

NETLANG PPA: Personalized Network Engineering and Causal Neuromodulation for Language Restoration in Primary Progressive Aphasia

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Project Keywords: Primary Progressive Aphasia (PPA), Language Network Biomarkers
Multimodal Neuroimaging, Artificial Intelligence and Machine Learning, Causal Neuromodulation, Cerebral Network Excitability, Precision Cognitive Rehabilitation, Digital Neurohealth Engineering

Background

Human language is a uniquely complex cognitive function supporting social interaction, learning, and cultural development. Although often studied in isolation, evidence from cerebrovascular and neurodegenerative disorders demonstrates that language relies on interactions with domain-general cognitive systems such as executive control, working memory, and attention. These systems are supported by distributed cortical and subcortical networks—including the prefrontal cortex, inferior parietal lobule, temporo-parietal junction, striatum, and thalamus—which coordinate phonological, syntactic, and semantic processing. Primary Progressive Aphasia (PPA) is a group of rare neurodegenerative disorders primarily affecting language, with three main variants: non-fluent/agrammatic (nfv-PPA), logopenic (lv-PPA), and semantic (sv-PPA). Related syndromes such as Frontotemporal Dementia and Progressive Supranuclear Palsy also display language impairments. These conditions provide a natural framework to study the neural architecture of language, the mechanisms of selective vulnerability, and the interplay between domain-general cognition and linguistic processes. Advances in multimodal neuroimaging (structural MRI, DTI, resting-state fMRI, PET), electrophysiology (EEG/MEG), computational modeling, and non-invasive brain stimulation (NIBS, via tCS, TMS) now allow precise, quantitative investigations of language networks, enabling mechanistic insights and translational applications in rehabilitation.

Scientific Objective

The project is located at the intersection of biomedical engineering, digital health science, clinical neuroscience, and therapeutic neurotechnology design. It contributes to precision medicine by advancing quantitative models of cognitive network dysfunction and by developing translational methodologies linking neuroscience, computational modeling, and clinical validation of non-invasive brain stimulation technologies. Importantly, the work directly supports the scientific priorities of Institut Universitaire d'Ingénierie en Santé de Sorbonne Université (IUIS) by addressing the innovation chain, from conceptual modeling of disease mechanisms to clinical evaluation of health technologies.

Scientific Approach Justification

The current project aims to address fundamental and clinically applied challenges with regards to the organization of language systems (behavioral phenotypical expression and anatomical and electrophysiological correlates) and diagnosis and treatment of their dysfunctions in PPA by exploiting an existing datasets (PHRC CAPP) which is one of the largest cohort of PPA patients (n=91) and matched healthy-controls (n=24) ever collected in France and characterized at an early stage, including: detailed cognitive and language assessments, top-notch neuroimaging recordings (structural MRI, diffusion imaging, fMRI resting-state and PET-FDG), and biological biomarkers obtained from patient's CSF. To optimally address the phenotypic characterization challenge posed by early onset dementia, the project will add to that existing dataset two additional analogous cognitive, language and imaging datasets produced by our team: On the one hand, ICM sponsored pre-therapeutic protocol (STIMLANG) including astringently characterized PPA patients of the three variants (sv-PPA n=18, lgn-PPA n=6, lfv-PPA n=4), PSP patients (n=12) and bv-FTD (n=12), all submitted to a single session stimulation cross-over causal study with transcranial Direct Current Stimulation (tDCS) at three different modalities (Left anodal, right cathodal, sham) in three specific targets for PPA patients (Anterior temporal Lobe-ATL, Temporo-Parietal Junction-TPJ, and Inferior frontal Gyrus-Broca's IFG) respectively. Finally, a three-arm therapeutic clinical trial (PHRC National STIMSD) evaluating the impact on the above/mentioned domains of a multiday regime comparing 2 active strategies of transcranial Direct Current Stimulation (tDCS) to sham stimulation in semantic PPA (n=39 patients and n=20 healthy controls) using a randomized double-blind trial design versus placebo. All three datasets integrate a detailed evaluation of language performance (semantic access, fluency, reading task and speech-voice recordings). Also, a thorough evaluation and survey of cognitive status including memory, executive control, attention, perception, humor with well-established neuropsychological battery.

Conventional hypothesis-driven approaches, inferential statistics and analyses (correlational, multiple-regression models) will be applied to a first analysis of clinical, cognitive assessment and MRI, fMRI, PET and EEG datasets and their associations. Multimodal integration: Data from behavioral, imaging, electrophysiology, and biological sources will be combined using statistical models and machine learning (univariate/multivariate classifiers, deep learning) to extract biomarker-based phenotypes and predictive models. Network characterization: Structural and functional

connectivity analyses will map variant-specific phonological, syntactic, and semantic networks and identify vulnerable hubs and interactions. Causal probing & rehabilitation: Non-invasive brain stimulation (tCS/TMS) will target variant-specific nodes identified in prior analyses. Behavioral and neurophysiological outcomes will assess efficacy, optimize parameters via individualized modeling (SimNIBS), and guide personalized rehabilitation strategies. Validation & cross-cohort analysis: Multimodal biomarkers and stimulation outcomes will be validated across cohorts to ensure robustness and reproducibility. The priority will be given to more sophisticated Machine Learning approaches (Univariate and Multivariate classifiers, Deep learning IA) which will benefit from multiple cohorts of patients and matched-healthy participant datasets, allowing training and testing in different subsets facilitating cross-validation of identified biomarkers of language phenotypes. Overall, the PhD project will allow the candidate to address simultaneously 4 specific aims:

Aim 1/Workpackage 1: To identify new multimodal diagnostic biomarkers data and use them as a basis to establish new accurate classification dimensions for language-impairing condition via the development of algorithms allowing the classification of PPA phenotypes based on neuroimaging, linguistic/cognitive and biological datasets.

Aim 3/Workpackage 2: To develop via, a stratification of PPA patient population according to their underlying pathological mechanisms and the identification if specific on nodes and networks showing high vulnerability to neurodegeneration, hence early onset prognostic value.

Aim 2/Workpackage 3: To further characterize via anatomo-linguistic correlations of the structural and functional interaction between nodes of neural networks subtending different components of language processes (phonology, syntax, semantics) and identify PPA variants associated to specific networks, probed causally with NIBS

Aim 4/Workpackage 4: To employ MRI current field distribution models (SimNIBS) to identify and evaluate the optimal non-invasive stimulation strategies to improve variant-specific language impairments in PPA, as a stepping-stone to extend these approaches to other cognitive disability, with emphasis placed on patient-customization.

Scientific environment

The NETLANG PPA project will be supervised and coordinated by Dr. Antoni Valero-Cabr  (DR CNRS ICM, PhD & HDR, Team FRONTLAB) and Dr. Marc Teichmann (PH, PhD & HDR, Im2A APHP) Clinician and researcher at the IM2A-Piti -Salp tri re with complementary expertises and long experience studying the neural basis of language cognition and their impairments with clinical evaluations, computer-based paradigms, prosody and speech content analysis, neuroimaging approaches (MRI, PET, fMRI, DTI), electrophysiological (scalp EEG) including causal exploratory, pre-therapeutic and therapeutic studies (TMS, tCS). Ongoing collaborations, with Jacobo Sitt (DR INSEMR ICM, MD PhD/ HDR, Team PICNIC) and Dr. Ninon Burgos (DR CNRS ICM, PhD & HDR, Team ARAMIS) in Machine Learning, and Deep learning approaches for patient Neuroimaging datasets (PET-MRI), Prof. Aur lie Kas (PU-PH, PhD HDR, APHP Salp tri re Nuclear Med Sorbonne Univ.) for MRI-PET imaging, Prof. Nadya Pyatigorskaya (PU-PH, PhD HDR, APHP Salp tri re Neuroradiology, ICM Team MOVIT lab) for Diffusion Imaging and Dr. Raffaella Migliaccio (CR INSERM, PhD & HDR, Team FRONTLAB) for resting state fMRI, will warrant success.

Profile and skills required

The ideal candidate for this PhD will hold a Master's degree in neuroscience, cognitive science, psychology, biomedical engineering, or a related field. Strong interest in language, neurodegeneration, and cognitive rehabilitation is required. Experience in neuroimaging (MRI, fMRI, DTI), electrophysiology (EEG/MEG), or brain stimulation (tDCS/TMS) is highly desirable. Proficiency in programming and data analysis (Python, MATLAB, R) and statistical modeling is expected. Familiarity with machine learning and network analysis is an advantage. The candidate should demonstrate autonomy, critical thinking, and problem-solving skills. Good organizational skills and ability to manage complex datasets are important. Strong written and oral communication skills in English are required; French is advantageous. Motivation for multidisciplinary collaboration in clinical and basic neuroscience is essential. The candidate should be committed to high ethical standards and research integrity.

Selected Relevant References of supervisors for the project (see additional ones in associated CVs)

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