Neurofeedback as a Neurorehabilitation Tool for Memory Deficits
A Phase 0 Clinical Trial

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1 OBJECTIVES

Although underexplored, the idea of using brain computer interfaces (BCI) for behavioral and cognitive rehabilitation is based on recent evidence suggesting that not only self-regulated brain signals, but also involuntary brain signals may provide useful information about the BCI user. These BCI systems, also called passive BCIs, acquire brain waves from an electroencephalographic (EEG) amplifier and then utilize the biomarkers derived from the brain signal and adapt to the user's performance without the purpose of voluntary control of the system (Zander & Kothe, 2011).The aim is to apply neuro-physiological regulation to foster cortical reorganization and compensatory cerebral activation by targeting brain-wave correlates of functional deficits, thus promoting Central Nervous System (CNS) plasticity (Duffau, 2006). Critically, CNS plasticity has been observed in early-stages of dementia, thus constituting a great challenge for the development of "cognitive BCIs" focused on the rehabilitation of brain functions in neurological patients (Hill et al., 2011). The main goal of this project is to promote CNS plasticity, and therefore cognitive reserve, through neurofeedback training in subjects with Subjective Memory Complaints (SMC) related to attentional deficits. It is a Phase 0 clinical trial.

2 METHODS

Several EEG markers were developed in the literature for Alzheimer's disease (AD) detection and their efficiency was largely proven in the state-of-the-art (Cibils, 2002; Babiloni et al., 2004; Ilh et al., 1996; Vialatte et al., 2011; Houmani et al., 2015). In this project, we will transpose these biomarkers to the framework of our BCI-system and apply them in subjects with Subjective Memory Complaints (SMC). Such markers can be reduced to small sets of EEG channels: we conducted simulations, and obtained stable classifications results using a set of four EEG channels. Experiments will involve 40 SMC subjects, recruited at the Institut de la Mémoire et de la Maladie d'Alzheimer, in the Salpêtrière's hospital, in Paris. Subjects will be assigned randomly to either the neurofeedback or the sham task. The procedure will be double-blinded. Subjects will participate in 20 (neurofeedback or sham) sessions, twice per week over a period of maximally 10 weeks. At the end of each neurofeedback/sham session, the state of the patients will be assessed in order to evaluate for any adverse effect. In case such effects were to be observed, the protocol would be interrupted. Each session of 30 minutes will start and end with a recording of 1 minute of rest EEG with eyes opened. In addition, subjects will be administered a pre-trial and a post-trial standardized neuropsychological battery, lasting 1 hour. The individual results (n=40) will be analyzed with a reliable change index (RCI; Jacobson & Truax, 1991). Additional analyses between neurofeedback and sham groups will be performed. The training protocol will be personalized. This is critical, since each subject has his/her own EEG pattern. Moreover, the use of one standard protocol could be ineffective or even adverse.

3 RESULTS

We expect the development of a cognitive BCI that allows **1)** an electrophysiological reorganization of subjects' brain activity, directly correlated with **2)** subjective and objective improvement of subject's memory and attentional functions, as measured by a previously validated Memory Complaints Questionnaire and specific neuropsychological tests, all administered to each subject pre- and post-trial.

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4 DISCUSSION

Subjective Memory Complaints (SMC) are reports of problems with, or changes in, memory, being often a source of distress among older adults (Yates et al., 2017). Indeed, although the subjective decline lies within the normal limits of cognitive ageing, it negatively influences everyday functioning. However, attentional resources have been found to be critical for subjects' perception of everyday memory functioning, which seems related to the role of prefrontal attention systems for memory retrieval (Davidson et al., 2006). Furthermore, it has been demonstrated that depression or anxiety may also influence the expression of SMC (Balash et al., 2013). Therefore, the examination of memory efficiency in older subjects requires not only memory tasks, but additional measures of cognitive function (focusing on attention), as well as mood examination. Criticaly, recent evidence from both neuroimaging and behavioral outcomes research supports the ability of the brain to adapt, modify, and learn throughout, at a minimum, the early stages of dementia. For instance, evidence from functional neuroimaging has shown that AD patients can use additional neural resources in the prefrontal cortex to compensate for losses attributable to the degenerative process of the disease (Grady et al., 2003). Moreover, neurofeedback (NFB) training has been found to improve attention abilities in elderly people (Angelakis et al., 2007; Wang & Hsieh, 2013). Taken together, these findings suggest that NFB may have a place in the treatment of individuals with Subjective Memory Complaints, as well as in patients in very mild stages of Alzheimer's disease. Importantly, Alzheimer's disease (AD) is a chronic neurodegenerative disorder that leads to progressive decline of cognitive functions, along with behavioral disturbances and insidious loss of autonomy in daily living activities (Dubois et al., 2014). Its incidence increases exponentially with age, and doubles every 5 years after the age of 65 (Kukull et al., 2002; Qiu et al., 2009; Corrada et al., 2010), being the most common cause of dementia in late adult life. Accordingly, and because of the unprecedented level of aging in developed countries, the health care costs associated with AD are exceptional high, imposing a tremendous burden on modern societies. Currently, two classes of drugs, cholinesterase inhibitors [ChE-I] and N-metil-D-aspartate [NMDA] receptor antagonist, are recommended for the symptomatic treatment of AD, each targeting a different neurochemical component thought to underlie the condition (Cummings, 2000). Unfortunately, none of the available treatments is able to stop or reverse the disease progression, and their cost-effectiveness has been questioned (Loveman et al., 2006). Thus, continuing efforts are required, with an urgent need for the development of novel therapeutic strategies, envisaging not only pharmacological but also non-pharmacological interventions. This project represents a first step on this path, even though considerable development and controlled clinical trials will be required before these BCI interventions earn a place in our standard of clinical care.

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