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MUSICAL LEARNING AND SINGING IN CEREBRAL RECOVERY: EFFICACY OF MUSIC-BASED INTERVENTIONS IMPROVED TAKING INTO ACCOUNT SOCIOMOTIVATIONAL FACTORS IN STROKE REHABILITATION

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1. Abstract of the original project

The project "*Playing and Singing for the Recovering Brain: Efficacy of Enriched Social-Motivational Musical Interventions in Stroke Rehabilitation*" aims to investigate the effectiveness of music playing and singing on motor and language recovery in chronic stroke patients. Two novel approaches of music-based intervention were designed, combining individual home-based sessions with group sessions of musical training. Both interventions emphasize the role of intrinsic motivation and social factors, which have been found to optimize stroke recovery.

Stroke is the leading cause of acquired long-term disability worldwide. Public health care provides formal rehabilitation programs for the first six months post stroke, the period during which the brain shows increased plasticity. However, most patients do not achieve full recovery after this period, and the scarcity of public rehabilitation resources prevents them from continuing rehabilitation. The novel group- and home-based rehabilitation model implemented in this project provides a more accessible and easily applicable intervention in comparison with conventional therapist-led individual rehabilitation. In order to evaluate the rehabilitative efficacy of the novel music-based interventions, two randomized controlled trials (RCTs) were conducted by three research groups: **Study 1** comprised **Subproject 1** (directed by Dr. Rodríguez-Fornells) and **Subproject 3** (directed by Dr. Arcos); and **Study 2**, comprised **Subproject 2** (directed by Dr. Särkämö).

Subproject 1 (Dr. Rodríguez-Fornells), which shared tasks with **Subproject 3** (Dr. Arcos), aimed to explore the effectiveness of music playing on the recovery of upper limb motor function in chronic stroke patients. To do so, a prospective, single blind, two-arm parallel group RCT was implemented (n = 35). The music-based intervention protocol was designed by adapting music-supported therapy (MST) for home use and adding group music therapy sessions. The novel version was called enriched music-supported therapy (*eMST*) and added two important aspects to the previous benefits observed in MST: (i) increased autonomy and self-regulated behaviors via the home-based self-training sessions; and (ii) increased social reward and reintegration into community life via the group music therapy led sessions. The *eMST* intervention consisted of a 10-week rehabilitation program of 4 one-hour sessions per week (3 self-training sessions and 1 group session). The control intervention applied was a

conventional home-based motor rehabilitation program previously validated in chronic stroke patients called Graded and Repetitive Arm Supplementary Program (*GRASP*). Patients were evaluated before and after completing the intervention, as well as 3 months post-intervention (follow-up). The **primary outcome** was the **upper extremity function**. Secondary outcomes were motor impairment, grip strength, functional movements, dexterity, motor performance in everyday tasks, cognitive functions, emotional well-being, quality of life (QoL), and self-regulated behaviors. The baseline evaluation included the assessment of patients' musical perception skills, musical hedonism, and social support.

Subproject 3 was responsible for the technological development of the app to support home-based eMST sessions. In order to increase patients' engagement and motivation, the artificial intelligence (AI) platform incorporated the following elements: 1) continuous monitoring of patient activities; 2) personalization and tailoring of exercises; 3) incorporation of positive feedback and gamification strategies; and 4) empowerment of patients to self-regulate their training sessions. The implementation of AI algorithms in the app was considered to support therapists and to boost user engagement by personalizing the interventions according to patient needs and preferences.

Subproject 2 aimed to explore the effectiveness of a novel singing intervention in aphasia rehabilitation of chronic stroke patients. Secondary aims were to explore the preservation of singing skills and music learning in aphasia. To do so, a cross-over RCT was performed ($n = 60$). Patients were randomly allocated in two groups: the AB group received the singing intervention during the first 4-month period, and the BA group during the second 4-month period. The novel singing intervention was designed for aphasic patients and their family members (FMs), and combined (i) a group training part involving traditional choir singing and singing-based speech training using melodic intonation therapy (MIT) adapted for a group setting, and (ii) self-training part of the choir song material at home with a tablet computer and special software. The software performed acoustic analyses of the vocal production, provided online feedback, and tracked the amount of home training. The intervention consisted of a 16-week rehabilitation program doing 3 self-training sessions per week (30 min. per session) and 1 group training session per week (1.5 h per session). Patients were evaluated at baseline, at 4-month stage, and at 9-month stage. The **primary outcome** was the

language recovery, and secondary outcomes were cognitive and auditory functions, singing skills, mood, QoL, and social functioning. Vocal-motor training-related structural and functional neuroplasticity was also assessed in a subsample of 30 patients who underwent structural and functional magnetic resonance imaging (s/fMRI) and diffusion tensor imaging (DTI) measurements at the three time points.

2. Results

Study 1. This part included: (1) the development of an app for electronic tablets to apply eMST, and (2) the evaluation of the effectiveness of the eMST intervention in improving upper limb motor functions of patients with chronic stroke.

Development of an app for eMST. The process of the app development was conducted following three steps. First, the **theoretical research** and understanding of the benefits of music-based interventions on upper limb motor function recovery, which were reported in a review (Grau-Sánchez et al., *Neuroscience & Behavioral Reviews* 2020). This allowed us to develop the app with a solid foundation in basic neuroscience and previous clinical research. Second, the **technological development of the app**, on which computer engineers and neuroscientists worked together to add all the necessary elements on the AI platform to conduct the home-based self-training eMST sessions (Sanchez-Pinsach et al., *Artificial Intelligence Research and Development* 2019). Finally, testing the **usability of the novel app** and the **feasibility of the eMST intervention** in a pilot study with five chronic stroke patients (Segura et al., *Brain Injury* 2021). In this study, patients clinically improved in upper limb motor function in most of the motor tests post-intervention. In addition, they overall showed to play faster in the piano evaluation exercises throughout the intervention demonstrating a tendency to reach controls' performance, which means an improvement in their fine motor function. The technical features of the first version of the app were enhanced throughout the intervention according to patients' feedback. Finally, the last version of the app received high usability scores post-intervention. This allowed us to improve the usability of the app before testing the effectiveness of the intervention.

Evaluation of the effectiveness of eMST. We conducted an **RCT** to test the effectiveness of the eMST intervention in improving upper limb motor functions of chronic stroke patients. The completion of the RCT coincided with the coronavirus pandemic. Two research members from **Study 1** (Dr. Grau-Sánchez) and **Study 2** (Dr. Särkämö) participated in an online discussion of the problems arising under the pandemic on applying music research protocols and the possible solutions to how to overcome them (Papatzikis et al., *Frontiers in Psychology* 2020). In order to conduct the RCT in this context, we modified the evaluation protocol applying preventive measures and adapting the music therapy group sessions to be conducted remotely (via Zoom). Before starting the RCT, the protocol of the novel home-based eMST intervention was published (Grau-Sánchez et al., *BMC Neurology* 2021) and the trial was registered in *ClinicalTrials.gov* (identification number: NCT04507542). Due to the coronavirus pandemic, the RCT has not yet completed the follow-up evaluations. Therefore, the results presented here are preliminary and include 35 patients with chronic stroke that completed the intervention (*eMST* or *GRASP*) and follow-up evaluations. A **characterization of participants** for the trial was made considering relevant sociodemographic and clinical variables that play a role in stroke recovery: age, stroke etiology, lesion location, time since stroke, and level of motor impairment. Groups did not differ in any descriptive variables, which allow generalization of research results to the general stroke population. Regarding the **effect of the intervention group** (*eMST* vs. *GRASP*), the preliminary results showed clinically relevant changes in upper limb motor function in both groups after completing the intervention. Importantly, the eMST group clinically improved equally or higher than the control group in the different motor outcomes. This means that ***our novel music-based rehabilitation program can be as effective as a previously validated conventional rehabilitation program (GRASP) in upper limb motor recovery.*** Specifically, only the eMST group clinically improved when measuring upper limb function (the primary outcome) post-intervention, while both groups did so at follow-up. Regarding the secondary motor outcomes: i) both groups clinically improved in motor tests assessing motor impairment and motor performance in everyday tasks, and ii) the control group clinically improved in dexterity in both evaluations, while the eMST group did so only in the follow-up evaluation.

Study 2. This part included: (1) the evaluation of the preservation of singing skills in aphasia, and (2) the evaluation of the effectiveness of a novel singing intervention in aphasia rehabilitation for chronic stroke patients.

Preservation of singing production ability in aphasia. Baseline sMRI data provided converging results that, in contrast to spontaneous speech production, which was linked to a large left fronto-temporoparietal network, ***spontaneous singing production was linked to more focal regions in the damage in the anterior and posterior parts of the left superior and middle temporal gyri.*** These results were supported by the baseline DTI data, which showed that spontaneous speech production was associated with higher quantitative anisotropy (QA, indicating better connectivity) in both dorsal [arcuate fasciculus (AF)] and ventral [inferior fronto-occipital fasciculus (IFOF)] pathways in the left hemisphere whereas spontaneous singing production with higher QA only in the left ventral pathway [IFOF and inferior longitudinal fasciculus (ILF)]. Additionally, a *post hoc* subgroup analysis of severely aphasia patients who were able to produce no or very little spontaneous speech was performed. In this subgroup, patients with preserved ability to produce words through singing had higher QA in the left ILF, IFOF, and posterior AF as well as in the posterior (tapetum) part of the corpus callosum (CC, connecting the left and right posterior temporal lobes) compared to those patients who could not produce words either through speaking or singing. Together, these findings provide highly novel, crucial insights into the structural correlates of singing in chronic aphasia and may potentially also serve as biomarkers in predicting treatment response to singing-based aphasia rehabilitation.

Effectiveness of the singing intervention in aphasia rehabilitation. The behavioral RCT results showed that compared to standard care ***the novel singing intervention enhanced self- and caregiver-reported communication ability and social interaction,*** improved performance in responsive speech production, and reduced the stress and burden experienced by the FMs. The longitudinal DTI and sMRI results showed that compared to standard care the singing intervention enhanced: (i) **structural white matter QA** in the left AF, bilaterally in the CC, frontal aslant tract (FAT), superior longitudinal fasciculus (SLF), and corticostriatal tract; and (ii) **grey matter volume in language-related frontal regions,** including the Broca's area and ventral premotor cortex (vPMC). Importantly, the neuroplasticity changes in the left IFG, AF, and FAT correlated with longitudinal improvement in responsive speech, suggesting that they were closely linked to the clinical efficacy of the intervention.

These findings provide new and pioneering evidence that singing-based rehabilitation is effective in chronic aphasia, both in terms of the communicative and social functioning of the patients and the psychological well-being of their caregivers and is underpinned by structural neuroplasticity changes in the bilateral language network.

3. Relevance and possible future implications

In this project we have followed the framework for developing and evaluating complex interventions of the Medical Research Council (United Kingdom) to ensure the transferability of the group and self-training versions of eMST and MIT to clinical practice. In this sense, the following aspects of the project contribute to its transferability potential:

- **Previous research and theoretical understanding of the interventions.** Both playing and singing novel interventions have been developed with a strong grounding in basic neuroscience music research and previous clinical research. Our research teams have been exploring for more than 15 years the effectiveness of applying MST and MIT interventions at the hospital with individual led sessions in the recovering of motor and language functions of stroke patients. Previous positive results encouraged us to improve the interventions in the present project to increase the effectiveness and allow a wide implementation in clinical and community settings.
- **Pragmatism.** Two pragmatic RCTs were conducted to test that the effectiveness of the MST and MIT remains the same when implemented under real circumstances: participants represented different profiles of sociodemographic backgrounds and clinical circumstances, and the intervention was carried out at home without changing any other aspect of their routine.

Considering the high prevalence of stroke and the burden caused by upper limb motor deficits and aphasia on the survivors, there is an urgent need for new effective and widely applicable treatments. The implementation of the novel playing and singing interventions has direct **clinical implications** for patients, caregivers, and health care professionals:

- **Study 1** shows the effectiveness of applying eMST as a form of telerehabilitation. Patients treated with eMST recovered from upper limb motor deficits, which contributes to increasing the number of options of evidence-based interventions.

This provides a **more cost-effective solution for rehabilitation services** to address the needs of chronic stroke patients providing them with the opportunity of continuing rehabilitation at home, avoiding returning to the hospital and promoting participation in community life. Importantly, the novel app was **co-designed** with patients following the principles of **responsible research and innovation** and **citizen science**, which promote the inclusion of affected individuals as **active members in the research process**. In addition, the creation of the app for applying the eMST intervention as a form of telerehabilitation allows **valorisation of the research results**. The novel app has the potential to become a medical device, which could be of great benefit to society and public health, and it is in turn an indicator of the **transferability** of our results.

- **Study 2** shows the effectiveness of applying a group and home-based version of MIT intervention in enhancing communication ability, social interaction, and caregiver well-being. The results **uncover the structural neural basis of the clinical efficacy of singing in aphasia**, which can help in targeting and further developing the singing intervention to optimize its efficacy. The study also provides the **first-ever multimethodological neural mapping** underlying the impairment and preservation of spontaneous singing production ability in aphasia. The results can shed new light on the **clinical phenotype of aphasia** that can broaden our understanding of a positive aspect (singing) in this otherwise debilitation condition.
- The improvement of the general health status and the autonomy of chronic stroke patients has a direct effect in the health system since can reduce the burden that close family members and formal and informal caregivers may experience. Although this aspect needs further research, the reduction of the burden may lead to better emotional and physical health and QoL of caregivers.

3. Publications derived from this research

From this project, a total of **6 papers** have been published: 1) a **study** of the AI platform created to conduct the home-based eMST sessions (Sanchez-Pinsach et al., 2019; 2) a **pilot study** that presents the feasibility results of the eMST with the use of the novel app (Segura et al., 2021); 3) a **protocol study** of the eMST that presents the theoretical basis and characteristics of the intervention (Grau-Sánchez et al., 2021); 4) a **neuroimaging study** of speech and singing production in aphasia

(Martínez-Molina et al., 2022); 5) a **review** of the benefits of music-based interventions on upper limb motor function recovery (Grau-Sánchez et al., 2020); and 6) an **online discussion** of the problems arising under the coronavirus pandemic on applying music research protocols and the possible solutions (Papatzikis et al., 2020). Additionally, 4 original research articles are in preparation or submitted for publication.

Martínez-Molina N, Siponkoski S-T, Pitkäniemi A, Moisseinen N, Kuusela L, Pekkola J, Laitinen S, Särkämö E-R, Melkas S Kleber B, Schlaug G, Sihvonen AJ, **Särkämö T**. (2022) Neuroanatomical correlates of speech and singing production in chronic post-stroke aphasia. *Brain Communications*. Doi: 10.1093. Q3 (Clinical Neurology). Number of citations: 0.

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Sanchez-Pinsach, D., Mülâyim, M.O., **Grau-Sánchez, J., Segura, E.,** Juan-Corbella, B., **Arcos, J.L.,** Cerquides, J.,Messaggi-Sartor, M., Duarte, E.& **Rodríguez-Fornells, A.** (2019) Design of an AI Platform to Support Home-Based Self-Training Music Interventions for Chronic Stroke Patients. *Artificial Intelligence Research and Development*. Doi: 10.3233/FAIA190120. Number of cites: 3.