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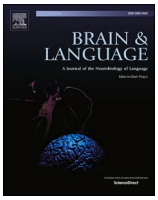

Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study

Marcelo L. Berthier [a,b], Lisa Edelkraut [a,b,c], Francisco J. López-González [d,e], Diana López-Barroso [a,b,c], Bettina Mohr [f], Friedemann Pulvermüller [g,h], Sergio E. Starkstein [i], Ricardo E. Jorge [j], María José Torres-Prioris [a,b,c], Guadalupe Dávila [a,b,c,*]

[a] Cognitive Neurology and Aphasia Unit, Centro de Investigaciones Médico-Sanitarias, University of Malaga, Malaga, Spain
[b] Instituto de Investigación Biomédica de Málaga - IBIMA, Malaga, Spain
[c] Area of Psychobiology, Faculty of Psychology and Speech Therapy, University of Malaga, Malaga, Spain
[d] Molecular Imaging Unit, Centro de Investigaciones Médico-Sanitarias, General Foundation of the University of Malaga, Malaga, Spain
[e] Molecular Imaging Group, Radiology Department, Faculty of Medicine, University of Santiago de Compostela, Galicia, Spain
[f] Zentrum für Neuropsychologie und Intensive Sprachtherapie – ZeNIS, Berlin, Germany
[g] Brain Language Laboratory, Department of Philosophy and Humanities, WE4, Freie Universität Berlin, Germany
[h] Berlin School of Mind and Brain, Humboldt Universität zu Berlin, Germany
[i] Faculty of Health and Medical Sciences, The University of Western Australia (M704), Perth, Australia
[j] Department of Psychiatry and Behavioural Sciences, Baylor College of Medicine, Houston, TX, United States

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ABSTRACT

This study explored the feasibility and effectiveness of a short-term (10-week) intervention trial using Donepezil administered alone and combined with intensive language action therapy (ILAT) for the treatment of apathy and depression in ten people with chronic post-stroke aphasia. Outcome measures were the Western Aphasia Battery and the Stroke Aphasia Depression Questionnaire-21. Structural magnetic resonance imaging and ^{18}fluorodeoxyglucose positron emission tomography were acquired at baseline and after two endpoints (Donepezil alone and Donepezil-ILAT). The intervention was found to be feasible to implement. Large treatment effects were found. Donepezil alone and combined with ILAT reduced aphasia severity, while apathy and depression only improved with Donepezil-ILAT. Structural and functional neuroimaging data did not show conclusive results but provide hints for future research. Given these overall positive findings on feasibility, language and behavioral benefits, further studies in larger sample sizes and including a placebo-control group are indicated.

1. Introduction

Post-stroke aphasia (PSA) is frequently associated with long-lasting neuropsychiatric symptoms, including apathy and depression (Døli et al., 2017; Edelkraut et al., 2022; Jorge et al., 2010; Laures-Gore et al., 2020). Apathy occurs in more than half of the persons with aphasia (PWA) (Kennedy et al., 2015), and about two-thirds show depression even one year after stroke onset (Laures-Gore et al., 2020). Post-stroke apathy and depression are clinically dissociable and result from disruptions of different subcomponents of networks regulating motivated behavior and mood (Jorge et al., 2010; Kos et al., 2016; Le Heron et al., 2018; Riva-Posse et al., 2019; Starkstein & Brockman, 2018). Yet, the neural signatures of these two symptoms are heterogeneous and do not seem to result from damage to a single brain region (Balaev et al., 2018; Starkstein & Brockman, 2018).

Several studies have shown improved language and communication deficits in chronic PSA after administering intensive language-action therapy (ILAT) (*for a review, see* Pulvermüller et al., 2016). Treatment gains can be augmented and speeded up with cognitive enhancing drugs and non-invasive brain stimulation (Basilakos et al., 2022; Berthier et al., 2009; Berthier, 2021). For instance, a randomized controlled trial (RCT) in chronic PSA showed that the glutamatergic modulator Memantine alone and in combination with ILAT produced significant language and communication benefits, which resulted in an increase of

* Corresponding author at: Unidad de Neurología Cognitiva y Afasia, Centro de Investigaciones Médico-Sanitarias, Universidad de Málaga, Marques de Beccaria 3, 29010 Málaga, Spain.
E-mail address: mgdavila@uma.es (G. Dávila).

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neural activity in both hemispheres (Barbancho et al., 2015; Berthier et al., 2009). Furthermore, an open-label case-controlled study and a cross-over RCT also showed that two weeks of ILAT produce significant improvements in depressive symptoms in PWA (Berthier et al., 2022; Mohr et al., 2017). However, the effects of combining ILAT with the cholinergic agent Donepezil[1] upon symptoms of apathy and depression in PWA have not been explored.

Based on studies reporting that Donepezil improves language, depression, and apathy in individuals with stroke and dementia (Berthier et al., 2006; Chen et al., 2010; Cummings et al., 2006; Whyte et al., 2008), we evaluated the feasibility of a therapeutic intervention and the preliminary effects of pharmacotherapy administered alone and combined with ILAT on symptoms of apathy and depression in chronic PSA. We predicted that this intervention would be associated with a decrease of apathy and depressive symptomatology and that these improvements would be greatest during the combined pharmacological-behavioral treatment phase.

The central cholinergic system is necessary for mediating complex forms of functional and structural plasticity (Picciotto et al., 2012). Experimental studies show that cholinergic depletion attenuates rehabilitation-induced recovery by hampering neural plasticity (Wang et al., 2016), whereas treatment with Donepezil prompts remodelling of cholinergic boutons in brain areas with loss of cortical cholinergic terminals (Ginestet et al., 2007). In humans, functional neuroimaging studies reveal complex reorganization patterns of brain connectivity using Donepezil in both healthy subjects (Chuah et al., 2009; Chuah & Chee, 2008; Péran et al., 2021; Wirsich et al., 2018) and patients with Alzheimer's disease (Cheng et al., 2019; Goveas et al., 2011; Griffanti et al., 2016; Li et al., 2012; Solé-Padullés et al., 2013). Therefore, besides the feasibility of the treatment implementation the present study is further aimed to explore preliminary treatment-related changes in brain structure and metabolic activity by using multi-method brain imaging approaches. We hypothesize that improvements in motivation and mood under Donepezil alone and in combination with ILAT could be associated with region-specific structural and/or functional plasticity in brain networks that regulate motivation and mood.

Accumulating evidence suggests that high-dose interventions for PSA administered over short periods improve efficacy and may maintain stability of gains in the long-term (Doppelbauer et al., 2021; Dreyer et al., 2021; Harvey et al., 2021; Pulvermüller et al., 2001). Furthermore, the addition of pharmacotherapy to intensive therapy for PSA can increase and accelerate the benefits provided by the behavioral intervention (Berthier et al., 2009, Berthier, Dávila et al., 2014; Walker-Batson et al., 2016). Therefore, in this feasibility trial we applied a shorter time window of Donepezil (10 weeks) than in our own previous studies (e.g., 16 weeks in Berthier et al., 2003; 2006) and added ILAT during the last two week of drug intake. The rationale for implementing this short-term feasibility trial with Donepezil and combined with ILAT was thus based on the following data: (*i*) significant benefits in aphasia severity, input–output phonology, single-word lexical-semantic processing (picture naming) and sentence comprehension in the initial four weeks of a trial treating chronic PSA with low doses of Donepezil (5 mg/day); more than half of these participants were responders to treatment at this endpoint (Berthier et al., 2003; Berthier, 2005); (*ii*) significant better outcomes in a case-series study of participants with chronic PSA receiving eight weeks of Donepezil combined with massed sentence repetition training (40 h) in comparison with 16 weeks of Donepezil plus distributed speech-language therapy (40 h) in the same sample (Berthier, Dávila et al., 2014); and (*iii*) significant improvement of depressive symptoms after two weeks of ILAT in two recent non-pharmacological intervention trials in persons with chronic non-fluent and fluent aphasias (Berthier et al., 2022; Mohr et al., 2017).

In the present trial we only included participants with mild-to-moderate PSA (Western Aphasia Battery-Aphasia Quotient [WAB-AQ] $\geq$ 51) (Kertesz, 2007), because persons with severe language deficits (WAB-AQ $\leq$ 50) usually do not respond to cholinergic stimulation with Donepezil, even when given in combination with intensive aphasia therapy (Berthier et al., 2011; Berthier, 2021; Woodhead et al., 2017).

2. Material and Methods

2.1. Study design

A 10-week feasibility open-label trial was conducted to assess the implementation process and treatment effects of Donepezil alone and combined with ILAT on depression and apathy in ten persons with chronic PSA at the University of Málaga, Spain. Treatment consisted of the administration of Donepezil alone for eight weeks (weeks 1–8) and combined with ILAT for two additional weeks (weeks 8–10). Small group studies are generally recommended to explore the feasibility of new, complex interventions (i.e., combination of pharmacotherapy and behavioral interventions) before moving on to larger and more refined studies (Bowen et al., 2009). Regarding the research and intervention process, the main questions to answer were: (1) Can appropriate participants be recruited considering eligibility criteria?; (2) How convenient are the outcome measures for the intended sample and the objectives of this trial?; (3) Are the procedures and interventions acceptable to the participants in terms of procedures, attendance, and participation of the trial?; (4) Does the research team possess sufficient expertise, resources, and time to conduct the trial?; and 5) Does this intervention program (Donepezil alone and in combination with ILAT) promise preliminary benefit for apathy, and depression outcomes? (Orsmond & Cohn, 2015; Whitehead et al., 2014).

The study was carried out in accordance with the Declaration of Helsinki. The protocol (DON-IIG-165; WS3006624) was approved by the Local Community Ethics Committee for Clinical Trials and by the Spanish Medicines and Health Products Agency (AEMPS). Written informed consent was obtained from all participants and caregivers. The study is registered with EudraCT (2008–008481-12).

2.2. Participants

Participants were recruited through community aphasia rehabilitation centers in Malaga, Spain. Out of 25 PWA who were screened for this feasibility trial, ten participants (eight males, mean age ± SD: 51.6 ± 8.52 years) met eligibility criteria. Inclusion criteria were: (1) age between 18 and 70 years; (2) Spanish native speakers; (3) left perisylvian stroke lesions; (4) diagnosis of aphasia according to WAB-AQ scores $\geq$ 51 to include only participants with mild-to-moderate aphasia (Kertesz, 1982); and (5) duration of aphasia for over six months. Exclusion criteria were: (1) presence of a severely reduced verbal output (WAB fluency score $<$ 4) including severe apraxia of speech, neologistic jargon; (2) severely impaired auditory comprehension (WAB comprehension score $<$ 4); (3) severe visual agnosia and/or limb apraxia; (4) history of any other neurological diseases or psychiatric disorders impairing language and communicative ability (e.g., dementia, schizophrenia); (5) pregnancy; and (6) ongoing medication with agents interfering with Donepezil (e.g., anticholinergics).

2.3. Pharmacological treatment

All participants received 5 mg of Donepezil (orally disintegrating tablets) for four weeks; the dose was titrated to 10 mg for another four weeks and maintained stable during the following two weeks of combined therapy (Donepezil-ILAT). Monitoring of adverse drug reactions was carried out throughout the trial.

[1] Donepezil is a specific inhibitor of the enzyme acetylcholinesterase, whose main physiological function is to hydrolyze the neurotransmitter acetylcholine eventually leveraging the brain availability of the neurotransmitter.

2.4. Intensive language-action therapy (ILAT)

Between weeks 8 and 10 of the study, all participants received three hours of ILAT per day for a total of 30 h in addition to the ongoing treatment with Donepezil. The Spanish version of ILAT (*REGIA* – Berthier, Green-Heredia et al., 2014) was applied by an experienced speech-language therapist who was blind to the aims of the study. ILAT was administered in small group settings (two to three participants plus the therapist), whereby participants were grouped according to their aphasia profile and severity (Berthier et al., 2022; Mohr et al., 2017).

2.5. Outcome measures

For the present study the WAB-AQ (Kertesz, 1982) and the apathy and depression subdomain scores of the Stroke Aphasia Depression Questionnaire-21 - SADQ-21 (Sutcliffe & Lincoln, 1998) were used as outcome measures. To ensure the stability of language deficits, the WAB-AQ was administered twice at baseline (two weeks apart), showing small, non-significant statistical differences between the two evaluations (mean ± SD, 0.45 ± 1.36; t (9) = 1.05, $p = 0.322$). To independently assess apathy and depression-related symptoms, the SADQ-21 was divided into: (1) 14 items assessing symptoms of depression; and (2) 7 items assessing apathy symptoms. This division was based on the factor analysis of the original scale (Sutcliffe & Lincoln, 1998), in which one factor consisted of six items (SADQ items: 4, 11, 12, 15, 17, and 20) considered to assess symptoms of apathy. An additional item (14: "Does the patient remain seated without doing any activity?") was considered to assess apathy based on a panel agreement composed of three post-stroke depression and apathy experts (MLB, SES, REJ). The remaining 14 items of the scale were considered to measure depression. Depression was diagnosed based on the shortened 10-item version of SADQ-21 (Stroke Aphasia Depression Questionnaire-10; SADQ-10) (Sutcliffe & Lincoln, 1998), which provides valid cut-off scores to detect depression (scores ≥ 14 points) and subthreshold depression (scores ≥ 6 points) (Berthier et al., 2022; Lincoln et al., 2000; Sutcliffe & Lincoln, 1998). Both evaluations (WAB-AQ and SADQ-21) were performed the day after ending each intervention. To ensure stability of mood, the SADQ-21 was administered twice at baseline (two weeks apart), showing small, non-significant statistical differences between the two evaluations (mean ± SD, 0.40 ± 0.16; t (9) = 0.16, $p = 0.872$[2].) The SADQ-21 was completed by a reliable caregiver during the three evaluations, as this instrument was specifically devised and validated for proxy-administration purposes (Lincoln et al., 2000; Sutcliffe & Lincoln, 1998).

2.6. Statistical analyses

Repeated measures ANOVA tests with "treatment" (Baseline, Donepezil, and Donepezil-ILAT) as a within-subject factor were used to assess changes over time in the WAB-AQ and apathy and depression subdomains of the SADQ-21. When a significant main effect was found, Bonferroni corrected post hoc t-tests were conducted. All tests were two-tailed, and the significance threshold was established at $p < 0.05$. Effect sizes were calculated for all comparisons. All statistical analyses were performed using JASP software (JASP 2020 version 0.14.1).

2.7. Neuroimaging acquisition

Structural magnetic resonance imaging of the brain (MRI) and ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) were acquired from the 10 PWA at three time points (T1: baseline, T2: Donepezil alone, and T3: Donepezil-ILAT). Both neuroimaging studies were acquired within a time window of 48 h after the evaluations with the aim of measuring changes in grey matter volume and metabolic activity, respectively. The baseline ^{18}FDG-PET was also acquired from 25 healthy controls (15 males; mean age: 58.25 ± 12.72 years; range: 48–67 years). Three-dimensional T_1-weighted images were acquired on a 3-T MRI scanner (Philips Intera Best, The Netherlands). ^{18}FDG-PET acquisition was performed on a Discovery ST PET/CT camera (General Electric, Milwaukee, WI). Acquisition parameters have been reported elsewhere (Torres-Prioris et al., 2019).

2.7.1. Voxel-based morphometry (VBM)

VBM was performed to investigate whether treatments effects co-varied with changes in brain structure. First, using MRIcron software, a binary mask was hand drawn to delineate the areas of the brain affected by the injury in each subject's native space T_1-weighted images acquired at T2. Subsequently, the mask of each PWA was coregistered to match the images acquired at T1 and T3. Cost function masking was used (Rorden & Brett, 2000), and then the T_1- as follows: T2 minus T1, T3 minus T1, and T3 minus T2. The resulting SPM (t) images were entered into a simple linear regression model to identify changes in grey matter volume associated with changes in apathy and depression scores. A statistical threshold of $p < 0.05$ corrected for multiple comparisons (FWE-corrected) at cluster level was applied. Further, results at an exploratory uncorrected level of $p < 0.001$ are also reported in Supplementary Results.

2.7.2. ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET)

Detailed methodology for ^{18}FDG-PET analysis has been reported elsewhere (Torres-Prioris et al., 2019). Briefly, PET images were co-registered with the T_1-weighted images and spatially normalized onto the MNI space. Grey and white matter-based intensity normalization was applied to the smoothed PET images. After pre-processing, the resulting PET images excluding lesioned tissue were used to assess longitudinal changes in metabolic activity across time points. As in VBM analysis, images were subtracted at each time point, resulting in three sets of images. Simple regression analysis was used to assess changes in the whole brain associated with changes in apathy and depression scores. Further, a set of regions of Interest (ROIs) (Fig. S1) were selected to study the correlation between their metabolic activity and changes in apathy and depression scores (see Supplementary Methods and results section). The preprocessing of VBM and PET and statistical analyses were performed with the Statistical Parametric Mapping program package, version 12 (SPM12, https://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2017b (Mathworks Inc., Natick, MA, United States).

2.8. Data availability

The behavioral data that support the findings of this study are available in Table 2. Access to MRI and PET data is limited by institutional policies, which requires signed data use agreements to ensure appropriate use by the academic community.

3. Results

3.1. Intervention overview

Key questions regarding the feasibility of study implementation were addressed. In terms of participant recruitment, 25 potential candidates were initially screened for eligibility, and of these ten PWA (40 %) met inclusion criteria for trial participation. Sociodemographic and clinical information is shown in Table 1 and Table 2. Twelve screened subjects were excluded due to the severity of aphasia (WAB-AQ ≤ 50), two other subjects because they had foreign accent syndrome with no aphasia (Mariën et al., 2019) and another individual for having bi-hemispheric lesions. PWA were provided with trial information via a language-

[2] WAB first baseline evaluation score (75.44 points) and two weeks later (75.89 points). SADQ21 first baseline evaluation score (18.2 points) and two weeks later (17.8 points).

Table 1
Demographic, clinical, lesion, and language profiles of participants.

Participant	Sex, Age & Handedness	Education (school years)	Stroke duration (months)	Lesion volume (cc) †	Lesion etiology and location	Antidepressants	Aphasia type
1	M, 51, R	10	33	198.62	Infarction, FT, INS	Escitalopram, 10 mg/day	Anomic
2	M, 59, R	13	30	175.29	Infarction, FTP, INS, BG, PVWM	No	TCMA
3	F, 41, R	8	15	23.11	Infarction, FTP, INS	No	TCMA
4	M, 52, R	12	7	20.24	Infarction, TP, PVWM	No	Conduction
5	M, 47, R	14	73	96.51	Infarction, TP, INS	No	Anomic
6	F, 53, R	10	42	72.43	Infarction, F, INS, BG, PVWM	No	Anomic
7	M, 50, R	15	9	50.31	Hemorrhage, TP, INS	Escitalopram, 10 mg/day	Anomic
8	M, 47, R	17	16	48.58	Infarction, TP, INS, PVWM	Escitalopram, 20 mg/day	Anomic
9	M, 56, R	15	53	141.12	Infarction, INS, PWVM	Escitalopram, 10 mg/day	Anomic
10	M, 60, Mx	8	23	89.59	Infarction, INS, P, BG	Sertraline, 50 mg/day	Anomic
Mean ± SD	51.6 ± 5.82	12.2 ± 3.12	30.1 ± 21	91.58 ± 62.04			

M: Male; F: Female; R: Right-handed; Mx: Mixed-handed; F: Frontal; P: Parietal; FT: Frontotemporal; FP: Frontoparietal; FTP: Frontotemporoparietal; TP: Temporoparietal; INS: Insula; PVWM: Periventricular white matter; P: Putamen; BG: Basal Ganglia; WAB-AQ: Western Aphasia Battery-Aphasia Quotient; TCMA: Transcortical Motor Aphasia. †Lesion volume was extracted from each individual lesion mask normalized to the MNI standard space.

Table 2
Behavioral profile at different timepoints of participants.

Participant	WAB-AQ Baseline	WAB-AQ DP	WAB-AQ DP-ILAT	Depression Baseline	Depression DP	Depression DP-ILAT	Apathy Baseline	Apathy DP	Apathy DP-ILAT
1	76.7	82.9*	87.5*	17	16	12	6	6	3
2	65.0	78.0*	78.9*	4	1	1	6	3	2
3	74.9	87.6*	92.0*	7	5	1	3	1	2
4	84.8	87.3	88.9	18	16	14	4	4	1
5	80.2	84.7	86.8*	11	9	7	3	2	2
6	78.2	84.1*	87.3*	10	6	6	3	0	0
7	61.6	69.4*	76.3*	19	24	21	6	8	6
8	87.7	90.4	92.4	18	18	17	3	0	0
9	70.6	76.0*	79.5*	7	7	7	8	0	0
10	79.2	83.8	84.2*	17	17	16	8	6	5
Mean ± SD	75.9 ± 8.2	82.4 ± 6.2	85.4 ± 5.4	12.8 ± 5.6	11.9 ± 7.2	10.2 ± 6.8	5.0 ± 2.0	3 ± 2.9	2.1 ± 2.0

Note = WAB-AQ: Western Aphasia Battery-Aphasia Quotient; DP: Donepezil; ILAT: Intensive Language Action Therapy. *Participants are classified as responders based on a WAB-AQ difference ≥ 5 points compared to baseline evaluation. The depression and apathy scores are derived from the sum of the item responses of each construct of the SADQ-21. Maximum depression score = 42 points; Maximum apathy score = 21 points. The identification of each participant receiving antidepressant treatment is bolded and underlined.

friendly visual presentation based on national guidelines recommendations. In addition, none of the participants had received aphasia therapy for at least three months before the beginning of the study nor were they treated with cognitive-enhancing drugs. PWA taking medication, including antidepressants, were instructed to maintain the doses unchanged during the length of the trial. All participants who met eligibility criteria agreed to participate in the study after specific provision of trial information. The recruitment of all participants took 6 months. Participants and caregivers showed understanding of the evaluation process and treatment to receive. In terms of the appropriateness of data collection procedures and outcome measures, the WAB and SADQ-21 are validated instruments for this population and frequently used in research studies (for example, see Laures-Gore et al., 2017; Wang et al., 2018). The SADQ-21 requires a proxy to assess depressive symptomatology (Sutcliffe & Lincoln, 1998), while the WAB must be administered and scored by an experienced evaluator (Kertesz, 1982). In terms of retention, all participants, and their caregivers completed the full duration of the study. Participants received 30 h of ILAT (3 h/day) and compliance with Donepezil intake was accomplished (participants returned the empty blisters after cessation of trial and all assured to have taken the drug). In terms of fidelity to therapy, the ten participants completed all training sessions, confirming thus the good compliance of chronic PWA to ILAT (Stahl et al., 2018). After the provision of Donepezil, three participants showed adverse events in the form of mild irritability, mild sleep problems, and occasional headaches, but none of them led to a reduction in dose or discontinuation of drug treatment at any time point. Regarding ILAT provision, specific adaptations were not needed at the university facilities, and sufficient resources and therapy material were available for the correct implementation of the therapy. The feasibility of applying the Spanish version of ILAT (REGIA) has been demonstrated in a randomized controlled trial (Berthier et al., 2009) and in a case-controlled study (Berthier et al., 2022). The present study further confirmed that it is achievable to provide ILAT in a group format of two or three participants in the foreseen time frame. No specific incidents were recorded for behavioral therapy. In terms of acceptability, after the end of trial all participants verbally expressed their desire for continuing receiving Donepezil intake. Based on the maintenance of gains in language provided by the Donepezil in a 6-month extension phase in a previous PSA study (Berthier, 2005) some participants asked their doctors to continue taking the drug as an "off-label" prescription. All participants also expressed satisfaction for receiving ILAT as already reported in previous studies (Berthier et al., 2009; 2022). In fact, 8 out of 10 participants asked for ILAT to be much longer in duration. No therapy disadvantages were reported by the participants or caregivers.

3.2. Language results

Statistical results of repeated measures ANOVA for WAB-AQ showed

a large treatment effect (F (2, 18) = 36.98, $p = < 0.001$, $\eta^2 = 0.80$[3].) Post-hoc tests showed that, compared to baseline, WAB-AQ scores increased significantly after administration of Donepezil alone ($p < 0.001$) and after Donepezil-ILAT treatment ($p < 0.001$); and from Donepezil alone to Donepezil-ILAT evaluations ($p = 0.003$). Based on changes in individual WAB-AQ scores over time, six participants were classified as responders (based on an increase of ≥ 5 points in the WAB-AQ) (Berthier et al., 2009) to Donepezil alone (AQ improvement [mean ± SD]: 6.5 ± 3.6), and eight participants were responders to Donepezil-ILAT (AQ improvement [mean ± SD]: 9.5 ± 4.6 points).

3.3. Neuropsychiatric results

When considering the separated components of the SADQ-21, large treatment effects were found for apathy (F (2, 18) = 9.6, $p = 0.001$, $\eta^2 = 0.52$) and depression scores (F (2, 18) = 7.0, $p = 0.005$, $\eta^2 = 0.44$) as revealed by eta-squared. Post-hoc tests showed that apathy scores improved significantly from baseline to Donepezil-ILAT (mean change: −2.9 ± 2.2; $p = 0.007$), but not with Donepezil alone (mean change: −2.0 ± 2.7; $p = 0.125$) (Fig. 1A). No significant differences were observed in apathy scores for the comparison of Donepezil alone with Donepezil-ILAT (mean change: −0.9 ± 1.4; $p = 0.203$). A significant reduction in depression symptoms was found with Donepezil-ILAT treatment compared to baseline (mean change: −2.6 ± 2.5; $p = 0.028$), but not with Donepezil alone compared to baseline (mean change: −0.9 ± 2.5; $p = 0.837$). Significant improvement in depression scores was also observed with Donepezil-ILAT compared to Donepezil alone (mean change: −1.7 ± 1.6; $p = 0.023$) (Fig. 1B). Based on the cut-off score of the SADQ-10 scale, participants were either diagnosed with depression (four participants) or subthreshold depression (six participants) at baseline. Improvement of depression was observed over time. At the end of the trial, four participants did not have depression anymore, four remained with subthreshold symptoms, and only two participants remained with depression. The five participants receiving selective serotonin reuptake inhibitors (SSRIs) showed negligible improvement in depression scores (mean ± SD: −1 ± 0.9 points) from baseline to the end of the trial, while participants without SSRIs treatment showed greater improvement (mean ± SD: −4.2 ± 0.5 points) in the depression subscale from baseline to week 10.

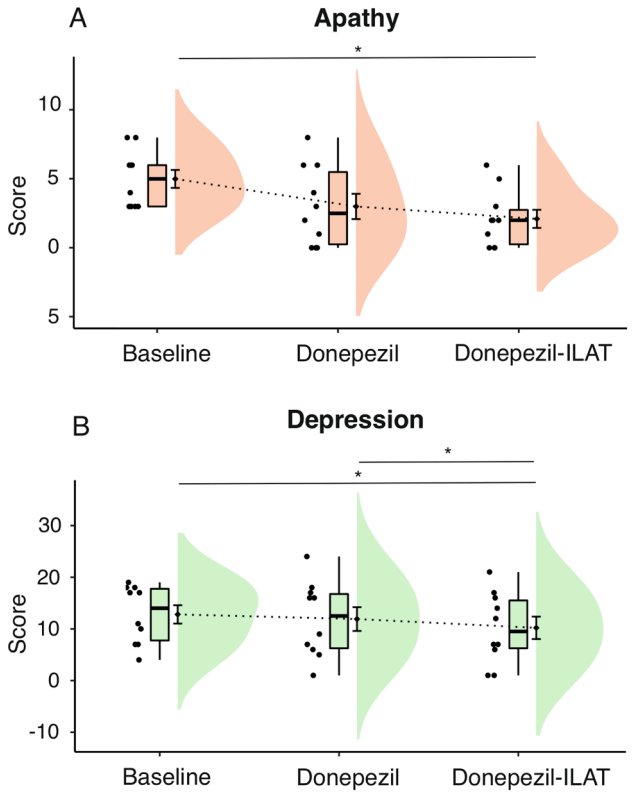

Fig. 1. Raincloud plots for apathy (A) and depression (B) scores at baseline, after treatment with Donepezil alone and after Donepezil-ILAT. Black dots indicate the score for each of the 10 persons with post-stroke aphasia. In the box-plot, the horizontal line dividing the box represents the median of the group, while the top and bottom lines represent the upper and lower quartiles, respectively. Whiskers represent the highest and lowest values. Dot and lines over the probability distribution represent the mean and standard error, respectively. Asterisks (*) index statistically significant effects. Graphs were generated with RainClouds R scripts.

3.4. Neuroimaging results

The lesion overlap map for the 10 participants is shown in Fig. 2. All lesions involved the left perisylvian regions, which presumably compromised the *lateral* cholinergic pathway in the frontoparietal operculum, insula, and superior temporal gyrus (Selden et al., 1998; Simić et al., 1999). The lesions spared the mesial frontoparietal cortex through which travels the *medial* cholinergic pathway (Selden et al., 1998). Whole brain VBM analysis at the selected statistical threshold ($p < 0.05$, FWE corrected) did not reveal any result. Uncorrected whole-brain VBM analyses showed that treatment with Donepezil alone and Donepezil-ILAT induced grey matter volume changes that were associated with changes in apathy and depression scores after treatment (see Supplementary Results, Table S1, Table S2 and Fig. S2). For ^{18}FDG-PET, no cluster survived the whole-brain analysis. ^{18}FDG-PET ROI-based analysis are reported in the Supplementary Results.

4. Discussion

In this feasibility study, we examined the intervention implementation process and the preliminary treatment effect of the acetylcholinesterase inhibitor Donepezil alone and in combination with ILAT on apathy, and depression in people with chronic PSA and left perisylvian lesions. The two phases of the trial (Donepezil alone and Donepezil-ILAT) were feasible to implement, and the intervention processes were satisfactorily designed and completed. Only mild adverse events with Donepezil were experienced in 3 participants. Strong interest in participation must be highlighted in lieu of the invasive ^{18}FDG-PET proceedings that required intravenous injection of a radiotracer. The retention rate for this 10-week trial was 100 % both for participants and their caregivers and verbal acceptability was expressed by both. In fact, all participants wished to maintain Donepezil intake and 8 out of 10 participants expressed their desire to receive more intensive and longer in duration ILAT.

We found treatment effects for apathetic and depressive symptoms with combined Donepezil-ILAT treatment, but not with Donepezil alone. At baseline, all participants showed depressive symptoms, whereas at the end of the trial four participants were symptom-free, two improved from depression to residual subthreshold symptoms and two remained depressed. Participants with stable antidepressant treatment improved less on depression scores than participants receiving no antidepressants. The interpretation of this finding is not straightforward and future studies are required to identify biomarkers (e.g., serotonin transporter gene polymorphisms, location of the injury) that would predict the response of depressed PWA to treatment with antidepressants alone (Fridriksson & Hillis, 2021; Hillis et al., 2018; Lee et al., 2018; Stockbridge et al., 2021) and combined with acetylcholinesterase inhibitors.

[3] For eta squared, threshold values are interpreted as small (0.01), medium (0.06), and large effects (0.14). (Cohen et al., 2002).

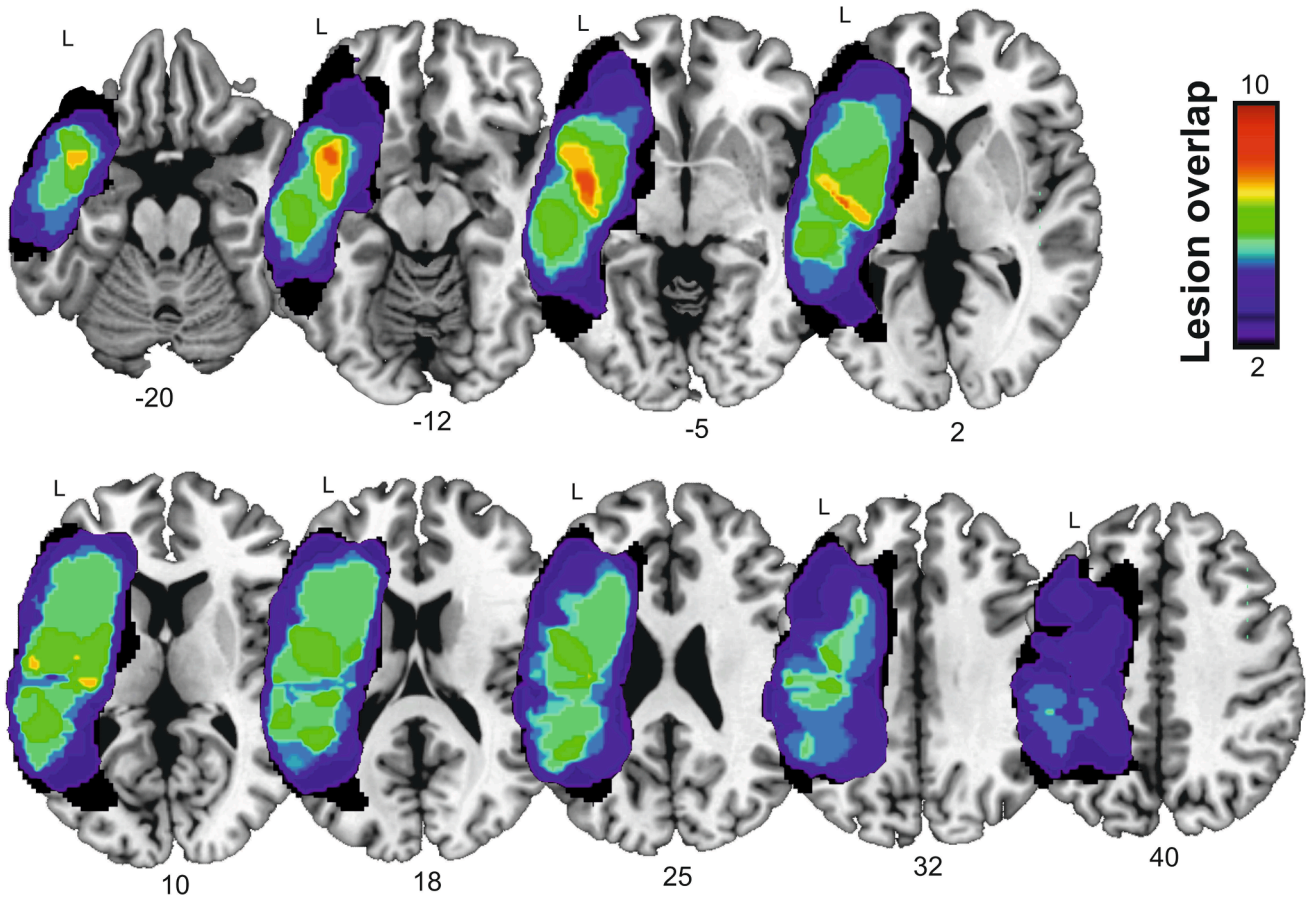

Fig. 2. Lesion overlay map of stroke lesions in persons with aphasia (n = 10). All lesions were restricted to the left perisylvian area in the vascular territory of the middle cerebral artery showing the maximum overlap in the insula and the superior temporal gyrus. Maps are overlaid on a standard template. The color scale indicates the number of participants with damage in that location, from 2 to 10. Warmer areas indicate greater lesion overlap. Lesions were manually drawn, binarized, and normalized to MNI reference space. MNI coordinates are reported below each axial slice. L: left.

Regarding language, scores on the WAB-AQ improved significantly with both interventions; six out of ten participants were responders to Donepezil alone, and eight of them further benefited from combined therapy.

A key question that deserves an answer is why apathetic and depressive symptoms in PSA can be improved with ILAT? One of the main pillars of this therapy is the strengthening of the spectrum of socio-communicative actions and interaction schemes (Pulvermüller et al., 2016). Therefore, it is possible that in our previous studies (Berthier et al., 2022; Mohr et al., 2017) and in the present trial two weeks of intensive training of behaviorally relevant verbal communication in social context may have contributed to improve motivation and mood by increasing the drive to use language for communicative purposes in everyday activities (McClung et al., 2010). Furthermore, the language and communication gains promoted by ILAT may increase the perception of self-efficacy and this, in turn, could have increased motivation and mood (Biel et al., 2018).

Structural MRI at baseline showed consistent involvement of the left insula and the superior temporal gyrus among the ten participants with PSA. Lesions involving these two regions together with the frontoparietal operculum were ideally suited to deplete cholinergic neurotransmission due to damage to the perisylvian division of the *lateral* cholinergic pathway that innervates distant cortical areas and deep nuclei (Selden et al., 1998; Simić et al., 1999). However, VBM and ^{18}FDG-PET results in our small sample could not provide reliable data about the brain changes presumably promoted by the interventions (see further discussion in Supplementary Material).

Despite these methodological issues, we hypothesize that the improvement in symptoms of apathy and depression in our sample might be related to changes in brain regions that receive dense cholinergic input from the basal forebrain (Mesulam, 2013; Selden et al., 1998) and brainstem nuclei (Mena-Segovia & Bolam, 2017; Mesulam, 2013). Some support for this hypothesis comes from the idea that deep grey nuclei (thalamus, striatum) and cerebellum showing exploratory uncorrected structural or functional changes associated with apathy and depression improvement in our participants are the sites of greater selective binding of Donepezil to acetylcholinesterase demonstrated with [5-^{11}C-*methoxy*]donepezil PET in healthy subjects (Hiraoka et al., 2009). However, modulation of the cholinergic system with Donepezil influences the activity of other neuromodulators (Furey, 2011; Mena-Segovia & Bolam, 2017; Picciotto et al., 2012). Therefore, it remains to be explored in future placebo-controlled trials whether ascending projections from the upper brainstem cholinergic complex to midbrain and forebrain structures could also improve apathetic symptoms by enhancing cholinergic-dopaminergic interactions (Mena-Segovia & Bolam, 2017). Altogether these findings might suggest that the unaltered regions and the networks' subcomponents in which they are embedded may be recruited to aid behavior modulation.

Our findings should be interpreted considering other methodological limitations. First, our trial enrolled a small number of participants and employed a feasibility design and, as such represents a low level of evidence. It should be noted, however, that we previously demonstrated the safety and efficacy of Donepezil and distributed aphasia therapy in language and communication deficits in chronic PSA in a double-blind, placebo-controlled, parallel group study (Berthier et al., 2006) and that similar benefits in language have also been reported in a controlled

study of acute PSA (Chen et al., 2010). Therefore, our objective in the present feasibility study was to evaluate the intervention process when combining, for the first time, Donepezil with ILAT. We have provided preliminary findings on treatment effects of drug intervention alone and combined with ILAT not only in language deficits, but also in mood and motivational deficits. Future trials enrolling larger sample sizes must include a placebo control group. In addition, it could be argued that it is difficult to rule out the continued increase of Donepezil effects in the two subsequent weeks (weeks 8 to 10) when combined with ILAT, therefore masquerading the true effect of adding behavioral intervention to the ongoing Donepezil treatment. Our preliminary results show that Donepezil improved language deficits, while the addition of ILAT further augmented gains in language performance and induced a different change, that is, a significant improvement in apathetic and depressive symptoms. An exclusive effect of Donepezil on the final therapy period, where also ILAT was applied, is in fact ruled out by the observation of a drug effect on language behavior in the first phase, before ILAT came in. Note that our study did not have a blind and inter-rater evaluation of efficacy. Future randomized controlled studies should include these aspects and add a long-term evaluation of maintenance of treatment effects after withdrawing the combined treatment.

Feasibility intervention trials initially explore the question "*can it work?*" (Orsmond & Cohn, 2015). The administration of Donepezil alone and in combination with ILAT appears to work and its implementation is feasible, conditioned by the presence of experienced physicians and speech-language therapists. ILAT can be administered in hospital, community, and academic settings. The next question that arises is "*does it work?*" Preliminary behavioral data show that language, apathy, and depression improve over the course of the short-term trial.

In conclusion, in the case that our current preliminary results are replicated in an adequately powered controlled intervention trial, Donepezil-ILAT treatment can be implemented as intervention program for PWA to improve apathetic and depressive symptoms, thus expanding our previous finding of depressive symptoms-reduction with ILAT alone in this population (Berthier et al., 2022; Mohr et al., 2017). Since there is a spectrum of neuropsychiatric symptoms in chronic PSA (Edelkraut et al., 2022), devising new effective intervention strategies is imperative. Our preliminary behavioral findings in this feasibility study using a combined therapy open potential new therapeutic options that deserve further research.

Author contributions

All authors contributed to the article and approved the submitted version. MLB, MT-P, DL-B, GD, FP, BM, SES and REJ were involved in conception and design, acquisition of data, or analysis and interpretation of data. MLB, LE and GD were involved in language and neuropsychiatric testing. FJL-G, MT-P and DL-B interpreted neuroimaging data. MLB, LE, MT-P, DL-B, GD, BM, SES and REJ drafted the article and revised it critically for important intellectual content.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was conducted as an independent research grant funded by Pfizer Spain and Eisai and it was designed, conducted, and controlled by principal investigators. Pfizer Spain provided the donepezil.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandl.2022.105205.

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