Optimal Stimulation Sites and Networks for Deep Brain Stimulation of the Fornix in Alzheimer's Disease

Ana Sofía Ríos, M.D.*[1], Simón Oxenford, M.Sc.[1], Clemens Neudorfer, M.D.[1], Ningfei Li, PhD[1], Alexandre Boutet, M.D., PhD[2,3,4], Gavin J.B. Elias[2,3], Jurgen Germann, M.Sc.[2,3], Aaron Loh, M.D.[2,3], Wissam Deeb, M.D.[5], Fuyixue Wang[6,7] ,Kawin Setsompop[6,7,8], Ph.D., Bryan Salvato, B.S.[9], Leonardo Almeida, M.D.[5], Kelly D. Foote, M.D.[5], Robert Amaral, B.Sc.[10], Paul B. Rosenberg, M.D.[11], David F. Tang-Wai, M.D.C.M.[12,3], David A. Wolk, M.D.[13], Anna D. Burke, M.D.[14], Stephen Salloway, M.D.[15], Marwan N. Sabbagh, M.D.[14], M. Mallar Chakravarty, Ph.D.,[10,16,17], Gwenn S. Smith, Ph.D.[11], Constantine G. Lyketsos, M.D.[11], Michael S. Okun, M.D.[5], William S. Anderson, Ph.D., M.D.[19], Zoltan Mari, M.D.[19,20] , Francisco A. Ponce, M.D.[18], Andres M. Lozano, M.D., Ph.D.[2,3], Andreas Horn, M.D., PhD[1,21,22]

Affiliations:
1. Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Movement Disorders and Neuromodulation Unit, Department of Neurology, Charitéplatz 1, 10117 Berlin, Germany.
2. Division of Neurosurgery, Department of Surgery, University Health Network and University of Toronto, Toronto, M5T2S8, Canada
3. Krembil Research Institute, University of Toronto, Toronto, M5T2S8, Canada
4. Joint Department of Medical Imaging, University of Toronto, Toronto, M5T1W7, Canada
5. Norman Fixel Institute for Neurological Diseases, Departments of Neurology and Neurosurgery, University of Florida, Gainesville, FL
6. Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Harvard MedicalSchool, Massachusetts General Hospital, Charlestown, MA, USA
7. Harvard-MIT Health Sciences and Technology, MIT, Cambridge, MA, USA
8. Department of Radiology, Stanford University, CA, USA
9. Florida State University, Tallahassee, FL, USA
10. Cerebral Imaging Centre, Douglas Research Centre, Montreal QC, Canada
11. Department of Psychiatry and Behavioral Sciences and Richman Family Precision Medicine Center of Excellence, School of Medicine, Johns Hopkins University, Baltimore, MD, USA
12. Department of Medicine, Division of Neurology, University Health Network and University of Toronto, Toronto, M5T2S8, Canada
13. Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
14. Barrow Neurological Institute, Phoenix, AZ
15. Department of Psychiatry and Human Behavior and Neurology, Alpert Medical School of Brown University, Providence, RI, USA
16. Department of Psychiatry, McGill University, Montreal, QC, Canada
17. Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada
18. Department of Neurosurgery, Barrow Neurological Institute, Phoenix, AZ, USA
19. Johns Hopkins School of Medicine, Baltimore, MD, USA
20. Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA
21. Center for Brain Circuit Therapeutics, Departments of Neurology and Psychiatry, Brigham and Women's Hospital, MA, USA
22. Departments of Neurology and Neurosurgery, Massachusetts General Hospital, MA, USA

INTRODUCTION

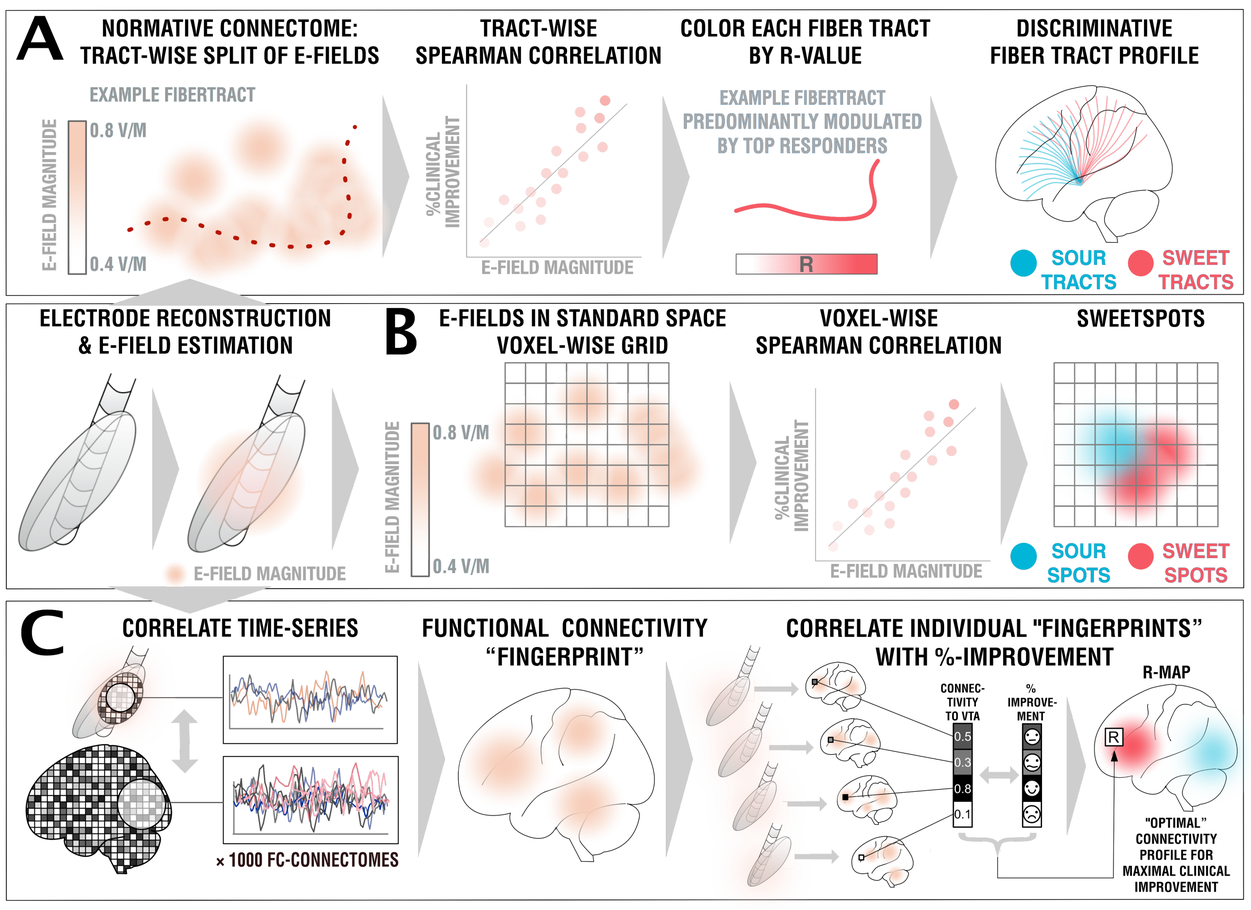
Alzheimer's Disease (AD) is the most common neurodegenerative disease burdening healthcare attention without an effective treatment to date[1]. Deep brain stimulation (DBS) to the fornix is under investigation for mild AD with completed phase I and II trials[2,3], showing cognitive improvement in some patients and deterioration in others[3]. As observed in other conditions treated with DBS[4–6], an explanation of these outcomes could lie in variance in electrode placement engaging distinct neural circuits.

OBJECTIVES

To identify optimal electrode location by investigating effects of stimulation on three levels:
1) Fibertract: white matter tracts traversing Electric-fields informed by a high resolution normative connectome[8].
2) Sweetspot: local-level voxel-wise analysis to identify an optimal stimulation site.
3) Network Mapping: whole-brain network effect informed by resting state fMRI data of 1000 healthy subjects[9].

METHODS

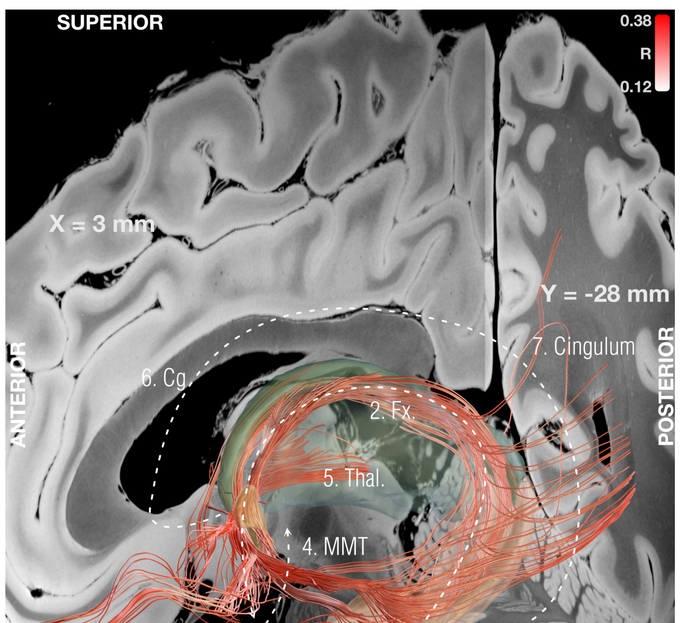
Retrospective analysis of a multi-center cohort of 50 patients (25 female, mean age: 67.5 ± 7.9 years) who underwent fornix-DBS to treat mild AD. Pre- and post-operative MRI volumes of the participants were processed using the lead-DBS pipeline (lead-dbs.org)[7], normalization and electrode localization were manually refined (WarpDrive tool) and clinical outcomes were measured by changes in the Alzheimer's Disease Assessment Scale-cognitive subscale 11 (ADAS-cog score).
At the fibertract level, the subjects were randomly assigned to a Training cohort (n=30) or Test cohort (n=20). Streamlines correlated to clinical improvement were identified in the Training cohort (Leave-one-out and K-fold approaches) and then used to predict clinical improvement of the Test cohort (cross-prediction). For the sweet spot and network mapping analyses, optimal sites and networks were investigated using the whole cohort and results were cross-validated with a Leave-one-out and multiple K-fold approaches.

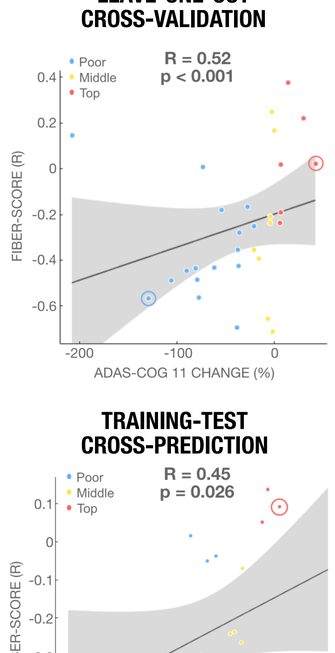


RESULTS

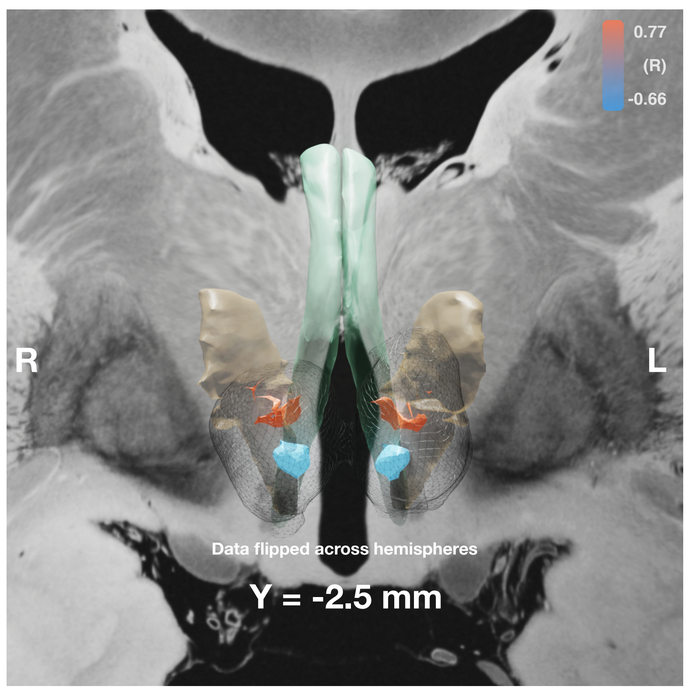
These analyses demonstrated that:
1) Modulation of the Papez' circuit and stria terminalis associated with cognitive improvement (R = 0.45 at p = 0.026).
2) Optimal stimulation site resided at the interface between fornix and bed nucleus of the stria terminalis (R = 0.29 at p 0.016).
3) Modulating specific distributed brain networks accounted for optimal outcomes (R = 0.30 at p = 0.015).

FIBER-TRACT LEVEL

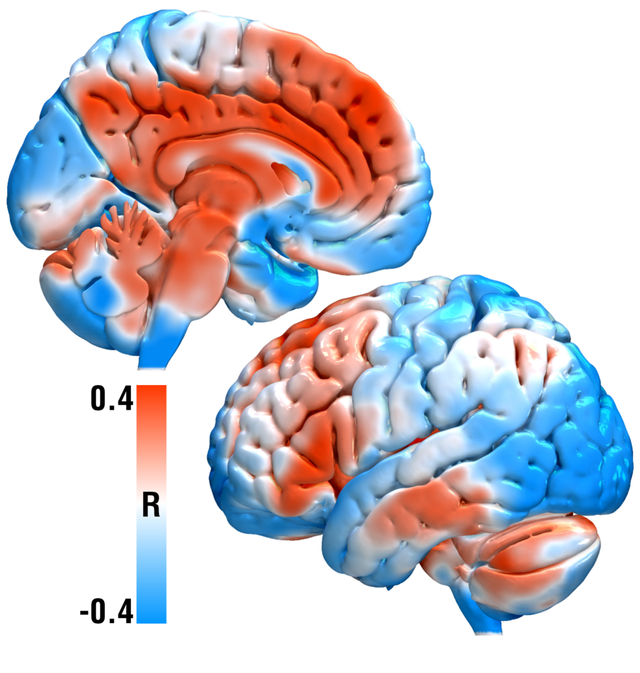




SWEETSPOT LEVEL



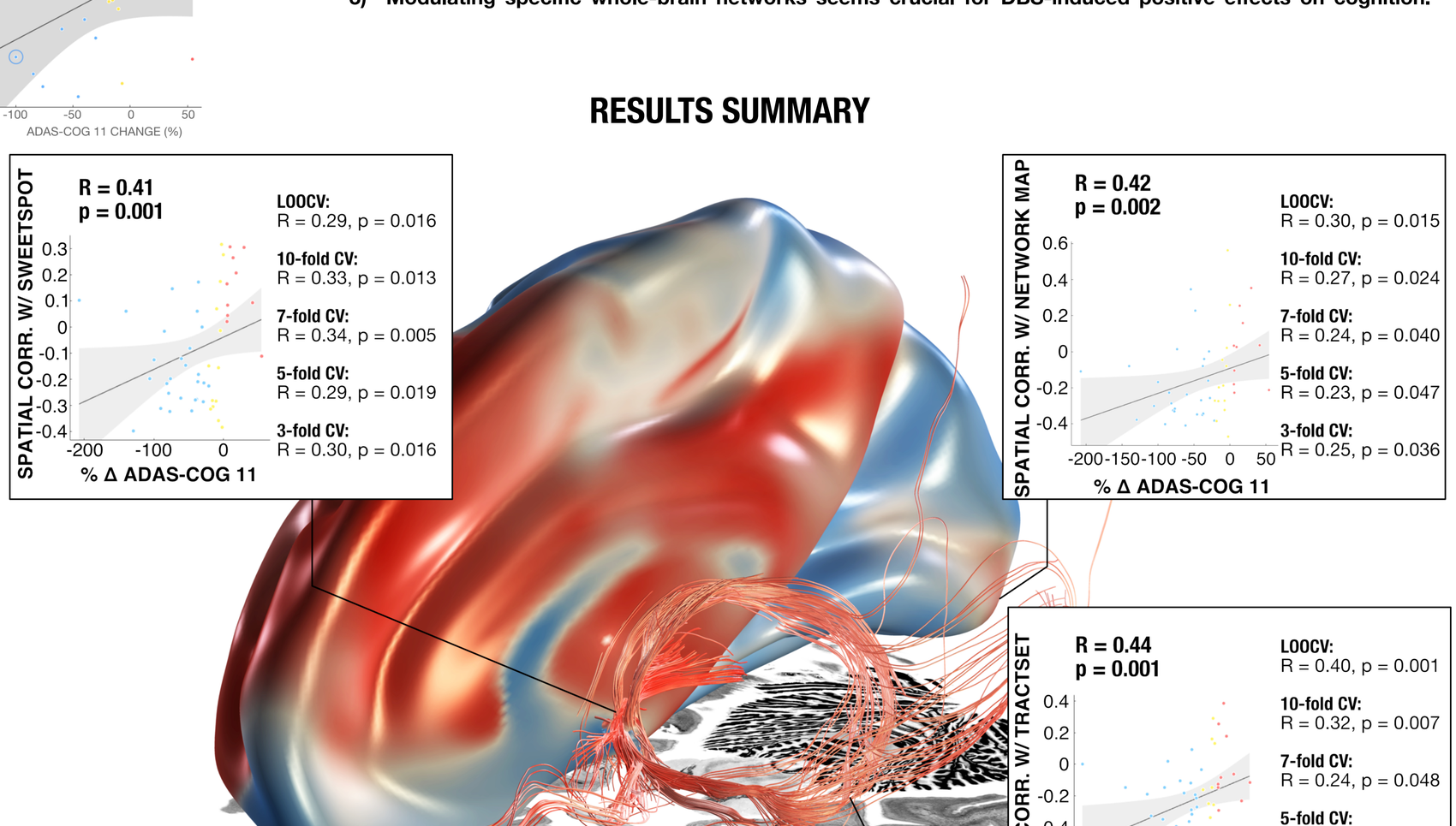
NETWORK MAPPING LEVEL



CONCLUSIONS

A potential optimal stimulation target for Alzheimer's Disease treatment with fx-DBS is proposed.
1) Stimulation of Papez' circuit and bed nucleus of the stria terminalis associated with cognitive improvement.
2) Optimal stimulation site: intersection between fornix and bed nucleus of the stria terminalis.
3) Modulating specific whole-brain networks seems crucial for DBS-induced positive effects on cognition.

RESULTS SUMMARY



Results summary including DBS fiber filtering, sweetspot mapping and network-mapping models. Three levels of analysis explain similar amount of variance of clinical outcomes when analyzed in circular nature (scatterplots ~16-19%) and led to significant cross-validation of clinical outcomes across leave-one-patient-out and k-fold designs. For visualization, patients were distributed into three groups based on their ADAS-cog score results a year after stimulation (poor responders: blue, middle responders: yellow and top responders: red). Gray shaded areas represent 95% confidence intervals. Analysis results were superimposed on slices of Big Brain atlas in MNI 152 space.

REFERENCES

1. Alzheimer's Disease Neuroimaging Initiative *et al.* (2016). J. Alzheimers Dis. 54, 983–993.
2. Laxton, A. W. *et al.* (2010). Ann. Neurol. 68, 521–534.
3. Lozano, A. M. *et al.* (2016). J. Alzheimers Dis. 54, 777–787.
4. Horn, A. *et al.* (2017). Ann. Neurol. 82, 67–78.
5. Li, N. *et al.* (2020). Nat. Commun. 11, 3364.
6. Choi, K. S. *et al.* (2015). JAMA Neurol. 72, 1252–1260.
7. Horn, A. *et al.* (2019). Neuroimage 184, 293–316.
8. Wang, F. *et al.* (2021). Sci. Data 8, 122.
9. Yeo, BT. *et al.* (2011). J. Neurophysiol. 106, 1125-1165.

For figures background and structures:
1. Edlow, B.L., *et al.* (2019) Sci Data 6, 244.
2. Amunts, K., *et al.* (2020). J Science 369,
3. Neudorfer, C., *et al.* (2020) Sci Data 7, 305.
4. Amaral , RSC., *et al.* (201(418). Neuroimage 170, 132-150.

FIND OUT MORE ABOUT THE TOOLS USED FOR THIS WORK HERE

Contact:
ana.rios@charite.de
@sofiari.91
@netstim_org
@leaddbs