Psychiatria Danubina, 2019; Vol. 31, Suppl. 3, pp 467-474 *Conference paper*

THE EFFECT OF MOZART'S MUSIC IN SEVERE EPILEPSY: FUNCTIONAL AND MORPHOLOGICAL FEATURES

Chiara Bedetti[1], Massimo Principi[2], Antonio Di Renzo[2], Marco Muti[3], Domenico Frondizi[4], Massimo Piccirilli[1,5], Patrizia D'Alessandro[1], Moreno Marchiafava[1], Antonella Baglioni[1], Marina Menna[1], Marilena Gubbiotti[1] & Sandro Elisei[1,6]

[1]Serafico Institute, Assisi, Perugia, Italy
[2]Neuroradiology Unit, "Santa Maria" Hospital, Terni, Italy
[3]Sanitary Physics Unit, "Santa Maria" Hospital, Terni, Italy
[4]Department of Neurosurgery and Neuroscience, "Santa Maria" Hospital, Terni, Italy
[5]Department of Experimental Medicine, University of Perugia, Perugia, Italy
[6]Department of Philosophy, Social and Human Sciences and Education, University of Perugia, Perugia, Italy

SUMMARY

Music is a very important factor in everyday life, involving mood, emotions and memories. The effect of music on the brain is very debated. Certainly, music activates a complex network of neurones in auditory areas, mesolimbic areas, cerebellum and multisensory areas. In particular, music exerts its effects on the brain of patients with epilepsy, having a dichotomous influence: it can either be seizure-promoting in musicogenic epilepsy or antiepileptic. Several studies have shown that seizure-prone neural networks may be stimulated by certain periodicities while other frequencies may prevent seizure activity. There are a lot of data in the literature about the so-called "Mozart effect" (Rauscher et al. 1993). In previous studies we observed that in institutionalized subjects with severe/profound intellectual disability and drug-resistant epilepsy, a systematic music listening protocol reduced the frequency of seizures in about 50% of the cases. In this study we are conducting a survey on the observation of what happens to the brain of patients suffering from drug-resistant epilepsy through electroencephalographic investigations, brain MRI and behavioural analysis before and after six months of listening to Mozart music (Sonata K.448). The first step is to present the data of the first patient under investigation.

Key words: *EEG - epilepsy - intellectual disability - autism - MRI*

* * * * *

INTRODUCTION

Data literature has revealed much evidence supporting the positive effects of music in neurological disease, including Parkinson's disease, senile dementia, sleep disorder, depression and epilepsy. Since 1952 Gheerbrant found a relaxant effect in Mozart's music on native Indians during his expedition to the Amazon region (Gheerbrnat 1952). Since then, many reports have been published on the effects of Mozart' music, named "Mozart effect" (Rauscher et al. 1993). The expression "Mozart effect" refers to an increase or normalisation of higher brain function associated with listening to Mozart's music (Grylls et al. 2018). In epilepsy this effect was first characterised by Hughes et al, who observed a decrease in electroencephalographic epileptiform activity in 23 patients out of 29 while they were listening to Mozart's music (Hughes et al. 1998). After this work some authors have studied electroencephalographic activity before, during and after listening Mozart's Music (Turner et al. 2004) and its effects on the seizure frequency in children (Lin et al. 2010, Lin et al. 2011, Grylls et al. 2014, D'Alessandro et al. 2017, Bedetti et al. 2019). Regarding seizure frequency, a randomized controlled study carried out over 24 months in children with initial unprovoked seizures revealed that those children who were under musical treatment had a 76.8% reduction in epileptic seizures compared to the 37.2% reduction of the children in the control group (Lin et al. 2014). Studies of Lin et al. have confirmed previous sporadic and anecdotal observations (Lahiri & Duncan 2007, Kuester et al. 2010) and overall have stimulated further investigations on this subject.

Understanding why music, and in particular Mozart's music, have this positive effect is very difficult.

Data literature shows that music listening improves neuronal connectivity in specific brain regions and musical activities promote neural plasticity and induce grey and white matter changes in multiple brain regions, especially frontotemporal areas (Wan et al. 2010, Schlaugh et al. 2015, Vaquero et al. 2016).

The approach to music, both as a passive listening activity and as direct use of musical instruments, is able to influence the functionality of numerous brain areas. From several studies in literature we can see the involvement of brain areas that go beyond the classical structures connected to sensory perception (Habibi et al. 2018), in particular the structures appointed to interconnect intra-and inter-hemispheric brain areas to be called into question (Moore et al. 2014), including the corpus callosum (Schlaug et al. 1995, Lee et al. 2003).

Among the mechanisms that can explain this link with music and the development of brain structures dedicated to interconnection, we find not only the activation of the areas assigned to perception and secondary integration to musical listening, but also the ones for the activity of "abstraction" of the emotional meaning that the brain performs in response to the complex auditory stimulus (Sachs et al. 2018).

Musical processing involves a complex network of neurones in auditory areas, mesolimbic areas, cerebellum and multisensory areas, so music can be used in the fields of cognitive neuroscience, auditory perception, memory, sensorimotor processing, brain plasticity and mirror neuron system. The brain, like music, generates waveforms that may create harmony or disharmony (Maguire 2016).

Mozart's music in particular seems to act through different mechanisms. Studies on the organisational structure of the neocortex of the brain showed that nerve cells are highly structured in longitudinal cell columns, forming an organisational unit (Mountcastle 1957, Rakic 1988). Hughes et al. noted that Mozart's music is also highly organized (Hughes et al. 1998), with a unique, repetitive structure. Considering that the cerebral cortex and Mozart's music have a similar arrangement, they may communicate to each other, normalising the suboptimal functioning of the cortex (Liao et al. 2015).

Mozart's music, compared to that of other composers, shows long-term periodicity, so melody repetition is more frequent than in other musical works (Hughes 2001). These characteristics may resonate with the structure of the cerebral cortex (Liao et al. 2015).

Other authors suggested that mirror neurons are involved in the antiepileptic effect, activating through music listening and regulating neuronal activity (Molnar et al. 2006, Buccino et al. 2005).

Lin et al. observed that, in sixty-four epileptic children, there was a significant reduction of epileptiform discharges during and right after listening to Mozart's music (sonata K448 and K545); at the same time, in the majority of the patients, a reduction in heart rate was observed representing the autonomic function; so the authors conclude that there is a possible increase in parasympathetic tone during the exposure to music (Lin et al. 2013).

Dopamine may also play a role in the effect of music on epilepsy. Reflex epilepsy and in particular musical epilepsy are connected to the other side of the effect that music can have on the brain. This phenomenon can be explained by the different roles of dopamine receptors: the D2 receptors activation is associated with an anti-epileptic effect, the activation of selective D1 receptors lowers the seizure threshold and induces epilepsy (Al-Tajir & Starr 1990).

Taking into consideration everything that has been said, this work aims to verify whether after an intervention with Mozart's music (sonata K448) we can identify changes in seizure frequency through EEGs, in the brain structure and functionally through brain MRI and on the behavioural level through the administration of specific scales.

For this survey the model is communicated by describing a single case report.

SUBJECT AND METHODS

This project has been approved by the Ethics Committee of the Umbria Region (prot. Number 13236/18/ESS). An informed consent form was signed before the study began. A 27-year-old boy affected by profound intellectual disability, QI=20 evaluated by Vineland II (Sparrow et al. 2005), autism spectrum disorder, intermittent explosive disorder, drug-resistant epilepsy with atonic and tonic-clonic seizures (EEG characterized by very frequent and generalised epileptiform discharges), microcephaly, facial and limbs dysmorphisms. Figure 1 shows a brain MRI of the patient characterised by a reduction of the cranium diameters, diffuse cortical atrophy, dysmorphic corpus callous (reduced volume at the level of the body), malacic areas in the frontal and occipital lobes bilaterally, reduced representation of the subcortical white matter, slight left ventricular prevalence.

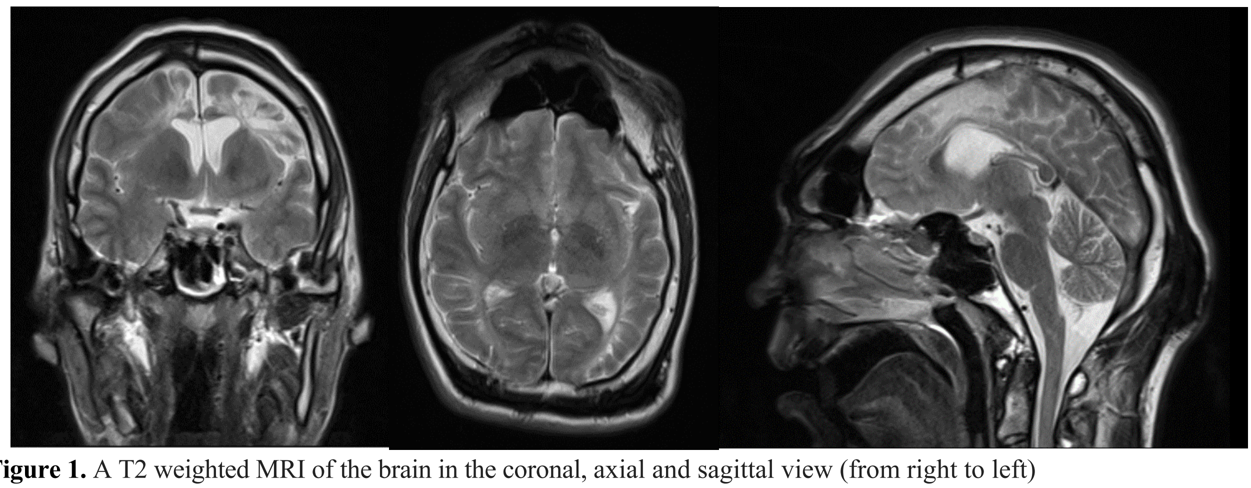

Figure 1. A T2 weighted MRI of the brain in the coronal, axial and sagittal view (from right to left)

He was subjected to EEG (duration: 180 minutes in the waking state) and brain MRI before (baseline: T0) and after (T1) a six-months-long period of listening to music 30 minutes a day (Mozart's piano sonata K448). Then we detected differences in epileptiform activity and in brain MRI between baseline and T1. Even the seizure frequency (seizure/month) had been monitored 6 months before and during the 6-months-period of listening to music. For the behavioural aspects we used the Brief Psychiatric Rating Scale (BPRS) and the Modifies Overt Aggression Scale (MOAS).

As regards changes on the EEG, we programmed the measurement of the number of epileptic discharges between an exam performed before the music period and an exam performed immediately after the music period. The seizure frequency has been calculated like total of seizures 6 months before compared with total of seizures during the music period of 6 months listening to Mozart. We also measured the monthly average in the number of seizures of the previous six months and of the six months during music listening.

To perform the MRI it was necessary to sedate the patient with midazolam 0.35 mg/Kg mg i.v. and then with propofol (2 mg/Kg i.v. for the induction and 8 mg/Kg/h for maintenance).

The two brain MRI exams were obtained using a Siemens (Erlangen, Germany) 3T Verio MRI scanner with a 12-channel head coil. Anatomical images were obtained using a T1-weighted sagittal magnetisation-prepared rapid gradient echo (MPRAGE) series (repetition time [TR] 1900 ms, echo time [TE] 2.52 ms, slice thickness 1 mm), from which it was obtained a linear volumetric measurement of the dimensions of the corpus callosum. We followed the Hofer's criteria which divided the corpus callosum into 5 sections/regions: region I as the most anterior segment covers the first sixth of the corpus callosum and contains fiber projecting into the prefrontal region; the rest of the anterior half of corpus callosum is region II, which contains fiber projecting to premotor and supplementary motor cortical areas. Region III was defined as the posterior half minus the posterior third and comprises fiber projecting into the primary motor cortex; region IV, the posterior one-third minus posterior one-fourth refers to primary sensory fiber. Callosal parietal, temporal and occipital fiber cross the corpus callosum trough region V which is defined as the posterior one-fourth (Hofer & Frahm 2006), (Figure 2).

The DTI sequence was acquired using a single shot echo planar imaging with a 12-channel head coil (TR 12200 ms, TE 94 ms, 2 mm thickness, isotropic voxels) from the foramen magnum to the vertex (whole brain acquisition). The diffusion gradients were applied along 30 non-collinear directions with two effective b values: 0 and 1000 s/mm2. Image data processing was performed with the FSL 6.0 software package (FMRIB Image Analysis Group, Oxford, UK).

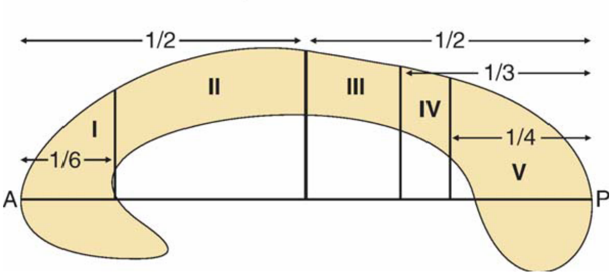

Figure 2. Sagittal section of the corpus callosum and subdivision into its functional components, according to Hofer's criteria (Hofer & Frahm 2006).

Diffusion data were corrected for motion and distortions caused by eddy current artifacts; the FMRIB's Diffusion Toolbox was used for local fitting of diffusion tensors. Two regions of interest (ROI) were defined for each exam (pre and post-music period): the first one included the entire corpus callosum displayed on the sagittal anatomical image, with a thickness of 6 mm on the midline; the second one included only the V portion of the corpus callosum, region made up of callosal parietal, temporal and occipital fiber (Hofer et al. 2006), with the same thickness on the midline. For each ROI the average FA and MD with the respective standard deviation (SD) were calculated with FSL. The first measurement was made the day before the beginning and the second was made the day after the end of the six months of music listening. A measurement of the tractography from the corpus callosum was also performed before and after the music period.

For the behavioural aspects we used the Brief Psychiatric Rating Scale (BPRS) that is a rating scale which may be used to measure psychiatric symptoms (24 items) such as depression, anxiety, hallucinations and unusual behaviour; each of the 24 items is rated 1-7, in an increasing order of gravity. The scale is one of the oldest, most widely used scales to measure psychotic symptoms (Overall & Gorham 1962). We also used another method for the evaluation of the behaviour, in particular the aggressive one, which can be performed through the use of an internationally validated scale, which is the Modified Overt Aggression Scale (MOAS), a versatile and prompt compilation tool for the caregiver and for health professionals. It evaluates four different forms of aggressiveness (verbal, physical towards objects, physical towards third parties, physical towards oneself) (Yudofsky et al. 1986).

Professional cares assessed the behaviour of the patients through blinded administration of these scale both before and after the musical listening period.

RESULTS

There was a significant decrease in the frequency of generalized epileptiform discharges on 180 min-awake-EEG performed on the last day of listening to music (160) compared to the 180 min-awake-EEG performed

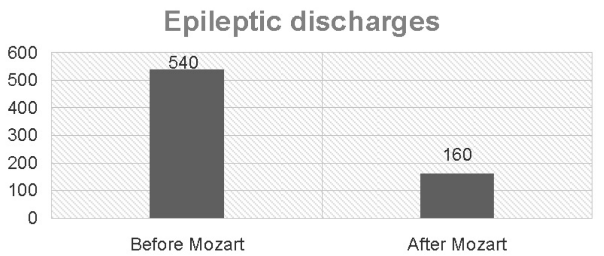

Figure 3. Comparison of the number of epileptic discharges counted manually through the 180 min-awake EEG performed the day before the beginning of period of listening to music (Before Mozart: equal to 540) and the last day of the period of listening to music (After Mozart: equal to 160)

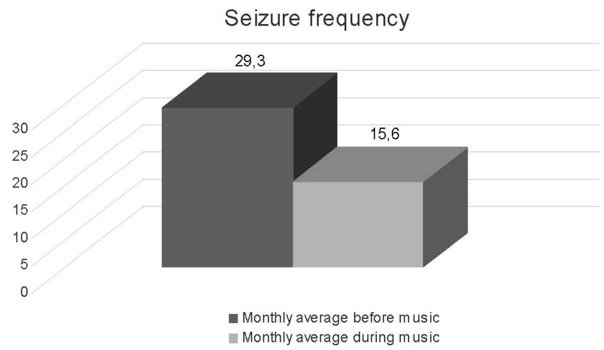

Figure 4. Seizure frequency: monthly average of seizures comparing the 6 months before (black column) and during (grey column) the period of listening to Mozart's music

the day before the beginning of listening to music (540). Epileptic discharges were counted manually (Figure 3). During the music listening period no pharmacological changes have been made.

The total number of seizures in the 6 months prior to listening to music was 176, while that of the six months during which the patient was listening to music was 94 (a reduction of 46.6%).

As shown in figure 4 even the seizure frequency (calculated as a monthly average in the 6 months before and during music listening) presents a marked reduction with a 6 month average percentage of reduction of 53.4%.

In particular, tonic-clonic seizures have been reduced to a greater extent than atonic ones, respectively 54.1% and 29.7% (Figure 5).

The analysis through brain MRI consists in calculating the volume of the corpus callosum according to a linear model, that divides the structure in 5 regions according to Hofer's criteria based on the connections between different areas. The same measurement was made before and after the musical listening period (Table 1).

Table 1 shows how the linear volumetric measurements of the corpus callosum are substantially unchanged between the T0 control and the T1 control.

The volumetric analysis of the corpus callosum was also conducted through the definition of Region of Interest (ROI) contouring the corpus callosum on a brain sagittal image and obtaining a measurement of fractional anisotropy (FA) and mean diffusion (MD) for a thickness of 6 mm for both the whole structure of corpus callosum and only the V portion. The same measurement was made before and after the musical listening period (Table 2).

The Corpus callosum data showed in Table 2, detect a reduction in FA and an increase in MD for both the whole corpus callosum and only its V portion.

The corresponding images obtained through DTI before the listening to music period (Figure 6) and after the listening to music period (Figure 7) provide a visual feedback of the performed study.

The behavioural aspects were assessed using two scales: the BPRS and the MOAS. The first, 24 items scale, useful to evaluate psychiatric symptoms such as elation/euphoria, agitation/aggression, irritability/lability and unusual behaviour; each of the 24 items is rated 0-7, where 0=not assessed, 1=absent and 2-7 in increasing order of gravity. The second scale measures the aggressiveness of the patients (verbal, physical towards objects, physical towards third parties, physical towards oneself) giving a score from 0 to 4 with increasing gravity.

Table 1. Corpus callosum measurement according to Hofer's criteria (Hofer & Frahm 2006), which divides the structure into 5 regions based on the connections within the different brain areas. The table shows the values of the 5 sections before and after the period of music listening

Corpus callosum sections	I	II	III	IV	V
Before music	9.5	19.1	9.5	4.7	14.3
After music	9.5	19.1	9.5	4.8	14.3

Table 2. Region Of Interest (ROI) for the volumetric measurement of the corpus callosum and of the only V portion expressed in average (Mean) and standard deviation (DS). FA=fractional anisotropy. MD= mean diffusivity

	Before Music		After Music	
	Mean	DS	Mean	DS
ROI Corpus callosum (whole)				
MD	0.001397	0.000566	0.001538	0.000866
FA	0.366932	0.240215	0.253316	0.101850
ROI Corpus Callosum (V posterior)				
MD	0.001299	0.000393	0.002398	0.000537
FA	0.472133	0.214866	0.306006	0.119977

Table 3 shows a reduction (from 88 to 73 equal to 17.1%) in the total score of the BPRS after the period of music listening. Considering the individual scores a reduction was observed for the items: hostility (from 7 to 5), elevated mood (from 6 to 5), bizarre behaviour (from 6 to 5), blunted affect (from 6 to 5), emotional withdrawal (from 6 to 5), tension (from 7 to 6), uncooperativeness (from 7 to 5), excitement (from 6 to 5), distractibility (from 6 to 4), motor hyperactivity (from 6 to 5), mannerism and posturing (from 7 to 6). Values equal to "0" were assigned based on the severity of the patient's intellectual state which does not allow the evaluation of these items. No items have increased.

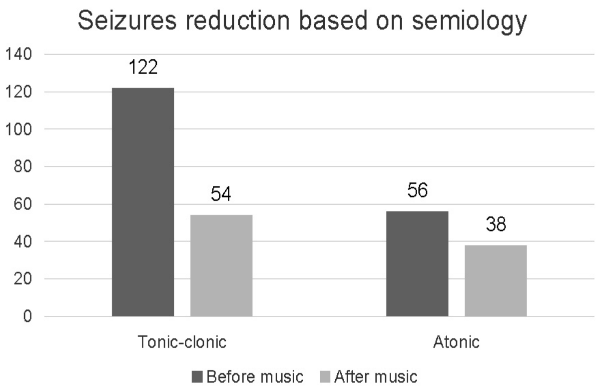

Figure 5. Reduction of seizures frequency in the six months before (black columns) and during (grey columns) music listening distributed by tonic-clonic and atonic semiology

Table 3. Single and total scores obtained from the administration of Brief Psychiatric Rating Scale (BPRS) before and after the period of listening to music

BPRS	Before Music	After Music
Somatic Concern	0	0
Anxiety	0	0
Depression	0	0
Suicidal	1	1
Guilt	0	0
Hostility	7	5
Elevated mood	6	5
Grandiosity	0	0
Suspiciousness	0	0
Hallucination	1	1
Unusual thoughts content	0	0
Bizarre Behaviour	6	5
Self Neglect	6	5
Disorientation	3	3
Conceptual disorganisation	6	6
Blunted affect	6	5
Emotional withdrawal	6	5
Motor Retardation	1	1
Tension	7	6
Uncooperativeness	7	5
Excitement	6	5
Distractibility	6	4
Motor hyperactivity	6	5
Mannerism and Posturing	7	6
Total	88	73

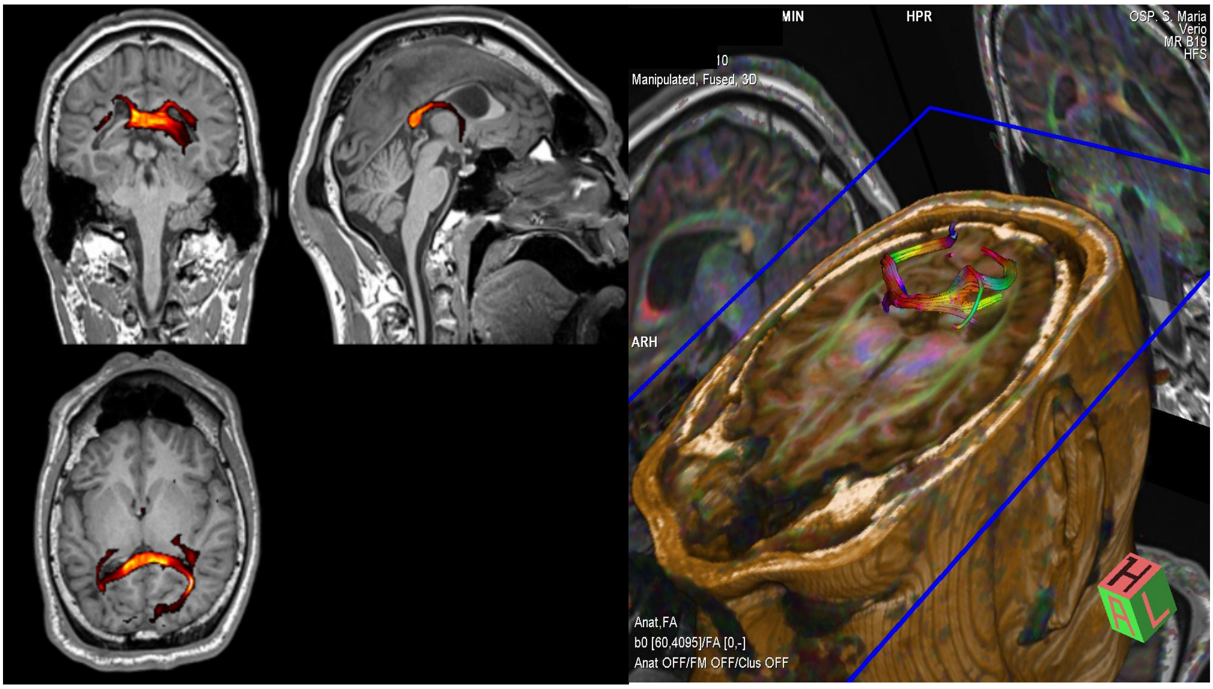

Figure 6. Pre-music MRI exam: to the left bundles of splenium fiber of the corpus callosum (DTI sequence: TR 1.22 ms; TE 94 ms; thk 2 mm; directions: 30), superimposed on anatomical images (3D T1-weighted images: TR: 1900 ms; TE: 2.52 ms; thk: 1 mm). On the right the 3D reconstruction

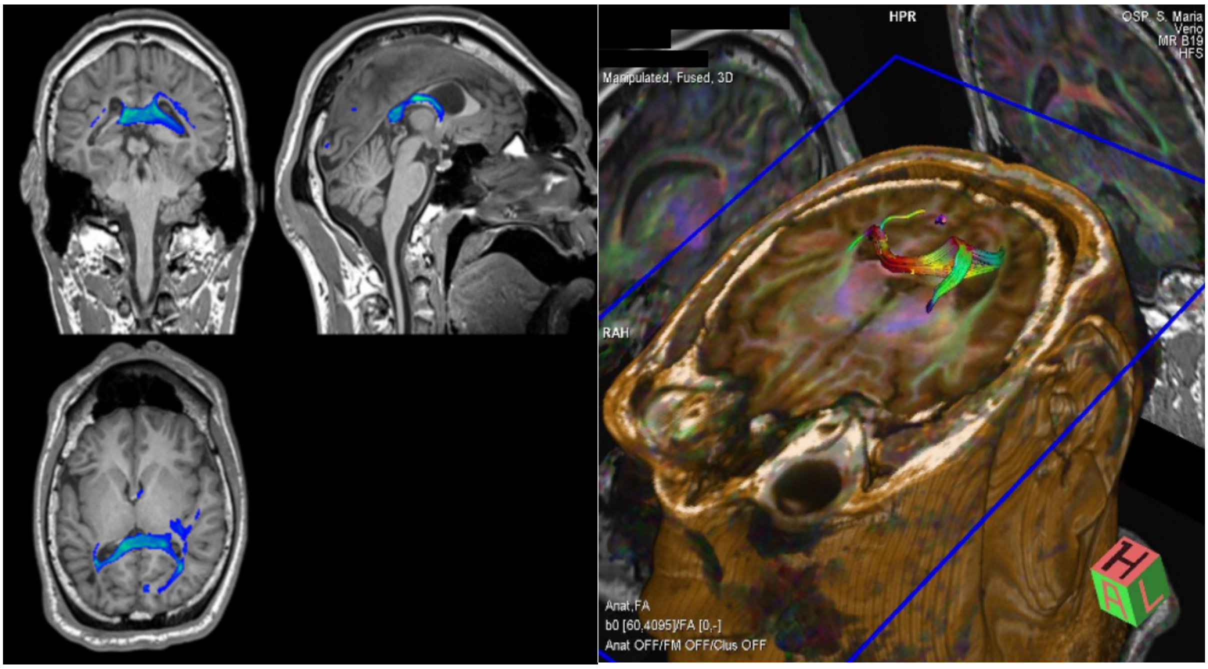

Figure 7. Post-music MRI exam: to the left bundles of splenium fiber of the corpus callosum (DTI sequence: TR 1.22 ms; TE 94 ms; thk 2 mm; directions: 30), superimposed on anatomical images (3D T1-weighted images: TR: 1900 ms; TE: 2.52 ms; thk: 1 mm). On the right the 3D reconstruction

Even the MOAS shows an improvement of behavioural aspects, in particular of the aggressiveness, which has been reduced by almost 50%, especially for the items of verbal aggression (from 4 to 2), aggression against property (from 2 to 1) and self-aggression (from 4 to 2) (Table 4).

Table 4. Single and total scores obtained from the administration of Modified Overt Aggression Scale (MOAS) before and after the period of listening to music

MOAS	Before Music	After Music
Verbal Aggression	4	2
Aggression against property	2	1
Self-aggression	4	2
Physical aggression	4	3
Total	14	8

DISCUSSION

The purpose of this work was to analyse what happens in the brain when Mozart's music (Sonata K448) is systematically administered, for a period of 6 months. This purpose has been achieved by carrying out assessments before and after the musical listening period. In particular we observed and analysed the electroencephalographic characteristics, the frequency of epileptic seizures, brain MRI data (volumetric measurement of the corpus callosum and its connections), and the behavioural aspects (through the administration of two scales: the BPRS and the MOAS).

The analysis of EEG aspects obtained by manual counting of generalized epileptic discharges between the track performed before and after the music listening session shows a marked reduction (70.4%) in line with the literature data that shows reduction in epileptic activity on the EEG, in particular of generalized ones, during and after the administration of Mozart's music (Turner et al. 2004, Lin et al. 2010, Lin et al. 2011, Lin et al. 2014, Grylls et al. 2014). Equally in agreement with the literature data, our research presents a reduction in the frequency of epileptic seizures during the 6 months of listening to music, in particular for tonic-clonic seizures, compared to atonic ones, notes for the poor response to pharmacological treatments (Kelley & Kossoff 2010).

Brain MRI data concerning the volumetric acquisitions of the corpus callosum show linear data that can be substantially overlapped between before and after listening music period, it is possible that the already damaged structure (atrophy of the body, MRI Figure 1), is not able to show significant variations, considering also that the presence of drug-resistant epilepsy contributes to the damage of brain structures such as the corpus callosum.

The measurement through FA and MD at T0 e T1 shows the reduction of FA and the increase of MD. This data can be interpreted in line with some network activity studies with analysis of FA and MD carried out on patients suffering from migraine, through which it is hypothesised that the reduction of FA reflects the shrinkage of neuronal and glial cells or the gain of directional organisation (Mandl et al. 2008, Coppola et al. 2014, Coppola et al. 2016). However these data obtained from the study of a single patient, with a strongly compromised cerebral development, are presented as an example and they cannot be attributed neither statistical nor clinical value yet. A correct interpretation can only be extrapolated when the analysis is conducted on the whole group of our patients.

The behavioural aspects show an improvement that mainly concerns the significant reduction of aggression (measured by the MOAS). Even trough the BPRS have highlighted a reduction of hostility, elevated mood, bizarre behaviour, blunted affect, emotional withdrawal, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerism and posturing. All aspects are very difficult to control in a patient with autism spectrum disorder and gain greater value even in the context of a relatively short follow-up period.

CONCLUSIONS

The study was designed to develop a method of investigation and presented the preliminary data of the first patient analysed. It shows very positive data and in line with the literature regarding the marked reduction of epileptic discharges to EEG after the listening period of the Mozart's music and the sharp reduction in the frequency of seizures during this period.

Brain MRI data need, for a correct clinical interpretation, the implementation of the sample, also in consideration of the gravity of the clinical picture studied.

The behavioural aspects showed a good outcome with reduction of aggressive behaviours and with reduction of motor stereotypes with the attainment of less distractibility and greater collaboration, after the listening to music period, in a patient with autism spectrum disorder.

Acknowledgements:

The authors wish to thank Lorenzo Buzzao, the professional carer of the Serafico Institute who accompanied with passion and professionality the patient on the diagnostic path and the Disabled Assistance Centre of the "Santa Maria" Hospital of Terni, in particular Donatella Perugini and Lorella Angeli who organized and lived the hospital journey of our patient.

Conflict of interest: *None to declare.*

Contribution of individual authors:

Chiara Bedetti, Massimo Piccirilli, Patrizia D'Alessandro & Domenico Frondizi: conception and preparation of the study.

Chiara Bedetti, Massimo Principi & Antonio Di Renzo: acquisition of data and their interpretation.

Antonella Baglioni, Marina Menna & Moreno Marchiafava: preparation of the study.

Sandro Elisei, Massimo Piccirilli, Marilena Gubbiotti, Antonella Baglioni & Marina Menna: revision of the manuscript.

References

1. *Al-Tajir G, Starr MS: Anticonvulsant action of SCH 23390 in the striatum of the rat. Eur J Pharmacol 1990; 191:329-36*
2. *Anderson JR, Jones BW, Yang JH, Shaw MV, Watt CB, Koshevoy Pet al.: A computational framework for ultrastructural mapping of neural circuitry. PLoS Biol 2009; 7:e1000074*
3. *Bedetti C, D'Alessandro P, Piccirilli M, Marchiafava M, Baglioni A, Giuglietti M et al: Mozart's music and multidrug-resistant epilepsy: a potential EEG index of therapeutic effectiveness. Psychiatr Danub 2018; 30(Suppl 7):567-571*
4. *Buccino G, Riggio L, Melli G, Binkofski F, Gallese V & Rizzolatti G: Listening to action-related sentences modulates the activity of the motor system: a combined TMS and behavioral study. Brain Res Cogn Brain Res 2005; 24:355-63*
5. *Coppola G, Tinelli E, Lepre C, Iacovelli E, Di Lorenzo C, Di Lorenzo G et al: Dynamic changes in thalamic microstructure of migraine without aura patients: a diffusion tensor magnetic resonance imaging study. Eur J Neurol 2014; 21:287-e13*
6. *Coppola G, Di Renzo A, Tinelli E, Di Lorenzo C, Di Lorenzo G, Parisi V et al: Thalamo-cortical network activity during spontaneous migraine attacks. Neurology 2016; 87:2154-2160*
7. *D'Alessandro P, Giuglietti M, Baglioni A, Verdolini N, Murgia N, Piccirilli M et al: Effects of music on seizure frequency in institutionalized subjects with severe/profound intellectual disability and drug-resistant epilepsy. Psychiatr Danub 2017; 29(Suppl 3):399-404.*
8. *Gheerbrnat A: L' expédition Orénoque Amazone, 1952 1st ed.Gallimard, Paris*
9. *Grylls E, Kinky M, Baggot A, Wabnitz C & McLellan A: Study of the Mozart effect in children with epileptic electroencephalograms. Seizure 2018; 59:77-81*
10. *Habibi A, Damasio A, Ilari B, Elliot Sachs M & Damasio H. Music training and child development: a review of recent findings from a longitudinal study. Ann N Y Acad Sci Epub ahead of print, 6 mar 2018*
11. *Hofer S & Frahm J: Topography of the human corpus callosum revisited - Comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuro Image 2006; 32:989–994*
12. *Hughes JR, Daaboul Y, Fino JJ & Shaw GL: The Mozart effect on epileptiform activity. Clin Electroencephalogr 1998; 29:109–19*
13. *Hughes JR: The Mozart effect. Epilepsy Behav 2001; 2:396-417*
14. *Kelley SA & Kossoff EH: Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. Dev Med Child Neurol 2010; 52:988-93*
15. *Kuester G, Rios L, Ortiz A & Miranda M: Effect of music on the recovery of a patient with refractory non-convulsive status epilepticus. Epilepsy Behav 2010; 18:491–3*
16. *Lahiri N & Duncan JS: The Mozart effect: encore. Epilepsy Behav 2007; 11:152–3*
17. *Lee DJ, Chen Y & Schlaug G: Corpus callosum: musician and gender effects. Neuroreport 2003; 14:205-9*
18. *Liao H, Jiang G & Wang X: Music therapy as a non-pharmacological treatment for epilepsy. Expert Rev Neurother 2015; 15:993-1003*

19. Lin LC, Lee WT, Wu HC, Tsai CL, Wei RC, Jong YJ et al.: Mozart K.448 and epileptiform discharges: effect of ratio of lower to higher harmonics. Epilepsy Res 2010; 89:238-45
20. Lin LC, Lee WT, Wang CH, Chen HL, Wu HC, Tsai CL et al.: Mozart K.448 acts as a potential add-on therapy in children with refractory epilepsy. Epilepsy Behav 2011; 20:490-3
21. Lin LC, Lee MW, Wei RC, Mok HK, Wu HC & Tsai CL: Mozart K.545 mimics Mozart K.448 in reducing epileptiform discharges in epileptic children. Evid- Based Complement Altern Med 2012; 2012
22. Lin LC, Chiang CT, Lee MW, Mok HK, Yang YH, Wu HC et al.: Parasympathetic activation is involved in reducing epileptiform discharges when listening to Mozart music. Clin Neurophysiol 2013; 124:1528-35
23. Lin LC, Lee WT, Wu HC, Tsai CL, Wei RC, Jong YJ et al.: Mozart K.448 listening decreased seizure recurrence and epileptiform discharges in children with first unprovoked seizures: A Randomized Controlled Study. BMC Complement Altern Med 2014; 14:17
24. Maguire M: Epilepsy and music: practical notes. Pract Neurol 2017; 17:86-95
25. Mandl RC, Schnack HG, Zwiers MP, van der Schaaf A, Kahn RS, Hulshoff P: Functional diffusion tensor imaging: measuring task-related fractional anisotropy changes in the human brain along white matter tracts. PLoS One 2008; 3:e3631
26. Molnar-Szakacs I & Overy K: Music and mirror neurons: from motion to 'e'motion. Soc Cogn Affect Neurosci 2006; 1:235-41
27. Moore E, Schaefer RS, Bastin ME, Roberts N & Overy K: Can musical training influence brain connectivity? Evidence from diffusion tensor MRI. Brain Sci 2014; 4:405-27
28. Mountcastle VB: Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 1957; 20:408-34
29. Overall JE, Gorham DR: The brief psychiatric rating scale. Psychological Reports 1962; 10:799-812
30. Rakic P: Specification of cerebral cortical areas. Science 1988; 241:170-6
31. Rauscher FH, Shaw GL & Ky KN: Music and spatial task performance. Nature 1993; 365:611
32. Sachs ME, Habibi A, Damasio A & Kaplan JT. Decoding the neural signatures of emotions expressed through sound. NeuroImage 2018; 174:1–10
33. Schlaug G, Jaencke L, Huang Y & Steinmetz H: Increased corpus callosum size in musicians. Neuropsychologia 1995; 33:1047–1055
34. Schlaug G: Musicians and music making as a model for the study of brain plasticity. Prog Brain Res 2015; 217:37–55
35. Sihvonen AJ, Särkämö T, Leo V, Tervaniemi M, Altenmüller E & Soinila S: Music-based interventions in neurological rehabilitation. Lancet Neurol 2017; 16:648-660
36. Sparrow SS, Cicchetti VD & Balla AD: Vineland adaptive behavior scales. 2nd edition. 2005 Circles Pines: American Guidance Service
37. Turner RP: The acute effect of music on interictal epileptiform discharges. Epilpesy Behav 2004; 5:662-8
38. Vaquero L, Hartmann K, Ripollés P, Rojo N, Sierpowska J, François C, et al.: Structural neuroplasticity in expert pianists depends on the age of musical training onset. Neuroimage 2016; 1:106–19
39. Wan CY & Schlaug G: Music making as a tool for promoting brain plasticity across the life span. Neuroscientist 2010; 16:566–77
40. Yudofsky SC, Silver JM, Jackson E, Endicott J & Williams D: The Overt Aggression Scale for the Objective Rating of Verbal and Physical Aggression. Am J Psychiatry 1986; 143:35-9

Correspondence:
Chiara Bedetti
Istituto Serafico di Assisi
Viale Guglielmo Marconi, 6, 06081 Assisi, Perugia, Italy
E-mail: chiarabedetti@serafico.it