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# Te.M.P.O., an app for using temporal musical mismatch in post stroke neurorehabilitation: A preliminary randomized controlled study

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**Abstract**.
**BACKGROUND:** Recently, the potential rehabilitation value of music has been examined and music-based interventions and techniques such as the Negative Mismatch (MMN) have been increasingly investigated in the neurological rehabilitation context.
**OBJECTIVE:** The aim of this study was to investigate the effectiveness of a negative mismatch-based therapy on the disability and quality of life in patients with stroke in sub-acute phase.
**METHODS:** Thirty patients with a stroke diagnosis in sub-acute phase were randomly assigned to one of two groups: Mismatch (Mg) or Control (CTRLg) group. Both groups used an innovative Android application: Temporal Musical Patterns Organisation (Te.M.P.O). The Disability Rating Scale (DRS), the Modified Barthel Index (MBI) and the Stroke Specific Quality of Life scale (SSQoL) were used at the baseline (T0) and after four weeks of training (T1), in order to assess changes over time.
**RESULTS:** Statistical analysis was performed using the data of 24 (Mg = 12, CTRLg = 12) subjects. The results show a major improvement of the Mg with respect to the CTRLg in all clinical scales score.
**CONCLUSION:** The temporal negative mismatch-based therapy performed with the Te.M.P.O. application could be useful in improving the disability and the quality of life in stroke survivors in a sub-acute phase.

Keywords: Stroke, mismatch, music rehabilitation, cognitive rehabilitation

## 1. Introduction

Music represents a unique stimulus, capable of evoking a brain response that requires the activation of many neural processes not strictly assigned to the auditory reception of the acoustic stimulus, such as areas of language decoding (Zatorre et al., 2002). For this reason, in the past, many scientific research used music as a means of understanding the functioning of different cortical processes (Peretz et al., 2005). More recently, its potential rehabilitation value has been recognized and music-based interventions have been increasingly investigated in the neurological rehabilitation context, opening a new hotspot of research (Sihvonen et al., 2017; Besson et al., 1994; Damasio et al., 1978; Tervaniemi et al.,

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1997). Several studies (Mainka et al., 2018; Cha et al., 2014; Murgia et al., 2018) have already investigated the effects of music-based therapeutic techniques in patients with neurological diseases such as Rhythmic Auditory Stimulation (RAS).

The use of this type of stimulation comes from the fact that researchers have already amply demonstrated that humans are regularly exposed to a perception, "underlying pulse", called the "beat" or "tactus' (Ullén et al., 2008). This kind of stimulation causes spontaneous synchronized movement, such as toe tapping or head nodding (Su et al., 2012). Among the various properties that music can play, an important role is given by its temporal structure which neural corelates have already been mapped by neuroimaging studies (Levitin et al., 2005). When we talk about the structure of music, we refer to the perception of an ordered sequence from a random sequence of musical events (Levitin, 2009). Usually, the human brain performs these processes during the decoding of sensory stimuli thanks to the numerous peripheral processing structures, such as sensory receptors. Therefore, this process of temporal "reordering" of musical events which can take place progressively (horizontally) or simultaneously (vertically), allows not only its correct perception, but also the possibility of associating meaning to music (Levitin, 2009). One technique based on these cognitive properties of the brain is the Mismatch Negativity (MMN), a deviation-specific component of auditory event-related potential (ERP) which detects a deviation between a sound and an internal representation (e.g., memory trace) (Yu et al., 2015). MMN is closely related to deviations between different sound features, such as pitch, timbre, location of sound source, intensity, rhythm, and abstract rule (Vuust et al., 2012). Specifically, MMN peaks at around 100–200 ms after deviation onset with the amplitude and latency altering depending on deviation magnitude and perceptual discriminability (Yu et al., 2015). The MMN has opened an unprecedented window to the central auditory processing and the underlying neurophysiology, affected in a large number of different clinical conditions (Näätänen et al., 2019). The MMN could enable to reach a new level of understanding of the brain processes forming the attentional processes controlling for the access of auditory sensory input to conscious perception and higher forms of memory (Näätänen et al., 2019). Talking about perception and mismatch in musical language, we need to refer to semiotic (Eco, 1975) and the role of the listener in sense attribution (Nattiez, 1989). Structural essential features, in fact, at the level of "matter of the musical object" are memory and the flow of sounds over time. Music is matter forming over time, almost a kind of chronological form and it also works via deviations from the prebuilt pathand the prebuild path is mnemonic (Baker, 1887).

The MMN technique has already been used in rehabilitation protocols for patients with various neurological problems including stroke, obtaining good results (Ilvonen et al., 2003). In addition to linguistic rehabilitation where excellent results have already been reported (Ilvonen et al., 2004), it has been proposed as an index of cognitive impairment (Näätänen et al., 2014).

In consideration of the scientific evidence exposed so far, the rehabilitation protocols that take advantage of the MMN can represent a valid tool not only for the rehabilitation of specific cognitive faculties but also and above all to help the re-learning of transversal skills essential to face simple tasks of daily life. In particular, we refer to the possibility of exploiting the MMN to enhance executive functions required for the execution of motor acts in patients such as those who have experienced a stroke.

In this context, we built a protocol in which patients had to recognize the mismatch and to give it a negative connotation. The aim of this study was to investigate the effectiveness of a temporally negative mismatch on the disability and the quality of life of patients with stroke in sub-acute phase.

## 2. Methods

### 2.1. Study design

This was a two-arm, single-blind randomized controlled trial (Fig. 1). The guidelines for Good Clinical Practice, and the Consolidated Standards of Reporting Trials (CONSORT), were followed. This trial was approved by the Local Ethics Committee of Fondazione Santa Lucia (FSL) Institute for Research and Health Care (Protocol CE/PROG.729); all participants or their legal guardians gave their written informed consent for participation.

A researcher who was not involved in the intervention sessions assessed the patients' eligibility to participate based on the inclusion and exclusion criteria. Participants were randomly assigned to one of two groups: Mismatch Real (MRg) or Mismatch Sham (MSg) group.

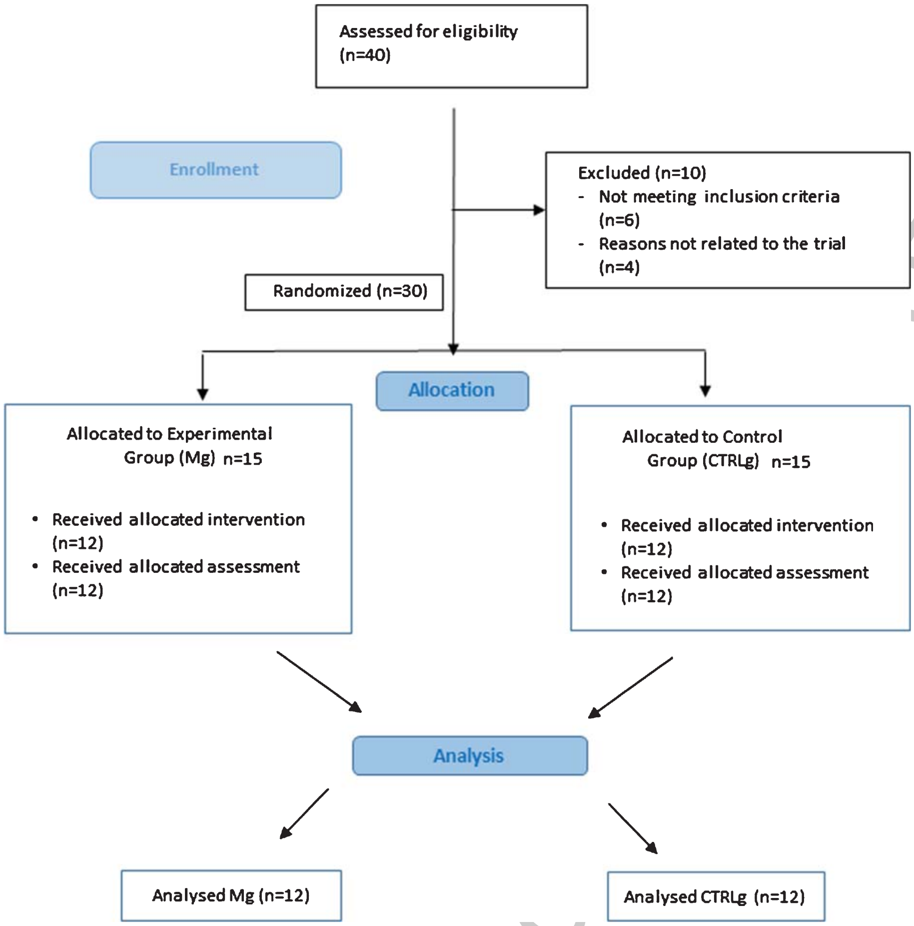


Fig. 1. Flowchart of the study.

### 2.2. Participants

Thirty inpatients (13 males, mean age 57.53 ± 13.33 years) with a diagnosis of stroke (<6 months after stroke) were recruited and enrolled on the basis of consecutive sampling at the FSL from June 2018 to January 2020. Inclusion criteria were stroke with unilateral hemiplegia at most in the previous six months. Subjects were aged between 18 and 65 years.

Exclusion criteria were: cognitive deficits affecting the ability to understand task instructions (Mini-Mental State Examination > 24); severe unilateral spatial neglect (diagnosed with a test battery that included the Letter Cancellation test, Barrage test, Sentence Reading test and the Wundt-Jastrow Area Illusion Test), presence of degenerative diseases, tumors or other comorbidities. Demographic characteristics of the sample are reported in Table 1.

Table 1
Demographic characteristics at baseline

| | Group | |
|---|---|---|
| | Mg | CTRLg |
| Age [Years] | 50.87 ± 12.37 | 64.20 ± 10.94 |
| Gender | 6M | 7M |
| Time since stroke [Months] | 1.86 ± 2.07 | 2.60 ± 2.77 |
| Stroke location | 4R | 5R |
| Stroke type, ischemic | 8I | 13I |

Mean ± standard deviation; M = Male; R = Right; I = Ischemic.

## 3. Interventions

Two different protocols were created, one based on the mismatch technique (Real) and the other in which there was no stimulation with mismatch (Sham). For both interventions, each session lasted 20 minutes. Both groups performed the allocated intervention


Fig. 2. Exercises and choice setting interface screenshots.

three times a week for 4 weeks, in addition to the standard cognitive rehabilitation.

### 3.1. Real mismatch

The experimental intervention was performed using the Temporal Musical Patterns Organisation application (Te.M.P.O.). The Te.M.P.O. application was conceived and designed by the musician and composer GP, an example of the app interface is shown in Fig. 2. The application can be use on Android system and allowed to exercise the cognitive functions using sudden variation of music tone during the listening of a sequence of different music themes. In the Real protocol, the tasks required the patient to listen simple musical themes (composed ad hoc), executed with different tones, and mixed together. It asked patients to identify and report any mismatch (discrepancy between themes) in the listened music sequence and to give the right order for avoiding any theme mismatch.

### 3.2. Sham mismatch

The sham approach was performed using the Te.M.P.O application. The task was the same as for the experimental approach and the musical themes sequences were also similar. The difference between the real approach and the sham one was that in the sham approach there were no mismatches in the listened music theme sequences. However, as in the real approach, patients were asked to listen the music sequences to identify and report any mismatches, and eventually to assemble one theme without any mismatch. Each session lasted 20 minutes.

### 3.3. Conventional therapy

All subjects performed both cognitive and motor standard rehabilitation. The standard cognitive rehabilitation techniques were performed in order to enhance the injured cognitive functions with particular attention on executive functions. It was performed three times a week for four weeks and each session lasted 45 minutes (Morone et al., 2019). The standard physiotherapy was performed five times a week for four weeks and each session lasted 40 minutes. It consisted of exercises aimed at the recovery of voluntary motor functions and of balance, including the active-assisted mobilization, the muscle stretching, the facilitation of movements on the paretic side, balance training and gait training. (Morone et al., 2014).

## 4. Outcome measures

At enrolment, clinical and demographic data were collected. All patients were evaluated before the treatment (T0) and after four weeks of training (T1) using the Disability Rating Scale (DRS) (Gouvier et al., 1987), the Modified Barthel Index (MBI) (Shah et al., 1989) and the Stroke Specific Quality of Life scale (SSQoL) (Williams et al., 1999). All evaluation scores were collected by a speech therapist blinded to the group allocation.

## 5. Blinding

A researcher not involved in the intervention sessions carried out the randomization. Block randomization was performed with a computer-generated randomization list using a block size. Allocation concealment was ensured by using opaque envelopes. The researcher responsible for the randomization process deposited the list in a secure web-based storage.

## 6. Statistical analysis

IBM SPSS Statistics software (v23, IBM Corp., Armonk, NY, USA) was used. The sample size complied with the minimum number of participants

Table 2
Clinical scale scores

| | Mg | | CTRLg | | Mg vs CTRLg |
|---|---|---|---|---|---|
| | T0 mean ± SD | T1 mean ± SD | T0 mean ± SD | T1 mean ± SD | *p* value comparison at T1 |
| MBI | 55.00 ± 26.11 | 73.75 ± 27.31* | 37.08 ± 25.36 | 50.42 ± 26.50* | $p = 0.019$** |
| SSQOL | 145.42 ± 37.85 | 170.58 ± 39.66* | 123.00 ± 22.76 | 130.08 ± 21,76* | $p = 0.017$** |
| DRS | 5.83 ± 2.44 | 3.42 ± 3.03* | 7.42 ± 2.84 | 6.67 ± 3.08 | $p = 0.017$** |

Mean ± standard deviations of clinical scales scores at T0,T1; Mg = Experimental Group; CTRLg = Control Group; MBI = Modified Barthel Index; SSQOL = Stroke Specific Quality of Life; DRS = Disability Rating Scale *=significant for $p < 0.05$ in the within subjects analysis; **=significant for $p < 0.05$ in the between-subjects analysis at T1.

recommended by a statistical analysis performed on preliminary data ($\alpha = 0.05$; $\beta = 0.8$; ES = 0.5) for nonparametric between-group comparisons (Cohen, 1977). We used the latency data of patients with a time from stroke lower than three months of a previous study on the mismatch negativity paradigm (Ilvonen et al., 2003).

Data were reported in terms of means and standard deviations. The Wilcoxon signed ranks test was used for the within-subjects comparison for both groups at times T0–T1. The Mann-Whitney U test was used to compare data between groups at T0 and T1. The descriptive analysis was performed using [(T1 score − T0 score / maximal score-T0 score) × 100] (Shah et al., 1990) in order to calculate the percentage of effectiveness in the two groups.

## 7. Results

Thirty patients met the inclusion criteria and were enrolled in the study; four patients were released before the end of the training and two dropped out for reasons not related to the trial (Fig. 1). The statistical analysis was performed using the data of 24 (Mg = 12, CTRLg = 12) subjects.

At the baseline (T0), the patients in the two groups did not differ significantly in term of demographic characteristics, time since stroke, stroke location, stroke type and mean scores on the administered scales ($p > 0.05$). As shown in Table 2, both groups enhanced all the clinical scales' scores over time.

The within-subjects comparison showed a significant improvement both in Mg and CTRLg in MBI (Mg $p = 0.005$, CTRLg $p = 0.041$) and SSQOL scale (Mg $p = 0.002$, CTRLg $p = 0.037$). Additionally, the Mg showed a significant improvement also in DRS ($p = 0.004$). Significant differences were found for the MBI score, SSQOL and for the DRS at T1, in the between-subjects analysis of the Mg with respect to the CTRLg, all clinical scales scores are reported in Table 2.

Table 3
Percentage of effectiveness in the two groups

| | Mg | CTRLg | Mg vs CTRLg |
|---|---|---|---|
| | Increase T1vsT0 Mean±SD (%) | Increase T1vsT0 Mean±SD (%) | *p* value |
| MBI | 60.24 ± 25.21 | 30.37 ± 22.10 | $p = 0.175$ |
| SSQOL | 28.76 ± 17.04* | 9.33 ± 6.55 | $p = 0.009$* |
| DRS | 53.74 ± 28.05* | 18.60 ± 26.37 | $p = 0.025$* |

Mean ± standard deviations of effectiveness related to clinical scales scores between T0 and T1; Mg = Experimental Group; CTRLg = Control Group; MBI = Modified Barthel Index; SSQOL = Stroke Specific Quality of Life; DRS = Disability Rating Scale; the percentage increase was calculated as follow: $\left[(\text{T1 score} - \text{T0 score}/\text{maximal score-T0 score}) \times 100\right]$; *=significant for $p < 0.05$ in the between-subjects analysis.

The analysis of effectiveness revealed that, compared with baseline (T0), the percentage of improvement in all the clinical scales' scores was greater in the Mg group than the CTRLg (Table 3). Significant differences in effectiveness were found in the between-subject analysis of SSQOL and DRS scores.

## 8. Discussion

The aim of this study was to investigate the effect of the temporally negative mismatch technique on the disability and quality of life in patients with stroke in a sub-acute phase.

The within-subjects analysis showed significant improvements over time in the two groups both about the independence in daily life activities (MBI) and the health-related quality of life (SSQoL). In addition, the Mg group showed a significant reduction of disability assessed with the DRS.

The comparison between the two groups showed significant differences at T1 in all the considered scales. This result, combined with the effectiveness analysis showing a higher percentage of improvement in the experimental group with respect to the control group, shows a greater overall improvement in the experimental group than in the control group.

Sounds, which are the raw material of music, maintain a temporality and a sequencing that are useful in temporal patterns of the cognitive function formation; they represent an useful aid in the formation of temporal patterns of the cognitive functions, and constitute an assembly or framework that facilitates the learning of sequential information processing, such as memory (Jauset-Berrocal et al., 2018).

The mismatch negativity (MMN) is related to an electrophysiological change-detection response of the brain stimulated when there is any discernible change to a repetitive sequence of sound, occurring even in the absence of attention; it is an automatic response and causes an involuntary attentional shift, representing a function which is of vital significance (Näätänen et al., 2019).

Different studies have shown that the ability to identify a mismatch in sound sequences is related to the improvement of cognitive abilities (Näätänen et al., 2019; Ilvonen et al., 2004; Näätänen et al., 2012). Moreover, in a wider prospective, the applications of music therapy in cognitive neurorehabilitation is proven to be useful in improving cognitive abilities such as memory and attention (Jauset-Berrocal et al., 2018; Magee, 2005; Kleinman, 2007).

Patients who have experienced a stroke and are in the subacute phase have underestimation deficits in their motor skills (Carter et al., 2010). In severe cases, these patients have to re-learn the way to perform the targeted gestures (Uswatte et al., 2006), in other cases, no less disabling, they have to deal with awareness deficit (Yates et al., 2002). In fact, it has been reported that many stroke patients fall because they do not correctly estimate the time required to perform the movement adequately (Yates et al.,2002). The timing of motor sequences is made possible by cortical areas that reside in the frontal lobes which share neural circuits with those involved in an MMN task (Schubotz et al., 2000; Lappe et al., 2013). Therefore, protocols based on MMN could stimulate the same circuits that allow the perception of the temporal structure of the action.

Given these considerations and the showed results, we may speculate that the improvement of the cognitive abilities, induced by the training with the temporally negative mismatch, may lead to improvements in daily life activities and to a reduction of disability with significant consequences on improvement of the quality of life in stroke survivors.

Furthermore, the Te.M.P.O. application used in this study allows to create different music sequences and to modify the exercises both regarding the difficulty and regarding the required tasks. Moreover, the application is enabled to save and make available each patient's data in order to monitor the execution's progress over time. Te.M.P.O. is innovative, easy to use and it could be installed on any Android device. Considering its characteristics, we believe that it could be a useful tool to use in order to perform the MMN technique. Despite it, the present study has some limitations. The study sample included different types of stroke (i.e., haemorrhagic and ischemic, right and left hemiparesis) generating a heterogonous group.

At the moment there are no studies that have considered MMN as an indirect stimulation for the improvement of stroke patients. The aim was to evaluate whether patients reported an improvement in quality of life and in daily life activities following MMN training. Therefore, only cognitive tests that ascertained participants' inclusion criteria were administered.

Further studies should be able to verify how the use of MMN can act cortically and lead to an improvement in disability in these stroke patients.

A current limitation of the study was that when using the Te.M.P.O it did not allow to register the patient test but it was only possible to perform the exercises in the form of training. Further studies could investigate the improvement of patients in the various sessions, being able to access to trial data when the app will be released in its full version.

## 9. Conclusions

In light of the results obtained and considering the utility of the Te.M.P.O. application, we believe that it could be useful to add to the standard neurorehabilitation a specific training performed with the Te.M.P.O. application and based on the temporal negative mismatch technique, in order to improve the disability and the quality of life of stroke survivors in a subacute phase.

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## Conflict of interest

The authors declare that there is no conflict of interest. The authors also do not report financial support.

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