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Music to the Survivors' Ears

The role of music in mitigating neurocognitive impairments of childhood acute lymphoblastic leukemia survivors

Childhood acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer and, due to high survival rates, there is an ever-growing population of survivors. Many childhood ALL survivors experience neurocognitive late effects that can affect intelligence, working memory, and processing speed, and which may be linked to chemotherapy received during treatment. Some clinical interventions have been tested in this population, but with minimal success. Music has been suggested as a therapeutic intervention for childhood cancer survivors at large, but not specifically for childhood ALL survivors. A review of the literature suggests that music may provide important benefits in all areas of neurocognitive difficulty for childhood ALL survivors. Therefore, music may be a promising form of intervention for the late effects of childhood ALL survivors, and it is necessary to develop and pilot such an intervention for this population.

Keywords: Childhood acute lymphoblastic leukemia, neurocognition, late effects, music

There are approximately 10,000 children currently living with cancer in Canada, 30% of whom have been diagnosed with leukemia. Acute lymphoblastic leukemia (ALL) accounts for 75% of all cases of childhood leukemia. ALL has a high survival rate, with a large number of ALL survivors consequently attempting to reintegrate into academic and work life; however, a growing number of these survivors also experience important neurocognitive impairments, often referred to as late effects (Iyer et al., 2015). Some remediation programs have been piloted to aid these survivors (Butler & Copeland, 2002; Conklin et al., 2007), but with limited success, leaving a great need for more effective clinical interventions. Music has been shown to generate important cognitive benefits (Hiscock et al., 2013), which suggests that it may help to mitigate the neurocognitive impairments experienced by childhood ALL

survivors. This review aims to assess the specific mechanics of ALL, the resulting neurocognitive impairments, and the potential healing role of music.

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia is a type of cancer that affects the bone marrow and the blood and is characterized by the over-production of immature lymphoblastic cells (Orkin et al., 2009). ALL is often called a childhood disorder, as two thirds of cases arise during childhood or adolescence (Pui & Evans, 2006), with a peak prevalence between the ages of two and five years old (Pui et al., 2008). Given this high frequency of occurrence, ALL is in fact the most common form of childhood and adolescent cancer (Pui & Evans, 2006). Due to the fact that treatment has evolved dramatically since the 1950s, the survival rate is currently estimated around 90%. Thus, there is an ever-growing number of childhood ALL survivors (Simon, 2019).

Several treatment options currently exist for children suffering from acute lymphoblastic leukemia, the most common being chemotherapy. Patients are given a cocktail of various chemotherapy agents, which include methotrexate, vincristine, glucocorticoids, anthracyclines, and L-asparaginase (van der Plas et al., 2015). These agents must be given in fairly high doses, and directly into the central nervous system via the cerebro-spinal fluid in order to eliminate all of the cancerous cells and prevent relapse (Pui et al., 2008). In addition to chemotherapy, some children with high risk ALL may also undergo a stem-cell transplant in order to help promote the healthy regeneration of lymphoblasts (Pui et al., 2008). Another option for patients in the high-risk group is to receive prophylactic cranial irradiation, a form of radiation therapy, although it is discouraged due to harmful side effects (Pui et al., 2009). Finally, the newest type of treatment available is targeted therapy, which aims to eliminate specific cancer cells using drugs or other substances, without harming normal surrounding cells. This is still a relatively rare form of treatment that is still being studied heavily to be further developed in children with ALL (National Cancer Institute, 2016).

LATE NEUROCOGNITIVE EFFECTS IN ALL SURVIVORS

Given the growing number of childhood ALL survivors, it has become increasingly possible to study late effects that may develop in these individuals. Late effects can be defined as adverse health consequences that appear two or more years after the completion of treatment (Moleski, 2000). Today it appears that 40–60% of childhood ALL survivors who were treated with chemotherapy only experience late neurocognitive impairments. These impairments can be quite serious, affecting a variety of components in a survivor's life, such as mental health, academic performance, success in a work environment, and overall quality of life (van der Plas et al., 2015).

When neurocognitive impairments were first studied in ALL survivors in the 1970s and 1980s, they were initially evaluated within a psychosocial framework. Research at the time pointed to the traumatic experiences that children with ALL had to endure, such as long-term hospitalization and painful treatments (Kellerman, 1980). Even though some researchers did find significant neurocognitive deficits in ALL survivors, particularly in verbal intelligence (Stehbens et al., 1981), these deficits were quite often attributed to psychosocial factors, or even discredited as statistical artifacts (Kellerman et al., 1982). Although these psychosocial interpretations are still valued and recognized, contemporary research now links the neurocognitive impairments in ALL survivors to treatment methods (van der Plas et al., 2015). It was established that cranial irradiation consistently caused impairments in intellectual and neuropsychological functioning, among other negative effects on the survivor's health (Butler et al., 1994). Chemotherapy is now the most common form of treatment, and researchers have established that this too may be linked to neurocognitive impairments, although less so than cranial irradiation (Moleski, 2000).

Iyer et al. (2015) conducted a review of the neurocognitive impairments of childhood ALL survivors who were treated with chemotherapy only. Survivors experience a decrease in IQ of 6–8 points lower than healthy controls. Although both verbal and verbal IQ scores seem to be affected, the most pronounced effect was found in the verbal IQ score. Childhood ALL survivors were also found to show a significant decrease in working memory and in information processing speed. Attention/concentration, verbal and visual memory, fine motor functioning, visual construction, and executive function were also examined. The literature remains inconclusive on these neurocognitive impairments, although certain studies do identify these as potential issues (Iyer et al., 2015).

Additionally, certain brain abnormalities have been detected in ALL patients and survivors, and have been linked to various neurocognitive late effects. Up to 80% of ALL patients who have been treated with chemotherapy experience lesions in the white matter of the brain, whether transient or persistent (Bhojwani et al., 2014). Reddick et al. (2014) found that ALL survivors had an overall reduced volume of white matter, which was correlated with lower scores in intelligence, attention, and academic success. Recent studies have also identified abnormalities in the grey matter of childhood ALL survivors who were treated with chemotherapy, with smaller cortical surface area and reduced cortical thickness in certain areas (Tamnes et al., 2015). In addition, survivors who displayed reduced cortical surface area in the prefrontal cortex experienced significant problems in executive functioning (Tamnes et al., 2015).

INTERVENTIONS FOR NEUROCOGNITIVE LATE EFFECTS

In order to aid survivors of childhood ALL and other forms of childhood cancers that experience late neurocognitive impairments, Butler and Copeland (2002) created a Cognitive Remediation Program (CRP). This program combines elements from the areas of brain injury rehabilitation, educational psychology, and clinical psychology. The CRP utilizes several different techniques including drill practices, learning skills and strategies, and cognitive-behavioral therapy; however, the CRP was designed primarily to improve attentional difficulties, so it does not address all of the neurocognitive impairments that survivors of childhood ALL may experience. In addition, a multicentre clinical trial of the CRP method in childhood cancer survivors showed that although participants showed some improvement in academic success and their parents rated their attention abilities as improved, the neuropsychological batteries did not reveal significant improvement (Butler et al., 2008).

In addition to this cognitive training approach, researchers have attempted to treat these neurocognitive impairments pharmacologically. Conklin et al. (2007) completed a double-blind cross-over clinical trial of methylphenidate, which appeared to have promising effects on attention, cognitive flexibility, and processing speed; however, certain children fared better with this pharmacological intervention, particularly males with a higher level of intelligence and who were treated at an older age (Conklin et al., 2007). Thus, there seems to be a necessity to develop more effective clinical interventions for all childhood ALL survivors.

MUSIC AND THE BRAIN

Music has been shown to improve many abilities, such as spatial-temporal reasoning, numerical reasoning, phonemic awareness (Rauscher & Hinton, 2011), attention, processing speed (Roden et al., 2014) and linguistic abilities (Moreno et al., 2009). In this field of study, the direction of causality is often questioned: are the bright children taking music lessons or can music cause an increase in cognitive function? Causal studies—rather than correlational studies—are now being conducted, such as Schellenberg's (2004) study on intelligence and a 2011 study (Roden et al.) on attention and processing speed. Such studies provide further support for the cognitive benefits that music offers.

Music training has also proven to alter a variety of brain structures. Even at an amateur level of musicianship, music training is associated with an increase in grey matter, notably in the motor, auditory, and visual-spatial areas of the brain (Gaser & Schlaug, 2003). Grey matter appears to increase in the ventral premotor cortex, which is the area of the brain that integrates sensory and motor information (Bailey et al., 2014). Also, the corpus callosum is more developed and larger in musicians, particularly in area 3, but only if they began musical training before the age of seven (Schlaug et al., 2009). Musicians with at least ten years of formal training are also found to have increased cortical thickness, especially in the superior temporal and

dorsolateral frontal regions, which are implicated in the processing of complex sounds (Bermudez et al., 2009).

The blooming field of music therapy takes advantage of the various benefits that music may offer in order to apply them to individuals with a variety of physical or psychological issues. In essence, music therapy is the prescribed use of music administered by a certified professional used to improve or maintain health. This can be an effective strategy for individuals with traumatic brain injury, developmental disabilities such as autism, physical disabilities, pain management, dementia, and many more (Canadian Association for Music Therapy, 2014). The effectiveness of music therapy with such individuals helps to support the fact that music may provide benefits not only for healthy individuals but also for those with brain abnormalities (LaGasse, 2014; Ridder et al., 2013; Weller & Baker, 2011).

MUSIC FOR CHILDHOOD ALL SURVIVORS

Music currently plays a role in childhood ALL patients; however, this musical engagement takes place primarily pre-remission while the child is still being treated in hospital (Tucquet & Leung, 2014). An Australian national review of the usefulness of music therapy during childhood cancer treatment conducted by Tucquet and Leung (2014) revealed that music therapy plays a significant role in parent-child bonding, emotional support, self-expression, pain management, and anxiety management during treatment.

Hiscock et al. (2013) reviewed existing literature on the topics of late neurocognitive effects in childhood cancer and the cognitive benefits of music, and concluded that a music-based intervention would likely help alleviate survivors' neurocognitive impairments. The article provides a strong foundation in this field, but it is important to look specifically at the neurocognitive impairments of childhood ALL survivors, as they can differ significantly from impairments in other types of childhood cancer.

First, it is crucial to examine whether music may aid the three most pronounced cognitive impairments of ALL survivors: intelligence, working memory, and information processing speed (Iyer et al., 2015). Schellenberg's (2004) revolutionary causal study demonstrated that 36 weeks of music training in children at age 6 led to an increase of 2.7 IQ points in comparison to the control group. In terms of working memory, musicians outperformed non-musicians on tasks of this ability both behaviourally and on an electrophysiological level (George & Coch, 2010). To assess information processing speed, Roden et al. (2014) compared two groups of children who received either musical training or natural science training for 18 months. At the end of this period, children who had received musical training showed a significant increase in information processing speed. Thus, evidence suggests that these three common neurocognitive impairments in childhood ALL survivors—

intelligence, working memory, and information processing speed—could potentially be aided with music.

In addition, five potential neurocognitive impairments in childhood ALL survivors that were identified by Iyer et al. (2015) are worth considering: attention/concentration, verbal and visual memory, fine motor function, visual construction and executive function. Several studies have shown that music can improve attention and concentration, including visual attention (Roden at al., 2014) and auditory attention (Dege et al., 2011). Verbal memory (Dege et al., 2011) and visual memory (Ferreri et al., 2013) have also been shown to improve with music training. In terms of improvements in fine motor functioning, Weller and Baker (2011) found that music in physical rehabilitation programs could aid certain aspects of physical functioning, such as fine motor functioning. Visual-construction skills involve the ability to perceive a picture or an object as a set of individual parts and then to reconstruct it from this set of parts. This skill essentially combines visual-spatial abilities and fine motor functioning (Mervis et al., 1999). Although the impact of music on visual-construction abilities has not been studied directly, music has been proven to improve visual-spatial abilities (Tai, 2010). In combination with the effect of music on fine motor functioning, it appears promising that music may also increase visual-construction abilities. Finally, there is evidence that music also seems to improve executive functioning abilities (Moreno et al., 2011). Overall, evidence indicates that music could improve any of the neurocognitive impairments that childhood ALL survivors may experience.

Additional benefits that music training or music therapy may provide for a child are also worth considering. In general, music is a natural and important part of a child's life and is thus quite enjoyable (O'Callaghan et al., 2011). Children may also benefit from other components of music education, such as the development of creativity. It can also help the child survivor cope with certain traumatic experiences associated with their cancer (e.g., long-term hospitalization, medical trauma) as well as any persistent stress or anxiety (Tucquet & Leung, 2014). Therefore, music is a harm-free form of treatment and may be beneficial to the child survivor of ALL in more ways than intended.

CONCLUSION

In conclusion, music appears to be a very promising form of treatment for mitigating the known neurocognitive impairments of children who have survived ALL. The ultimate goal for childhood acute lymphoblastic leukemia is to develop less harmful treatment methods, and music has the potential to alleviate the harm current treatment may cause. To confirm this method of treatment, a music therapy or music instruction program created specifically for ALL survivors should be devised, to target the particular impairments that these children experience. Such a program should then be tested with survivors in order to prove the efficacy of a musical intervention

in this population. It is important to note that a program of this nature highlights the value of interdisciplinary work: the neuroscientist and the musician can work innovatively and productively together rather than independently.

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