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Influence of music therapy on the rehabilitation of children with severe brain damage

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Abstract

The aim of this experiment was to test for the efficiency of a music therapy (MT) program implemented at the Centro Internacional de Restauracion Neurologica (CIREN), La Habana, Cuba. All the children who participated in this study had severe neurological disorders and were involved in an intense neuro-restoration program for 4 to 8 weeks. Children were randomly assigned to the MT group or to a control group. Overall results from questionnaires filled in by the occupational and speech therapists showed that all children improved from Week 1 to Week 4 on three dimensions (motor, social and emotional behaviours). Importantly, improvements on the motor behaviour dimension were larger for children in the experimental MT group than for children in the control group. Moreover, results in the MT group revealed that improvements on musical tests were larger after 8 weeks than after 4 weeks of MT. Finally, although analyses of the Event-Related brain Potentials (ERPs) showed large inter-individual variability, it was nevertheless possible to isolate subgroups of children with similar patterns of results (P250 vs N300 components). Taken together, these results are encouraging in showing that the use of different methodologies can provide complementary information on the efficiency of neuro-restoration and MT programs

1. Introduction

Music Therapy (MT) defined as the use of music for clinical purposes has been used for a long time (e.g., Van de Wall, 1946) and MT is often recommended as a treatment for infantile autism, for instance (Accordino, et. al. 2006). Until the past ten years, however, empirical support for MT was relatively scarce and not entirely convincing for several reasons. First, support was mainly coming

42 from case studies conducted by music therapists with limited use of controlled research
43 methodologies. Second, when conducting group studies, a number of factors were not controlled. For
44 instance, groups involved in MT were often heterogeneous without control groups matched on age,
45 sex, level of school education, socio-economic status of the family etc... Patients were not randomly
46 assigned to the experimental (MT) or control group. Data were not always analyzed using appropriate
47 statistical tools and the number of participants was often too small to obtain statistically reliable
48 results (Mrazova&Celec, 2010). Finally, and may be most importantly, these first studies were not
49 theoretically-based and the reasons for using MT in clinical settings were not explicitly described.

50 Importantly, these shortcomings have been fully considered and rigorously controlled studies have
51 been conducted in the past ten years to test for the effects of MT in different groups of patients (see
52 Robb et al. 2011; Robb & Carpenter, 2009 for reviews of music-based interventions and Wan et al.
53 2010, for a review of singing therapy). For instance, Särkämö (Särkämö et al., 2008) and
54 collaborators tested a group of 60 stroke patients with acute middle cerebral artery stroke in left or
55 right hemisphere to determine whether music listening improved cognitive recovery and mood.
56 Patients were randomly assigned to music listening (20 patients), audiobook listening (20 patients) or
57 to a control group (20 patients). Brain magnetic activity, Magnetoencephalography (MEG) was
58 recorded and the Mismatch Negativity (MMNm) was analyzed. The MMN is considered as a good
59 index of preattentive auditory processing (Näätänen et al. 1978). The main advantage of the MMN is
60 that it can be recorded under passive listening conditions from many different types of patients
61 without requiring any specific action from their part (Kujala & Naatanen, 2010). Patients typically
62 watch a silent movie while a sequence of sounds is delivered that comprises standard and deviant
63 stimuli. The MMN is computed by subtracting the Event-Related Potentials (ERPs) to the standard
64 stimulus from the ERPs to the deviant stimuli. Results of Särkämö et al. showed that both music and
65 audiobook listening enhanced recovery of auditory sensory memory functions as reflected by
66 enhanced amplitude MMNm compared to the control group. However, only music listening
67 improved cognitive recovery (verbal memory and focused attention) and prevented depression in the
68 6 months following the stroke. In a subsequent study from the same group (Forsblom et al. 2010), the
69 authors tried to disentangle two factors that may have contributed to improved cognitive recovery
70 and mood in the stroke patients tested by Särkämö (Särkämö et al., 2008), namely enhanced neuronal
71 plasticity and stimulation or emotional and psychological factors related to the music listening
72 experience. Using a phenomenological approach based on the analysis of the patients' own
73 narratives, they found that both types of activities were considered as refreshing stimulations and that
74 both evoked thoughts and memories. However, only music listening was considered as favoring
75 relaxation and increased motor activity and as contributing more than audiobook listening to
76 recovery and positive mood changes.

77 Still with stroke patients, Rodriguez-Fornells and collaborators (Grau-Sanchez et al., 2013;
78 Rodriguez-Fornells et al., 2012), tested the hypothesis that by improving auditory-motor coupling
79 (e.g., Bangert et al., 2006; Baumann et al., 2007; Lahav et al. 2007), playing a musical instrument can
80 promote neuroplastic changes in the motor cortex and the restoration of motor abilities. Patients were
81 involved in a Music-Supported-Therapy (MST) program (Schneider, et al. 2007) during 4 weeks (20
82 individual sessions of 30min each) in which they trained on a MIDI-piano for fine movements and on
83 an electronic drum set for gross movements. Improvements in motor abilities were monitored using
84 3D movement analysis and clinical motor tests. The authors also employed different brain imaging
85 methods, functional Magnetic Resonance Imaging (fMRI) coupled with functional connectivity
86 analyses and Trans-Magnetic Stimulation (TMS). Patients involved in MST showed restored
87 activation in different brain regions (primary auditory cortex, precentralgyrus, inferior frontal regions

88 and supplementary motor area) as well as increased functional connectivity between these different
89 brain regions. Moreover, applying TMS revealed changes in the excitability of the motor cortex and
90 in the organization of sensori-motor cortex accompanied by a reduction of motor deficits. The
91 authors suggested that MST may restore the inherent dynamics of the auditory–motor loops involved
92 in music processing. While these results are highly promising, one caveat is that no patients were
93 involved in another activity as interesting and motivating as MST that would allow controlling for
94 attention and motivation. This is important insofar as neuroplasticity may depend on the motivational
95 value of the activity (Sanes & Donoghue, 2000).

96 MT has also been used with Alzheimer patients. For instance, Narme (Narme et al., 2012) compared
97 musical (12 patients) vs non-musical (painting: 10 patients or cooking, 5 patients) interventions (2
98 hours, twice a week) in 27 patients with moderate to severe dementia (Mini-mental state: 3-18/30).
99 The largest improvements in emotional states were found in the music group both immediately and 2
100 weeks after the interventions. Särkämö and collaborators, (Särkämö et al., 2013) tested a larger
101 number of patients (89) with mild to moderate dementia and involved in singing (n = 30), music
102 listening (n = 29) or in usual care (control group, n = 30) for 10 weeks. Results showed positive
103 changes in the mood and the quality of life of the patients immediately after the musical intervention
104 and 6 months after. Results of neuropsychological assessments also revealed improvements in
105 general cognition, orientation, short-term memory, attention and executive functions after singing
106 and music listening. They concluded that simple musical activities that are easy to implement can
107 have positive long-term cognitive, emotional, and social benefits in mild/moderate dementia. Another
108 example of cost-effective music-based interventions is provided by the results of Janata (2012)
109 showing that playing individually-selected music programs in the rooms of patients with moderate-
110 to-severe dementia, several hours per day each day for 12 weeks reduced the average levels of
111 agitation and depression among the residents.

112 Music listening was also shown to facilitate motor activities and the initiation of walking in
113 Parkinson patients (McIntosh et al. 1997) as well as to reduce the speech deficits often associated
114 with Parkinson disease (see Wan et al., 2010, for review). More generally, Stahl et al (2013) showed
115 that singing and rhythmic therapies in non-fluent aphasic patients did facilitate the production of
116 formulaic phrases but only standard therapy allowed transfer to the production of unknown phrases
117 (non formulaic language). These results led the authors to conclude that propositional (left
118 perilesional brain regions) and formulaic speech (right corticostriatal areas) may rely on different
119 neural pathways. Similarly, recent results from Schlaug and collaborators (Vines et al. 2011; Wan et
120 al., 2010) showed that combining singing therapy with trans-Direct Current Stimulation (t-DCS), to
121 increase the excitability of the right posterior inferior frontal gyrus known as a key region for the
122 recovery of aphasia, improved the fluency of speech in non fluent aphasic patients. To our
123 knowledge, only a few controlled randomized studies have tested the effects of MT in children. For
124 instance, Kim and collaborators (Kim et al. 2008; Kim et al. 2009) employed a single subject
125 comparison design to investigate social interactions between children with autism and the therapist
126 during improvisational music therapy and toy play. Within these two conditions they measured
127 emotional, motivational and inter-personal responsiveness in the children during joint engagement
128 episodes using video recordings (analyses of facial expressions, eye contacts...). Results indicated
129 more and longer events of joy, ‘emotional synchronicity’ and ‘initiation of engagement’ behaviors in
130 improvisational music therapy than in toy play sessions.

131 In sum, this short review of the literature shows that the number of well-controlled studies, including
132 random assignment of patients to experimental or control groups and large groups of patients is
133 rapidly increasing. Overall, results are positive and encouraging but this may also result from a

134 publication bias with negative results remaining unpublished. Importantly, mechanisms underlying
135 the positive influence of MT in several pathologies as described above are currently investigated
136 using different behavioral and brain imaging methods.. Several hypotheses have been proposed. For
137 instance, music listening and performance engage extensive brain networks that are also involved in
138 other perceptual, cognitive and motor activities. Moreover, many results have shown that music
139 training promotes neuroplastic changes in different brain regions (see Münte et al. 2002, for review)
140 including auditory (e.g., Meyer et al. 2007) and motor-related brain areas (e.g., Bangert et al., 2006;
141 Baumann et al., 2007; Lahav et al., 2007), thereby enhancing auditory-motor coupling (Rodriguez-
142 Fornells et al., 2012). It has also been proposed that the preservation of the medial prefrontal cortex
143 may explain why familiar music is still remembered and able to evoke emotions in persons with
144 severe and advanced dementia (Janata, 2012). The short-term positive effects of music on mood and
145 arousal are possibly mediated by the dopaminergic mesolimbic [reward] system and noradrenaline
146 system (Särkämö & Soto, 2012). Finally, results of epidemiological studies have shown that
147 stimulating cognitive activities (and cognitive reserve) in late life have protective effect against
148 dementia (Verghese et al., 2003) and can slower cognitive decline in dementia (Hall et al., 2009;
149 Treiber et al., 2011). Findings from Alzheimer transgenic mice are interesting in this respect: they
150 showed that enriched environments can protect against cognitive impairment, decreased beta-amyloid
151 deposition, and increased hippocampal synaptic immunoreactivity (Cracchiolo et al., 2007).
152 Following Mrazova and Celec (2010), “The ultimate goal of mechanistic research is the molecular
153 understanding of music therapy”. While this goal may still require time to be reached, important
154 progress is made in this direction (e.g., Gomez-Pinilla & Hillman, 2013).

155 The aim of the present research project was to implement an experiment aimed at investigating the
156 influence of MT in children with severe brain damages. These children were patients from the
157 “Centro Internacional de RestauracionNeurologica (CIREN)”, directly dependent from the Ministry
158 of Health of Cuba. This center is well-known for receiving patients (adults and children) from all
159 over the world and, in particular from Latin America (but also Portugal, Spain, United States...). The
160 general procedure is similar for all incoming patients. The first week is dedicated to complete
161 evaluation of the patient by a multi-disciplinary team of neurologists, neuropsychologists,
162 neurophysiologists and clinicians to establish a diagnostic. Based upon this diagnostic, individualized
163 therapies are implemented to fulfill the specific needs of the patients (e.g. motor, cognitive, speech,
164 memory etc...). Typically, patients are involved in these different therapies from 8:30 until 12:00 am
165 and from 2:00 until 5:30 pm every day except Sundays (Saturday from 8:00 to 12:00). Each therapy
166 session lasts for one hour minimum. Importantly, at least one member of the family remains at the
167 CIREN during the entire stay of the patient to take care of him(her) when (s)he is not involved in the
168 therapies. The neuro-restorative program lasts for a minimum of 4 weeks but may last longer
169 depending upon the patient needs and the family economic situation.

170 We took advantage of the organization of the neuro-restorative program at the pediatric clinic of the
171 CIREN to implement a protocol based on a Test – Training – Retest procedure. We had three main
172 objectives. First, we aimed at testing whether 10 to 15 min of MT would increase children’s attention
173 and motivation in the subsequent speech and cognitive therapies that they received several times a
174 day. Second, it was of importance to determine whether music therapy improved musical abilities,
175 social behavior (verbal and nonverbal) and the quality of life of the children enrolled in the program
176 and of their parents. To reach the first and second aim, speech and occupational therapists were asked
177 to fill in questionnaires specifically designed for this experiment based on standard questionnaires
178 (see methods) and parents expressed their opinions in interviews. Finally, we aimed at testing the
179 feasibility of recording the Mismatch Negativity (MMN) from these children. As mentioned above,

180 the MMN is recorded under passive listening conditions and is taken to reflect preattentive auditory
181 processing (Kujala & Näätänen, 2010; Näätänen et al., 1978). In this project, we implemented a
182 typical MMN design with sequences of standard syllables intermixed with deviant syllables varying
183 in pitch, duration and Voice Onset Time (VOT, a phonological parameter that allows differentiating
184 “Ba” from “Pa”, for instance). Our aim in recording the MMN from a sample of the children included
185 in the present experiment was to gain objective information on the specific acoustic cues (pitch,
186 duration or VOT) that the child would be most sensitive to and thereafter use this cue to orient
187 subsequent speech therapy. For instance, if one child is most sensitive to frequency, this is interesting
188 information for the speech therapist that can then use voice frequency modulations in the speech
189 therapy program. Moreover, it was also of specific interest to examine changes in MMN amplitude
190 and/or latency before and after the restorative program and the MT.

191 2. Materials and methods

192 2.1. Participants

193 A total of twenty-seven children participated to this project that lasted from January to October 2013.
194 The inclusion criteria were as follows: participation in the neuro-restorative program at CIREN for at
195 least 4 weeks, age between 3 and 12 years old; Spanish as native language; functional Auditory
196 Brainstem Responses (ABRs) and parents’ consent. Out of the 27 children, all from Latin American
197 countries (Argentina, Chile, Mexico and Venezuela), 17 were randomly assigned to the experimental
198 group (7 girls) and 10 to the control group (3 girls). The mean age of the children was not
199 significantly different in the experimental (mean=6.83, SD=3.22) and in the control group
200 (mean=6.80, SD=3.77; U-Mann Whitney test for independent samples: $p=0.44$). The socio-
201 economic background of the family was assessed based on the family income as determined from the
202 parent(s) profession (scale from 1 to 4: Working class=1, Low middle class=2, Middle class=3,
203 Upper middle class=4) and was not significantly different between the experimental (mean = 2.66,
204 SD= 1.18) and control groups (mean=2.55, SD=1.13; $p=0.71$). The level of education of the parents
205 was also assessed based on the number of years of education (including primary school) and was
206 again not significantly different between the experimental (mean= 14.3 years, SD=4.14) and control
207 groups (mean= 13.1 years, SD=4.9; $p=0.36$).

208 During the first evaluation week, a comprehensive battery of standard psychometric and
209 neuropsychological tests (Progressive Matrices Test (Raven et al.1998), Wechsler intelligence scale
210 children WISC-r (Wechsler, 1974), Brunet-Lezine psychomotor scale (Brunet & Lezine, 1978),
211 Children neuropsychological scale ENI (Rosselli et al. 2001), as well as routine
212 ElectroEncephaloGram (EEG) recordings and neuroimaging (structural anatomy using Magnetic
213 Resonance Imaging (1.5 T MRI) were performed to establish or to confirm neurological diagnosis
214 and to propose individualized neuro-restorative programs. Screening included search for associated
215 epilepsy, mental retardation, ophthalmologic and/or hearing impairments, speech and language
216 disorders as well as oral-motor dysfunctions. Cognitive assessments revealed a high proportion of
217 mental and psychomotor retardation ($n=6$), apraxia ($n=12$) and attention ($n=16$) impairments.
218 Moreover, out of the 27children with brain damage, 19 suffered from Static Lesions of the Central
219 Nervous System (SLCNS; 12 in the experimental group and 7 in the control group) of prenatal and/or
220 perinatal origins that were expressed in cerebral palsy ($n=12$, with spastic diparesia subtype) or in
221 cognitive and/or language disorders ($n=9$). Seven children (5 in the experimental group and 2 in the
222 control group) were diagnosed with other disorders including Autistic Spectrum Disorder (ASD,
223 $n=2$), generalized dystonia ($n=1$), neurofibromatosis ($n=1$) and paraplegia due to spinal cord injury
224 ($n=2$). Finally, 12 children showed abnormal EEG, 6 children had unilateral impairments in the
225 Auditory Brainstem Responses (ABRs) and MRI showed that 22 children had brain structural

226 abnormalities (see Table 1). While we are aware that ideally, homogenous groups of patients should
227 be included in such an experiment, this was not possible considering the heterogeneity of the specific
228 lesions and associated behaviors of the children who were enrolled at CIREN.

229 **2.2. Ethics**

230 This study was approved by the scientific council of CIREN and received necessary support from the
231 direction of the hospital. The project was conducted in accordance with norms and guidelines for the
232 protection of human subjects. Informed consent from the doctors and therapists of the neuro-pediatric
233 clinic was granted before the start of the project. Parents were informed in details of the procedure
234 (see below) and on the music training program that was described as an interesting and rewarding
235 experience for their children. Parents who agreed with the project signed an informed consent form.

236 **2.3. Occupational and speech therapy questionnaires**

237 The study comprised three phases: Test – Rehabilitation –ReTest.

238 During the evaluation week (Week 1), the occupational and speech therapists met the child and filled
239 a questionnaire build from standard questionnaires (MacArthur-Bates Inventario I and II, (Jackson-
240 Maldonado et al. 2003); Escala Autónoma Asperger-Autismo, (Belinchon et al., 2008); CUMANIN,
241 (Portellano Perez et al. 2000) around three main dimensions: motor behavior, social behavior and
242 emotional behavior. The therapists received specific training to use the quantitative scale (no
243 reaction= 1, relevant reaction= 5 best). Both therapists filled the same questionnaires again at Week 4
244 (and at Week 8 for the children that remained at CIREN for 8 weeks).

245 **Data Analysis:** Data from the questionnaires filled in by the occupational and speech therapists were
246 analyzed first, by computing the means and standard deviation related to the three dimensions. These
247 data were then submitted to non-parametric Sign-tests and to the Kruskal Wallis one way ANOVA to
248 compare results in the Experimental MT group and in the Control group.

249 The parent's questionnaire was administered by a specialist in Physical Medicine and Rehabilitation
250 in an interactive interview that took around one hour and that was conducted twice, once at Week 1
251 (evaluation week) and once at the end of the restoration program (Week 4 or Week 8, depending
252 upon how long the children remained at CIREN). The overall aim was to determine whether the
253 parents observed changes in the behavior of their children (from MT or control groups) and how they
254 evaluated different aspects of the rehabilitation program. Moreover, parents from children included in
255 the MT program were also asked whether they felt that their children was happy to participate in the
256 MT and whether they considered that MT increased the quality of life of their children.

257 **2.4. Music Therapy**

258 MT was implemented three times a day, three days per week during 4 to 8 weeks for 10 to 15 min.
259 before the speech and cognitive therapies (Total MT=360 min after 4 weeks and 720 minutes after 8
260 weeks). Musical stimuli were presented to the children in a quiet, dedicated room, using a computer
261 and external speakers. MT involved active music listening: while listening to the different musical
262 excerpts the music therapist played games with the children to orientate their attention toward
263 specific aspects of the music and to favor their active participation (e.g. throwing a ball to other child
264 when changing from one music excerpt to the other, clapping hands/feet/fingers/moving head in
265 rhythm with the music, etc...). Four different sequences of musical excerpts were prerecorded and
266 each was used in different sessions to avoid habituation. Musical pieces with different characteristics

267 (rhythm, melody, intensity and timber) were selected based on a pilot study conducted in the same
268 clinical settings at CIREN (April to July 2012) with a sample of 17 pediatrics patients (the list of
269 musical pieces is available upon request and included excerpts from, Vivaldi, Benny More, Mozart,
270 Piazzola, etc.). Each sequence was built in such a way as to start with quiet music pieces, continue
271 with more dynamic, entraining musical pieces and end with more quiet pieces.

272 Children in the control group were not involved in extra activity equivalent to MT, but they received
273 more of the classic neuro-restoration program. Ideally, it would have been important for children in
274 the control group to participate in an extra activity to control for attention and motivation but this was
275 not possible to implement for practical reasons.

276 2.5. Evaluation of children in the music therapy group

277 The level of performance of the children in the experimental group was evaluated by the music
278 therapist by using three different tests. **Performance Scale:** this scale comprised 5 domains: motor
279 ability, attention, emotion, imitation and communication. At the end of each MT day, the therapist
280 filled a 5 points scale for each child (from 0 -poor level of performance- to 5 -high level of
281 performance). Averaged individual scores were computed weekly (i.e., over 9 MT sessions).
282 Comparisons are reported between Week 1, Week 4 (all children) and Week 8 (for the subset of
283 children who stayed for 8 weeks).

284 **Rhythm test** (subtest of CUMANIN, (Portellano Perez et al., 2000): children were asked to reproduce
285 a rhythmic sequence played by the therapist by clapping her hands. The number of taps and their
286 grouping increase in difficulty (from level 1 to 7). Rhythmic performance was evaluated using a 5
287 points scale (0 poor and 5 exact reproduction). For data processing, a score equal or superior to 4 was
288 considered as an index of successful rhythmic reproduction.

289 **“Musical” test:** this test was developed by KMM & MB to evaluate the orientation response,
290 perceptual discrimination and attention. Fifteen music excerpts were presented twice to the children,
291 once in their original version and once in a modified version that included abrupt changes in timber,
292 harmony and melody. This test was presented twice, under implicit and explicit conditions. In the
293 implicit condition, the music therapist watched the child reaction (1:no reaction and 5: child clearly
294 reacted to the changes). In the explicit conditions, children were given the following instructions:
295 “We are going to play a little game. You listen to the music and you raise a finger/arm/foot/leg/move
296 your head... if you hear something surprising” (scores varied from 1: (no reaction to 5: (detect
297 surprising events at the right time).

298 The Rhythm and “musical” tests were administered to each child individually at different time points
299 during the therapy (Week 1, Week 4 and Week 8) and scores corresponding to the three time points
300 were compared using pairwise nonparametric Sign Tests and Kruskal Wallis one-way ANOVA.

301

302 2.6. Electrophysiology experiment

303 **Stimuli:** Children were presented with a sequence of syllables (Consonant-Vowel structure) with the
304 syllable "Ba" serving as standard stimulus and deviant stimuli in vowel frequency, vowel duration
305 and Voice Onset Time (VOT; the syllable “Pa”). The standard stimulus “Ba” had a fundamental
306 frequency (F0) of 103 Hz, vowel duration of 208 msec and VOT of -70msec for a total duration of
307 the stimulus of 278 msec. For frequency deviant syllables, the F0 of the vowel was increased to 155
308 Hz using Praat (Boersma & Weenink, 2001). For duration deviant syllables, vowel duration was
309 shortened by 75 msec using Adobe Audition, for a total syllabic duration of 203 msec. Finally, for
310 VOT deviant syllables, the VOT was 70 msec. shorter than for the standard syllable for a total
311 duration of 208 msec.

312 **Procedure:** The EEG was recorded from a subset of 12 children (out of 17) from the experimental
313 MT group (mean age 7.78, SD 3.01; 5 girls) and from 6 children (out of 10) from the control group
314 (mean age 7.47, SD 3.7; 2 girls; see Table 1). Children who required anesthesia for EEG recordings
315 during the first evaluation week were not included in the subgroup because we did not want to repeat
316 the anesthesia at the end of the MT program (Retest session, see below). Thus, EEG was recorded pre
317 and post training without anesthesia. During EEG recordings, children were told to watch a silent
318 movie without paying attention to the sounds that were presented through headphones. Standard
319 syllables and frequency, duration, and VOT deviant syllables were randomly presented within the
320 auditory sequence with a fixed Stimulus Onset Asynchrony of 600 msec. A total of 920 stimuli were
321 presented binaurally and pseudo-randomly (at least one standard stimulus between each deviant
322 stimulus) with 76% standard stimulus and 8% for each type of deviant stimulus. All stimuli were
323 presented within a single block that lasted for 8 min.

324 **Recordings:** EEG was recorded continuously at a sampling rate of 200 Hz using a MEDICID IV
325 amplifier system (Neuronic, Cuba) from 19 active Ag-Cl electrodes at standard positions of the
326 International 10/20 System (Jasper, 1958): Fp1, Fp2, F7, F8, F3, F4, C3, C4, T5, T6, T3, T4, P3, P4,
327 O1, O2, Fz, Cz, Pz and nose. Data were re-referenced off-line to the algebraic average of the left and
328 right mastoids and filtered with a bandpass of 1-30 Hz (12 dB/oct).

329 **Data analyses:** EEG data were analyzed using EEGLab (Delorme & Makeig, 2004) and the Neuronic
330 Analysis software (Version 3.0.2.0; www.Neuronicsa.com). EEG recordings were segmented into 600
331 msec. epochs (from -100 msec. until 495 msec. post-stimulus onset) time-locked with stimulus
332 presentation. Epochs with electric activity exceeding baseline activity by $\pm 100 \mu\text{V}$ were considered
333 as artifact and were automatically rejected from further processing. The percent of rejected trials was
334 calculated by experimental condition (25% standard, 24% frequency, 22% duration, 25% VOT). The
335 selected EEG artifacts free trials of each child were averaged for the four types of stimuli (standard,
336 frequency, duration and VOT) in the PRE and POST conditions.

337 3. Results

338 3.1. Comparison between Experimental MT group and Control group

339 Results are reported for the comparisons between Week 1 (before therapies started) and Week 4
340 (after therapies started). The number of children who remained at CIREN for 8 weeks was too
341 unbalanced (Occupational therapy: MT $n=8$ and Control $n=4$) or too small (Speech therapy: MT $n=3$
342 and Control $n=3$) to conduct further analyses.

343 **Occupational therapy:** This questionnaire relates to all children involved in the neuro-restoration
344 program (MT: $n=17$ and Control = 10). Using pairwise Sign-tests, results showed significant
345 improvements on motor behavior: Week 1 (mean=3.30) and Week 4 (mean=3.76, $z=2.69$, $p=0.007$),
346 social behavior: Week 1 (mean=2.64) and Week 4 (mean=3.33, $z=3.20$, $p=0.001$) and emotional
347 behavior: Week 1 (mean=3.07) and Week 4 (mean=3.60, $z=2.91$, $p=0.003$).

348 Using the Kruskal Wallis non parametric one way ANOVA, results showed that the main effect of
349 Group was only significant for motor behavior ($\text{ChiSq}(2) = 3.84$, $p < .04$) with larger improvements
350 from Week 1 to Week 4 in the experimental MT group (0.66) than in the control group (0.35). No
351 significant between-groups differences were found on the other dimensions.

352 **Speech therapy:** This questionnaire relates to the subset of children who followed speech therapy
353 (MT: $n=9$ and Control = 8). For the three main dimensions that were considered, motor behavior,
354 social behavior and emotional behavior, results of pairwise Sign-tests showed that the improvement
355 between Week 1 and Week 4 was significant for motor behavior ($z=2.75$, $p < 0.005$) but not

356 significant for the other dimensions.

357 Using the Kruskal Wallis non parametric one-way ANOVA, results showed that the main effect of
358 Group was also significant for motor behavior ($\text{ChiSq}=4.5$, $p<.03$): the improvement between Week 1
359 and Week 4 was larger in the MT group (1.0) than in the control group (.69).

360 **Evaluation of the parents' interview:** Complete information was obtained from 18 parents (MT, $n=$
361 15 and Control, $n=3$). Because of the unbalanced number in the two groups, it was not possible to
362 conduct quantitative analyses. Qualitative observations are reported below.

363 In the initial interview, all parents ($n=18$) reported that their children enjoyed music and were able to
364 pay attention to music. They also believed that music can help their children in their everyday life.
365 Only one question, related to rhythmic movement associated with music, was negatively rated by
366 parents ($n=4$) of children with spasticity or dystonia. The majority of children had previous
367 experiences with different types of music therapy in their countries and parents generally agreed on
368 the importance of this intervention.

369 In the final interviews, the positive aspects noted by parents of children in the MT group ($n=15$) were
370 related to increased motivation, sociability and auditory attention. In particular, they noted that MT
371 improved motivation so that children more easily engaged in functional games during the speech and
372 occupational therapies, were less angry and less irritable and were more likely to allow facial
373 massages. Related to sociability, parents noted that their children were more understanding and
374 complying with complex requests and that the collaboration with adults was improved. Overall,
375 children seemed more communicative and more relaxed. Finally, related to auditory attention, parents
376 noted that their children listened more carefully to adult' speech, that they tend to apply during
377 speech and occupational therapies the listening strategies learned during MT and that they paid more
378 attention to music outside the MT therapy. Some children spontaneously started singing songs to
379 their parents. May be most importantly, parents noted that their children were very happy to go to the
380 music therapy sessions.

381 The positive aspects noted by the parents of children in the control group ($n=3$) were mainly related
382 to social behavior (e.g., improved verbal and nonverbal communication, increased contact with other
383 children and adults). Finally, two parents (from one child in MT group and from one child in control
384 group) also mentioned negative aspects related to increased irritability in their children, possibly
385 because children were taking new anti-epileptic medications.

386 **3.2. Evaluation of children in the experimental MT group**

387 **Behaviour:** the music therapist did evaluate the level of performance of the children at Week 1
388 ($n=17$), Week 4 ($n=17$) and at Week 8 ($n=9$) on five psychological scales related to motor ability,
389 attention, emotional behaviour, imitation and communication. Using pairwise Sign tests, results
390 revealed significant improvements from Week 1 to Week 4 on all dimensions (all $p<0.005$,) and
391 from Week 1 to Week 8 (all $p<0.04$) but only marginally significant improvements from Week 4 to
392 Week 8 (all $p<0.08$; see Table 2).

393 Using Kruskal Wallis tests, results showed that the main effect of Session was significant for each
394 dimension ($p<.001$, see Table 2). Moreover, results of post hoc Tukey HSD tests revealed that the
395 improvements from Week 1 to both Week 4 and Week 8 were significant for each dimension ($p<.05$)
396 but improvements from Week 4 to Week 8 were not significant ($p>.05$) except for the attention and
397 communication dimensions ($p<.05$; see Table 2).

398 **Specific music tests:** Three children could not perform either the rhythm reproduction tests or the
399 "musical" test. The rest were tested at Week 1 ($n=14$), at Week 4 ($n=14$) and at Week 8 ($n=9$).

400 **Rhythm reproduction test** (subtest of CUMANIN): Using pairwise Sign-tests, results showed that
401 the improvement was not significant from Week 1 (mean=0.43, Std=1.16, median=0) to Week 4
402 (mean=1.43; std=2.14, median=0; $z=1.22$, $p>.22$) and from Week 1 to Week 8 (mean=2.75, std=1.83,
403 median=2.50; $z=1.51$, $p>.13$). However, the improvement was significant from Week 4 to Week 8
404 ($z=2.27$, $p<.03$), that is for the subset of children ($n=9$) that remained longer.

405 Using the Kruskal Wallis test, results showed that the main effect of Session was significant
406 ($\text{ChiSq}(2) = 10.13$, $p<.007$). Results of post hoc Tukey HSD tests showed significant improvements
407 from Week 1 (0.43) to Week 8 (2.75, $p<.05$). However, mean scores in Week 4 (1.43) were in
408 between and not significantly different either from Week 1 or from Week 8 (both $p>.05$).

409 **Explicit “musical” test:** Using sign tests, results showed increased level of performance from Week
410 1 (mean score = 23.57, Std = 11.48, median = 19.00) to Week 4 (mean score =34.00; std= 14.28,
411 median=29.50; $z=2.60$, $p<0.01$), from Week 1 to Week 8 (mean score =46.88, std=12.14,
412 median=47.00; $z=2.47$, $p<0.02$) and from Week 4 to Week 8 ($z=2.47$, $p<0.02$).

413 Using the Kruskal Wallis non parametric test, results showed that the main effect of Session was
414 significant ($\text{ChiSq}(2) = 12.17$, $p<.003$). Results of post hoc Tukey HSD tests showed significant
415 improvements from Week 1 to Week 8 ($p<.05$). However, mean scores in Week 4 were in between
416 and not significantly different from Week 1 or Week 8 ($p>.05$).

417 **Implicit “musical” test:** Using pairwise Sign-tests, results showed increased level of performance
418 from Week 1 (mean score=29.43, std=11.61, median=27.50) to Week 4 (mean score=41.21,
419 std=16.33, median=42.50; $z=2.77$, $p<.006$), from Week 1 to Week 8 (mean score=54.13, std=13.34,
420 median=53.50; $z=2.47$, $p<.02$) and from Week 4 to Week 8 ($z=2.47$, $p<.02$).

421 Using the Kruskal Wallis non parametric test, results showed that the main effect of Session was
422 significant ($\text{ChiSq}(2) = 11.49$, $p<.004$). Results of post hoc Tukey HSD test showed improvements
423 from Week 1 to Week 8 ($p<.05$). Again, mean scores in Week 4 were in between and not
424 significantly different from Week 1 or Week 8 ($p>.05$).

425 Finally, results of pairwise Sign-tests showed that implicit mean scores were higher than explicit
426 mean scores at Week 1 ($z=3.18$; $p<.0002$), Week 4 ($z=3.18$; $p<.0002$) and Week 8 ($z=2.47$; $p<.02$).
427 Results of the Kruskal Wallis test also showed that mean scores in the implicit musical test were
428 significantly higher than mean scores in the explicit test ($\text{ChiSq}(1) = 4.32$, $p<.04$).

429 **3.3. Correlation analyses between different instruments**

430 To determine whether results at the different scales and questionnaires employed in our study were
431 correlated, we compared scores at Week 1 and at Week 4 using one-tailed Spearman correlation
432 coefficient. Importantly, results revealed significant correlations between the social behavior subscale
433 of the parent’s interview and the subscales of the occupational therapy questionnaire: social behavior
434 ($p=0.009$), emotional behavior ($p=0.04$) and motor behavior ($p=0.05$). Thus, the improvements noted
435 by the parents were in agreement with the ratings of the occupational therapists. Turning to results in
436 the MT group, scores on emotional behavior were significantly correlated in MT performance and
437 speech therapy subscales ($r=0.528$, $p=0.02$).

438 **3.4. ERPs data**

439 Close examination of the ERPs data revealed large inter-individual variability which was expected
440 due to the heterogeneity of the various brain lesions and neurological disorders of the children tested
441 in this study. No clear pattern emerged from a quantitative comparison of the experimental and
442 control group. Nevertheless, on the basis of visual inspection of the data, two suggestive patterns

443 emerged, independently of whether children belonged to the experimental or to the control groups:
444 For a group of children, called the “P250 responsive group”, ERPs were more positive between 200
445 and 300 ms post-stimulus onset (P250 component) after the neuro-restoration and MT programs than
446 before this intervention.
447 For the other group of children, called the “N300 responsive group”, ERPs were more negative
448 between 300 and 400 ms post-stimulus onset (N300 component) after the neuro-restoration and MT
449 programs than before this intervention.
450 Thus, we computed separate averages for these two sub-groups of children both in the experimental
451 and in the control groups.

452 For the P250 responsive group, as can be seen in Figure 1, the ERPs to standard stimuli and VOT
453 deviant stimuli overlap for the experimental and control subgroups before the start of the restoration
454 and MT programs. By contrast, after the programs, the amplitude of the P250 components elicited by
455 standard stimuli and VOT deviant stimuli were clearly larger in the experimental than in the control
456 group. The parietal scalp distribution of this positive component is an indication that this component
457 may belong to the P3 family (P3b) and may reflect increased auditory reactivity after the MT
458 program.

459 For the N300 responsive group, as can be seen on Figure 2, the pattern of results is quite different
460 from the P250 responsive group. Again, there is good overlap of the ERPs to standard stimuli and
461 VOT deviant stimuli in the experimental and control subgroups before the start of the restoration and
462 MT programs. By contrast, after the programs, a negative component peaking around 300 ms (N300)
463 developed after both standard stimuli and VOT deviant stimuli, with larger amplitude in the
464 experimental than in the control group.

465 While these observations are encouraging for further studies, the small number of children included
466 in the subgroups (from 3 to 6), precluded to conduct further analyses

467 **4. Discussion**

468 Overall results of this experiment showed that all children improved from Week 1 to Week 4 on the
469 three dimensions (motor, social and emotional behaviors) that were tested through the occupational
470 and speech therapies questionnaires. Children from the experimental MT group only differed from
471 children in the control group on the motor behavior dimension. Moreover, children in the MT group
472 showed improvements on the five dimensions (attention, emotion, imitation, communication and
473 motor behavior) of the psychological scales with larger improvements from Week 1 to Week 4 than
474 from Week 4 to Week 8. By contrast, overall results of the specific music tests (rhythm reproduction
475 and explicit and implicit “musical” tests) showed significant improvements from Week 1 to Week 8
476 but not from Week 1 to Week 4. Importantly, in the MT group and for the emotional dimension,
477 scores on the psychological scale were correlated with scores in the speech therapy questionnaire.
478 More generally, results of correlation analyses showed that the improvements noted by the parents
479 were correlated with those reported by the occupational therapist on the social, emotional and motor
480 behavior subscales. Finally, results of parents’ interviews revealed that they considered that MT had
481 a positive influence on their children motivation, sociability and auditory attention. These different
482 aspects are considered in turn in the following discussion.

483 Considering first results from the occupational and speech therapies questionnaires for all children
484 enrolled in the experiment, the finding of significant improvements from Week 1 to Week 4 on the
485 three dimensions that were tested (social, emotional and motor behaviors) shows the positive impact
486 of the neuro-restoration program implemented at the neuro-pediatric clinic of the CIREN. However,
487 one can argue that since the occupational and speech therapists were involved in the rehabilitation,
488 there is a potential bias toward obtaining positive results. While this may be the case, correlation

489 analyses showed that the improvements noted by the occupational therapist were correlated with
490 those reported by the parents (who tend to be more critical because of their high expectations
491 regarding the outcome of the program) on the social, emotional and motor behavior subscales. Even
492 if results converge in showing improvements on these dimensions, it will be important in future
493 experiment for children to be tested by occupational and speech therapists that are not directly
494 involved in the neuro-restoration program at CIREN.

495 Results from the occupational and speech therapies questionnaires revealed significant between-
496 groups differences for the motor behavior dimension with larger motor improvements in the MT
497 group than in the control group. The neuro-restoration program includes motor rehabilitation and all
498 children involved in the experiment were receiving this therapy to variable extents depending upon
499 their specific impairments. However, dancing (or moving any part of the body) was encouraged
500 during music therapy and children very much enjoyed this aspect. Thus, MT provided increased
501 motor training possibly linked to an increased motivation to move due to the entraining function of
502 music (e.g., salsa, tango etc...). These two effects may contribute to the further improvement found in
503 the MT group. This interpretation is in line with results of McIntosh et al. (McIntosh et al., 1997)
504 showing that music facilitates initiation of walking in Parkinson patients. Forsblom et al (Forsblom et
505 al., 2010) also showed that the stroke patients tested in their study considered music listening as
506 favoring engagement in motor activity. Based on these results, it would be useful to implement motor
507 rehabilitation programs associated with entraining musical pieces.

508 Turning to children in the MT experimental group, results also showed improvements on the five
509 dimensions (attention, emotion, imitation, communication and motor behavior) of the psychological
510 scales. Several results in the psychology of music and neuroscience of music literature have shown
511 that music training is associated with increased attentional abilities (Tervaniemi et al., 2009); see
512 Besson et al. (2011) for a review). For instance, recording brain electrical activity and analyzing
513 ERPs, Marie (Marie et al. 2011) reported shorter latency and larger amplitude of ERP components
514 associated to categorization and decision processes (N2/N3 and P3b components, respectively) in
515 adult French musicians compared to nonmusicians in a same-different task on tone and segmental
516 variations in Mandarin Chinese. These results were interpreted as reflecting enhanced auditory
517 cognitive and attentional abilities in musicians. Similarly, Bauman (Baumann et al., 2007) showed
518 that focussed attention on sine wave tones was associated with an early negative component in
519 musicians but not in nonmusicians which again suggested that music training influenced top-down
520 attentional processes. Moreover, Särkämö (Särkämö et al., 2008) also reported enhanced focussed
521 attention in stroke patients after music listening. While fewer studies have been conducted with
522 children, Chobert (Chobert, et al. , 2011) reported enhanced preattentive processing of French
523 syllables varying in pitch, duration and VOT in musician than in nonmusician children.

524 The relationship between music and emotion has been extensively studied and it is common
525 knowledge that different types of music can induce different emotions and mood. Importantly, and as
526 mentioned in the introduction, Forsblom (Forsblom et al., 2010) found that music listening
527 contributed more than audiobook listening to recovery and positive mood changes in stroke patients
528 and Särkämö (Särkämö et al., 2008) showed that only music listening prevented depression in the 6
529 months following the stroke. Moreover, Narme (Narme et al., 2012) showed that music interventions
530 were associated with larger improvements in emotional states than painting or cooking interventions.
531 Similarly, Särkämö and collaborators (Särkämö et al., 2013) showed positive changes in the mood
532 and the quality of life of Alzheimer patients immediately after and 6 months after the music
533 intervention and Janata (Janata, 2012) reported reduced level of agitation and depression in
534 Alzheimer patients listening to music programs several hours per day. Finally, our results showed
535 that MT improved imitation and communication possibly because the music therapist encouraged
536 children to reproduce the movements that she performed on-line with the music (e.g., clapping hands

537 in rhythm with the music, rising hands or fingers or moving the head with melodic changes in the
538 musical excerpts, etc...). Children were also encouraged to share with each other's the emotions and
539 movements induced by the music.

540 However, and as discussed above for the results of the occupational and speech therapies
541 questionnaires, the music therapist was at the same time providing the MT interventions and filling
542 up the questionnaires to test for the results of the therapy. Even if the therapist performing the
543 therapy is probably the best person to evaluate changes in children's behavior because she worked
544 with them regularly three days per week, there is a potential bias toward obtaining positive results.
545 However, two sets of results provide evidence that such a bias is not the unique explanatory source.
546 First, correlation analyses showed that for the emotional dimension, scores on the psychological scale
547 were correlated with scores in the speech therapy questionnaire and the two therapists did not discuss
548 results together. Moreover, analyses of the parents' interviews also revealed that they considered that
549 MT had a positive influence on motivation, sociability and auditory attention. Second, results showed
550 larger improvements from Week 1 to Week 4 than from Week 4 to Week 8 which is not expected
551 based on the hypothesis of a positive bias toward "more music therapy better results". Note that the
552 reasons why the effects of MT were smaller during the second month of the intervention are unclear
553 but it may be that children tend to habituate to the music sessions with decreased positive effects of
554 MT with longer therapy. Based on these results, it would be of interest in future experiments to test
555 for the effect of an On-Off music therapy program (e.g., On for 4 weeks, Off for 2 weeks, On for 2
556 weeks...). It would also be important to compare the results obtained by the music therapist
557 performing the therapy and those obtained by another therapist not directly involved in the
558 rehabilitation program.

559 It is interesting to note that in contrast to results showing larger improvements from Week 1 to Week
560 4 than from Week 4 to Week 8 on the several dimensions of the psychological scales, results of the
561 rhythm reproduction test (CUMANIN) showed significant improvements from Week 1 to Week 8
562 but not from Week 1 to Week 4. Thus, a rather long period of training is necessary for the
563 improvement in rhythmic reproduction to be significant. The level of performance of the children in
564 Week 1 was 0.43, a score close to what reported for children with Down syndrome (0.36, SD= 0.50;
565 (Barba Colmenero & Robles Bello, 2012)). In the subset of children who stayed for 8 weeks, the
566 level of performance increased to 2.75 (SD= 1.83) which should not, however, be considered as
567 normal level (2.72, SD = 1.70) (Barba Colmenero & Robles Bello, 2012) because level 4 rather than
568 level 7 was considered as correct reproduction and some of the children were older than in the Barba
569 Colmenero 2012 study. That music therapy improved the reproduction of rhythmic patterns with
570 increasing complexity was expected based on several results showing that musicians are more
571 sensitive to several aspects of the music rhythmic structure than nonmusicians (e.g, (Vuust et al.,
572 2006). However, it is important that similar results can be obtained from children with severe
573 neurological impairments as those tested in the present study.

574 Turning to the "musical" test, results were somewhat different depending upon the statistical test that
575 was used to conduct the analyses (Sign-tests vs Kruskal Wallis tests). While results from the Sign-
576 tests revealed significant improvements from Week 1 to Week 4, results of the more conservative
577 Kruskal Wallis tests only showed significant improvements from Week 1 to Week 8. Thus, more
578 than one month of MT seems to be necessary for the children tested here to increase their sensitivity
579 to abrupt changes (i.e., a combination of timber, harmonic and melodic changes) in the musical
580 pieces. Finally, while similar results were obtained in the explicit and implicit music tests, mean
581 scores in the implicit test were higher, as expected, than mean scores in the explicit test.

582 In sum, results of this experiment are encouraging in showing effects of music therapy both on
583 specific music tests (rhythm reproduction and detection of timber, harmonic and melodic changes in
584 the musical pieces) and on more general aspects of the children behavior, in particular motor

585 behavior. In line with the literature, we used questionnaires to assess the effectiveness of music
586 therapy (Mrazova & Celec, 2010). However, two caveats are in order. First, while the questionnaires
587 that we used were built from questionnaires published in the literature (MacArthur-Bates Inventario I
588 and II, (Jackson-Maldonado et al., 2003); Escala autónoma Asperger-Autismo, (Belinchon et al.,
589 2008), they were not normalized with children without neurological problems. Second, our results are
590 based on the analyses of questionnaires filled by therapists actively involved in the neuro-restoration
591 program or the MT so that these measures may not be objective. Moreover, the use of questionnaires
592 may not be sensitive enough to detect subtle changes in the children's behavior. However, because
593 the group of children involved in this program was very heterogeneous, including children with
594 different types of brain damage and diverse etiologies (see methods and Table 1), it was not possible
595 to find an experimental test that can be performed by all of them. Moreover, the number of children
596 was not sufficiently larger to allow making subgroups of children with similar neurological problems.
597 In an attempt to find an objective measure of the influence of the neuro-restoration and MT
598 programs, we analyzed the ERPs from a subset of children at Week 1 (evaluation week) and at Week
599 4 (end of the neuro-restoration and MT programs). While the sample of children was too small to
600 compute statistical analyses and to draw firm conclusions from these data, they nevertheless lead to
601 interesting observations. First, while individual averages were highly variables from one child to the
602 other, it was nevertheless possible to note differences between Week 1 and Week 4. Furthermore, in
603 some children it was also possible to detect the type of deviants they were more sensitive to. While
604 these individual differences are difficult to quantify, it is our hope that new methods are developed
605 for analyzing clinical data (e.g., (Aarts et al., 2014) and for allowing the use of electrophysiological
606 measures as biomarkers of the prognosis and the efficacy of the therapeutic intervention. Second,
607 even if the individual data were variable, it was nevertheless possible to identify two sub-groups of
608 children with similar patterns of results (i.e., the P250 responsive group and the N300 responsive
609 group). While the small number of children in these subgroups precluded further analyses, these
610 between-group differences are encouraging us to collect more data in this experimental design.
611 In conclusion, results of this study provided clear indications that MT had a positive influence on
612 motor behavior, possibly because the children in the MT group benefitted from the entraining and
613 motivational effects of music. Moreover, they are encouraging in showing that the use of different
614 methodologies based on the analyses of questionnaires, specific tests and recording of the ERPs
615 provide complementary information on the efficiency of the neuro-restoration and MT programs.

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760 **7. Figure legends**

761 **Figure 1.Sub-averages for the “P250 responsive group”**. ERPs elicited by Standard stimuli (left
762 side) and deviant stimuli in Voice Onset Time (VOT) before and after rehabilitation are compared in
763 the Control (blue trace) and Experimental (red trace) groups. After rehabilitation, the amplitude of
764 the parietally-distributed P250 component was larger in the Experimental than in the Control group.
765 Time is in abscissa and the amplitude of the effects is in ordinate in microvolt (μV).

766 **Figure 2.Sub-averages for the “N300 responsive group”**. ERPs elicited by Standard stimuli (left
767 side) and deviant stimuli in Voice Onset Time (VOT) before and after therapy are compared in the
768 Control (blue trace) and Experimental (red trace) groups. After rehabilitation, amplitude of the
769 frontally-distributed N300 component was larger in the Experimental group than in the Control
770 group.

771 8. Tables

772 Table 1. Clinical Characteristic of the Children

Patient/gender	Age	Nationality	Type of disease	Expressed by	MRI	EEG/ MMN	ABRs
Experimental Group							
D.F./f	6.85	Argentina	SLCNS	Cognitive Deficit	Dysplasia in left temporal region	EA /MMN	Ok
A.J./f	9.93	Chile	SLCNS	Cerebral Palsy	Cortical atrophies in insular region. Vascular lesion at left occipito- mesial area. Lesion at caudate nucleus	MMN	Abn.
A.E.V. */f	9.22	Mexico	SLCNS	Cognitive deficits	Bilateral atrophy of hippocampus.	Abn /MMN	Ok
C.A.P./m	8.79	Mexico	SLCNS	Spastic Cerebral Palsy	Cortical heterotopias deforming lateral ventricles at oval centers. Hypoxia signs.	MMN	Abn.
Y.D./m	5.43	Venezuela	SLCNS	Cerebral Palsy	Left fronto-parietal sulci absents	EA /MMN	Abn.
A.Y.H./m	7.67	Venezuela	SLCNS	Cerebral Palsy	Subcortical lesions adjacent to upper lateral ventricles. Mild bilateral hippocampal atrophy. Pineal gland cyst.	MMN	Ok
B.A.A. */f	11.6	Mexico	SLCNS	Cerebral Palsy	Cortical heterotopias deforming lateral ventricles. Right frontal atrophy.	MMN	Ok
D.A. */m	8	Mexico	Neurodevelopment Disorder	Non-verbal Learning Disability	Mild right fronto-temporal atrophy	EA /MMN	Ok
C.G.*/m	4	Mexico	SLCNS	Language impairment	Ok	MMN	Ok
A.H.H./m	3.2	Venezuela	SLCNS	Cerebral Palsy	Hypoxic lesions in peri- ventricle areas	MMN	Ok
S.C./m	3.1	Venezuela	SLCNS	Cerebral Palsy	Subcortical lesions adjacent to lateral ventricles. Mild atrophy left temporal lobe. Hypoplasia Corpus Callosum	MMN	Ok
X.B.L. */f	7	Mexico	SLCNS	Cognitive deficit	Ok	Abn/ MMN	Ok
A.S.N./f	6	Venezuela	Spinal Cord Lesion	Paraplegia	Ok	No	Ok
L.Y.T./f	11	Venezuela	Idiopathic Dystonia		Cortical atrophy (temporal lobe). <i>Cavum vergae</i> . Brainstem hypoplasia	No	Ok
M.S./m	7	Angola	Neurofibromatosis		Tumor. Frontal atrophy.	EA	Abn.
D.F.*/m	4.2	Mexico	SLCNS		Bilateral atrophy hippocampus.	EA	Ok
O.E.T.*/m	5.8	Mexico	ASD		Left occipital lesion related to heterotopia area	EA	Abn
Control Group							
D.N.Q./f	9.48	Venezuela	SLCNS	Cerebral Palsy	Cortical atrophy. <i>Cavum vergae</i> .	Ok/ MMN	Ok
A.J.B./m	12	Venezuela	Spinal Cord Lesion	Paraplegia	Ok	No/ MMN	Ok
E.C./m	4.71	Mexico	SLCNS	Cognitive deficits	Left occipital lesion (heterotopia)	EA /MMN	Ok
S.G.*/f	3.99	Mexico	ADS	Rett Syndrome	Mild cortical atrophy more evident at temporal lobes.	EA /MMN	Abn
J.P.M./m	3.95	Venezuela	SLCNS	Cerebral Palsy	Periventricular heterotopias	MMN	No
K.P.R.*/f	9.64	Mexico	SLCNS	Cerebral Palsy	Ok	SW /MMN	Ok
L.A.C./m	3	Venezuela	SLCNS	Cerebral Palsy	Periventricular heterotopias. Corpus Callosum hypoplasia		No
A.A.M.*/m	4.96	Mexico	SLCNS	Language Disorder	Diminished cranial diameter. Temporal Operculum atrophy	EA	Ok
E.H.S./m	12	Mexico	SLCNS post surgery	Cognitive Deficit	Generalized cortical atrophy. Hypoxic lesion at basal ganglia	Abn.	Abn
J.P.R.*/m	4.6	Mexico	SLCNS	Cerebral Palsy	Periventricular heterotopias	EA	ok

773 SLCNS: Static Lesions of the Central Nervous System (when not explicit is by prenatal and/or perinatal causes); ASD: Autistic
774 Spectrum Disorder. ABRs: Auditory Brainstem responses. * = quit after 4 weeks. Sex f=feminine, m=masculine. EEG/MMN:
775 EA indicates Epileptiform abnormalities, SW: predominant slow waves, Abn: abnormal EEG or ABRs.

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777

778 **Table 2.** Results of questionnaires related to five dimensions administered in the MT group. Means,
 779 Standard deviations (STD) as well as p-values from the non-parametric Kruskal-Wallis test and from
 780 post hoc Tukey HSD tests (correcting for multiple comparisons) are reported to compare scores in
 781 Week 1 (17 children), Week 4 (17 children) and Week 8 (9 children).

Item	Week 1		Week 4		Week 8		K-W ChiSq(2)(pval)	W1 vs. W4	W1 vs. W8	W4 vs. W8
	Mean (STD)	Median	Mean (STD)	Median	Mean (STD)	Median				
Motor ability	1.95 (0.39)	1.79	3.42 (0.80)	3.38	4.48 (0.52)	4.63	30.01 (<4e-07)	<0.05	<0.05	> 0.05
Attention	1.69 (0.48)	1.83	3.17 (1.10)	3.17	4.64 (0.55)	4.88	26.63 (<2e-06)	<0.05	<0.05	<0.05
Affection	2.74 (0.75)	3.20	3.77 (0.70)	3.88	4.60 (0.64)	4.99	21.69 (<2e-05)	<0.05	<0.05	> 0.05
Imitation	1.45 (0.40)	1.67	3.73 (0.71)	3.95	4.58 (0.58)	4.75	33.81 (<5e-08)	<0.05	<0.05	> 0.05
Communication	1.58 (0.48)	1.75	2.85 (0.98)	3.10	4.45 (0.64)	4.75	26.94 (<2e-06)	<0.05	<0.05	<0.05

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Figure 1.TIF

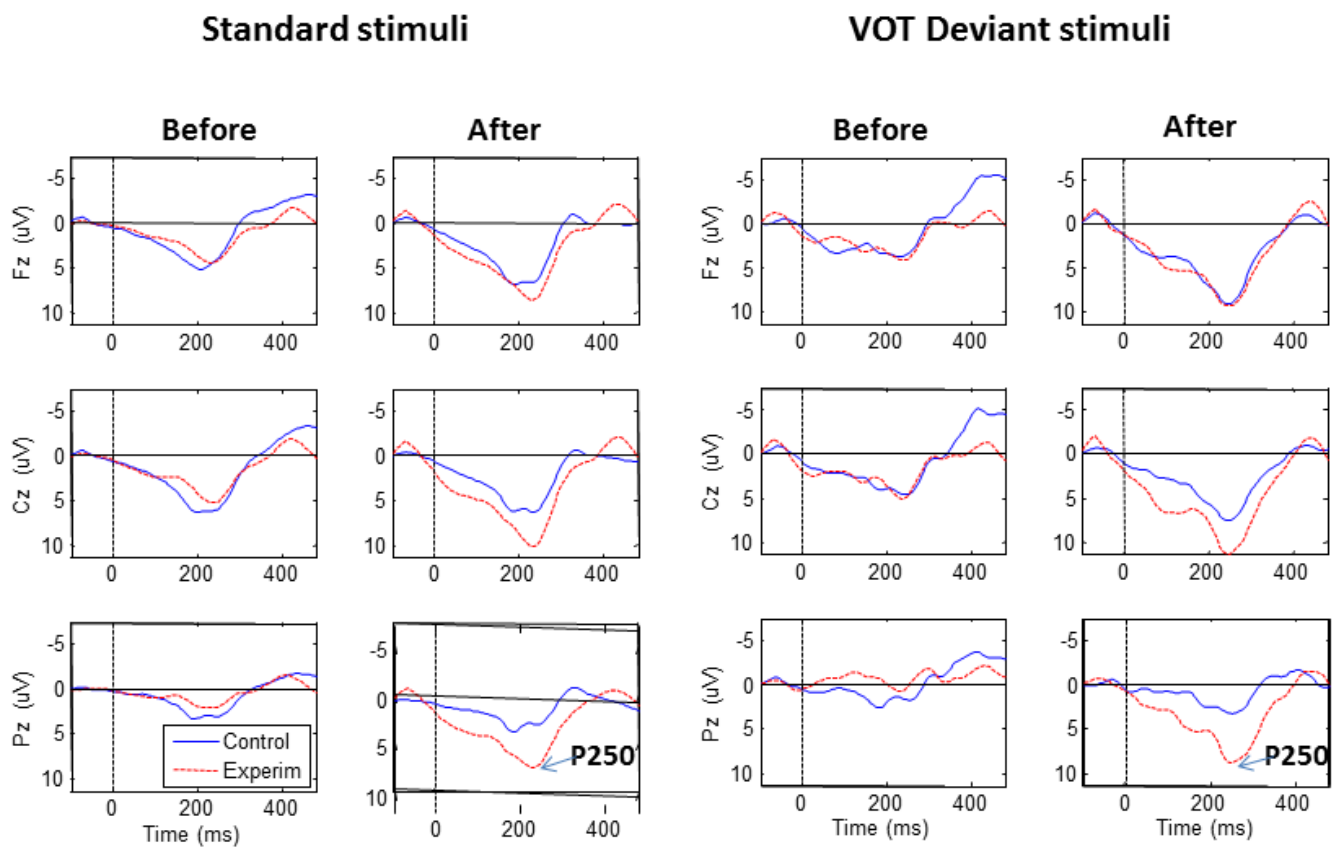


Figure 2.TIF

