Neural signatures of treatment-induced benefits in apathy and depression amongst persons with aphasia

Marcelo L. Berthier[1,2], Francisco J. López González[3,4], Lisa Edelkraut[1,2,5], Núria Roé-Vellvé[6], Diana López-Barroso[1,2,5], Bettina Mohr[7], Friedemann Pulvermüller[8,9], Sergio E. Starkstein[10], Francisco Alfaro[3], Guadalupe Dávila[1,2,5], María José Torres-Prioris[1,2,5]

[1] Cognitive Neurology and Aphasia Unit, Centro de Investigaciones Médico-Sanitarias, University of Malaga; [2] Instituto de Investigación Biomédica de Málaga - IBIMA, Malaga, Spain; [3] Molecular Imaging Unit, Centro de Investigaciones Médico-Sanitarias, General Foundation of the University of Malaga, Malaga, Spain; [4] Molecular Imaging and Medical Physics Group. Department of Psychiatry, Radiology and Public Health, University of Compostela, Galicia, Spain; [5] Area of Psychobiology, Faculty of Psychology and Speech Therapy, University of Malaga, Malaga, Spain; [6] Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain; [7] Department of Psychiatry. Charité Universitätsmedizin Berlin | Charité · Berlin. Germany; [8] Brain Language Laboratory, Department of Philosophy and Humanities, WE4, Freie Universität Berlin, Germany; [9] Berlin School of Mind and Brain, Humboldt Universität zu Berlin, Germany; [10] Faculty of Health and Medical Sciences. The University of Western Australia (M704), Perth Australia

BACKGROUND

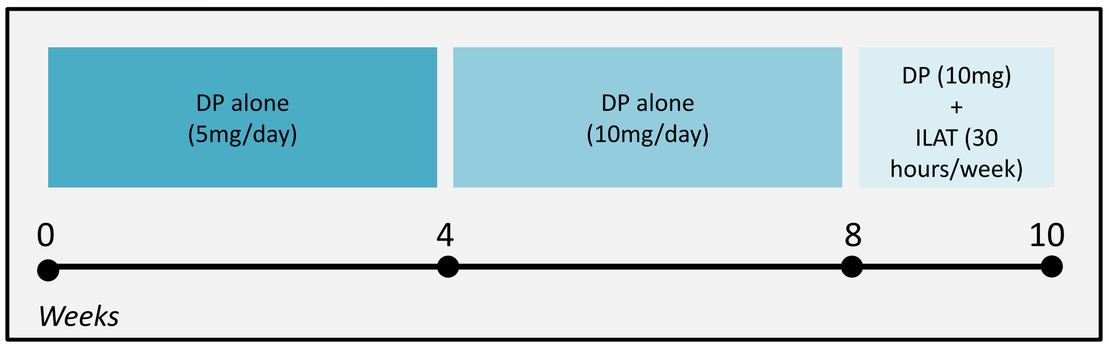
- Depression is one of the 10 research priorities in stroke aphasia (Franklin et al., 2018). In fact, around 40 % of persons with aphasia (PWA) develop apathy and depression after stroke.
- Until recently there was no information on the treatment of apathy and depression in PWA. In this line, Mohr et al. (2017) have found that intensive language-action therapy (ILAT) reduces symptoms of depression in PWA, but the neural correlates of such improvement remain unexplored.
- ILAT is a group language therapy that follows massed practice and action-embedded language use that may be useful for daily live (Difrancesco, Pulvermuller and Mohr, 2012). The behavioral improvements associated to ILAT can be potentiated when applied in combination to cognitive-enhacement drugs such as the cholinesterase inhibitor donepezil (DP) (Berthier, 2006, 2003).

AIMS

- To explore the neural underpinnings of improvements in apathy and depression associated to DP alone and combined with ILAT.

METHODS

- Participants: 10 persons with post-stroke chronic (> 6 months) aphasia (8 men; mean age: 51.8 (SD 5.71).
- Study design: 10-week open-label pilot study



- Primary outcome measures: Western Aphasia Battery (WAB), the Communicative Activity Log (CAL), the Stroke Aphasic Depression Questionnaire (SADQ) and the Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39). The severity of apathy and depression were measured with different items from the SADQ.
- Neuroimaging evaluation: Structural MRI and [18]fluorodeoxyglucose PET ([18]FDG-PET) were acquired at weeks 0, 8 and 10.
- Neuroimaging analyses: Voxel-based morphometry (VBM) with a $p < 0.001$ (uncorrected; threshold: 50) was used. For [18]FDG-PET the correlation between signal differences at each ROI and the differences in each of the subscales of the SADQ (apathy and depression) were studied.

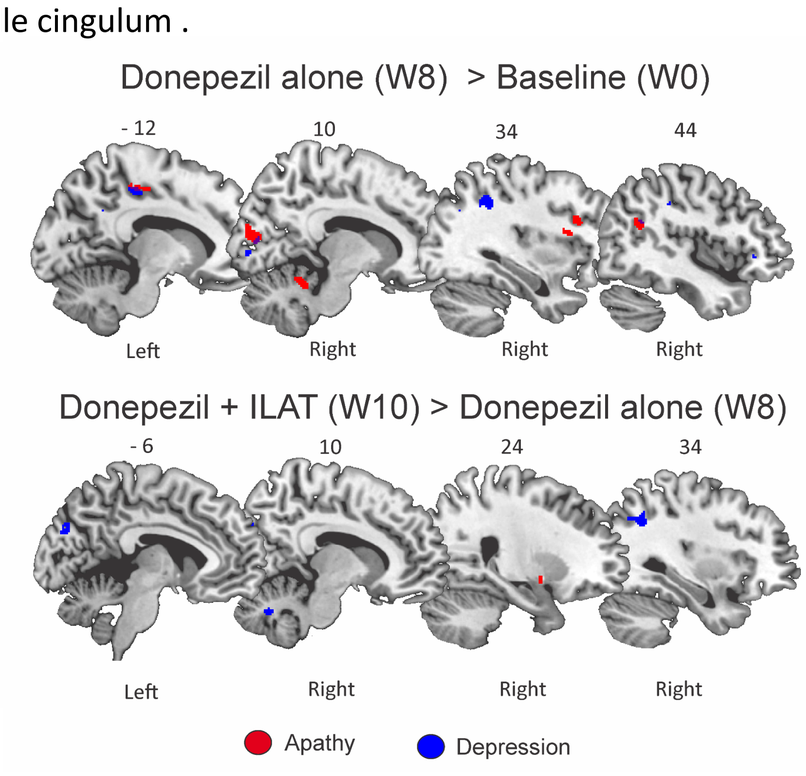
RESULTS

- Behavioral results showed improvements with DP alone and under DP-ILAT in AQ-WAB, CAL and SAQoL-39. **[18]FDG-PET analysis** revealed that DP alone induced significant increments in metabolic activity in the ventral tegmental area (VTA), left anterior cingulate cortex (ACC) and right superior temporal gyrus that were correlated with improvement in apathy. Although depression improved there were no metabolic changes under DP alone. However, reduction in depressive symptoms under DP-ILAT showed increased metabolic activity (compared to baseline) in the VTA, right ACC, left and right middle temporal gyrus, left and right inferior frontal operculum and orbitofrontal cortex.

	DONEPEZIL > BASELINE	DONEPEZIL + ILAT> DONEPEZIL	DONEPEZIL + ILAT> BASELINE
APATHY	L Anterior Cingulate L Anterior Temporal R Superior Temporal Bilateral Thalamus Ventral tegmental	L&R Cuneus L&R Posterior Cingulate L Subgenual	R Substantia Nigra L Superior Temporal Ventral tegmental area
DEPRESSION	-	L Anterior Cingulate R Fornix	R Anterior Cingulate L&R Frontal Inferior L&R Middle Temporal R Orbitofrontal Cortex R Substantia Nigra

L: left; R: right

- The **VBM analysis** revealed that DP alone treatment induced increases in grey matter density in the cuneus and right deep frontal operculum-anterior insula region associated to improvements in apathy and in right intraparietal sulcus associated to improvements in depression. Combined DP-ILAT improved apathy and induced changes in the right ventral striatum and right cerebellum compared with baseline (see figure). Conjoint analysis of PSA and PSD disclosed increases in grey matter density in the left middle cingulum .



CONCLUSIONS

- In conclusion, treatment with DP alone and combined with ILAT improved aphasia, communication and quality of life as well as associated apathy and depression by modulating regions innervated by the left medial, right lateral and brainstem cholinergic pathways.

References

Difrancesco S et al. Aphasiology 2012, Vol 26(11), 1317-1351.
Franklin S et al. Aphasiology 2017, Vol 32(11), 1388-1395.
Mohr B et al. Neurorehabilitation and Neural Repair 2017, Vol. 31(12) 1053-1062.
Berthier, M L et al., 2003. Neurology, 60(7), 1218-1219.
Berthier, M. L et al., 2006. Neurology, 67(9), 1687-1689.