An integrative cognitive rehabilitation using neurologic music therapy in multiple sclerosis
A pilot study

Federica Impellizzeri, PsyD®, Simona Leonardi, PsyD®, Désirée Latella, PsyD®, Maria Grazia Maggio, PsyD®, Marilena Foti Cuzzola, PsyD®, Margherita Russo, MD, PhD®, Edoardo Sessa, MD®, Placidio Bramanti, MD®, Rosaria De Luca, MSc®, Rocco Salvatore Calabrò, MD, PhD®

Abstract
Background: Multiple sclerosis (MS) is a demyelinating disease, affecting both the sensorimotor and cognitive systems. The typical pattern of cognitive impairment includes reduced speed of information processing, decreased phonological and semantic speech fluency, deficits in verbal and visual episodic memory, as well as attention and executive dysfunctions. We aimed to investigate the influence of the neurologic music therapy (NMT) on mood, motivation, emotion status, and cognitive functions in patients with MS.

Methods: Thirty patients with MS were randomly divided in 2 groups: the control group (CG) undergoing conventional cognitive rehabilitation (CCR), 6 times a week for 8 weeks, and the experimental group (EG) undergoing CCR 3 times a week for 8 weeks plus NMT techniques, performed 3 times a week for 8 weeks. All the participants were submitted to the same amount of treatment. Each patient was evaluated before (baseline: T0) and immediately after the end of each training (T1).

Main outcomes measures: We used as main outcome measure; the brief repeatable battery of neuropsychological test to assess various cognitive abilities; and the multiple sclerosis quality of life scale (MSQoL-54).

Results: Both the groups benefit from 8 weeks of CR. In particular, the EG got better results in cognitive function, with regard to selective reminding test long term storage ($P < .000$), long term recall ($P = .007$), and delayed recall of the 10/36 spatial recall test ($P = .001$), as compared with the CG. Moreover, the improvement in emotional status, motivation, mood and quality of life (with regard to the mental component; $P < .000$) was more evident in the EG.

Conclusions: NMT could be considered a complementary approach to enhance CCR in patients affected by MS.

Abbreviations: AMMT = associative mood and memory training, BDI = Beck depression inventory, BRB-N = brief repeatable battery of neuropsychological test, CCR = conventional cognitive rehabilitation, CG = control group, CR = cognitive rehabilitation, EG = experimental group, ICR = integrative cognitive rehabilitation, MPC = music in psychosocial training and counseling, MS = multiple sclerosis, NMT = neurologic music therapy, QoL = quality of life.

Keywords: cognitive and behavioral deficits, cognitive rehabilitation, multiple sclerosis, music, neurologic music therapy

1. Introduction

Multiple sclerosis is a chronic disease involving the central nervous system that is caused by a complex interplay between genetic and environmental factors.[1–4] In addition to motor involvement, other clinical manifestations significantly affect the quality of life of both the patients and their caregivers,[5] including fatigue, pain, dysphagia, psychiatric disorders, and cognitive deficits.[1–7]

In recent years, an increasing amount of attention has been paid to cognitive impairment in MS. Cognitive impairment, in fact, is a common and debilitating symptom in people with MS, although is poorly managed by pharmacotherapy. The prevalence of cognitive dysfunction ranges from 43% to 70%, and have been reported in all stages and clinical types of MS.[8] Patients with MS may experience cognitive dysfunction in several domains, especially in attention, visual and verbal memory, and processing speed.

The typical pattern of cognitive impairment includes reduced speed of information processing, decreased phonological and semantic speech fluency output, deficits in verbal and visual...
episodic memory, attention and executive dysfunctions.\[^9\]\nOtherwise, language function seems to remain relatively intact.\[^10\]\nLanguage impairments usually involve poor word recall and verbal fluency (phonological and semantic fluency).\[^11\]\nCognitive deficits can often be identified through a neuropsychological assessment and subsequent cognitive rehabilitation (CR). Indeed, specific trainings have been acknowledged as promising behavioral approaches for managing MS-related cognitive impairment to improve overall cognitive abilities and quality of life (QoL). In addition, MS can have consequences on mood and patients’ behavior, leading to depression, anxiety state, and a condition of excessive stress. The lifetime risk of major depression in people with MS has been estimated to be as high as 50% compared with the percentage of general population which is calculated at 10% to 15%.\[^12,13\]\nIn most cases, these disorders derive from: subjective reactions to the diagnosis, ability to adapt and face the disease, response to possible changes in their lifestyle and relationships with others, one’s own history, personality and the environment they have lived in, and last but not least, the support of the family and caregivers. Taking into account a multimodal and ecological rehabilitation approach, which also includes the psychological problems related to MS, it could be appropriate to focus the treatment on an integrative cognitive rehabilitation (ICR). In the last decades, the potential of musical stimuli to activate “perception” and “production” areas in the human brain has been investigated with the aim to provide a series of therapeutic applications to sensory, cognitive, and motor dysfunctions due to neurological diseases. To this aim, a new integrative therapeutic approach, which was established 20 years ago in the United States, called neurologic music therapy (NMT)\[^14\]\nhas provided various benefits to the conventional rehabilitative approaches on controlling mood disorders. This may help the patient to be prone to cognitive and behavioral change in therapy.\[^15\]\n
A typical NMT technique is the Associative Network Theory of Mood and Memory, which suggests that when an event or information is processed, neural connections are established together with other elements (emotional status, odors, environmental background, etc.) of that event, and stored as nodes in memory. Later, this neural node can be activated by music stimuli. Furthermore, the social nature of the musical experience has been investigated by various authors. Clark suggested that music provides shared experience, promoting self-identity, healthy relationships, and quality of life,\[^16\]\nwhereas Dunphy underlined the intrinsic social character of the creative arts therapies and their efficacy in reducing depression symptoms.\[^17\]\nMoreover, Sarkimo et al.\[^18\]\nproposed that, since many therapeutic music exercise methods offered opportunities for social learning, a neurologic music therapist should develop strategies and music-based applications that are better targeted at specific brain processes and at individual rehabilitation needs of patients. For this purpose, Music in Psychosocial Training and Counselling is another NMT technique, which uses music-based methods to help people with neurological problems to improve their psychosocial functioning (mood control; affective expression; cognitive coherence; reality orientation; and appropriate social interactions). Considering that depression and mood disorders still remain under-diagnosed and under-treated in neurological patients,\[^19\]\nand the side effects of the pharmacological treatment, music, and NMT may represent a valid support in reducing such depressive symptoms, improving mood and adherence to treatment while contributing to the functional recovery, including the cognitive one, at the same time. In this pilot study, we sought to investigate the effects of NMT on mood, motivation, emotion status, and cognitive functions in patients with MS that are receiving CR.

2. Materials and methods

2.1. Trial design

The study was a single-blind randomized controlled trial aimed to investigate the influence of NMT on mood, motivation, emotion status, and cognitive functions in patients with MS. It was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethical Committee (study number registration 07/2017). Each patient was adequately informed about the study, and offered their collaboration and signed a written consent.

2.2. Participants

Patients attending the Multiple Sclerosis Centre of IRCCS Centro Neurolesi “Bonino-Pulejo”, Messina, Italy, from November 2017 to December 2018 were invited to enter the study. For the enrollment procedures, see Consort 2010 flow diagram (Fig. 1). Thirty patients affected by relapsing-remitting, primary and secondary progressive MS, were randomly assigned to either the experimental group (EG; n = 15) or the control group (CG; n = 15), in order of recruitment. For a more detailed description of the sample, see Table 1.

Inclusion criteria were: MS diagnosis according to Lublin criteria; an Expanded Disability Status Scale between 3 and 7; to love/enjoy music, either performed instrumentally or listened; absence of disabling sensory alterations (i.e., hearing and visual loss); absence of severe medical and psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)\[^20\]\nand International Classification of Diseases (ICD-10).\[^21\]\n
2.3. Interventions

We applied 2 different rehabilitative approaches: the CG received conventional CR (CCR), 6 times a week for 8 weeks, whereas the EG received CCR (but with a different frequency, i.e. 3 times/wk, for a total of 24 sessions) and a specific NMT 3 times/wk for 8 weeks (for a total of 24 sessions). Each single session lasted about 60 minutes. Thus, both the groups received the same amount of treatment. We used 2 NMT techniques: the Associative Mood and Memory Training (AMMT) and the Music in Psychosocial Training and Counseling (MPC) (see Table 2). AMMT involves music to induce a specific mood state that is associated with material stored in long-term memory, specifically autobiographical memories that belong to the self and one’s past experiences. Through dedicated music listening or singing, the patient experiences a shift of mood, or intensification in their current mood, that activates an associative memory network, creating access to memories of information or events from the past. The primary goals of MPC include emotion identification and expression, mood control, social competence, and self-awareness. These goals are stimulated through guided music listening, musical role-playing, expressive improvisation or singing, and composition exercises.
2.4. Main outcomes measures

Each participant was evaluated by a trained neuropsychologist before (baseline: T0) and immediately after the end of the training (T1). The clinical assessors (who were different from the neuropsychologist who performed the training), and the statisticians were blinded to group allocation.

The neuropsychological battery included: the brief repeatable battery of neuropsychological test (BRB-N)[22,23] which was used to assess various cognitive abilities (attention, orientation, spatial abilities, memory, language); the multiple sclerosis quality of life-54 (MSQoL-54)[24] a specific questionnaire for MS patient’s quality of life, divided into physical and mental subitems; the Beck depression inventory (BDI)[25] used to assess mood; the emotion awareness questionnaire (EAQ)[26] to evaluate emotional component. EAQ is planned with a 6-factor structure defining 6 aspects of emotional functioning: differentiating emotions, verbal sharing of emotions, not-hiding emotions, bodily awareness of emotions, analyses of own emotions, attention to others’ emotions. The EAQ consists of a total of

![Figure 1. Flow diagram of the study population.](image-url)
Memory abilities

Memory training is performed on paper-and-pencil activities: patients have to remember verbal or visual-spatial stimuli previously seen on a book or a sheet.

Social skills

Social skill training (SST). These techniques are based on a series of principles of social learning such as learning by observation (modeling), verbally praising the steps of the social ability performed correctly (reinforcement), strengthen subsequent approximations to the desired final behavior (shaping), its automatization and generalization, transferring the learned ability in the training group to other contexts of reality.

Mood and motivation

Cognitive restructuring of dysfunctional attitudes caused by hospitalization and disease to produce an increase in mood, acceptance of their state of health and increase of motivation for cognitive rehabilitation.

Emotional awareness

Knowledge and auto-regulation of emotions through training of emotional awareness (recognition of own and others emotions) and training for emotional self-regulation (regulate their emotions according to context and situation).

The patient is asked to pay attention to a specific music. After, questions and comments are asked the patients to understand their effective responses to the song (title, author, meaning, instruments, specific words in the lyrics etc) together with their associated personal experience (AMMT).

Leading and follow: form a circle with plenty of room for playing musical instruments; the therapist can model initial improvisation, taking the leadership role and one by one (if they are capable of this) the group members take the leadership role with a changes of volume, rhythm, and tempo (MPC).

Musical mood induction: guided music listening to gain access to positive networks of thought and emotions. The therapist select and plays a song/music and then the patient’s feeling in response to music are discussed (MPC/AMMT).

Emotional continuum: each group member selects an instrument that will use to represent an emotion, each individuals plays a specific emotion the others will try to guess what emotion is been played (MPC).

30 items. Last, we also administered McClelland Motivational Factors,[27] which assess subject motivation, consisting of 3 components, that is, power, competition, and affiliation; specifically, the authors recognized 3 motivators which are believed all people have: a need for achievement, a need for affiliation, and a need for power. Different characteristics will depend on the subject’s dominant motivator and will act accordingly. Moreover, each experimental patient was asked to fulfil a Musical-Sound Anamnesis Form, to guide the NMT approach due to the EG.

### 2.5. Randomization and blinding

Patients with M5 were randomized to undergo either the NMT together with conventional CR (EG) or CR alone (CG). Patients were assigned in a 1:1 ratio using a computer-generated randomization list assessed by statisticians, which was blinded to the training allocation. Patients received instructions not to tell other patients anything about what they do during NMT training techniques.

### 2.6. Statistical methods

Data were analyzed using IBM https://www.ibm.com/products/spss-statistics SPSS Statistics 25, considering a \( P < .05 \) as statistically significant. The descriptive statistics were analyzed and presented as a mean + standard deviation (SD) for continuous variables and as frequencies (%) for categorical variables for the 2 groups (Table 1).

The Student \( t \) test for paired samples was used to compare each group between T0 (baseline) and T1 (intra-group analysis). Moreover, a double-tailed Student \( t \) test for paired samples was used to compare test score variations and discover whether in EG, a higher statistical significance was found rather than in CG (inter-group analysis). In particular, for each clinical test score we computed the differences between the 2 different evaluation times at T0 score and T1, as explained in Table 2.

### 3. Results

A total of 30 patients underwent randomization, and 15 were assigned to each group (see Fig. 1). No harms or unintended effects were found in both groups.

Firstly, at baseline T0, no significant differences between EG and CG were found concerning age, sex instruction, and disability states as shown in Table 1. The between group comparison of the test score variations from baseline (T0) to the end of the treatment (T1) highlighted improvements in various sub-scales of the cognitive evaluation battery (BRB-N) in the EG, as compared with CG (Table 3). In particular, in the EG a significant improvement was found concerning selective reminding test long term storage \( (P < .000) \), long term retrieval \( (P = .007) \), and delayed recall of the 10/36 spatial recall test \( (P = .001) \). Regarding the quality of life test results, the EG showed a more significant improvement in mental sub-test \( (P < .000) \) than the CG \( (P = .928) \). Moreover, in the EG, we observed a significant improvement in mood, as shown by the BDI test scores \( (P < .000) \), as compared with the CG \( (P = .278) \). Both groups revealed significant improvements in patients' emotional status, mood, and expressing emotions, as shown by the final scores in the EAQ (Table 3). However, in the EG, the scores obtained were statistically higher concerning verbal sharing of emotions \( (P < .000) \), not hiding emotions \( (P < .000) \), attending to others emotions \( (P < .000) \), and the analysis of own emotions \( (P < .000) \). Finally, only in the EG a significant improvement in motivational factors was observed, with the highest significance level in affiliation component \( (P < .000) \), compared with competition and power components final scores \( P = .002 \) and \( P = .008 \) respectively (see Table 3).
Multiple sclerosis quality of life (MSQOL) 

et al,

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4. Discussion

Our pilot study supported NMT as a possible effective additional method to improve mood, motivation, emotional status (aware-

and expression), and cognitive functions in patients with MS. There is growing evidence suggesting how music may help to elicit images from memory, based on associative memory network operations,
helping to retrieve mood/emotional quality of a particular life situation in the imaging process. MS patients have been observed to recall individual words or song lyrics better when presented in sung than spoken format. According to VanArsdall et al, animate stimuli are better remembered than matched

imagine stimuli in free recall because the encoding and retrieval of

are not a passive adaptation but active paths of discrimination: “Increasing the encoding of memories generally improves retrieval performance (. . . ) because it increases the percentage that the distinguishing features of encoding will come into play.” These findings are in agreement with our data, as music

stimulus helped the retrieval of information acting like an

external cue, which triggers environmental, interior, physical, emotional, and even very personalized neural pathways. In fact, we found significant cognitive improvements in attention control and long-term memory storage, as well as retrieval of verbal inputs and delayed recall of visual-spatial information.

Emotional and behavioral disturbances with a polymorphic symptomatology are often connected to neurological disorders such as MS. In line with Galisńska, our results showed that music may help to organize therapeutic experiences according to the affective and motivational values for the individual, and could lead to re-thinking personal problems, changing perception of others, learning new coping skills, processing significant life experiences, dealing with fears and setting new goals.

In this regard, increasing evidence highlighted the triggering of “eco-mirror neurons” during the execution of music-related movements (playing instruments, singing, clapping hands, stamping feet) or even during the imagination of a song or a melody. Indeed, it has been proposed that another important aspect of music is the ability to evoke and alter emotional reactions promoting motivation.

Recently, Hodgens and Hodgens and Sebard described affective-mood responses to music and concluded that: music evokes emotional reactions, including emotional peak experiences, music can alter a listener’s mood, emotional and mood responses to music are accompanied by physiological changes, and existing mood, musical preference, cultural expectations, and arousal needs also play a role in determining affective responses. This is probably due to the ability of music to stimulate the production of dopamine, through activation of the tegmental ventral area. This neurotransmitter exerts different effects in various regions and pathways throughout the brain. In fact, in the mesolimbic pathway, dopamine is believed to be involved in motivation and addiction due to the

| Clinical assessment | T0 | T1 | Change (95% conf. int.) | P-value | T0 | T1 | Change (95% conf. int.) | P-value |
|---------------------|----|----|------------------------|---------|----|----|------------------------|---------|
| Brief repeatable battery of neuropsychological tests in multiple sclerosis (BRB-II) | 27.82 | 40.25 | 12.43 (−17.89 to −6.96) | <.000* | 27.55 | 31.41 | −3.86 (−7.89 to −0.80) | .054 |
| SRTT-CLTR | 19.63 | 26.58 | −6.95 (−11.72 to −2.17) | .007* | 20.50 | 21.73 | −1.22 (−4.33 to −1.88) | .413 |
| SPART | 15.68 | 17.00 | −1.31 (−4.73 to −2.09) | .422 | 15.39 | 16.25 | −0.85 (−3.97 to −2.26) | .566 |
| SDMT | 32.01 | 36.24 | −4.22 (−11.97 to −3.53) | .262 | 24.33 | 26.93 | −2.59 (−5.95 to −0.76) | .120 |
| PASAT3 | 29.81 | 35.15 | −5.34 (−10.91 to −0.23) | .059 | 26.97 | 25.65 | 1.31 (−3.29 to −5.93) | .551 |
| PASAT2 | 22.04 | 23.33 | −2.38 (−7.13 to −0.55) | .088 | 19.40 | 18.97 | 0.42 (−4.38 to −5.22) | .853 |
| SRTD | 5.92 | 7.02 | −1.10 (−2.02 to −0.18) | .021 | 5.99 | 6.70 | −0.70 (−1.53 to −0.12) | .088 |
| SRRTD | 4.40 | 5.85 | −1.44 (−2.14 to −0.73) | .001* | 5.66 | 6.54 | 0.92 (0.65 to 0.71) | .936 |
| WLD | 18.01 | 19.35 | −1.34 (−3.88 to −1.19) | .275 | 20.14 | 18.14 | 2.00 (−0.36 to 4.38) | .004 |
| Multiple sclerosis quality of life (MSQOL) | 89.83 | 104.75 | −14.92 (−28.69 to −1.14) | .036 | 26.93 | 67.14 | 4.01 (0.62 to 7.41) | .024 |
| MSQOLPH | 53.21 | 75.21 | −21.99 (−28.54 to −15.44) | <.000* | 25.65 | 55.74 | 2.77 (−6.13 to 6.68) | .928 |
| Beck depression inventory (BDI) | 12.07 | 6.47 | 5.60 (3.47 to 7.72) | <.000* | 13.20 | 13.87 | 0.66 (−1.93 to 0.60) | .278 |
| Mood awareness questionnaire (EAO) | 1.84 | 2.14 | −0.30 (−0.47 to −0.12) | .002* | 1.56 | 1.48 | 0.08 (−0.03 to 0.12) | .003* |
| EAQAE | 1.39 | 1.80 | −0.41 (−17.89 to −6.96) | .006* | 1.54 | 1.40 | 0.14 (−0.04 to 0.23) | .009 |
| EAQOHE | 1.43 | 1.63 | −0.20 (−11.72 to −2.17) | <.000* | 1.52 | 1.41 | 0.10 (−0.04 to 0.16) | .001* |
| EAQOBE | 1.42 | 1.74 | −0.32 (−4.73 to −0.25) | .001* | 1.38 | 1.28 | 0.10 (−0.03 to 0.18) | .007* |
| EAQAOE | 1.60 | 2.03 | −0.43 (−11.97 to −0.11) | <.000* | 1.58 | 1.40 | 0.18 (0.06 to 0.29) | .005* |
| EAQAQON | 1.84 | 2.17 | −0.33 (−10.19 to −0.14) | <.000* | 1.70 | 1.44 | 0.25 (0.12 to 0.37) | .001* |
| McClelland motivational factors (MF) | 61.53 | 69.27 | −7.73 (−7.13 to −0.28) | .002* | 56.80 | 55.87 | 0.93 (−2.25 to 4.11) | .540 |
| MFAC | 58.87 | 78.47 | −19.60 (−20.02 to −0.19) | <.000* | 54.67 | 55.20 | −0.33 (−6.09 to 5.42) | .903 |
| MFA | 44.67 | 59.53 | −1.93 (−214 to −3.42) | .008 | 47.47 | 46.40 | 1.06 (−12.98 to 15.11) | .873 |

BDI = Beck depression inventory; EAQAE = emotional awareness questionnaire, attending to others emotions; EAQOAON = emotional awareness questionnaire, differentiating emotions; EAQAOE = emotional awareness questionnaire, not hiding emotions; EAQVSE = emotional awareness questionnaire, not hiding emotions; EAQAOE = emotional awareness questionnaire, verbal sharing of emotions; FMAC = motivational factors, affiliation; FMA = motivational factors, achievement; FMP = motivational factors, power; MSQOLPH = multiple sclerosis quality of life physical; PASAT2 = paced auditory serial addition test; PASAT3 = paced auditory serial addition test; SDMT = symbol digit modalities test; SPART = 10/36 spatial recall test; SRT-D = delayed recall of the 10/36 spatial recall test; SRT-DCLTR = selective reminding test, consistent long term retrieval; SRT-DLTS = selective reminding test long term storage.

*Significant differences between treatment effects are in bold. Before (T0) and after (T1) are expressed as means ± standard deviations; change and different variables as mean (95% confidence interval).

... statistics between baseline T0 and post-training scores T1 using t test for paired samples.
feelings of reward and pleasure associated with its release, while, in the mesocortical pathway, dopamine is linked to emotional and motivational activities. Music can stimulate each neural pathway by linking the neurotransmitter to the musical input. This may be partly the reason why EG had, during NMT, a highest need for affiliation, with a consequent improvement in their behaviour. Indeed, within a short space of time from the beginning of NMT treatment, patients themselves referred that they enjoyed and wanted to belong to that “musical” group, because they felt better personal acceptance and affiliated to the rest of the group (these results that are confirmed by MSQOL, EAQ, and BDI outcomes measures). Finally, they preferred collaboration to competition, as shown by the MC Lelland Motivational Factors final scores (higher especially in Affiliation sub-scale).

4.1. Study limitations
The main limitation of the study is the small sample size that limits the generalization of our results. Larger sample studies, using specific structural and functional examinations (such as EEG, and IMRI) in addition to neuropsychological evaluation, should be fostered to confirm these findings. Moreover, a more structured and homogeneous intervention is needed to guarantee better results.

5. Conclusions
NMT uses primarily the potential of musical stimuli to activate perception and production areas in the human brain, providing a series of additional therapeutic applications to sensory, cognitive, and motor dysfunctions resulting from neurological disease. When applied to neurological disorders, such as MS, NMT may promote functional recovery, collaborate in neuro-rehabilitation programs, and improve social and psychological outcomes including socialization, motivation, mood, and depression.

Author contributions
Conceptualization: Federica Impellizzeri, Margherita Russo, Rocco Salvatore Calabrò.
Data curation: Federica Impellizzeri, Simona Leonard, Desìre Latella, Marilena Foti Cuzzola, Rosaria De Luca.
Formal analysis: Federica Impellizzeri.
Investigation: Simona Leonard, Desìre Latella, Maria Grazia Maggio, Marilena Foti Cuzzola, Rosaria De Luca, Rocco Salvatore Calabrò.
Methodology: Federica Impellizzeri, Desìre Latella, Maria Grazia Maggio, Marilena Foti Cuzzola, Margherita Russo, Rosaria De Luca, Rocco Salvatore Calabrò.
Project administration: Edoardo Sessa, Placido Bramanti.
Supervision: Marilena Foti Cuzzola, Margherita Russo, Placido Bramanti, Rocco Salvatore Calabrò.
Validation: Edoardo Sessa, Placido Bramanti.
Visualization: Simona Leonard, Maria Grazia Maggio, Edoardo Sessa.
Writing – original draft: Federica Impellizzeri, Marilena Foti Cuzzola.
Writing – review & editing: Margherita Russo, Rocco Salvatore Calabrò.

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