PROJECT SUMMARY

Dr M . Teichmann

Dpt. de Neurologie, Institut de la mémoire et de la maladie d'Alzheimer

Hôpital Pitié-Salpêtrière

Within the spectrum of frontotemporal lobar degeneration (FTLD) semantic dementia (SD) causes profound language dysfunction. SD damages semantic processing typically in the anterior temporal lobes (ATL). It is an early onset disease (often before 65 years of age) affecting about 4000 patients in France and for which no validated treatment is available.

For several years a growing number of studies have explored the effects of transcranial stimulation (TCS) on aphasic patients following stroke. Several studies have targeted left-sided language areas and/or homotopical right-sided regions with excitatory or inhibitory TCS, respectively, according to the principle of inter-hemispheric inhibition. In addition, repetitive multi-day TCS has provided evidence for long-lasting language effects (>6 months) presumably linked to stimulation-induced neuroplasticity (Naeser et al. 2005; 2011). Such investigations have provided promising results and have demonstrated that the stimulation site is a determining factor by showing that stimulation of cortical areas belonging to the language network usually results in more convincing effects than stimulating areas outside that network. Despite these findings the use of TCS in degenerative language diseases, such as primary progressive aphasias including SD, has only been explored in few small cohort studies (Cotelli et al., 2012; 2014; Roncero et al., 2017) and, surprisingly, most have not targeted language-related cortices. Also, despite the fact that the majority of these studies have shown effects of stimulation in language behavior they did not use neuroimaging (resting state fMRI or PET) or neurophysiological (resting state scalp EEG or MEG) recordings, able to capture the short-term and long-term impact of stimulation on the targeted regions and associated brain networks. Such measures allow for a better understanding of the effects of TCS and, recorded before and at the end of the stimulation regime, serve to characterize plasticity processes leading to enduring language effects.

This project proposes the application of multi-day repetitive TCS with direct current (tDCS) in a large population of SD patients (N=60). It is built on an exploratory investigation of our team which has used three single tDCS sessions in a double-blind sham-controlled study (Teichmann et al., 2016). Anodal (excitatory) and cathodal (inhibitory) tDCS to the left and right ATL, respectively, demonstrated highly significant transient effects (20 min) on semantic processing in 12 SD patients, providing 'proof of concept' and the rationale for this project. The aim here consists of using repetitive multi-day tDCS for a potential therapeutic outcome leading to long-lasting semantic improvement via neuroplasticity. The project is grounded on 2 hypotheses: i) tDCS to the ATL (left-anodal, right-cathodal) reactivates semantic processing in SD, ii) repetitive tDCS during ten days could induce neuroplasticity and therapeutic long-lasting language improvement.

The main objective is to evaluate the potential therapeutic efficacy of repetitive tDCS during 10 days on language/semantic impairment in SD via a double-blind sham-controlled study design. The evaluation criteria will be a significant improvement of language/semantic performances two weeks after tDCS as compared to base-line (before tDCS), contrasting subgroups receiving left-anodal or right-cathodal tDCS vs. sham tDCS. We will also assess the time course of potential language/semantic improvement through the application of language evaluations at several follow-up time-points: base-line (one week before tDCS), three days, two weeks and four months after tDCS. We will assess brain markers which could reflect stimulation-induced neuroplasticity that will be evaluated through a possible modulation of cortical metabolism (FDG-PET) and functional connectivity (resting-state fMRI, resting-state EEG), comparing base-line and the 'two-week' time-point. We will compare left-anodal and right-cathodal tDCS to reveal the most efficient stimulation modality. Finally, we will also try to improve the understanding of the semantic roles of the left and right ATL, and their potential anatomical connectivity, by comparing left and right ATL stimulation and using MRI-based fiber tracking. We expect patients receiving the active stimulation to show improvements in their language abilities, maintained for at least two weeks, and to show neuroplastic changes that can subtend the language improvement.

The duration of the study will be 41 months; 36 months being dedicated to patient inclusion. Participation duration of a patient will be of 4 months and 1 week to 4 months and 3 weeks maximum. First, patients will undergo a series

of standardized neuropsychological and language tests and inclusion criteria will be checked. After inclusion, the base-line visit will comprehend an MRI/PET, EEG recordings and a set of language/semantic tasks. Subsequently the ten stimulation sessions will be scheduled. They will take place during two consecutive weeks (20 minutes of tDCS). The tDCS sessions will be followed by three time-point visits: 3 days (time-point 2) and two weeks (time-point 3) after the last stimulation session patients will undergo the language/semantic tasks. At time point 3 the second MRI/PET acquisition and EEG recordings will take place. Finally, the visit of time-point 4 will be at four months after the last tDCS session, dedicated to a last application of language/semantic tasks.

Publications on the subject:

Cotelli, M., Manenti, R., Petesi, M., Brambilla, M., Cosseddu, M., Zanetti, O. et al. (2014). Treatment of Primary Progressive Aphasias by Transcranial Direct Current Stimulation Combined with Language Training. *Journal of Alzheimer's Disease, 39, 799–808.*

Roncero, C., Kniefel, H., Service, E., Thiel, A., Probst, F. and Chertkow, H. (2017). Inferior parietal transcranial direct current stimulation with training improves cognition in anomic Alzheimer's disease and frontotemporal dementia. *Alzheimer's & Dementia, 3, 247-253.*

Teichmann, M., Lesoil, C., Godard, J., Verbet, M., Bertrand, A., Levy, R. et al. (2016). Direct Current Stimulation Over the Anterior Temporal Areas Boosts Semantic Processing in Primary Progressive Aphasia. *Annals of Neurology, 80(5), 693-707.*