

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *The Neurosciences and Music IV: Learning and Memory*

The involvement of audio–motor coupling in the music-supported therapy applied to stroke patients

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Music-supported therapy (MST) has been developed recently to improve the use of the affected upper extremity after stroke. MST uses musical instruments, an electronic piano and an electronic drum set emitting piano sounds, to retrain fine and gross movements of the paretic upper extremity. In this paper, we first describe the rationale underlying MST, and we review the previous studies conducted on acute and chronic stroke patients using this new neurorehabilitation approach. Second, we address the neural mechanisms involved in the motor movement improvements observed in acute and chronic stroke patients. Third, we provide some recent studies on the involvement of auditory–motor coupling in the MST in chronic stroke patients using functional neuroimaging. Finally, these ideas are discussed and focused on understanding the dynamics involved in the neural circuit underlying audio–motor coupling and how functional connectivity could help to explain the neuroplastic changes observed after therapy in stroke patients.

Keywords: music-supported therapy; auditory–motor coupling; plasticity; stroke; functional connectivity

Music and neurorehabilitation in stroke patients

Research on brain plasticity during the last decades has provided evidence of the capacity to induce plastic changes and repair in the adult damaged brain from discoveries concerning neurogenesis and learning,^{1,2} neuroimaging,^{3–5} neuroscience, and epigenetics.^{6–8} Clear evidence already exists in neuroscientific literature that after brain damage, new neuronal connections and pathways can be formed in the brain, be reshaped, or be rewired.^{9–11} This new research provides a more optimistic view regarding the adult learning brain^{12–14} and the importance of designing new strategic interventions that target residual learning abilities in patients. For example, motor disabilities after stroke have been the target of several recently developed therapies that have proven to be more effective than stan-

dard rehabilitation approaches.^{15,16} Using this approach, the constraint-induced therapy (CIT) induces the use of the paretic limb over extended periods of time, leading to marked clinical improvements that are accompanied by neuroplastic changes.¹⁷

Music learning could be conceived as one of these potential intervention strategies,^{18–22} mostly because of the extensive brain network engaged in music listening and performance, which is indeed necessary for processing multimodal information conveyed by music (coordinating information from auditory, visual, and sensorimotor information). Moreover, music training shapes the development of the brain by producing long-lasting changes in children and adults (see Refs. 23–26) and several neuroscience studies have shown that music training produces rapid changes in motor-related brain areas.^{27–32}

Against this background, a new motor rehabilitation therapy has been developed recently (music-supported therapy (MST)) for the rehabilitation of motor deficits in neurological patients.³³ Musical instruments (an electronic piano and an electronic drum set designed to produce piano tones) are used to train fine (piano) and gross (drums) motor functions in patients suffering from mild-to-moderate paresis after stroke. In two large samples of acute stroke patients, this therapy showed highly significant and clinically relevant improvements (see details in Refs. 33 and 34).

The MST rehabilitation program was designed on the following principles, considering previous studies on motor rehabilitation and brain plasticity:^{33,35} (1) *Massive repetition* and exercising of simple finger and arm movements;³⁶ (2) *audio–motor coupling and integration*: reinforcement of movement effects due to immediate auditory feedback supporting the precise timing and control of movements and coupling of movements to auditory events permits the development of multimodal auditory–sensorimotor corepresentations of movements;^{27,29,37} (3) *shaping*: adapting the complexity of the required movements according to the individual's progress; and (4) *emotion–motivation effects*: increased motivation of the patients due to the playfulness and emotional impact of making music and acquiring a new skill.

This last aspect might be very important because according to animal studies, cortical plasticity is increased by the behavioral relevance of the stimulation and its motivational impact.¹² Emotional effects induced by music listening, learning, and performance could engage reward–learning networks and corresponding neurotransmitter systems in the brain,^{38,39} helping to consolidate new information, increasing the amount of reward experienced during the rehabilitation program, and increasing the probability of voluntary practicing the new movement exercises. In agreement with these ideas, a recent study of Särkämä and colleagues⁴⁰ showed that music listening significantly enhances cognitive functioning in the domains of verbal memory and focused attention in a music group compared to a control group. The music group also experienced less depression and confusion than the control groups. These results have been replicated recently in our study conducted on 20 chronic stroke patients (middle cerebral artery stroke; mean age, 59 ± 9

years; mean number of months after the first stroke, 30 months) with slight–moderate upper-extremity hemiparesis receiving MST (one-month intensive intervention program, 30-min daily music training sessions) (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results). As shown in Figure 1A, we see a clear and significant improvement of positive mood (pleasure) in our patient sample using daily evaluations of affective valence (using the Self-Assessment Manikin—SAM, a nonverbal pictorial assessment technique⁴¹). When this patient group was contrasted with a well-matched healthy sample (14 control participants; mean age, 56 ± 9 years; matched for age, sex, and education) and evaluated two times with the same interval between both assessments (approximately one month and a half), the patient group showed a clear reduction of depressive symptoms (assessed using the Beck Depression Inventory Scale) and significant improvement of positive affect (using the Positive and Negative Affect Schedule (PANAS));⁴² see Fig. 1B). These results converge with the previous findings from Särkämä *et al.*⁴⁰ and support the positive emotional effects induced by MST in a chronic stroke group. More importantly, the chronic group also showed motor improvements in the Action Research Arm Test (ARAT⁴³) after the MST program, this test being one of the most widely used in the evaluation of motor function in the upper extremity.⁴⁴ Thus, even considering the limits for amelioration in the motor domain in these patients, MST clearly helped to improve their fine and gross motor skills. Indeed, the comparison of the three studies in which MST has been used (see Fig. 1C) shows that the amount of improvement of the chronic group (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results) is about half of the effect observed in the acute patients for the ARAT test.^{33,34} Notice, however, that the chronic patient group has a better initial score in the ARAT test due to residual and moderate physical deficits, but they have a smaller range of improvement compared with the acute group.

In sum, until now, different studies^{33–35,45} have used MST in acute and chronic stroke patients and suggest a potential for exploiting residual learning abilities in these patients through indirect, intact brain pathways engaged by music performance. We will show in this study how neuroimaging techniques and, specifically, functional

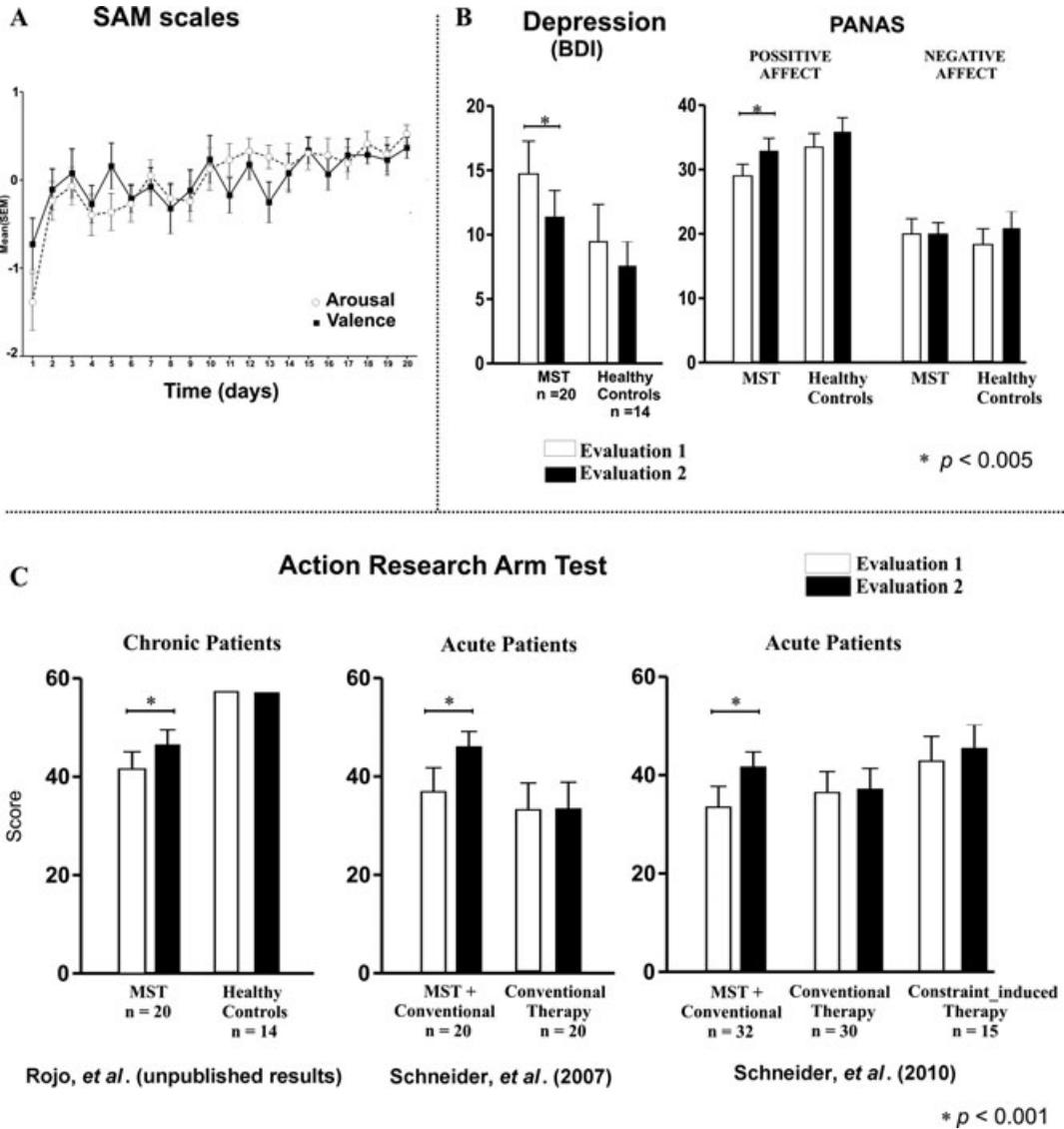


Figure 1. (A) Daily assessments of mood (pleasure and arousal) during each therapy sessions (intraindividual normalized Z mean values \pm SEM) for the chronic stroke patients (Rojo *et al.*, unpublished results; $n = 20$). A significant improvement was observed during the course of the therapy. (B) Significant reduction of the depressive symptoms posttherapy (second evaluation) when compared to pretherapy evaluations (first evaluation). Significant improvement was also observed for the positive affect but not the negative affect scales (PANAS). Notice that for the control group (healthy group that did not receive MST), no differences were observed for the BDI and the PANAS. (C) Comparison of the motor improvement effects evaluated with the ARAT of the three cohorts of stroke patients who received MST and the comparison with the respective control groups.

connectivity approaches, may help us to understand the neuroplastic changes observed after this new neurorehabilitation strategy. Finally, we will highlight the importance of audio-motor plasticity as a plausible mechanism to explain the success of MST for the neurorehabilitation of stroke patients.

Audio-motor coupling hypothesis in MST

Music performance is an extremely complex process that requires, in some cases, the integration between the auditory system, proprioceptive feedback, visual information, and motor control. The hypothesis of audio-motor coupling and an integration mechanism is based on the idea that

music performance requires the creation of fast feedforward and feedback loops to precisely coordinate auditory and motor information.²² Playing an instrument requires fine-grained mapping between a musical note (or a sound) and the motor movement that will be executed to produce that note. Forward information is important as it has been proposed that internal representations in motor control (or “internal models”;^{35,46,47} see Ref. 48) can be created to predict the outcome of a particular action using “efference copy”. Feedforward (bottom up) information could be transferred from the auditory system to the premotor cortices (PMC) using an internal model of the desired “sound” that will influence and modulate the motor output. Thus, well-trained motor responses associated with a specific sound will be primed or facilitated. However, the reverse is also possible; on-line motor actions might create internal representations of their actions (“efference copy”) and send them back to the auditory regions to evaluate the appropriateness of these actions for the goal of producing a specific note. In this last alternative, a learned action triggers top-down auditory expectations that will facilitate and refine auditory processing. This top-down influence is plausible considering data showing that auditory neurons are suppressed during vocalizations in monkeys and human speech production.^{49,50}

These feedforward and feedback connections between motor and auditory systems after learning to play an instrument could be used ultimately as fast nonconscious error-monitoring and correction systems that would allow the execution and correction of very fast movements in music performance (see Refs. 51, 52). These mechanisms might be especially relevant for string instrument players who have a continuum of note pitches without clear visual and/or kinaesthetic cues. In this particular case, fast corrections of movements could be necessary and be implemented via external auditory feedback mechanisms: the production of a partial erroneous note in the middle of a musical passage would be heard and correction would be implemented by the auditory cortex modulating the motor output. Indeed, this seems to be the case. For example, skilled cellists seem to require some constant motor recalibration using acoustic feedback guidance.⁵³

A growing number of studies have investigated the relevance of these auditory-motor coupling and

integration mechanisms (for a review, see Refs. 22, 27, 29, 37). On the one hand, motor and PMC activation (including the supplementary motor area (SMA)) can be elicited in musicians after passive listening of known melodies using functional magnetic resonance imaging or when playing familiar music pieces without auditory feedback (functional MRI (fMRI)^{27,28} and similar transcranial magnetic stimulation (TMS) evidence⁵⁴). In the study by Bangert *et al.*,²⁷ activation was also observed in the opercular part of the inferior frontal gyrus (IFG, BA 44), planum temporale, and supramarginal gyrus (SMG). More importantly, in a longitudinal study using nonmusicians, it was possible to follow the creation of these common auditory-motor representations during piano training. In this study, and after 20 min of training, the first signs of increased neuronal coupling between auditory and motor brain regions were observed when nonmusicians replayed the trained melodies. After five weeks, listening to piano tunes produced additional activity in the central and left sensorimotor regions. Finally, when trained participants played on a mute (soundless) keyboard, they produced additional activity in the auditory regions of both temporal lobes.³⁷ This experiment nicely demonstrates how fast and dynamic this auditory-motor plasticity mechanism can be.

Furthermore, in a similar and interesting fMRI study, Lahav *et al.*²⁹ showed that posterior middle ventral (PMC), but not the primary motor region (M1), was activated specifically when passive listening of trained simple but unfamiliar melodies in a group of nonmusicians (five-day training) was compared to a different untrained combination of the same notes. An important aspect of this study is the robust activation observed bilaterally in the left opercular part of the IFG as well as bilateral supramarginal activation when participants were listening to the trained melodies. The authors interpret these results in the left IFG as a support for the involvement of the mirror system, considering that this region is the homolog of area F5 (ventral PMC cortex) in monkeys where the mirror neurons have been located.⁵⁵ Thus, this region might be activated due its involvement in creating cross-modal repetitions and, specifically, for auditory-motor integration; these findings are also in agreement with previous ideas about the role of Broca’s area in sensorimotor integration.^{28,56}

However, the right IFG was constantly activated in all the conditions presented (trained and untrained), suggesting a different role of this region in music listening, most probably reflecting cognitive operations involved in music perception. Strong activations in this IFG region have also been observed in auditory object discrimination tasks.⁵⁷

Previous studies clearly suggest the possible role of this auditory-motor coupling mechanism in MST rehabilitation. Recently, in a single-case study, we provided preliminary evidence for a possible benefit of the MST in a chronic stroke patient who showed clinical improvement and an increase in the quality of rapidly alternating movements.⁴⁵ This result and new ones for the whole cohort evaluated (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results)⁴¹ suggest that MST, like other recently developed therapies such as constrained induced therapy,¹⁵ is capable of improving motor functions in patients with chronic stroke. Clinical improvements were accompanied by profound neural changes evidenced by both fMRI and TMS (J. Amengual, N. Rojo, M. Veciana, *et al.*, unpublished results), suggesting plastic changes in the contralateral sensorimotor cortex after therapy (see Fig. 2A). fMRI of hand movements showed a significant decrease of activation in the contra- and ipsilateral sensorimotor areas and PMC regions after therapy.^{58,59}

In addition, using a similar design inspired in previous studies,^{27,29} we showed the first evidence in favor of the idea that the mechanism that contributes to the efficacy of MST (besides massive practice of the paretic arm) is audio-motor coupling. A music

listening task was carried out in the MRI scanner (pre- and posttherapy) in which the patient had to passively listen to short and well-known familiar monophonic piano songs (songs that were going to be trained during the rehabilitation therapy) as well as well-known familiar songs (that were not going to be trained during the therapy). Alternating blocks of familiar-trained, familiar-untrained pieces, and rest blocks were presented inside the scanner.⁴⁵ As observed in Fig. 2B, the patient did not show activation in the PMC and IFG in the pretherapy session, but these regions were activated after therapy (notice also the activation observed in the SMA). The activation observed in this patient for passive music listening was replicated in the final protocol that consisted of 20 chronic stroke patients (14 patients could complete both scanning sessions) (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results). Interestingly, increased activation was observed after therapy on the caudal and ventral part of the PMC, posterior IFG, and SMA regions after music training, this being an effect significantly larger in the trained song condition. Thus, these results provided the first evidence of the involvement of audio-motor coupling and integration mechanisms in MST.

Functional connectivity evidence of audio-motor coupling in music processing

One question that arises from the previous experiments in MST and passive listening to familiar songs is to what degree the lack of activation in the chronic stroke patients in the pretherapy sessions could be

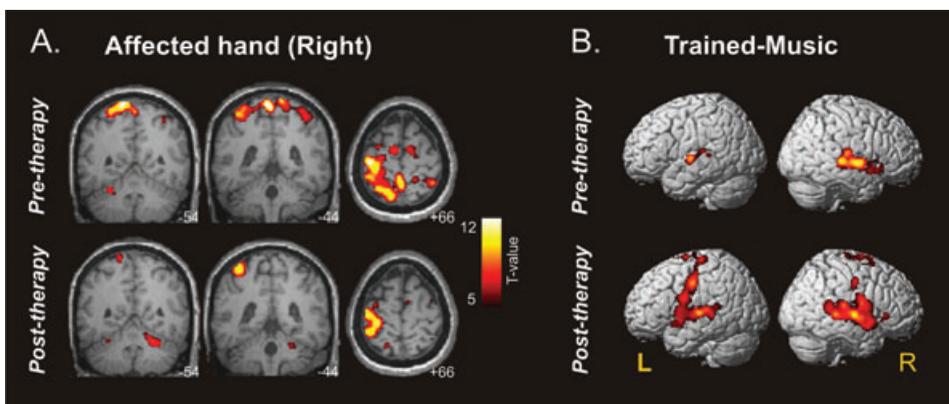


Figure 2. (A) fMRI activations in the motor task (superimposed on the patient's T1 image in standard stereotactic space ($P < 0.05$, family-wise error (FWE) corrected); (B) fMRI activation in the music listening task showing bilateral activation of motor-related brain regions when the patient was listening to trained music posttherapy but not pretherapy ($P < 0.05$, FWE corrected). Adapted from Rojo *et al.* (2011).

due to a decrease in connectivity in the auditory–motor circuit for music listening after the stroke instead of a clear effect of MST in increasing the activation of these feedforward–feedback loops for trained songs? In the previous experiments we observed that the neural network involved in these auditory–motor mechanism comprises the superior temporal lobe, inferior parietal lobe (probably SMG), ventral-caudal PMC, sensorimotor, and IFG regions. However, this strong coupling between auditory–motor regions observed in musicians and trained nonmusicians could also be observed in untrained people (see Fig. 2A depicted by Bangert *et al.* (2006) for nonmusicians²⁷). For example, ventral PMC activation has been observed during melodic discrimination⁶⁰ and while listening to consonant excerpts.⁶¹ Interestingly, in this last cited study, the activation in the PMC cortex was not observed when listening to unpleasant music. Besides, as we commented earlier, strong activation was also observed in the vPMC and IFG at the right hemisphere in the study by Lahav *et al.*—even for untrained songs. Thus, the automatic activation of the PMC/IFG cortex in passive listening in untrained musicians could be related to other cognitive functions in which this region is also involved; for example, working memory and rehearsal of tonal information,^{62,63} automatic transformation of auditory information in motor–premotor representations ((as has also been proposed in language learning)^{64–66}), the mirror neuron sensorimotor integrator,⁵⁶ or unconscious internal simulation and prediction of sequential auditory information.^{67,68}

In the rehabilitation study on chronic stroke and MST mentioned earlier (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results), we evaluated, using neuroimaging, a control healthy group well matched for age, sex, and education. This group was also evaluated two times (separated by approximately one and a half months) using the same fMRI passive listening task of well-known, familiar songs reported in Ref. 45. In Figure 3A, we can see the preliminary results of the activations of seven representative control subjects.^a The most important aspect here is that in both sessions the control healthy

participants showed strong robust activations when listening to popular songs in the STG, IFG, and ventral PMC. This activation pretherapy is not observed in the patient reported in Rojo *et al.* (Fig. 2B) or a subsample of the three chronic stroke patients reported (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results) (see Fig. 4A and B for the lesions in these patients). Instead, patients showed restored activation after therapy on this circuit (see Fig. 4A), including activation in the precentral gyrus, inferior frontal locations, and SMA.

The question that arises when observing these results is to what degree the connectivity of this audio–motor circuit is not reduced or dampened down because of the lesion? To answer this question, we evaluated the functional connectivity in the group of seven control healthy participants and three patients (N. Rojo, J. Amengual, P. Ripolles, *et al.*, unpublished results). This idea is plausible considering recent findings of large incidences of acquired amusia in patients with middle cerebral artery stroke,^{35,69,71} being at about 35% of the patients in chronic cases.⁷¹

To study the dynamics of the auditory–motor mechanism, we investigated the functional connectivity between the regions involved in this circuit, which is defined as the covariation between spatially remote neurophysiological processes.⁷² The underlying idea is that areas that are involved in the same brain network should show consistent correlations between their respective time courses.³⁸ We investigated functional connectivity in the control group shown in Figure 3 using first an *a priori* seed-based approach (selecting a specific region of interest in the network and correlating its time-course with the other target brain regions)^b and a multivariate approach (independent component analysis, ICA).^c

the standard MNI452 template. Finally, a smoothing kernel of 8 mm was applied. For each participant a statistical model was computed by applying a canonical hemodynamic response, and the conditions of interest were modeled in a GLM (see Ref. 45 for details).

^bFunctional connectivity analysis was conducted first defining four anatomical regions of interest (ROIs) in the auditory–motor circuit, and using picktalas software.^{73,74} The regions included the primary auditory cortex (PAC, BA 41, 42), IFG, SMA, and the precentral gyrus (including primary motor cortex, M1) in the affected hemisphere, according to the Talairach Daemon database atlases^{75,76} and the AAL atlas.⁷⁷ Once these areas were defined, and

^afMRI data was analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, London). Images were realigned between them and coregistered to their respective T1 before being normalized to

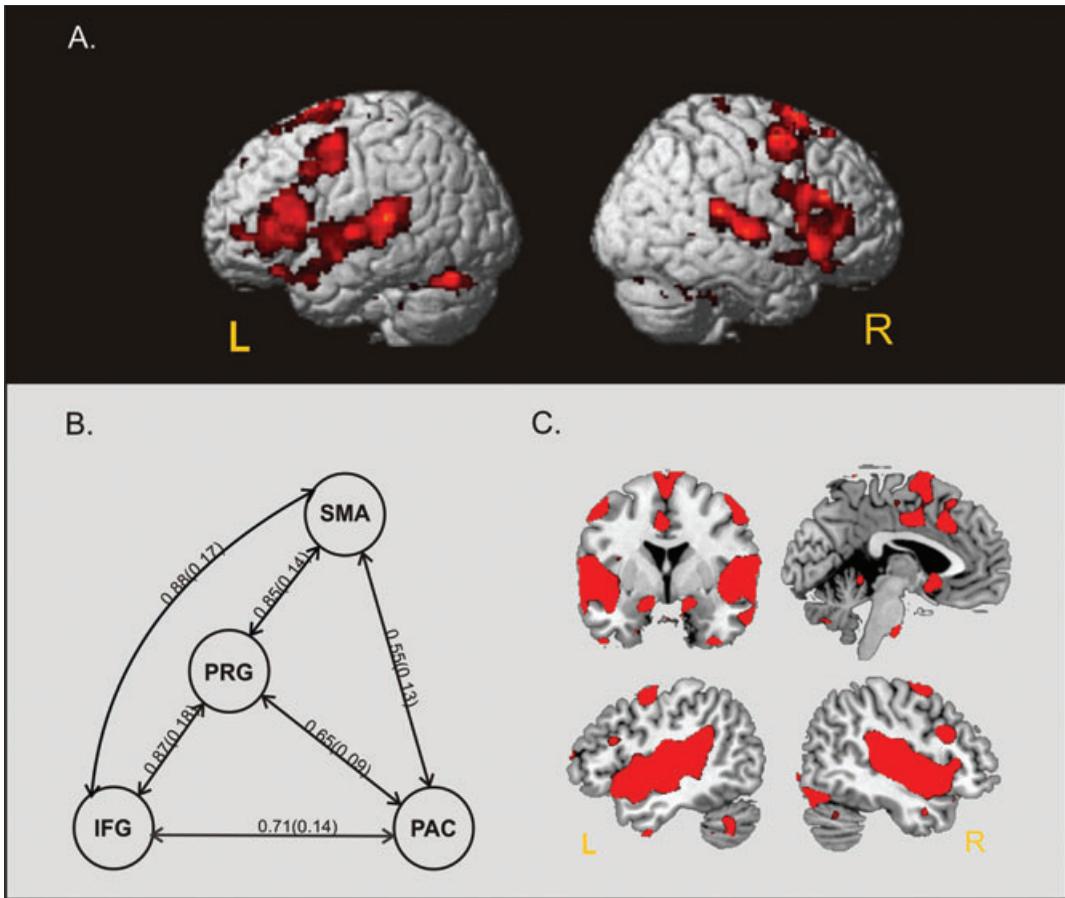


Figure 3. (A) Functional activation patterns in the passive music listening task in a sample of seven healthy participants and in the “Listening to Music” versus “Rest” contrast. Images were superimposed on a group-averaged structural MRI image in standard stereotactic space ($P < 0.01$, $n = 50$; uncorrected). (B) Mean functional connectivity (Fisher’s z-transformed) within the auditory-motor network (selected regions of interest: SMA, supplementary motor area; PRG, precentral gyrus (BA6/4); IFG, inferior frontal gyrus; PAC, primary motor cortex). (C) Audio-motor network component reconstructed using independent component analysis (ICA) on seven healthy participants.

for seven control participants (two evaluations) and three patients (patients were evaluated pre- and posttherapy), a set of voxels was selected inside an ROI using the fMRI results from the condition *Listening to Trained Music* in the patients or *Listening to Music* in controls. For each anatomical ROI, only the time courses from the voxels, which were activated in these contrasts, were extracted. Before averaging, all the time courses had the linear trend removed and were low-pass filtered using a MATLAB toolbox for functional connectivity.⁷⁸ Functional connectivity was calculated separately for each participant as a correlation between the activation time courses averaged over all the activated voxels in a pair of ROIs (as detailed in Ref. 79). Thus, six different correlations

(PAC-SMA, PAC-IFG, PAC-M1, M1-SMA, M1-IFG, and IFG-SMA) between ROIs were computed for each subject and Fisher’s r -to- z transformation was applied to each of them.

Independent component analysis (ICA). Functional images from the *Listening* experiment from 7 controls (previously preprocessed) were imported into the Group ICAfMRI Toolbox (GIFT v. 1.3i), and an ICA analysis was performed (see details in Refs. 80 and 81). To select a component related to the audio-frontal-motor network detected with parametrical maps, a functional template was created from the fMRI activations of the control group for the *Listening to Music* condition. This template was spatially correlated with all the ICA components, and the

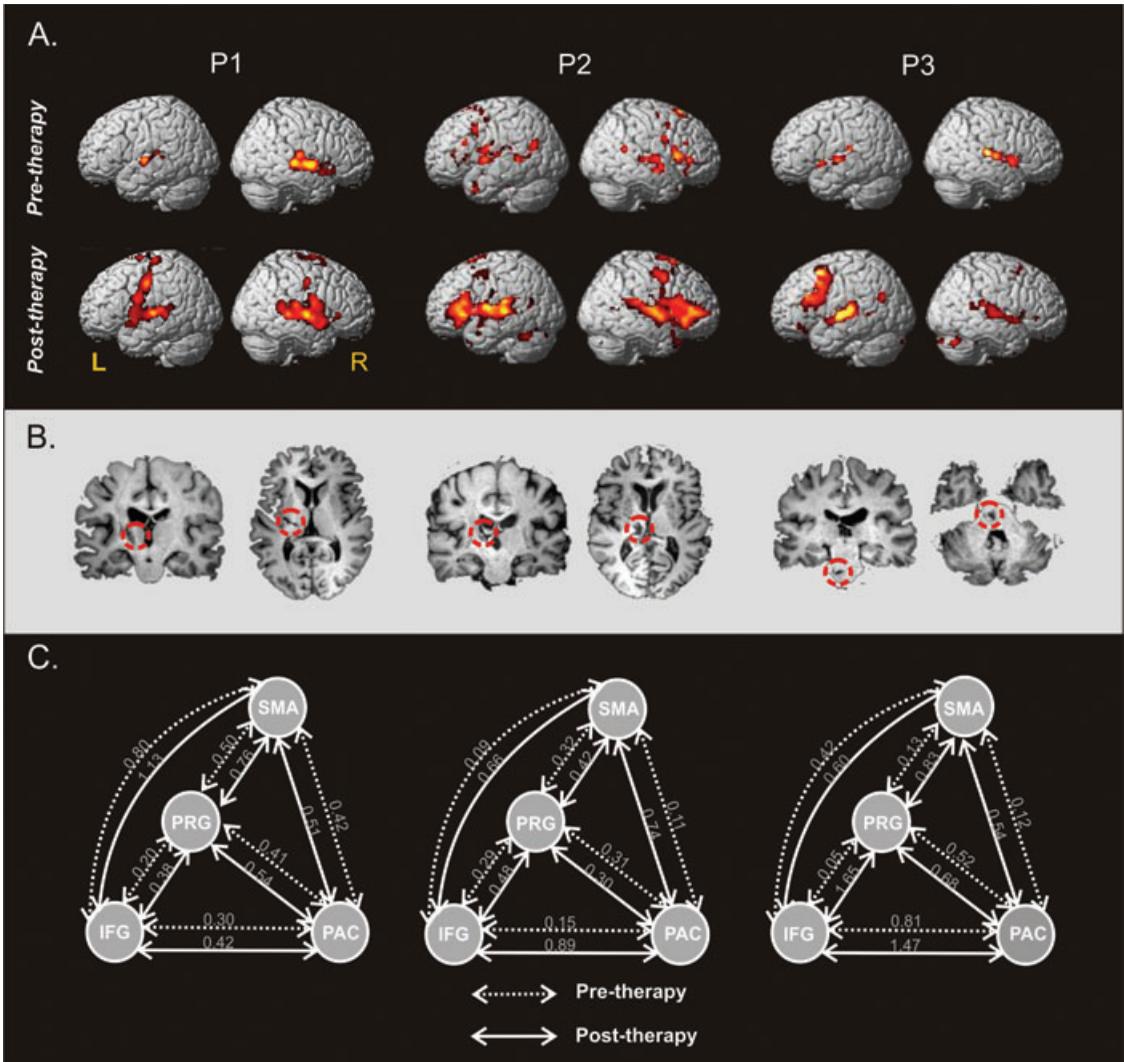


Figure 4. (A) fMRI activation in the music listening task in three chronic patients showing bilateral activation of the auditory-motor circuit when listening to trained music after but not before therapy (patient 1 (P1), $P < 0.05$, FWE corrected; P2, $P < 0.05$, uncorrected; and P3, $P < 0.001$, uncorrected). P1 is the same patient shown in Figure 2 (from Rojo *et al.*, 2011). (B) T1-weighted images showing the lesions of the three chronic patients (P1 includes thalamus, internal capsule, and posterior putamen; P2 thalamus; and P3 pons). (C) Individual functional connectivity (Fisher's z-transformed) within the audio-motor network reconstructed for each patient and for pre- and posttherapy (SMA, supplementary motor area; PRG, precentral gyrus; IFG, inferior frontal gyrus; PAC, primary auditory cortex). Notice the increase of functional connectivity in the different auditory-motor pathways involved in music listening.

In the standard *a priori* covariate approach, an initial ROI was selected in the primary auditory cortex, and we correlated its time course with the

component with the highest correlation ($r = 0.48$) was selected.

time course of the other regions involved in the pathway (precentral gyrus, including premotor and primary motor regions, the inferior frontal region, and SMA) in the passive music listening task. As can be seen in Figure 3B, strong connectivity was observed between the premotor and IFG regions (SMA-precentral, SMA-IFG, precentral-IFG) as well

as between the primary auditory cortex (PAC) and IFG (the same pattern was observed in both scanning sessions). The connectivity between the superior temporal cortex and premotor regions is somehow reduced, likely because this pathway is mediated by the dorsal connections between the posterior superior temporal cortex, inferior parietal lobe (probably through the SMG), and then through the connection to the prefrontal cortex via the superior longitudinal fasciculus.^{22,35,65,82–84} It is important also to reiterate that no direct connections exist between the STG and the primary motor region;⁸⁵ this influence is likely mediated via the dorsal route. This dorsal route might constitute the anatomical basis of the feedforward sounds-to-action loop. Importantly, the SMA is also highlighted in this pathway as a possible hub of strong connectivity in this auditory-motor network (Fig. 3B).

Especially relevant here is the anterior-ventral processing stream because of the strong connectivity observed between the STG and the IFG. This route is important as it has been proposed to be involved in auditory pattern recognition of complex sounds and auditory object identification.^{57,65,86} Important evidence also exists for the structural connectivity between the anterior temporal regions and the inferior frontal cortex from anatomical studies,^{87–89} also demonstrated by recent diffusion tensor imaging studies in humans.^{90–94} For example, a ventral connection through the extreme capsule (EmC) has been proposed connecting the middle section of the STG with the frontal operculum (FOP) close to the insular cortex.⁹⁵ White-matter individual differences in this pathway have been recently associated with success in a language learning task.⁹⁶ Thus, this pathway might be very relevant in the functional network related to music perception and learning and the implementation of audio-motor coupling loops (see Refs. 22, 65).

Finally, in Figure 3C we report the functional connectivity results but using the multivariate data-driven approach, ICA. This method allows for the decomposition of neuroimaging data into a set of spatial modes that capture the greatest amount of variance expressed over time and, therefore, identifying functional networks.³ As can be observed, ICA identified a very similar network when compared to the standard connectivity seed-based approach. This identified component comprised the

STG (from more anterior to posterior regions), PMC, IFG, SMA, and anterior cingulate regions (as well as the amygdala). Thus, both approaches showed strong convergence about the involvement of this network in music perception.

Finally, in Figure 4C we applied the same standard *a priori* connectivity approach to identify the weights of the connections between the different pathways in the three patients selected from N. Rojo, J. Amengual, P. Ripolles, *et al.* (unpublished results). The connectivity was assessed pre- and posttherapy. As demonstrated by the three connectivity pathways, an increase in connectivity between these regions was observed in practically all connections. Although this data is preliminary, the largest increases were observed between SMA and precentral and inferior frontal regions, as well as between the STG and the IFG (anteroventral stream). Thus, after MST, an increase in functional connectivity is exhibited in the three patients, suggesting a restoration of the inherent dynamics of the auditory-motor loops involved in music processing.

Conclusions

This study is an initial and preliminary report suggesting that MST could be effective in chronic stroke and acute patients and that it has a direct impact in the functional connectivity of the audio-motor networks that support musical perception and learning. One important result of the present research is that a clear increase in connectivity is evident in the auditory-motor circuit after MST. This finding suggests that MST affects the re-establishment of the default dynamics of this circuit in patients. This idea is convergent with the strong activation and connectivity observed in healthy untrained musicians in dorsal and anterior-ventral routes in the established auditory-motor circuit for music processing. Further studies are needed to understand how this auditory-motor plasticity mechanism helps in the amelioration of motor problems and positive affect and to clarify the impact of the different processes involved in MST (e.g., the role of auditory or proprioceptive feedback). In this regard, functional and structural connectivity neuroimaging information will be crucial to better understand the impact of certain training programs and to allow for the design of future specific neurorehabilitation programs based on preserved and undamaged brain connectivity (see Refs. 21, 97, 98).

Acknowledgments

This project has been supported by la Fundacio La Marato TV3 (Spain) and the DZNE (German Center for Neurodegenerative Diseases).

Conflicts of interest

The authors declare no conflicts of interest.

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