1), followed by a 12-week maintenance phase (10 mg/day of donepezil) (endpoint 2), and a 4-week washout phase of both donepezil and SLT (endpoint 3). Concomitant drug treatments included carbamazepine (200 mg/tid) and sodium valproate (chrono preparation; 500 mg/bid) to control epileptic seizures. She also received mianserine (20 mg/day) and propranolol (10 mg/day) to treat mild symptoms of depression and linguistic anxiety, respectively. The dosage of these concomitant medications was kept unchanged during the trial. Subject IMC received SLT on an individual basis administered by the same speech therapist. SLT was administered during the pharmacological phase (from week 0 to week 16) and it followed a syndrome-specific standard approach (Basso et al., 2013; Pulvermüller et al., 2001). The following domains were treated during one-hour sessions twice a week resulting in a total of 32 hours. (1) Naming of real objects and pictures; semantic and phonemic cues were provided when IMC produced commission errors. (2) Auditory comprehension of high-, medium-, and low-frequency words using spoken word-picture matching and of sentences of increased length and with different syntactic constructions (active/passive reversible and irreversible sentences); exercises tapping following command, and response to questions (e.g., Yes-No questions) were also used. (3) Repetition of digits, words, nonwords, and sentences of increased length were used as well as sentence completion with wide and narrow closures. (4) Conversations training on topics of the subject's own choice or interest were also included. Notice that given the characteristics of the trial, SLT was not specifically tailored to reduce SPs and semantic paraphasias.

2.4. Data analysis

The analysis of SP and other non-perseverative semantic errors (i.e., semantic paraphasias) was restricted to the Naming x Frequency subtest of the PALPA (Kay et al., 1992; Valle & Cuetos, 1995). The PALPA 54 is composed of 60 black and white drawings displayed in fifteen sheets with an arrangement of four items per sheet. These 60 items were selected on the basis of word length and nominal consensus. Items belong to nine semantic categories (animals, body parts, clothes, fruits/vegetables, house things, means of transportation, music instruments, tools, and others), but the number of exemplars in each category was different and not considered for item selection (Valle & Cuetos, 1995). The test contains 20 high-frequency nouns (e.g., "door"), 20 medium-frequency nouns (e.g., "lemon"), and 20 low-frequency nouns (e.g., "dromedary"). In each evaluation, subject IMC was asked to name all stimuli and her performance was audiotaped and transcribed. Afterwards, errors in each evaluation were analysed independently by two researchers who were blind to the different time-points.

For each trial, all responses in the picture naming task were classified as follows: (1) *Correct response*: production of the fully correct target word, or with minor deviations. (2) *Semantically related response*, including: (2.1) *semantic paraphasia* and (2.2) *semantic perseveration*. Semantic perseveration was defined as the production of a word semantically related to a previous response or stimulus, and semantic paraphasia as a word semantically related to the target but that has not been produced or heard before. To examine perseverations, responses for a given item were compared with previous ones, considering up to 15 trials backwards. The number of trials needed to go back to match the error will be, hereafter, referred to as *lag*. (3) Phonologically related response (share $\geq$ 50% of the target) including: (3.1) *phonological perseveration* and (3.2) *phonological paraphasia*. Phonological perseveration was defined as the production of a word or syllable phonologically related to a previous response or stimulus and phonological paraphasia as the production of a word phonologically related to the target that has not been produced or heard previously; (4) *Unrelated lexical response*: a real word not related semantically or phonologically (share < 50% of the target) to the target word. (5) *Unrelated non-lexical responses*: a nonword that does not bear a phonological resemblance to the target word (share <50% of the target). (5) Non-commission error: include omissions, descriptions, and circumlocutions.

To study the longitudinal changes in semantic errors promoted by the interventions, the number of SPs and semantic paraphasias in each of the three endpoints were compared to the results of the baseline testing using the statistic McNemar tests (two-tailed). Further, to study the temporal course of SPs at each time-point (baseline and endpoints 1 to 3), we performed a lag distribution analyses, a statistical approach developed by Cohen and Dehaene (1998), which is described in the *Analysis of semantic perseverations* section.

Further, to analyse the occurrence of SPs in IMC within a broader context, in the present we also report changes in language and communication variables at the individual level (group analyses were reported in Berthier et al., 2006). Treatment-induced changes from baseline to endpoint 3 were statistically compared using a McNemar test (two-tailed). Note that language and communication data of subject IMC were extracted from a randomised, double-blind, placebo-controlled trial of donepezil and SLT (Berthier

et al., 2006). In that trial, primary outcome measures for group analysis were the mean score change from baseline to the three endpoints on the Aphasia Quotient of the Western Aphasia Battery (WAB-AQ) (Kertesz, 1982) and the Communicative Activity Log (CAL) (Pulvermüller et al., 2001), a scale that assesses communicative behaviour in everyday life. Secondary outcome measures were selected subtests of Spanish version of the PALPA (Kay et al., 1992; Valle & Cuetos, 1995) to evaluate phonological and lexical-semantic processing at word and sentence levels, as well as auditory-verbal short-term memory.

2.5. Analysis of semantic perseverations

Cohen and Dehaene (1998) developed a suitable approach to study the time-course of VPs. This method involves the comparison of the observed lag distribution with a hypothetical random distribution (obtained after the application of the statistical procedure described below). This seminal study posited that VPs exhibit a characteristic temporal course, showing exponentially decreasing probability of occurrence after time; therefore, greater frequency of this type of errors is seen at short lags. In the present study, a similar methodology was used to analyse SPs in IMC.

Random distribution represents a reliable estimation to which the actual data can be compared with. The comparison between the observed and the random distribution allows to objectively determine if observed errors are genuine perseverative productions and do not represent a consistent participant´s bias for a given word, nor represent the selection of a readily accessible form. In this study, the random distribution data set was created by shuffling the sequence of trials (i.e., stimuli and its associated response) 20 times, thus, creating 20 new lists with 60 stimuli-response pairs in each. This was repeated for all four time-points. Accordingly, a total of 80 lists were analysed for SPs, using the same classification criteria as for the actual performance. By doing this, stimulus-error relationship is preserved, while serial organization between items is altered; hence, the greater occurrence of SPs at short lags expected in the observed distribution would disappear in a random distribution (Cohen & Dehaene, 1998). In their study of VPs, Cohen and Dehaene (1998) noted that random lists represent a decreasing function of time that fits well with the following logarithm formula [(1-P) L-1P] (P = probability of an error to occur, which is constant in absence of perseverations; L = the lag number for which probability of committing a perseveration is calculated).

Afterwards, a time correction was applied to the random distribution as in previous works (Cohen & Dehaene, 1998; Hsiao et al., 2009). Since the number of matched VPs for short lags is lower in the random distribution than in the observed distribution (and therefore, the number of non-matched errors is higher), there is a greater probability of obtaining a falsely higher number of VPs (i.e., matched errors) in lags other than lag 1. Therefore, to correct the random estimation of matched errors from lag 2 onwards, a proportion was calculated to consider the actual number of errors matched at the previous lag. For this, the number of matched errors estimated in the global analysis was divided by the remaining non-matched errors from the previous lag, and the result was multiplied by the remaining non-matched errors of the observed distribution. Thus, for example, time correction for matched errors in lag 2 (see "Time corrected analysis" column in Table 1) was calculated as follows: $0.20 \div 26.65 \times 22$ (Global analysis: Number of

Table 1. Illustration of lags distribution analyses in IMC for baseline evaluation.

	Observed distribution		Random distribution			
			Global analysis		Time-corrected analysis	
Lag	**N. matched errors**	**Remaining non-matched**	**N. matched errors**	**Remaining non-matched**	**N. matched errors**	**Remaining non-matched**
1	5	22	0.35	26.65	0.35	26.65
2	2	20	0.20	26.45	0.17	26.48
3		20	0.15	26.3	0.11	26.37
4		20	0.15	26.15	0.11	26.26
5	2	18	0.20	25.95	0.15	26.10
6		18	0.05	25.9	0.03	26.07
7		18	0.30	25.6	0.21	25.86
8		18	0.45	25.15	0.32	25.54
9		18	0.30	24.85	0.21	25.33
10		18	0.05	24.8	0.04	25.29
11	1	17	0.15	24.65	0.11	25.19
12		17	0.15	24.5	0.10	25.08
13	1	16	0.20	24.3	0.14	24.94
14		16	0.05	24.25	0.03	24.91
15		16	0.15	24.1	0.10	24.81
TOTAL	11	16	2.90		2.19	

matched errors in lag 2 [0.20]; Global analysis: Non-matched errors in lag 1 [26.65]; Observed distribution: Remaining non-matched errors in lag 1 [22]). This allows estimating the proportion of matched errors from the observed distribution, thus considering a real number of unmatched errors and not a falsely higher one. The application of this adjustment has two advantages. First, given the observed distribution, it allows inferring a random distribution instantly, just by calculating the perseveration probabilities from lags 1 to 15 using observed parameters. This greatly reduces the time needed to rearrange the lists and to analyse errors, yet enough trials are needed for reliable comparisons. Second, when this procedure is applied to the random distribution obtained by shuffling the list 20 times, it allows softening peaks in the distribution due to stochastic events and human errors.

The two distributions, observed and time-corrected random, were compared using a χ^2 goodness of fit. First, the observed distribution was statistically compared to the estimated time-corrected distributions globally and, afterwards, comparisons were performed at each of the 15 lags. These analyses allowed the exploration of the temporal course of SPs in IMC, and, importantly, of the longitudinal changes associated with the treatment.

3. Results

Results showed that naming errors committed by IMC were mainly semantic and rarely phonological or not related errors (Table 2). Inter-rater agreement was high (.90) and the instances of disagreement were solved by consensus. Following the aim of exploring treatment-induced changes in semantic errors, the results on SPs and semantic paraphasia are presented in greater detail below. Regarding general language deficits, Table 3 shows IMC´s changes from baseline scores to endpoint 1 (donepezil 5 mg/SLT), endpoint

2 (donepezil 10 mg/SLT), and endpoint 3 (washout) on primary and secondary outcome measures determined for the randomised clinical trial. She showed mild improvement in the WAB-AQ score after ending the starting dose of donepezil of 5 mg/day (week 4: change in AQ: 3.8). However, after finishing treatment with donepezil 10 mg/day (week 16: change in AQ: 8.6), she was classified as a "responder" to interventions (improvement ≥ 5 points in AQ) (Berthier et al., 2011; Katz & Wertz, 1997) and this gain remained for at least 4 weeks after treatment termination endpoint 3 (change in AQ: 8.4). Subject IMC also showed improvement in communication in activities of daily living test (CAL) at endpoint 1, which was then mildly reduced at endpoint 2 and at the washout phase. Secondary outcome measures also improved. Participant IMC's performance significantly improved in Naming x Frequency (PALPA 54, endpoint 1, donepezil 5 mg/day) as well as in Spoken Word-Picture Matching (PALPA 47) and Nonword Repetition (PALPA 8) at endpoint 2 (donepezil 10 mg/day) (Table 3). Other secondary measures were close to the maximum score at baseline, leaving little scope for improvement. During the trial, subject IMC did not show adverse events induced by donepezil and no epileptic seizures took place.

3.1. Treatment-induced changes in semantic perseverations and semantic paraphasias

The number of SPs in the picture naming test (PALPA 54) decreased with donepezil and SLT (baseline: 11 instances; endpoint 1: 3 instances; endpoint 2: 6 instances; endpoint 3: 6 instances). At endpoint 1 (week 4: donepezil 5 mg/day) the number of SPs was significantly reduced compared to baseline ~~($p = 0.008$),~~ while a trend to significance was found at endpoint 2 (week 16: donepezil 10 mg/day; $p = 0.063$) and endpoint 3 (week 20: washout; $p = 0.063$). Changes in the number of SPs across the different time-points are depicted in Figure 2.

At baseline, the comparison of the two lag distributions (observed distribution vs time-corrected random distribution) revealed a significant difference ($\chi^2_{(14)} = 102.24$; $p < 0.001$), indicating a distinctive time-course in the occurrence of SP between them. Analysis at each lag showed differences for lags 1 ($\chi^2_{(1)} = 61.77$), 2 ($\chi^2_{(1)} = 19.49$) and 5 ($\chi^2_{(1)} = 20.89$); $p < 0.001$ in all cases, as well as in late lags (lag 11: $\chi^2_{(1)} = 12.1$, $p < 0.01$;

Table 2. Classification of responses in the picture naming task.

Response classification	Endpoint 1		Endpoint 2	Endpoint 3
	Baseline	Donepezil 5 mg	Donepezil 10 mg	Washout
Correct responses	33	47	37	40
Types of errors				
Semantic				
Semantic perseveration	11	3	6	6
Semantic paraphasia	22	25	25	24
Phonological				
Phonological perseveration	0	0	0	0
Phonological paraphasia	0	0	2	0
Mixed phonological and semantic	3	0	4	3
Unrelated lexical	1	2	5	1
Unrelated non-lexical	0	0	0	2
Non-commission	4	0	3	4

Table 3. Language and communication testing.

Test	Baseline	Endpoint 1 Donepezil 5 mg	Endpoint 2 Donepezil 10 mg	Endpoint 3 Washout
Primary Outcome Measures				
WAB Aphasia Quotient (max = 100)	68.6	72.4	**77.2***	**77***
Information content (max = 10)	8	8	8	8
Fluency (max = 10)	5	6	7	6
Comprehension (max = 10)	7.1	7.0	7.6	7.7
Repetition (max = 10)	7.4	8.4	9.0	8.4
Naming (max = 10)	6.8	6.8	7.0	8.4
Communicative Activity Log (max = 108)	68	**86***	83	78
Secondary Outcome Measures				
Lexical-semantics				
Naming x frequency (PALPA 54) (max = 60)	33	**47***	37	40
Semantic fluency (animal naming – WAB) (max = 20)	7	4	7	15
Auditory word recognition (WAB) (max = 60)	37	47	39	41
Spoken word-picture matching (PALPA 47) (max = 60)	32	31	**39***	36
Auditory lexical decision (PALPA 5) (max = 160)	149	148	147	147
Auditory sentence comprehension (PALPA 55) (max = 60)	37	42	45	44
Phonology & short-term memory				
Nonword minimal pairs (PALPA 1) (max = 56)	50	54	51	55
Word minimal pairs (PALPA 2) (max = 56)	52	50	52	53
Repetition: syllable length (PALPA 7) (max = 24)	20	24	24	24
Repetition: nonwords (PALPA 8) (max = 24)	9	16	**19***	15
Digit production (PALPA 13) (max = 10)	2	3	4	4

Note: Asterisk (*) indicates $p < 0.05$ (McNemar test, two-tailed).

and 13: $\chi^2_{(1)} = 16.5$, $p < 0.01$). At endpoint 1, the difference in the global performance was no longer observed and the excess of errors for short lags disappeared, showing significance only in lag 6 ($\chi^2_{(1)} = 4.32$, $p < 0.05$). At endpoint 2 (donepezil10 mg/day) a significant difference between both distributions was observed ($\chi^2_{(14)} = 29.18$, $p < 0.05$), being SPs higher in the actual distribution for lags 5 ($\chi^2_{1)} = 7.74$, $p < 0.01$) and 12 ($\chi^2_{(1)} = 15.07$, $p < 0.01$). Finally, at endpoint 3, differences in the global performance persisted ($\chi^2_{(14)} = 71.52$, $p < 0.01$) as well as the excess of SPs reappeared for short lags (lag 1: $\chi^2_{(1)} = 54.12$, $p < 0.01$; lag 2: $\chi^2_{(1)} = 9.22$, $p < 0.01$ and lag 4: ($\chi^2_{(1)} = 9.40$, $p < 0.01$) but not for late lags. The actual and time-corrected distributions are shown in Table 1 and Figure 2.

Regarding semantic paraphasias, no significant changes were observed across the different time-points (baseline vs donepezil 5 mg: $p = 0.25$; baseline vs donepezil 10 mg: $p = 0.25$; baseline vs washout: $p = 0.50$). We observed 96 instances of semantic paraphasias (baseline: 22 instances; endpoint 1: 25 instances; endpoint 2: 25 instances; endpoint 3: 24 instances). These errors mostly occurred in medium- and low-frequency words. Predominantly, verbal paraphasias were presented in the form of semantic approximations to the target word (e.g., for the target *piano*, subject IMC responded: *accordion, violin, guitar, saxophone*). It was also observed that paraphasias were triggered by semantically related stimulus depicted on the same sheet. These errors are related to the way the test items of the PALPA-54 are presented (four items per sheet, two top and two bottom ones). For instance, when the target picture on the bottom left side of the sheet was a "mushroom" and the next target picture on the bottom right side of the sheet was

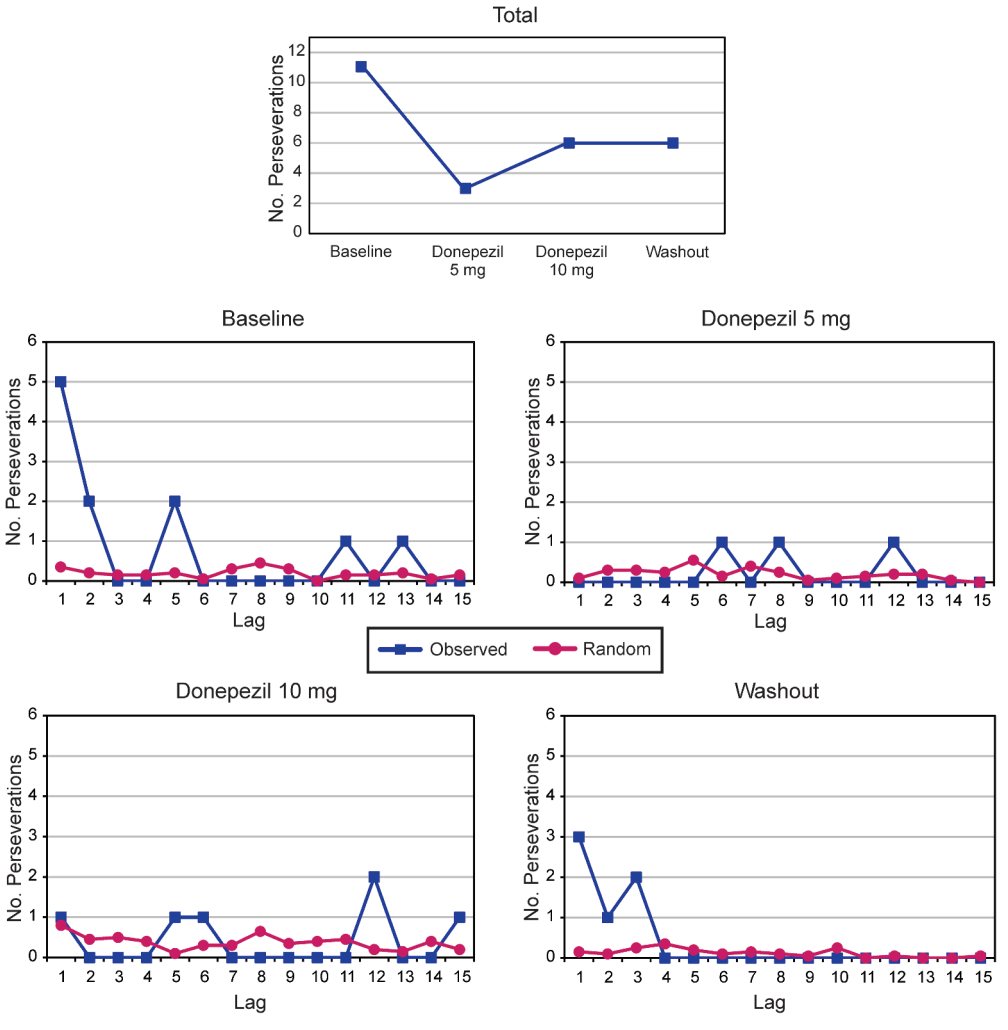

Figure 2. Distribution of semantic perseverations across the four evaluations. The top graph depicts the total number of perseverations at the different time-points. Note a clear decrease of semantic perseverations after the administration of donepezil (5 mg/day). The bottom graphics show the observed (blue line) and random (red line) lag distributions of semantic perseverations.

a "carrot", her response was "carrot, aubergine, zucchini". On some occasions, this also led to perseverations and non-related errors, although the latest were rare.

4. Discussion

This study explored the changes in SPs and semantic paraphasias in response to a combined treatment with donepezil and SLT in a subject with chronic fluent post-stroke aphasia. Our main finding was that the high occurrence of SPs at baseline significantly decreased with low doses of donepezil (5 mg/day) and SLT for 4 weeks but no change was observed in the occurrence of semantic paraphasia. Additionally, the interventions induced a significant improvement in more general primary outcome measures

tapping aphasia severity (WAB-AQ, endpoint 2 and endpoint 3) and communication in activities of daily living (CAL, endpoint 1). Significant improvements were also found in secondary outcome measures including phonological (nonword repetition – endpoint 2) and semantic processing (picture naming x frequency – endpoint 1 and spoken word-picture matching – endpoint 2).

Baseline testing revealed that in picture naming, subject IMC produced significantly more SPs than expected by a random distribution, in addition to semantic paraphasias mostly in the form of successive approximations to the target word. While the high rate of SPs suggests an activation deficit of the target word, the production of semantic approximations additionally points to a reduced inhibitory control (*see* Nozari, 2019). Interestingly, these deficits showed a dissociated response to the combined intervention. Low doses of donepezil (5 mg/day) in combination with SLT produced a fast and strong response, reducing SP (from 11 to 3 instances at endpoint 1), but no parallel reduction of semantic paraphasias. The rapid improvement of SPs may suggest that changes in neurotransmitter dynamics took place in very short periods of time, possibly generated by rapid reactivation of silent synapsis, reshaping neural networks not engaged in language before the stroke, or both (Berthier, 2021). Moreover, the use of SLT in combination with donepezil probably enhanced learning-dependent neural plasticity (Kiran & Thompson, 2019; Kleim & Jones, 2008) reliant on the essential role of cholinergic stimulation (Kilgard & Merzenich, 1998; Thiel, 2007). Higher doses of the drug (donepezil 10 mg/day) also contributed to reducing the number of SPs relative to baseline but such changes were less evident than those obtained with the initial dose of donepezil. In the same line, scores in picture naming significantly increased with donepezil (5 mg/day), but these changes were less noticeable with higher doses (10 mg/day). Nevertheless, improvements in aphasia severity, as measured with the WAB-AQ, were more evident with higher doses of donepezil (10 mg/day) (endpoints 3) relative to baseline testing. The increased number of SPs with high doses of donepezil (10 mg/day) relative to the lower doses (5 mg/day) raises the possibility of biochemical tolerance to the drug. Indeed, an inverted U-shaped dose-response effect to donepezil could be implicated in the mild decrement in performance under high doses of the drug (10 mg/day) (Berthier, 2021; Husain & Mehta, 2011; Woodhead et al., 2017).

By analysing the distribution of SPs along lags for each evaluation, we found a decreasing function in time with a high preference for lags 1 to 4, findings that align well with previous descriptions (Cohen & Dehaene, 1998; Corbett et al., 2008; Hsiao et al., 2009). This distribution trend disappeared after receiving donepezil (5 mg/day), mimicking a distribution comparable to the random one, except for altered late lags. This finding indicates that cholinergic modulation caused a dosage-dependent reduction of SPs in subject IMC with greater improvement at lower doses. Yet, the 5 mg/day and 10 mg/day doses of donepezil showed a remarkably similar distribution for short lags, indicating a similar time-course in both cases. In the washout period, the lag distribution changed showing a similar distribution to the baseline, but with a lower number of SPs (baseline: 11; washout: 6). The different distribution of SPs in baseline/washout periods compared with donepezil (5 mg and 10 mg) treatment suggests that leveraging cholinergic activity had an impact on the incidence and time-course of SPs, even though the response to higher doses of the drug (10 mg/day) was less noticeable. This fact highlights the importance of analysing the distribution of SPs along lags rather than just accounting

for the total number of perseveration instances. At baseline, we found a slightly higher number of SPs in late lags (above lag 8) compared to the random estimation, thus leaving little chance for improvement with the therapeutic interventions. The low occurrence of SPs in late lags has already been reported (Cohen & Dehaene, 1998; Corbett et al., 2008; Hsiao et al., 2009) but it should be noted that we did not consider lags later than 15.

Semantic paraphasias in IMC were mainly produced in the form of within-category semantic approximations, specially related to naming musical instruments, and fruits/vegetables. In subject IMC successive semantic approximations may be interpreted in the frame of co-activation of multiple representations during word production (see Nozari & Hepner, 2019 and commentaries). Such sequences of errors might have resulted from incompetent inhibitory control mechanisms, whereby the visual presentation of the target automatically activates neighbouring words belonging to the same category (Nozari, 2019). This is in line with the proposal of connectionist models of VPs that show that errors resulting from removal of connections, to simulate brain damage, often share a semantic relationship (harmonica → accordion) or a blended visual and semantic horizontal link to the target stimulus (guitar → violin), as objects that are both visually and semantically similar are closer together (Gotts & Plaut, 2004).

Further, on some occasions, item's display of the naming test (four items per sheet) induced the production of semantic paraphasias, where nearby semantically related target acted as a prime. These errors possibly resulted from difficulties in allocating visual attention to the target item in the presence of distractors presented simultaneously with the target. Thus, it is conceivable that the multiple stimuli display of PALPA 54 taxed visual spatial attention, eliciting these errors (Heuer & Hallowell, 2015; Heuer et al., 2017). Although treatment with donepezil in healthy subjects increases the spatial integration of visual responses across visual fields (Chuah & Chee, 2008; Kosovicheva et al., 2012; Silver et al., 2008), the very rare occurrence of these types of errors in subject IMC prevented us from examining the role of donepezil. In this regard, reducing the effects of involuntary shifts of spatial attention to visual distractors could have great clinical relevance for people with aphasia. Moreover, since there is evidence that people with aphasia frequently show task-based modulation of eye movements (Heuer & Hallowell, 2015; Smith et al., 2018), future studies using eye-tracking methodology would provide relevant information on this issue as well as on the potential changes promoted by cholinergic enhancement. Unexpectedly, the significant reduction in the number of SPs under low doses of donepezil was not paralleled by a similar decrease in the number of non-perseverative semantic paraphasias at different time-points.

As already mentioned, a high frequency of perseverations is only observed in some persons with aphasia (Gotts et al., 2002; Hirsh, 1998; Lhermitte & Beauvois, 1973). In the case of subject IMC, the high occurrence of SPs and non-perseverative semantic paraphasias might be attributed, at least in part, to lesions located in the left anterior temporal lobe and orbitofrontal cortex. The anterior-most portion of the lesion involved important regions for semantic processing such as the temporopolar region (Brodmann's area [BA] 38) (Mesulam et al., 2013), the posterior lateral orbitofrontal cortex (BA 47/12) (Petrides, 2005) and multiple ventral white matter pathways converging in the temporal pole (uncinate fasciculus, inferior longitudinal and inferior fronto-occipital fasciculi) (Bajada et al., 2015; Sierpowska et al., 2019). The temporopolar cortex is a paralimbic region involved in high semantic representation and/or processing (Lambon Ralph, 2014; Walker

et al., 2011), the orbitofrontal cortex participates in active retrieval and encoding of information (Petrides, 2005), and the ventral white matter tracts are implicated in semantic processing (Almairac et al., 2015; Sierpowska et al., 2019). Moreover, these cortical areas and some white matter tracts (uncinate fasciculus) are innervated by the cholinergic system (Lou et al., 1992; Mesulam, 2013). Therefore, it remains to be determined whether treatment with donepezil and SLT produce cortical remodelling in areas spared by the lesion innervated by the cholinergic system (Kilgard & Merzenich, 1998) and improve cerebral perfusion (Claassen & Jansen, 2006; Van Beek & Claassen, 2011).

Findings from the study of IMC should be interpreted in light of the following limitations. First, she was included in a group of persons with aphasia recruited for participation in a randomised controlled intervention trial aimed to improve aphasia; hence, this study was not specifically designed to investigate the impact of cholinergic modulation combined with SLT on perseverations. Language errors in the subject IMC were further evaluated because it was noticed that she produced numerous SPs in picture naming while other participants in this trial did not (Berthier et al., 2006). Our analysis of SPs in IMC was motivated by the fact that she was treated with a drug that may reduce them (Tanaka et al., 2006). Second, donepezil and SLT in IMC were administered in combination thus precluding knowing the independent effect of each intervention. Although previous studies of donepezil or SLT have shown a reduction in VPs when used as the only therapeutic strategy (Stark, 2018; Tanaka et al., 2006), further studies examining the role of pharmacotherapy alone and combined with model-based language therapies are needed. Third, even though IMC had abundant SPs and semantic paraphasias in naming tasks, due to the protocol of this trial her SLT was not specifically tailored to reduce such errors. Therefore, future studies combining drugs or other biological treatment (non-invasive brain stimulation) need to use specific therapies aimed to reduce SP and semantic paraphasias.

In summary, our findings are consistent with recent theoretical accounts on the mechanisms underpinning VPs (Buckingham & Buckingham, 2011; Cohen & Dehaene, 1998; Gotts et al., 2002; Martin & Dell, 2004, 2007; Stark, 2018). Based on modern connectionists approaches, VPs have been conceptualised as resulting from a deafferentation mechanism (Gotts et al., 2002; Martin & Dell, 2007). In other words, the mechanism by which brain damage induces SPs is by leaving a language network for the target word out of function, so that any previously activated networks could be able to resurge, producing a wrong, but semantically related word (Nozari, 2019). This study of a single subject suggests that leveraging the activity of the cholinergic system with donepezil in combination with SLT significantly reduce SPs and that such gains coexist with a general improvement in aphasia severity, picture naming, and everyday communication

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