

MOZART'S MUSIC AND MULTIDRUG-RESISTANT EPILEPSY: A POTENTIAL EEG INDEX OF THERAPEUTIC EFFECTIVENESS

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SUMMARY

Multidrug-resistant epilepsy is a pathological condition that affects approximately one-third of patients with epilepsy, especially those with associated intellectual disabilities. Several non-pharmacological interventions have been proposed to improve quality of life of these patients. In particular, Mozart's sonata for two pianos in D major, K448, has been shown to decrease interictal electroencephalography (EEG) discharges and recurrence of clinical seizures in these patients. In a previous study 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 cases. This study aims to assess electroencephalography as a quantitative (qEEG) predictive biomarker of effectiveness of listening to music on the frequency of epileptic discharges and on background rhythm frequency (BRF).

Key words: Mozart effect – EEG – music - drug-resistant epilepsy

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INTRODUCTION

Music is one of the most complex, fascinating and enigmatic human abilities and has been the object of numerous investigations from specialists of both humanistic and natural sciences. In recent years, neuroscience has made a substantial contribution to the comprehension of the peculiar characteristics of the musical experience. Classic neuropsychological studies have suggested that music is a highly complex stimulus consisting of a large number of components which are relatively autonomous of one another: indeed melody, harmony, rhythm, meter, memory, imagination, emotional response and so on may be compromised independently of each other (Peretz & Coltheart 2003, Piccirilli et al. 2000). Music processing requires an ongoing process of decomposition and recombination of these different components; from an anatomical perspective, it is a widespread function of the nervous system involving a highly complex neuronal network (Sacks 2008). More recently, currently available neuroimaging techniques have demonstrated that musical training is a powerful means of reorganization of brain structures (Bodner et al. 2001). Music may be considered an outstanding tool for promoting brain plasticity (Wan & Schlaug 2010). Changes which result involve both grey and white matter. This structural/functional reorganization affects the size, asymmetry and density of grey matter of specific cerebral regions, along with the size, volume, and composition of white matter fiber bundles. For example, with regards to brain development, six year-old children undergoing musical training who were followed for two years were found to have a marked

development of the arcuate fasciculus and corpus callosum when compared to a control group of children who were not exposed to any kind of musical training (Hyde et al. 2009). It should be kept in mind that these brain changes may be diversely detected in relation to specific expertise: as a matter of fact, changes are not present in an undifferentiated way but correlate with a number of characteristics linked to personal history and individual competence (Merret et al. 2013). These differences in musical competence may be responsible for significant differences in individual brain anatomical and functional organization. For example, the sensorimotor representation of the hands is different between violinists and pianists, and significant anatomical aspects can be found between professional musicians and those who just plays for fun (Bangert et al. 2006, Wan & Schlaug 2010). In other words, it is now well-documented that musical training can shape brain and improves the efficiency of the connections between different brain regions. Musicians possess a different connectome than non-musicians (Schlaug 2015). In this view, with regards to nervous system damage it is plausible that the reorganization of brain structures can result from musical training. The various components of music can be used in a differentiated manner in relation to the type of pathology in question, therefore justifying the effectiveness of music therapy in different clinical conditions such as parkinsonism, aphasia, neglect, dementia, learning disorders and autism (Altenmüller & Schlaug 2013, D'Alessandro 2016, Särkämö et al. 2016, Schlaug et al. 2010, Thaut et al. 2015). Actually, as Patel points out (2008), music may be considered a “transformative technology” of the mind.

MUSIC THERAPY AND EPILEPSY

Recently growing interest has been demonstrated by researchers studying the effects of music in epilepsy. In particular a considerable group of studies have been carried out by Lin and coll. (Lin & Yang 2015) investigating the so-called "Mozart effect" (Rauscher et al. 1993). Their investigations revealed that both seizure frequencies, recurrence of first unprovoked seizure, and epileptiform discharges are significantly reduced when listening to sonata K.448 of Mozart. With regards to epileptiform discharges, forty-seven (81%) of fifty-eight children between the ages of 1 year to 19 years 8 months showed a significant decrease in interictal discharges (Lin et al. 2010). In eighteen children with epilepsy under good pharmacological control a significant decrease in epileptiform discharges were found when compared with EEGs prior to listening to music (Lin et al. 2011a). In another study of sixty-four epileptic children 90.2% demonstrated decreased epileptiform discharges during and immediately following their listening to Mozart K.448 and 82.6% while listening to Mozart K.545 (Lin et al. 2013); similar results were obtained in other investigations (Lin et al. 2012). According to a recent meta-analysis, a reduction in interictal epileptic discharges appears to be significant in 84% of patients (Dastgheib et al. 2014). 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 37.2% of children in the control group (Lin et al. 2014a). Studies of Lin et al. have confirmed previous sporadic and anecdotal observations (Turner 2004, Lahiri & Duncan 2007, Kuester et al. 2010) and overall have stimulated further investigations on this subject. A first report of the Mozart effect on epileptic patients dates back to 1998: Hughes et al. found reductions in epileptiform activities in patients with status epilepticus or with periodic lateralized epileptiform discharges (PLEDs). More recently Grylls et al. (2008) evidenced a significant reduction in the frequency of epileptic discharges while listening to Mozart's music compared to baseline and to control music in their study of forty five children who had epileptiform activity on EEG (2–18 years; mean 7 years 10 months). In conclusion, the available data suggest that music may be considered a valuable non-invasive, non-pharmacologic treatment of epilepsy. In addition, further information about the Mozart effect has been discovered from a number of experimental and clinical investigations. Differential response of brain activity to the different characteristics of musical stimuli is well documented by both neurophysiological and functional neuroimaging investigations (Bodner et al. 2012, Verusio et al. 2015). Seizure frequencies and spontaneous discharges were reduced in Long Evans rats with spontaneous absence seizure during and after music exposure as compared to the pre-music stage (Lin et al. 2013b).

MOZART EFFECTS AND MULTIDRUG-RESISTANT EPILEPSY

The beneficial effect of Mozart music as an add-on treatment in the clinical management of epilepsy is particularly valuable in the case of drug-resistant epilepsy, accounting for 20-30% of all cases of epilepsy, where standard pharmacological treatments have not proven to be effective and where prevalence is related to degree of intellectual disability (Kwan et al. 2010, French et al. 2004). Regarding drug-resistant epilepsy, Lin et al. (2011b) observed a 53.6±62.0% reduction in seizure frequency; 72.7% of subjects (n=11) demonstrated a greater than 50% reduction, including 18.9% who were seizure-free. In their sample of 11 outpatients (age range 1.5 to 21 years) Coppola et al. (2015) observed a 51.5% reduction in seizure frequency. In a subsequent study (2018) significant seizure reduction was observed in 9 of 19 patients, two while listening to Mozart's sonata K448 and seven (including two seizure-free cases) while listening to a set of Mozart's compositions. In a randomized study conducted at a residential facility for individuals with heterogeneous neurological impairments, (age range 12-78 years), Bodner et al. (2012) observed a 24% reduction in seizure frequency and 24% of subjects were seizure-free. In our previous investigation of 12 institutionalized subjects with severe intellectual disability (age range 5-35 years), we observed a 20.5% reduction in seizure frequency; 50% of patients demonstrated a positive response to treatment, including 8% who were seizure-free (D'Alessandro et al. 2017). Since none of the patients in our sample worsened in seizure frequency, though the beneficial effect was lost following the end of the intervention, we have decided to continue music therapy in all our subjects. At a one year follow-up, the available data suggest some considerations:

- subjects who exhibited a very good response to treatment continued to maintain efficacy over time; there was no reduction in the effectiveness of music therapy; no adverse side effects were observed;
- on the contrary, subjects in our sample who were nonresponders had not benefited from the continuation of music therapy;
- the response obtained after the first month appears sufficient to determine whether such intervention is worth continuing;
- some variables appear to be associated to a favourable response: in our study, different responses of the subjects to music therapy can be inferred from the average monthly baseline seizure frequency. Age, gender, degree of intellectual disability as well as characteristics of epilepsy did not affect the results. The literature suggests that the largest seizure reduction is observed among patients with generalized or central epileptiform discharges; however, all types of epilepsy, both idiopathic and symptomatic, with the exception of those with occipital discharges, showed a significant decrease in epileptiform discharges (Lin et al. 2011b);

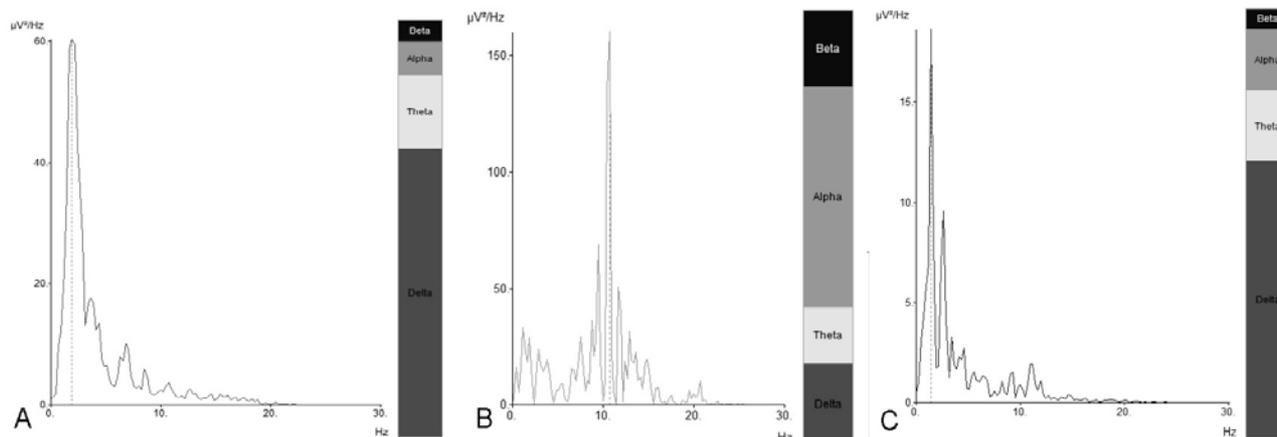


Figure 1. EEG background rhythm frequency before (A), during (B) and after (C) music listening

- considering the differences in responses between different subjects, it appears extremely important to search for any differential characteristics between responders and nonresponders. In this perspective, very interesting preliminary data suggest that some qEEG markers are able to identify subjects potentially sensitive to the positive effect of Mozart's music (Lin et al. 2014b). Our preliminary data suggest that subjects who positively respond to treatment with music listening show a difference in EEG background rhythm frequency (BRF) between the intervention period and the baseline period; in these subjects the pattern of brain wave activity shows less δ frequencies and more θ and α frequencies, while no changes in EEG activity are detected in our non-responder subjects (Figure 1).

Significant differences in the BRF between the baseline period (A), the intervention period (B) and post-intervention (C), in a 21 year-old male affected by the inv dup (15) syndrome, one of the most common chromosomal abnormalities associated with Drug Resistant Epilepsy (DRE). Distinctive clinical findings are represented by early central hypotonia, developmental delay, intellectual disability, epilepsy, and autistic behaviour. qEEG may be a useful model for predicting therapeutic effectiveness of music in patients with epilepsy.

CONCLUDING REMARKS

The frequency of epilepsy and drug-resistant epilepsy (DRE) remains higher in subjects with intellectual disability (ID), a population where a direct relationship between the severity of ID and the presence of DRE has been previously documented (Robertson et al. 2015). Living with ID and epilepsy represents many challenges for the individual, caregivers, and family. Medical science has failed to provide evidence-based data on the care of patients with ID and DRE (Devinsky et al. 2015). The presence of DRE in subjects with ID has therefore strongly stimulated research on new and innovative approaches to intervention, the effectiveness of which are still the subject of further investigation

(Jackson et al. 2015). In particular, in the absence of effective pharmacological and surgical therapies, non-pharmacological interventions are currently playing an increasing role. Listening to Mozart's music may be potentially useful as an add-on non-pharmacological therapy in the treatment of epilepsy, including multi-drug-resistant epilepsy. At the moment, due to the small sample sizes examined and methodological differences utilized, the truthfulness of this statement appears difficult to establish and various aspects of this issue need to be further investigated. The effect of music on patients with epileptic seizures is complex and at present poorly understood; it appears that some patients with seizures might benefit from musical exposure, whereas other patients may experience an exacerbation of their symptomatology. The dichotomous effect of music on epilepsy is an intriguing yet poorly understood phenomenon and the subject of ongoing research and debate. Music may act as an anticonvulsant via activation and enhancement of cortical areas involved in spatial cognitive processes that produce greater inhibition, either directly on surrounding motor areas or via inhibitory corticothalamic feedback loops (Maguire 2012). Similarly, music may act as proconvulsant in musicogenic epilepsy where anticipation of music and memory responses may enhance activity in the prefrontal cortex and associated frontostriatal connections (Leaver et al. 2009). However it is noteworthy that Mozart's music seems to be effective regardless of the different treatment protocols used in various studies. Mozart's music is supposedly the only piece to demonstrate beneficial effects on epilepsy. Mozart composed more than 600 works in his lifetime: his music is considered purely "cortical;" since he did not make corrections on paper it is said that his hand was only the "printer," and that his musical structure had a "direct line from his brain to that of the listener" (Greenberg 2000). In particular, Mozart composed with very repetitive melodic lines and his compositional structure reveals a highly detailed organization. In general, when comparing Mozart's music with the music of other composers such as Beethoven, Wagner or Chopin, or other types of music, this hypothesis seems

to be validated (Hughes 2001). Some authors evidence the peculiar characteristics of Mozart's music; Hughes et al. (2001) found that the long-term periodicity of the melodic line in Mozart's music was significantly more apparent and frequent when compared to the music of 55 other composers. Lin et al. (2010) compared the piano K.448 with a digitally computerized string version of the same musical stimulus: although these two kinds of music possessed the same melody, piano K.448 and string K.448 differed in their harmonics. The differences were particularly noteworthy at higher frequencies because the string K.448 was composed of stronger high frequency harmonics. Interestingly, lower harmonics found in piano K.448 work better to decrease seizure activity compared to higher harmonics found in string K.448. The hypotheses regarding the mechanism of action of Mozart's music are still under investigation; there is no value that can be attributed to the aspecific action of music on attentional processes or on mood (Bradt et al, 2010). A well-known typical effect of a musical experience is entrainment, the phenomenon by which a musical rhythm resonates with cerebral rhythms (Levitin 2006). Brain activity responds in different ways to the different characteristics of musical stimuli (Xing et al. 2016); music can therefore be considered a powerful agent of neuroplasticity given its ability to induce brain reorganization and favourably modify connections between neuronal networks. In conclusion, our data seems to justify further studies on Mozart effect as a potential add-on treatment for individuals with drug-resistant epilepsy, where standard pharmacological treatments have not proven to be effective.

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Contribution of individual authors:

Chiara Bedetti: study conception and preparation, acquisition of data, drafting manuscript;

Patrizia d'Alessandro, Antonella Baglioni, Marta Giuglietti, Domenico Frondizi, Marina Menna: study preparation, interpretation of data;

Moreno Marchiafava: interpretation of data;

Sandro Elisei, Massimo Piccirilli: revising manuscript.

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