MARCIA: Music-Assisted brain Reconnection in Cognitive Impairment After stroke

MARCIA aims at providing proof of concept that listening to music can improve cognitive performance after stroke by restoring brain connectivity. Our **main hypothesis** is that intensive listening to music may facilitate the reconnection of brain regions that have become isolated due to stroke and improve integration between the two hemispheres.

Context. Stroke interferes with blood supply in the brain, and is a frequent cause of severe and permanent disability. In addition to sensorimotor deficits, such as hemiplegia, stroke often provokes disabling cognitive deficits. Patients with strokes in the right hemisphere often find themselves living in a halved world, because of a profound inattention for left-sided events (spatial neglect)[1]; patients with left hemisphere strokes may become unable to speak or to understand language (aphasia). Our team has discovered that the state of anatomical and functional connectivity between the hemispheres can predict both spontaneous recovery and response to rehabilitation[2,3]: after a stroke in one hemisphere of the brain, perhaps the healthy contralateral hemisphere may learn to compensate for cognitive impairment[4]. However, in other cases the healthy hemisphere seems to exert a competitive activity against the lesioned one[5,6], resulting in a worse functional outcome. It is possible that the state of inter-hemispheric connectivity is critical for shifting the role of the non-lesioned hemisphere from exerting maladaptive effects, to promoting adaptive (compensatory) activity[7]. Music therapy has previously shown positive effects on neurological conditions including stroke[8-11], but its mechanisms are unknown. MARCIA leverages evidence that music processing induces coordinated bi-hemispheric activity in neurotypical individuals, with different aspects of music processing recruiting different brain regions and hemispheres[12,13], including the cerebellum[14], which is of special interest as it represents one of the largest inter-hemispheric pathways after the corpus callosum[15].

Objectives. To assess the effect of music listening on post-stroke cognitive recovery, with a focus on neglect and aphasia, and to understand its neural basis. We hypothesize that listening to music may reconnect isolated brain regions caused by the stroke and promote inter-hemispheric integration. MARCIA will use cognitive tests[3,16] and biomarkers[17,18] to assess this hypothesis.

Methods. 30 patients with chronic neglect or aphasia after a stroke will participate in a 4-week randomized, crossover study. Patients will act as their own control, and be assessed multiple times. Patients will be recruited and followed-up by Dr. E. Bayen in the NeuroRehabilitation Department of the Pitié-Salpêtrière hospital. Neuroimaging procedures will take place at the Cenir platform on the same site. Behavioral, neuroimaging and recruiting procedures with exclusion and inclusion criteria are already in use at the ICM[2,3]. Briefly, the main inclusion criterion is a first unilateral stroke inducing chronic signs of neglect or aphasia. Exclusion criteria will be impaired vigilance, confusion, general mental deterioration or psychiatric disorders, or prior history of neurological disease. Music composed by Haydn, Mozart, and Beethoven will be listened to for 2 hours/day for 2 weeks. This musical repertoire provides an optimal balance of expected and surprising events[19,20], because it is built on a shared set of "stock musical phrases"[21]. These compositional criteria result in a pleasant and engaging experience both for connoisseurs and non-experts. All patients will listen to the same playlist, which will be developed in collaboration with the Collegium Musicæ at Sorbonne University. Traditional rehabilitation will be provided to the control group. EEG and MRI biomarkers will be analyzed in collaboration with the IUIS.

Procedure. The procedure will consist of a 2-week period in which patients will listen to music on a daily basis and a 2-week period of standard of care, in a randomized, crossover study design. Neuroimaging and cognitive assessments will be performed at baseline, at crossover, and at the end of the study. A preliminary cognitive evaluation will be carried out two weeks before the start of the protocol to ensure that the patients exhibit chronic and stable deficits

Expected Results. Improved cognitive performance and improved brain connectivity, as indicated by better fMRI and EEG connectivity indices, are expected after listening to music compared to traditional rehabilitation.

Pilot Results. A grant attributed by AP-HP/Sorbonne Université and IUIS allowed us to collect pilot data. Two patients with no musical training and chronic, nonfluent aphasia after left hemisphere strokes participated to a preliminary version of the protocol, in different arms of the crossover design. Music-assisted rehabilitation, but not traditional rehabilitation, significantly improved their performance on a clinical aphasia battery. In one patient, behavioral improvement was accompanied by an increase of EEG long-distance theta weighted Symbolic Mutual Information[17] in the right, nonlesioned hemisphere. These promising results indicate the feasibility of MARCIA, and suggest its potential effectiveness.

Partnership. MARCIA brings together two teams with complementary expertise in neuroscience and neurorehabilitation. The project will also benefit from the interdisciplinary cooperation with Collegium Musicæ and IUIS at Sorbonne University.

1. The Paris Brain Institute (ICM), Pitié-Salpêtrière Hospital, is a multidisciplinary institute that performs basic and clinical research in neuroscience (molecular and cellular biology, neurophysiology, cognitive sciences), exploiting the best available current technology. The ICM team will be led by Paolo Bartolomeo (MD, PhD), coordinator of MARCIA (50% of time on MARCIA). Dr Bartolomeo, a clinical neurologist and a neuroscientist, leads the PICNIC Lab at the ICM, a group with recognized expertise in cognitive and neuroimaging research on brain-damaged patients. He has coordinated several EU and French projects (FP6 Era-Net Neuron Beyondvis, ANR Brandy and NeuroDataShare, Fondation AVC COM2C), has supervised 17 PhD theses and 5 post-doctoral researchers, and published more than 180 papers on international peer-reviewed journals (h-index 66). The Bartolomeo team has discovered connectional biomarkers of recovery from neglect[2,3]. Dr. Bartolomeo has received musical training in piano and harpsichord, and has co-authored studies on the impact of musical expertise on reading musical notation[13] and on music-assisted improvement of neglect[8].

2. The NeuroRehabilitation Department (NRD), is located on the campus of the large stroke unit of APHP-Sorbonne University (USI-NV), enabling a robust recruitment of participants in in- and out-patient care (average of 80 and 50 stroke patients per year, respectively). Dr Eleonore Bayen (MD, PhD), chief of the NRD, is a neurologist by background and holds a musical Diplôme de Fin d'Etudes in piano from the Conservatoire G. Fauré (Paris, 1992). She has published over 40 publications and has experience in neuropsychological assessment of neurological patients[22], in cognitive monitoring using connected objects[23], and in music-assisted neurorehabilitation[24].

A PhD candidate with some experience in neuropsychological evaluation and neuroimaging, and some musical training would be ideal, but musical training is not mandatory.

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