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Music perception and the effects of music listening interventions on agitation in hospitalized acute care patients with acquired brain injury

Par

Kirsten Anderson

Département de psychologie

Faculté des Arts et des Sciences

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Music perception and the effects of music listening interventions on agitation in hospitalized acute care patients with acquired brain injury

Présentée par

Kirsten Anderson

A été évaluée par un jury composé des personnes suivantes

Isabelle Peretz
Président-rapporteur

Elaine de Guise
Directeur de recherche

Nathalie Gosselin
Codirecteur

David Ellemberg
Membre du jury

Shantale Hegde
Examinateur externe

Résumé

Les traumatismes craniocérébraux (TCC) peuvent entraîner de lourdes conséquences physiques, cognitives, émotionnelles et comportementales. Parmi celles-ci, l'agitation est très fréquente et se caractérise par une hyperactivité motrice, une désorientation, des problèmes d'attention, une labilité émotionnelle, une désinhibition et de l'agressivité. Elle interfère avec le rétablissement et les processus de réadaptation, mais il n'existe pas à ce jour de consensus sur son traitement, outre la contention physique ou la prise de médicaments, qui peuvent respectivement causer des blessures ou entraver la récupération. De récentes données suggèrent que les interventions musicales peuvent réduire l'agitation chez les patients TCC mais la capacité des patients TCC à percevoir et traiter la musique pendant la phase aiguë post-blessure n'a pas été établie.

Le premier article de cette thèse visait à évaluer la perception musicale chez les patients TCC hospitalisés en phase aiguë. Dans la présente étude, 42 patients ayant subi un TCC ont été comparés à un groupe témoin. Tous les participants ont complété les tests de Scale et Rhythm de la Montreal Battery of Evaluation of Amusia pour mesurer la perception musicale, et le test d'empan numérique pour mesurer la mémoire verbale à court terme. Comparativement au groupe témoin, les patients TCC ont obtenu des performances significativement inférieures; 43% d'entre eux présentaient des déficits de traitement de la hauteur et 40% des déficits de traitement du rythme. Les patients présentant des lésions à l'hémisphère droit ont obtenu des résultats plus faibles que ceux présentant des lésions à l'hémisphère gauche. Les déficits de traitement de la hauteur et du rythme coexistaient dans 31% des cas, ce qui suggère l'existence de réseaux neuronaux partiellement dissociables.

Le deuxième article est une revue non systématique dont l'objectif était de caractériser l'agitation et son traitement. Plusieurs types d'interventions comportementales, dont les interventions musicales, ont été explorées dans cette revue. Les limites méthodologiques ont été discutées et des recommandations ont été faites pour une approche plus systématique de la recherche utilisant des études de cas et de séries de cas chez les patients agités.

Le troisième article est une étude pilote de phase II dans laquelle sont inclus des patients ayant subi un TCC modéré à sévère (n = 3) ou un accident vasculaire cérébral de l'artère cérébrale moyenne (n = 1). Ils ont été exposés à leurs musiques préférées, de la musique classique relaxante et un extrait sonore non musical (cascade) pendant la phase aiguë de récupération. Les comportements d'agitation ont été évalués à l'aide de l'Échelle d'Agitation (Agitated Behaviour Scale), de mesures actigraphiques et d'une observation qualitative. Les résultats indiquent que l'agitation a diminué lors de l'écoute de la musique classique relaxante et la cascade. L'agitation est restée stable lors de la musique préférée, mais certains patients ont exprimé des émotions positives ou présenté un comportement plus organisé, comme taper du pied ou chanter. Compte tenu des importantes limites méthodologiques dans ce champ d'études, la présente étude a permis d'explorer la faisabilité et l'effet d'une intervention musicale, ce qui permettra de guider les études futures.

Mots clés: agitation ; lésion cérébrale traumatique ; lésion cérébrale acquise ; perception de la hauteur des sons ; perception du rythme ; musique préférée ; musique relaxante ; cascade ; échelle de comportement agité ; actigraphie.

Abstract

Traumatic brain injury (TBI) has serious physical, cognitive, emotional, and behavioural consequences. Agitation is highly prevalent among patients with TBI, and is characterized by motor hyperactivity, disorientation, attention problems, emotional lability, disinhibition, and aggression. It often results in decreased engagement in rehabilitative treatment, and poorer functional outcomes. There is no consensus on the treatment for agitation. Most often, it is managed with medication and physical restraints, which may cause injury or impede cognitive recovery. Few studies examine novel non-pharmacological interventions for agitation in TBI patients. However, recent evidence suggests that music interventions may decrease agitated behavior in TBI patients. The ability of TBI patients to perceive and process music during the acute phase has not been established, though it may influence the efficacy of preferred music interventions.

The first article of this thesis evaluated music perception in acutely hospitalized TBI patients. Music perception deficits have been identified in populations with acquired brain injury due to epilepsy, stroke, and after aneurysmal clipping. However, few studies have evaluated deficits following TBI, resulting in an underdiagnosis in this population. Forty-two patients completed the Scale and Rhythm tests of the Montreal Battery for the Evaluation of Amusia to measure music perception, and Digit Span Forward to measure verbal short-term memory. TBI patients were more often impaired than controls, with 43% demonstrating pitch processing deficits, and 40% demonstrating rhythm processing deficits. Patients with right hemisphere damage performed more poorly than those with left hemisphere damage. Pitch and rhythm deficits co-occurred 31% of the time, suggesting partly dissociable neural networks. Results are discussed in the context of current research and clinical implications.

The second article was a non-systematic review in which we characterized agitation and its treatment. We explored behavioural interventions, including music interventions, occupational therapy, the Intervention Contingencies Awareness Relationship behavioural model, operant contingency management, and general therapeutic activities. The methodological limitations were discussed and recommendations made for a more systematic approach to research using case and case series studies in agitated patients.

The third article was a phase-II development-of-concept pilot study in which four patients with moderate to severe TBI (n = 3), and middle cerebral artery stroke: (n = 1) were exposed to preferred music, relaxing classical music, and a nonmusical control (waterfall) during the acute phase of recovery. Agitated behaviours were assessed using the Agitated Behavior Scale, actigraphy, and qualitative observation. Agitated behaviour decreased during relaxing classical music, and waterfall. It remained stable in the preferred music condition. However, certain patients expressed positive emotions and organized behaviour such as tapping or singing along. Given important methodological limitations in current studies, a phase-II study allowed for the evaluation of outcomes and the practicality of delivering music listening interventions, which may guide future studies.

Key words: agitation; traumatic brain injury; acquired brain injury; pitch perception; rhythm perception; preferred music; relaxing music; waterfall; agitated behaviour scale; actigraphy

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List of Acronyms

ABI	Acquired brain injury
ABS	Agitated Behavior Scale
CT	Computerized tomography
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
GCS	Glasgow Coma Scale
GOSE	Extended Glasgow Outcome Scale
ICHD-II	International Classification of Headache Disorders
IFG	Inferior frontal gyrus
MBEA	Montreal Battery of Evaluation of Amusia
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PTA	Post-traumatic amnesia
SPECT	Single-photon emission computerized tomography
STM	Short-term memory
TBI	Traumatic brain injury

I dedicate my thesis to my loving parents,

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CHAPTER I: General Introduction

Traumatic Brain Injury

Prevalence of traumatic brain injury

Traumatic brain injury (TBI) is a significant health, economic, and social issue, with an estimated worldwide prevalence of between 64 and 74 million cases per year (Dewan et al., 2018). This is considered to be an underestimation, as low- and middle-income countries tend to under-report head injury (Dewan et al., 2018). The US and Canada combined have the highest incidence of documented TBIs in the world, with rates of 4.6 million per year, or 1299 cases per 100,000 people (Dewan et al., 2018). However, even in North America, many individuals never seek medical care, or are treated in outpatient settings rather than emergency rooms, lowering the recorded numbers (Andelic et al., 2009; Dewan et al., 2018). Between 2006 and 2018, there were 399, 376 TBI-related hospitalizations documented in Canada. In the provinces of Ontario and Alberta alone, there were 5,074,239 emergency room visits annually, or roughly 1151 visits daily. Canadian hospitals reported approximately 53, 200 TBI-related deaths between 2002 and 2016 (Public Health Agency of Canada, 2020). The number of people who survive TBI and other types of acquired brain injury has increased in recent years due to advancements in emergency medical care (Oujamaa et al., 2017; Slifer & Amari, 2009). Thus, there is an increasing need to focus on functional outcomes following TBI, which are often poor (Andelic et al., 2012; Oujamaa et al., 2017).

Definition of TBI

Traumatic brain injury may be defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force." (Menon, Schwab, Wright, & Maas, 2010). "Alteration in brain function" refers to at least one of the following symptoms: 1) loss of consciousness; 2) a loss of memory of events that occurred before or after the injury (retrograde amnesia or post-traumatic amnesia); 3) an alteration in mental state at the time of injury (slowed thinking, confusion, disorientation); and/or 4) neurologic deficits (loss of balance, weakness, paralysis, vision changes, sensory loss)(Menon, Schwab, Wright, & Maas, 2010). Evidence of brain pathology may be confirmed visually, with imaging studies, and/or lab results.

An external force to the brain may result from the following events: 1) an object striking the head (eg. during recreational activities), the head striking an object (eg. striking the floor or furniture during a fall), an acceleration or deceleration movement with no external trauma (eg. whiplash sustained in a motor vehicle accident), penetration of the brain by a foreign object (eg. gunshot wound); or the force from an explosion (eg. in combat) (Menon, Schwab, Wright, & Maas, 2010).

Classification of TBI severity

The classification of TBI as mild, moderate, or severe is based primarily on clinical symptoms, as individuals may demonstrate impairment in the absence of neuroimaging findings (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013). Within mild TBI exists the sub-category "mild complicated," based on a radiological diagnosis of positive findings on CT. The Glasgow Coma Scale (GCS) is commonly used to determine the state of consciousness of the patient, with three categories: eye opening, motor response, and verbal response (Teasdale & Jennett, 1974). The GCS is used in conjunction with additional information, such as duration of loss of consciousness, neuroimaging results, neurological exam, and the presence and duration of post-traumatic amnesia (Table 1).

Table 1. Categories of traumatic brain injury severity

CHARACTERISTICS	TBI SEVERITY		
	MILD	MODERATE	SEVERE
Duration of loss or alteration of consciousness	0 to 30 minutes	30 minutes to 6 hours; maximum of 24 hours	24 hours to days; minimum of 6 hours
GCS Score	13 to 15	9 to 12	3 to 8
Lesions (fracture or intracranial lesion)	positive (complicated) or negative (uncomplicated) results on brain imaging	generally positive results on brain imaging (focal damage)	positive results on brain imaging
Neurological Exam	possible positive (focal signs possible)	positive (focal signs)	positive (focal signs)
Post-traumatic Amnesia (PTA)	$\leq$ 24 hours	1 to 14 days	several weeks

Note. Translated and adapted from the document "Orientations ministérielles du Québec pour le traumatisme craniocérébral léger 2005-2010" by the General Director of Health Services and University Medicine, Government of Quebec, 2005, pg. 71.

Pathophysiology of TBI

Mechanisms /phases of injury. There are two main mechanisms/phases that characterize the cellular and vascular degradation of TBI: primary injury, which occurs at the moment of impact; and secondary injury, which consists of a cascade of biochemical responses beginning just seconds after the initial impact (Hill, Coleman, & Menon, 2016; Werner & Engelhard, 2007). Primary injury involves mechanical tissue damage to axons and cell bodies, microglia, and vasculature of the cerebrum (Werner & Engelhard, 2007). Secondary injury is characterized by dysregulations in cerebral blood flow and cell metabolism. For example, imbalances in oxygen and glucose consumption result in the excessive release of excitatory neurotransmitters, allowing for a floodgate of debris to enter the cell. The debris is recognized as an antigen and removed through inflammation, resulting in cell death and scarring (Werner & Engelhard, 2007). Common conditions stemming from TBI that require management include oedema, paroxysmal sympathetic hyperactivity, post-traumatic hydrocephalus, and post-traumatic neuroendocrine disorders stemming from pituitary gland lesions (Oberholzer & Müri, 2019).

Patterns of injury location. TBI lesions are often observed in the brain parenchyma both cortically and subcortically, as well as in the subdural, subarachnoid, and/or epidural spaces. Injury may be classified as focal or diffuse. Focal damage is typically observed following direct head impact and commonly involves frontal and temporal regions. Diffuse injury may be observed following acceleration-deceleration injury, such as traffic accidents, and includes the widespread stretching and tearing of axons and cell bodies. However, focal and diffuse injury coexist in more than half of the individuals with TBI (Oberholzer & Müri, 2019; Skandsen et al., 2010).

Clinical symptoms and recovery following TBI

Mild TBI symptoms are fewer in number, severity, and duration than in moderate or severe TBI. They often resolve over weeks to months without therapy, though they may persist long term in a sub-group of patients (Van der Naalt et al., 2017). Moderate to severe TBI typically involves several stages of recovery, beginning with impaired consciousness, followed by a state of agitation and post-traumatic amnesia. Finally, there is a post-confusion period in which recovery of function is usually marked by persistent difficulties in physical, cognitive, emotional, and behavioural domains (Ganau et al., 2018; Oberholzer & Müri, 2019). Outcomes in moderate to severe TBI range from vegetative state to complete recovery (Ganau et al., 2018). Most individuals with moderate to severe TBI experience long-term disability (Königs, Beurskens, Snoep, Scherder, & Oosterlaan, 2018).

The structural and functional damage caused by TBI is typically demonstrated in a variety of disruptions to function. Physical symptoms may include motor dysfunction (Cavanaugh et al., 2005; Kim, Lee, Kim, Cho, & Paik, 2019), visual deficits (Armstrong, 2018), auditory deficits such as hyperacousia (Fausti, Wilmington, Gallun, Myers, & Henry, 2009), sensory deficits (Alwis, Yan, Morganti-Kossmann, & Rajan, 2012), and headaches, vertigo, nausea (Anderson, Tinawi, Lamoureux, Feyz, & de Guise, 2015; see Appendix), sleep disorders, and fatigue (Tomar, Sharma, Jain, Sinha, & Gupta, 2018). Cognitive symptoms may consist of impairments in attention, memory, processing speed (Hegde, 2014; Perbal, Couillet, Azouvi, & Pouthas, 2003), and executive function (Busch, McBride, Curtiss, & Vanderploeg, 2005). Emotional symptoms may include depression, anxiety, and difficulty at regulating emotions (Coetzer, 2018). Behavioural symptoms may include irritability, disinhibition, and agitation (Ganau, Lavinio, & Prisco, 2018). Agitation is one of the most common behaviours following

TBI, affecting up to 96% of TBI patients (Singh, Venkateshwara, Nair, Khan, & Saad, 2014). It poses significant safety threats to patients and caregivers, and requires management.

Agitation Following Traumatic Brain Injury

Definition of Agitation

Agitation may be thought of as a variation of delirium that is characterized by 1) cognitive symptoms, such as disorientation and reduced attention; 2) physical symptoms, such as motor hyperactivity; 3) emotional symptoms, such as anxiety and emotional lability; and 4) behavioural symptoms, such as physical and verbal aggression (Ganau, Lavinio, & Prisco, 2018; Ponsford, Janzen, et al., 2014). It is accompanied by post-traumatic amnesia, or a decrease in the ability to learn new information (Bogner, Corrigan, Fugate, Mysiw, & Clinchot, 2001). Disorientation to place and time is observed, as this would demand the storage and retrieval of new information (Baker, 2001).

Pathophysiological mechanisms underlying agitation

While the pathophysiological mechanisms underlying agitation are poorly understood, agitation is proposed to stem from structural and functional tissue damage that occurs when the neural network is being remodeled following injury. Metabolic changes, neuroinflammation, and neurotransmitter dysregulation are observed (Ganau, Lavinio, & Prisco, 2018; Rahmani, Lemelle, Samarbafzadeh, & Kablinger, 2021; Wang et al., 2021). For example, temporal base contusions may disrupt the cholinergic system, which is instrumental in mediating the processes of memory and attention (Arciniegas, Topkoff, & Silver, 2000), and disruption to dopaminergic neurotransmission is associated with behavioural changes following TBI (Jenkins, Mehta, & Sharp, 2016). Anatomically speaking, agitation appears to be linked with damage to structures in the limbic system (for example, the orbitofrontal cortex, hippocampus, entorhinal cortex, and amygdala), as this disrupts long-range cortico-cortical connectivity with frontal regions supporting higher cognitive functions, such as emotion regulation, behavioural coherence, and attention (Ganau et al., 2018; Hawkins & Trobst, 2000; Simpson, 2017). Damage to any of the components of this system may result in agitated behaviours, such as emotional lability, irritability, impulsiveness, and disinhibition (Ganau et al., 2018; Wang et al., 2021; Williamson et al., 2020).

Pharmacological management of agitation

Due to staff shortages, medication is often the treatment of choice for the management of agitation (Janzen, McIntyre, Meyer, Sequeira, & Teasell, 2014). However, a growing body of work demonstrates that pharmacological management of agitation may impede cognitive and functional recovery and is variable in its effectiveness (Bogner et al., 2015; Jackson, Clare, & Mannix, 2002; Phelps, Bondi, Ahmed, Olugbade, & Kline, 2015; Phyland et al., 2020). One of the chief difficulties that physicians face when managing agitation pharmacologically is balancing between promoting arousal in patients and provoking agitation (Wang et al., 2021). Given the disadvantages of pharmacological management, many clinicians and researchers propose a multi-faceted approach for the management of agitated behavior in the hospitalized patient (Alderman, 2003; Flanagan et al., 2009; Freeman, Yorke, & Dark, 2019).

Physical restraints

Physical restraints, such as mitts, straps, vests, and enclosed beds, are discouraged until other pharmaceutical, environmental and behavioral interventions have been exhausted (Ponsford, Bayley, et al., 2014). However, given the fact that hospital resources are usually insufficient to provide for a 24-hour sitter, restraints are often used in the clinical setting to prevent patients from harming themselves and others. Unfortunately, this approach may increase agitation (Beaulieu et al., 2008; Duraski, 2011; McNett, Sarver, & Wilczewski, 2012), or injure patients (Beaulieu et al., 2008; Bromberg & Vogel, 1996; Ponsford, Bayley, et al., 2014). Furthermore, many nurses report feeling uncomfortable applying restraints to patients (Freeman et al., 2019)

Environmental modifications

Minimizing environmental stimulation is recommended, as it may provoke arousal levels that exceed the patient's cognitive processing capacity (Flanagan et al., 2009). This includes noise (e.g. TV and radio) (Duraski, 2011); light, and visitors (Becker, 2012; Flanagan et al., 2009). Environmental modifications, though often helpful, are often insufficient on their own.

Rehabilitation after moderate and severe TBI

Agitated behaviour, in addition to posing risks of self-harm and harm of others, poses a special problem with respect to accessing rehabilitation services (Bogner et al., 2015; Williamson et al., 2020). Patients are often unable to comply with rehabilitative exercises due to aggressive behaviour and decreased concentration (Bogner et al., 2015). To add to this, treatment with sedatives may compromise patients' cognitive faculties, further reducing participation (Formisano et al., 2001). This is unfavourable for recovery, as early rehabilitation mitigates the long-term consequences of TBI (Andelic et al., 2012; Formisano et al., 2001; Mishra et al., 2021). Even small delays in rehabilitation worsen outcome in patients with moderate to severe TBI (Oujamaa et al., 2017; Tepas III et al., 2009). Typical treatment consists of multidisciplinary rehabilitation with a rehabilitative physician, speech pathologist, physical therapist, and occupational therapist (Choi et al., 2008; MacKay, Bernstein, Chapman, Morgan, & Milazzo, 1992), multisensory stimulation (Andelic et al., 2012; Megha, Harpreet, & Nayeem, 2013), or intensive cognitive rehabilitation (Cicerone, Mott, Azulay, & Friel, 2004). However, many researchers and clinicians recognize the need for cost-effective, easily applicable interventions beyond the traditional methods that currently exist (Sihvonen et al., 2017; Williamson et al., 2020). They would ideally complement traditional forms of rehabilitation in occupational therapy, physical therapy, speech therapy, and neuropsychology, while being offered independently of them (Sihvonen et al., 2017). With advancement in neuroimaging techniques in recent decades, music listening interventions have gained interest as a potential treatment to fill that gap (Särkämö, 2018; Sihvonen et al., 2017). Advantages are that music is culturally universal, enjoyed by most individuals, inexpensive, readily accessible, and applicable in numerous settings.

The Beneficial Effects of Music

There is ample evidence indicating that music enhances well-being and regulates stress in both healthy individuals and diverse clinical populations (Koelsch, 2014, 2020; Magee et al., 2011; Moreno et al., 2011b; Schafer, Sedlmeier, Stadtler, & Huron, 2013; Hole, Hirsch, Ball, & Meads, 2015). Music listening stimulates neural activity across widespread brain regions implicated in emotion (Blood & Zatorre, 2001b; Koelsch, Cheung, Jentschke, & Haynes, 2021), cognition (Cuddy, Sikka, & Vanstone, 2015; Kiss & Linnell, 2021; Zatorre, Chen, & Penhune, 2007) , sensory function, and motor function (Chen, Penhune, & Zatorre, 2008; Gordon, Cobb, & Balasubramaniam, 2018; Vroegh, Wiesmann, Henschke, & Lange, 2021). Thus, listening interventions may be well-suited for heterogeneous populations such as TBI patients, who have a range of cognitive, emotional, sensorimotor, and behavioural deficits.

The effects of music on cognitive networks

Keeping track of a melody within the musical structure of timing and phrasing demands cognitive flexibility and recruitment of executive functions (Särkämö, Tervaniemi, & Huotilainen, 2013; Hegde, 2014; Särkämö & Sihvonen, 2018). In order to support these demands, widespread frontal, temporal, parietal, subcortical and cerebellar networks are activated. When following the progression of a musical piece, one must keep the melody in mind. Thus, attention and verbal working memory are necessary. Melody perception engages the frontotemporoparietal network, which includes the superior temporal gyrus, dorsolateral prefrontal cortex, inferior frontal cortex, anterior cingulate, and intraparietal areas (Janata, Tillmann, & Bharucha, 2002; Peretz & Zatorre, 2005). Listening to familiar music engages the hippocampus along with other medial temporal areas and parietal regions involved in episodic memory (Särkämö & Sihvonen, 2018; Janata, 2012; Platel et al., 2003). When perceiving rhythm, motor areas are engaged, including the accessory motor cortices, basal ganglia, and cerebellum (Chen et al., 2008; Grahn & McAuley, 2009; Zatorre, Chen, & Penhune, 2007). These areas are involved in the coordination and sequencing of movement, gait, and fine motor control (DeLong & Wichmann, 2010). The processing of complex musical structures, such as harmonies and chords, recruits the superior temporal gyrus and inferior frontal gyrus (Peretz & Zatorre, 2005; Särkämö & Sihvonen, 2013). Thus, there is a particular interest in using music interventions in patients with fronto-temporal cognitive dysfunction, which is common following TBI (Oberholzer & Müri, 2019). Interestingly, music that is perceived as pleasant and arousing increases verbal working memory and attention in stroke patients (Särkämö & Soto, 2012).

The effects of music on networks of emotion and reward

Music listening engages areas of the brain that are not unique to music listening per se, but overlap with areas involved in reward-related behavior. For example, it elevates mood and regulates emotion (Koelsch, 2020; Koelsch et al., 2016; Schafer et al., 2013). The pleasurable feelings that arise while listening to music activate a phylogenetically-old reward network (Zatorre & Salimpoor, 2013). This network is also activated during motivation and consumption of primary rewards such as food, drink, and sex, and secondary rewards, such as money and power (Blood & Zatorre, 2001; Koelsch, 2014). Emotion interpretation depends on activity in key structures in the limbic system, such as the hippocampus, amygdala, ventral striatum and caudate nucleus (Gosselin, Peretz, Johnsen, & Adolphs, 2007; Gosselin et al., 2006; Simic et al., 2021). More specifically, it is proposed that music listening is associated with up-regulation of activity in the mesocorticolimbic "reward" system, particularly the striatum, and down-regulation of activity in the amygdala, an area associated with fear (Blood & Zatorre, 2001; Koelsch et al., 2011).

A cluster of behaviors indicates emotional lability in TBI patients during the agitated phase. These include spontaneous shifts between excessive crying or laughter (Corrigan, 1989; Corrigan & Bogner, 1994). Pathological crying and laughing are associated with prefrontal cortical lesions (Tateno, Jorge, & Robinson, 2004). It is proposed that damaged prefrontal areas may cause functional dysregulation in the limbic circuits, which may underlie the disturbed emotional expression and lability seen in pathological crying and laughing (Tateno et al., 2004). Since music listening has a regulatory effect on the mesocorticolimbic system, to the extent that there is dysregulation of the mesocorticolimbic system of TBI patients (Balasubramanian, Srivastava, Pawar, Sagarkar, & Sakharkar, 2020), music may aid in reducing the emotional lability that characterizes agitation.

The effects of music on arousal and the stress response

Stress occurs in situations perceived as novel and unpredictable, in which a lack of control over the situation is experienced (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). The biological stress response is characterized by hormonal and metabolic changes that occur following an unpleasant situation, injury or trauma (Desborough, 2000; Helmy, Vizcaychipi, & Gupta, 2007). It is well-established that music may modify the stress response by contributing to the maintenance of homeostasis (Chanda & Levitin, 2013; de Witte, Spruit, van Hooren, Moonen, & Stams, 2020; Khalfa, Bella, Roy, Peretz, & Lupien, 2003; Mishra et al., 2021; Ozturk, Hamidi, Yikilmaz, Ozcan, & Basar, 2019). For example, a decreased stress response is well-documented in patients who listen to music before, during, or after invasive medical and surgical procedures (Fu et al., 2019; Gogoularadja & Bakshi, 2020; Hole, Hirsch, Ball, & Meads, 2015; Ozturk et al., 2019; Padam et al., 2017), with one meta-analysis citing sufficient evidence for authors to recommend the availability of music to all patients undergoing surgical procedures (Hole, Hirsch, Ball, & Meads, 2015).

The stress response is evident in TBI patients through increases in cortisol, adrenaline, and other hormones (Helmy et al., 2007). The injury response includes activation of the hypothalamus-pituitary-adrenal axis. Hormones that are released from the pituitary gland act on the adrenal cortex and produce the stress steroid cortisol. The hypothalamus also activates the sympathetic responses, including catecholamine, from the adrenal medulla. The magnitude of the hormonal and sympathetic stress response is associated with the extent of trauma (Desborough, 2000). These stress responses can occur within the first hours after TBI, and can persist for weeks (Lemke, 2004). To the extent that the stress response is part of the agitation syndrome, the salutary effects of music on agitation may be related at least in part to reductions in sympathetic tone or cortisol release.

The stress response is modified differentially by parameters of music, such as tempo (slow, fast) (Conrad et al., 2007; Suda, Morimoto, Obata, Koizumi, & Maki, 2008; Bernardi, Porta, & Sleight, 2006). In fact, tempo may be one of the most important parameters in reducing the stress response (Bernardi, Porta, & Sleight, 2006; Björkman, Karlsson, Lundberg, & Frisman, 2013). Slower tempos are associated with decreased blood pressure and heart rate (Conrad et al., 2007). For example, Conrad and colleagues examined the response of critically ill patients to a one-hour music listening session in which only the slow movements of Mozart sonatas were played. After the session, decreases in heart rate and stress hormone levels were observed. Furthermore, patients in the music group required lower doses of sedatives to achieve the same level of sedation as patients in the no music group (Conrad et al., 2007). Sandstrom & Russo (2010) compared the effects of different music parameters on the stress response, as measured by heart rate and skin conductance. Participants were split into four music listening conditions with different valences (positive, negative) and arousal types (low, high). Participants in the low arousal and positive valence conditions demonstrated more rapid recovery from the stress response than those in the high arousal and negative valence conditions. This corresponded with their subjective reports of discomfort (Sandstrom & Russo, 2010).

Preferred music may also mitigate the stress response by creating a familiar environment, which may be particularly beneficial for individuals with dementia and TBI, who are often confused and disoriented. In a pioneering study in individuals with dementia, it was proposed that by creating a familiar environment through preferred music, the cognitive demands placed on the individual in trying to interpret a novel environment were lowered, thereby resulting in decreases in agitation (Gerdner & Swanson, 1993). To date, the majority of studies evaluating the effects of preferred music on agitation have been conducted in dementia patients, which has provided the foundation for similar studies in TBI patients.

Music Listening Interventions in Neurological Populations

Preferred music listening interventions

The effects of preferred music on agitation in dementia. There is considerable support for the use of preferred music in dementia patients (Sanchez, 2016; Scudamore et al., 2021; Harrison, 2021; Janata, 2012; Park, 2013; Hicks-Moore, 2008; Sung & Chang, 2005; Ragneskog et. al., 2001; Gerdner, 1997; Clark, 1998; Gerdner, 2000; Gerdner & Swanson, 1993; Schroeder et. al, 2018)**.** For example, one study demonstrated that six weeks of preferred music therapy with a trained therapist resulted in decreased agitation in dementia patients compared with patients receiving standard care. Furthermore, the preferred music group did not see an increase in their psychotropic medication, unlike the control group (Ridder, Stige, Qvale, & Gold, 2013). In another study, home-dwelling patients with dementia had significant reductions in agitation following just four 30-minute sessions of their preferred music over two weeks (Park, Williams, & Lee, 2016). Sung and colleagues found that home residents with Alzheimer's disease who listened to their preferred music twice a week for six weeks had lower levels of anxiety than those receiving standard care (Sung, Chang, & Lee, 2010). Finally, assisted-living facility patients with Alzheimer-type dementia demonstrated decreased levels of agitation and depression in response to preferred music streaming into their rooms (Janata, 2012). The compelling evidence of the effects of preferred music on agitation in individuals with dementia has encouraged curiosity as to whether this might be applied successfully to TBI patients.

The effects of preferred music on agitation in TBI patients. To our knowledge, two studies have examined the effects of preferred music listening interventions on agitation in TBI patients, with both demonstrating positive results. Baker (2001) examined the effects of preferred taped and live music on agitation in 22 patients with post-traumatic amnesia. The patients' preferred music was determined by family members. Following this, each patient received either taped, live, twice a day for six days, or no music. Agitation was measured using the Agitated Behavior Scale (ABS), an objective measure of agitation over time (Corrigan, 1989). Scores were computed at baseline and following the intervention. Scores were lower in the taped or live preferred music conditions compared to the no music condition. Baker also made qualitative observations. For example, some patients replaced disorganized motor behaviors, such as pacing and inappropriate movements, with organized movements, such as tapping along to the rhythm or pacing in time with the music.

In the same study, patients' scores on the Westmead Post-traumatic Amnesia Scale improved during the preferred music condition. This scale measures the ability to acquire new information, as well as orientation to person, place and time. Baker proposed that the predictability of a familiar song may also help patients with PTA to orient themselves in an unfamiliar and stressful environment. Preferred music induces positive mood and memories, further increasing the sense of orientation (Baker, 2001; Park et al., 2016), and possibly decreasing anxiety and agitation. Indeed, these results are in keeping with the fact that music listening activates the mesocorticolimbic "reward" system of the brain, which is linked to the experience of positive mood and emotion (Blood & Zatorre, 2001; Koelsch & Skouras, 2014).

In a case-crossover design study by Park, Williams and Lee (2016), agitation significantly decreased in a preferred music condition compared to a relaxing classical music condition or no music. The three-day intervention was conducted in 14 severely head-injured patients. Patients' preferred music was selected by family and friends. Each intervention lasted three hours. On the first day, during the first hour, no music was played. During the second hour, patients listened to either relaxing classical music or preferred music. Finally, during the third hour, no music was played. The second day was a washout period. The third day was similar to the first, except that listening conditions were counterbalanced between days. The ABS score was calculated for each condition. The finding that preferred music was more effective at reducing agitation than relaxing classical music supports the argument that preferred music is more effective than unpreferred music chosen by the researcher as relaxing.

Although these studies demonstrated benefits of music at reducing agitation in TBI patients, there were important methodological limitations that make it difficult to draw conclusions. First, the absence of a control condition makes it difficult to determine if the reduction in agitated behaviors was due to the music, or due to the simple fact that there was an intervention. Second, bathing and feeding routines occurred for some patients during the intervention, which may have altered behaviours. This is particularly impactful when using a case-crossover design in which each condition is only presented once. Third, the presence of the researcher in the room throughout interventions may have altered agitated behaviours. Fourth, the fact that the person rating behaviours was not blind to the condition elevates the risk of rater bias. Finally, it has not been determined how well individuals with acute TBI are able to perceive and process music.

The potential impact of music perception deficits on the enjoyment of music following TBI

Many of the structures implicated in pitch and rhythm processing are located in frontal and temporal regions, particularly in the right hemisphere (Albouy et al., 2013; Albouy et al., 2019; Rosslau et al., 2015; Särkämö et al., 2010; Tillmann, Lévêque, Fornoni, Albouy, & Caclin, 2016). Frontal and temporal areas are among the most common locations of damage following TBI (Oberholzer & Müri, 2019). Thus, TBI patients may be expected to have deficits in the processing of pitch and rhythm during the acute phase, when music interventions for agitation would ideally be introduced. Two previous studies have demonstrated deficits in pitch and rhythm processing in individuals during the chronic phase of TBI one to ten years post-TBI, when compared to healthy controls (Balzani, Mariaud, Schön, Cermolacce, & Vion-Dury, 2014; Léard-Schneider & Lévêque, 2020).

It is currently unknown as to how music processing deficits might alter emotional responsiveness or engagement in music after TBI. However, case studies in patients with acquired brain injury who have music processing deficits report decreased enjoyment of music (Griffiths et al., 1997; Peretz et al., 1994; Satoh et al., 2016). Furthermore, more than half of individuals with congenital amusia report not enjoying music (McDonald & Stewart, 2008; Omigie, Müllensiefen, & Stewart, 2012), compared to none (McDonald & Stewart, 2008), or 6% (Omigie et al., 2012) of healthy controls. Specifically, music is less prone to alter the mood of individuals with congenital amusia, and they incorporate it less into their everyday life than controls (McDonald & Stewart, 2008; Omigie et al., 2012). Applied to TBI patients, if they no longer enjoy music following their injury, it may not have the desired effect of reorienting them and attenuating the stress response. In fact a music intervention may have the potential to become a source of stress that may exacerbate agitation. It would therefore be important to systematically examine music perception in TBI patients during the acute phase to better characterize possible music deficits.

Limitations in the current literature on music listening intervention studies

Despite the ample number of studies that support the efficacy of music listening interventions on agitation, there is still a need for well-controlled studies (Samson, Clément, Narme, Schiaratura, & Ehrlé, 2015). Results from a sizeable portion of music intervention studies are influenced by numerous uncontrolled variables that may lead to exaggerated treatment effects (Samson et al., 2015). Examples include rater bias, multiple nursing staff inconsistently administering stimuli, and interruptions to testing, among other variables. Often, the reporting of methodology, music stimuli, and sample characteristics is incomplete, which thwarts attempts at replication. Finally, the majority of studies have no control condition, which limits the conclusions that can be drawn. The overarching result is a failure to translate results from research to consistent application in clinical practice. (Dobkin, 2009). In order to progress to more controlled studies, it may be useful to conduct smaller phase 2 studies designed to settle a number of questions. For example, it would be important to successfully operationalize the testing variable and determine whether the environment is conducive to testing procedures, outcome measures can be objectively and reliably measured, and raters can be blinded to the conditions. Smaller stage 2 studies allow for the adding or subtracting of components that might compliment the intervention (Dobkin, 2009). Failure to replicate previous studies or attain positive results should be reported.

Aims and Overview

The present thesis has three main objectives, each of which is explored in a separate research study.

The first objective is to systematically examine whether individuals hospitalized with TBI have music perception deficits. If deficits are detected, we will characterize them in the context of hemispheric lesion lateralization based on CT findings. We will also examine the comorbidity of pitch and rhythm, and the relationship of pitch and rhythm deficits to verbal short-term memory.

The second objective is to conduct a non-systematic literature review of non-pharmacological behavioural interventions for the management of agitation during acute and sub-acute care for TBI in order to provide a summary of several behavioural intervention studies. To this end, we will examine case studies and case series studies that use musical interventions, operant contingency management, occupational therapy, the Information Contingencies Awareness Relationship (ICAR) behavioral model for agitation management, and general therapeutic activities.

The third objective is to conduct a phase-II development-of-concept pilot study comparing the effects of preferred music, relaxing classical music, or a non-musical control condition on agitated behaviour in patients with acquired brain injury during acute hospitalization. We aim to assess outcomes for these listening conditions. We will also determine the practicality of applying and monitoring a music listening intervention on an acute care ward in a trauma centre.

CHAPTER II: Article 1

Pitch and Rhythm Perception and Verbal Short-Term Memory in Acute Traumatic Brain Injury

Kirsten S. Anderson [1,2,3,*], Nathalie Gosselin [1,3], Abbas F. Sadikot [4], Maude Laguë-Beauvais [4,5], Esther S. H. Kang [6], Alexandra E. Fogarty [7], Judith Marcoux [4,5], Jehane Dagher [2,5] and Elaine de Guise [1,2,8,*]

[1] Département de Psychologie, Université de Montréal, Montréal, QC, Canada

[2] Centre de Recherche Interdisciplinaire en Réadaptation du Montréal Métropolitain (CRIR), Montreal, QC, Canada

[3] BRAMS - International Laboratory for BRAin, Music and Sound Research (BRAMS), and Centre for Research on Brain, Language, and Music (CRBLM), Montréal, QC, Canada

[4] Neurology and Neurosurgery Department, McGill University Health Centre, Montreal, QC, Canada

[5] Traumatic Brain Injury Program, McGill University Health Centre, Montreal, QC, Canada,

[6] Faculty of Medicine, McGill University, Montreal, QC, Canada

[7] Department of Neurology, Division of Physical Medicine and Rehabilitation, Washington University School of Medicine, St. Louis, MO, USA

[8] Research Institute of the McGill University Health Centre, Montreal, QC, Canada, H4A 3J1

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Abstract

Music perception deficits are common following acquired brain injury due to stroke, epilepsy surgeries, and aneurysmal clipping. Few studies have examined these deficits following traumatic brain injury (TBI), resulting in an under-diagnosis in this population. We aimed to (1) compare TBI patients to controls on pitch and rhythm perception during the acute phase; (2) determine whether pitch and rhythm perception disorders co-occur; (3) examine lateralization of injury in the context of pitch and rhythm perception; and (4) determine the relationship between verbal short-term memory (STM) and pitch and rhythm perception. Music perception was examined using the Scale and Rhythm tests of the Montreal Battery of Evaluation of Amusia, in association with CT scans to identify lesion laterality. Verbal short-term memory was examined using Digit Span Forward. TBI patients had greater impairment than controls, with 43% demonstrating deficits in pitch perception, and 40% in rhythm perception. Deficits were greater with right hemisphere damage than left. Pitch and rhythm deficits co-occurred 31% of the time, suggesting partly dissociable networks. There was a dissociation between performance on verbal STM and pitch and rhythm perception 39 to 42% of the time (respectively), with most individuals (92%) demonstrating intact verbal STM, with impaired pitch or rhythm perception. The clinical implications of music perception deficits following TBI are discussed.

Keywords: traumatic brain injury; verbal short-term memory; music perception; pitch; rhythm

Introduction

Amusia is a disorder in music processing that is independent of musical training, and may be present despite normal intelligence, verbal memory skills, language skills, and auditory functioning (Peretz, Champod, & Hyde, 2003; Tillmann, Schulze, & Foxton, 2009). It is estimated that between 1.5% and 4.2% of the general population has congenital amusia (Peretz & Vuvan, 2017). Music perception deficits after acquired brain injury and neurosurgical interventions are often referred to in the literature as acquired amusia. Whereas acquired music perception deficits have been studied in the context of stroke (Hirel et al., 2017; Peretz, 1990; Särkämö et al., 2009; Sihvonen et al., 2016; Sihvonen, Ripolles, Rodriguez-Fornells, Soinila, & Särkämö, 2017; Sihvonen et al., 2019; Steinke, Cuddy, & Jakobson, 2001), surgical interventions following epilepsy (Liegeois-Chauvel, Peretz, Babai, Laguitton, & Chauvel, 1998; McChesney-Atkins, Davies, Montouris, Silver, & Menkes, 2003; Sihvonen et al., 2019; Zatorre, 1985, 1988), and the clipping of aneurysms (Ayotte, Peretz, Rousseau, Bard, & Bojanowski, 2000; Peretz, 1996; Peretz et al., 1994), few studies have examined deficits in music perception following traumatic brain injury (TBI) (Balzani et al., 2014; Hattiangadi et al., 2005; Léard-Schneider & Lévêque, 2020). Although patients with head injury may show evidence of acquired amusia to various degrees, these deficits have not been studied using rigorous quantitative measures integrated with brain imaging findings.

The majority of amusia studies examine musical pitch processing. Thus, amusia is often attributed to difficulty processing pitch, whether related to pitch-specific memory deficits (Albouy et al., 2013; Foxton, Dean, Gee, Peretz, & Griffiths, 2004; Gosselin, Jolicoeur, & Peretz, 2009; Schaal, Pfeifer, Krause, & Pollok, 2015; Tillmann, Leveque, Fornoni, Albouy, & Caclin, 2016; Williamson & Stewart, 2010), or pitch-specific perceptual deficits (Peretz, 2016;

Peretz, Champod, & Hyde, 2003). Deficits in pitch perception can interfere with rhythm discrimination (Foxton, Nandy, & Griffiths, 2006), and the ability to accurately perceive durations between notes (Pfeuty & Peretz, 2010). This may be due to simultaneous demands made on pitch and rhythm processing. However, evidence indicates that pitch deficits in amusia may be dissociable from rhythm deficits (Di Pietro, Laganaro, Leemann, & Schnider, 2004; Mavlov, 1980; Peretz, 1990; Peretz & Kolinsky, 1993). The Montreal Battery for the Evaluation of Amusia (MBEA) is the most widely-used measure to diagnose perceptual deficits (Vuvan et al., 2018), with subtests comprising both the melodic dimension (sequential variations in pitch) and temporal dimension (sequential variations in duration) (Peretz et al., 2003). Given the MBEA's usefulness in identifying music disorders following brain damage, the TBI population provides a novel opportunity to determine how performance on the MBEA relates to the lateralization of pitch and rhythm perception.

Neural networks underlying pitch and rhythm discrimination

Individuals with congenital amusia demonstrate pitch deficits associated with abnormalities in a predominantly right frontotemporal network (Albouy et al., 2013; Albouy et al., 2019; Rosslau et al., 2015; Särkämö et al., 2010; Tillmann et al., 2016). This is evidenced in increased grey matter density and decreased white matter density in the right inferior frontal gyrus (Hyde, Zatorre, Griffiths, Lerch, & Peretz, 2006), and right superior temporal gyrus (Hyde et al., 2007), compared with controls (Albouy et al., 2013; Peretz, 2016). The volume of the right arcuate fasciculus is reduced (Chen et al., 2015; Loui, Alsop, & Schlaug, 2009; Peretz, 2016). In addition, there is diminished connectivity between the right auditory cortex and the right inferior frontal gyrus (Albouy et al., 2013; Loui et al., 2009; Peretz, 2016), with anomalous recurrent processing between these regions (Loui et al., 2009; Peretz, 2016). Finally, there is increased activity between the left and right auditory cortices (Albouy et al., 2013). In sum, congenital amusia is associated with decreased activity between inferior frontal and auditory regions, and increased activity between auditory cortices (Hyde, Zatorre, & Peretz, 2011; Peretz, 2016).

Overlapping neural networks appear to underlie pitch and rhythm processing (Jerde, Childs, Handy, Nagode, & Pardo, 2011), and pitch and rhythm disorders may co-occur in individuals with congenital amusia (Lagrois & Peretz, 2019; Léard-Schneider & Lévêque, 2020; Léard-Schneider & Lévêque, 2020). However, several imaging studies demonstrate that pitch and rhythm processing are at least partly dissociable (Di Pietro et al., 2004; Jerde et al., 2011; Mavlov, 1980; Peretz, 1990; Peretz & Kolinsky, 1993; Samson, Ehrle, & Baulac, 2001), with more widespread neural activation occurring during rhythm processing (Phillips-Silver, Toiviainen, Gosselin, & Peretz, 2013). For example, a PET study of healthy individuals demonstrated that both pitch and rhythm activated a frontoparietotemporal network. However, only rhythm processing recruited the subcortical region of the cerebellum (Jerde et al., 2011). Indeed, rhythm involves activation of both cortical (ie. prefrontal cortex, premotor cortex, supplementary motor area, temporal lobe, and parietal cortex), and subcortical (ie. cerebellum, and basal ganglia) areas (Levitin, Grahn, & London, 2018; Penhune, Zatorre, & Feindel, 1999; Phillips-Silver et al., 2013). Therefore, either damage to a predominantly right frontoparietotemporal network or damage to subcortical areas can result in impaired interval timing and duration estimation (Piras et al., 2014). In summary, studies of pitch and rhythm indicate involvement of diffuse brain regions during musical processing, with most studies indicating right-hemisphere anomalies.

Acquired amusia in individuals with traumatic brain injury and stroke

Traumatic brain injury may be defined as “an alteration in brain function, or other evidence of brain pathology, caused by an external force” (Menon et al., 2010), and may result in disruption of attention, memory, and executive functions (Arciniegas, Held, & Wagner, 2002). Given the extensive cortico-cortical networks underlying amusia, TBI patients may have a higher incidence of music perception deficits than that observed in the general population. Indeed, a study conducted by Balzani and colleagues (2014) reported that mild TBI patients demonstrated impaired performance on the MBEA Rhythm test (p = .01) and a trend in poorer performance on the MBEA Scale test (p = .07) than controls (Balzani et al., 2014; Léard-Schneider & Lévêque, 2020). A recent study confirmed that TBI patients performed significantly worse than healthy controls on both the Scale and Rhythm tests of the MBEA (Léard-Schneider & Lévêque, 2020). Both studies evaluated TBI patients following a significant time lapse, from one to 10 years post-injury. Neither study evaluated regional abnormalities on brain imaging in TBI patients, relative to deficits on the Scale and Rhythm subtests of the MBEA. Furthermore, music perception was not examined in TBI patients during the acute period of recovery, defined here as the first three months following injury. Thus, to our knowledge, the present study is the first to examine and relate regional abnormalities on brain imaging to music perception in patients during the acute phase of TBI, when music interventions are often initiated.

Studies conducted in stroke populations report impaired performance on the Scale test, particularly in cases of right hemisphere damage (Hirel et al., 2017; Särkämö et al., 2009; Särkämö et al., 2010). For example, among patients with middle cerebral artery damage, those with right hemisphere damage have more severe pitch deficits on the MBEA than those with left hemisphere damage (Särkämö et al., 2010). This is particularly true for patients with damage to frontal and temporal regions (Särkämö et al., 2010). Together, these studies demonstrate that individuals with brain damage have poorer performance on the Scale and Rhythm tests than do healthy individuals.

The question of modularity in short-term memory for rhythm and pitch

The frontotemporoparietal network that is associated with amusia has also been associated with domain-general short-term memory (STM) (Brown & Martinez, 2007; Särkämö et al., 2010). Short-term memory is defined here as the maintenance of stored auditory or verbal information for seconds to minutes, without manipulation (Baddeley, 2010; Cowan, 2008). Therefore, an important question arises as to whether domain-general STM deficits underlie amusia, or whether a pitch-specific memory deficit underlies amusia (Albouy et al., 2019). Several studies provide evidence that verbal memory and pitch memory are shared domains (Chan, Ho, & Cheung, 1998; Särkämö et al., 2009; Särkämö et al., 2010; Schaal et al., 2015; Schendel & Palmer, 2007; Schulze & Koelsch, 2012). Indeed, a recent meta-analysis concluded that trained musicians perform significantly better at both verbal and tonal short-term memory tasks than non-musicians (Talamini, Altoe, Carretti, & Grassi, 2017). The fact that musical training is associated with greater verbal STM points to shared mechanisms between musical short-term memory and verbal short-term memory. Indeed, one study conducted in stroke patients found that acquired amusia was associated with deficits in domain-general attention, executive functions, and working memory (Särkämö et al., 2009).

However, other studies have proposed separate memory systems for pitch and verbal material (Defilippi, Garcia, & Galera, 2019; Deutsch, 1970; Salamé & Baddeley, 1989; Williamson & Stewart, 2010). Evidence for this has been demonstrated in healthy participants, who are impaired at recognizing and maintaining tones in STM when there is interference of irrelevant tones, but not words (Defilippi et al., 2019; Deutsch, 1970). Studies in congenital amusia also propose that STM for pitch and verbal STM are dissociable (Albouy et al., 2019; Williamson & Stewart, 2010), based on findings of spared verbal STM, with impaired pitch memory (Foxton et al., 2004; Jones, Zalewski, Brewer, Lucker, & Drayna, 2009; Tillmann et al., 2009). It is as yet unclear whether short-term memory mechanisms for music and verbal material are shared, overlapping, or separate. However, a recent fMRI study proposes that music perception deficits may be explained by an inability to integrate higher order processing, such as STM, with the elemental components of music (Albouy et al., 2019). Research in TBI patients, who commonly suffer attention and memory deficits, might further elucidate the mechanisms underlying music processing, and deficits associated with amusia.

Goals of the present study

We aimed 1) to evaluate the performance of mild to severe patients with TBI on pitch and rhythm processing during the acute phase of injury, compared with healthy controls. We hypothesized that a TBI patient population would demonstrate impaired performance on music perception tasks compared to healthy controls; 2) to determine and characterize the possible co-occurrence of pitch and rhythm disorders in TBI patients. We hypothesized that pitch and rhythm perception deficits would co-occur in TBI patients, who often have diffuse injury; 3) to determine in a TBI population whether damage predominantly located in the right or left hemisphere is associated with the hemispheric lateralization of pitch and rhythm discrimination. Based on studies conducted in individuals with congenital amusia and acquired amusia following stroke, we hypothesized that TBI patients with right hemisphere damage would have greater deficits than those with left hemisphere damage; and 4) to determine if verbal short-term memory is related to pitch and rhythm perception in TBI patients, who often have STM deficits. Given the fact that previous studies argue for at least partly overlapping mechanisms of verbal

STM and pitch STM, we hypothesized that TBI patients with lower scores on MBEA tasks would have lower scores on a verbal short-term memory task.

Materials and Methods

Participants

Forty-two mild, moderate, and severe TBI in-patients who were hospitalized on the neurology and neurosurgery ward at the McGill University Health Centre-Montreal General Hospital (MUHC-MGH) were included in this study (Table 1). Patients seen only in the emergency room were not included.

TBI patients who participated had an initial Glasgow Coma Scale test score of 3-15, and were admitted to our tertiary traumatology center. Scores from arrival, emergency, and post-resuscitation were collected by the research assistant from the patient's medical chart. A GCS score between 3 and 8 was considered to be a severe TBI, a score between 9 and 12 was considered moderate, and a score between 13 and 15 was considered mild (Fischer & Mathieson, 2001; Heilman, Safran, & Geschwind, 1971). Within the mild TBI population is a subgroup referred to as "mild complex," a radiological diagnosis applied to patients with positive findings on CT. The TBI diagnosis was confirmed by a physician, based on the Centers for Disease Control and Prevention criteria (Control & Prevention, 2015). Patients who were included in the sample had sustained a closed head injury, meaning that the there was no penetrating injury. Therefore, direct or indirect force (rotational and/or deceleration) to the head caused the injury.

Exclusion criteria for the study included a pre-morbid history of alcohol or drug abuse, an active diagnosis of psychiatric disorder, pre-existing neurological deficits, post-traumatic agitation precluding collaboration, aphasia, inner ear fractures, hemotympanum, and visual and hearing impairment. Hearing impairment was determined by asking each participant if they had suffered a hearing loss or had a history of congenital impairment, in addition to verifying with each individual that they were capable of hearing the sample musical excerpts with ease during practice trials. Assessments were not performed when patients were administered intravenous narcotic medication, or while they were still in the intensive care unit. Patients not fluent in English or French were excluded, as well as those who were unable to consent. To compare the performance on music perception tests, the TBI patients were matched for age and education with 42 healthy control participants selected from the norms of 421 participants who completed the MBEA (Peretz, et. al., 2003; see the Isabelle Peretz Research Laboratory website, https://www.peretzlab.ca/publications/2003/page2). Matching was done based on age and education level only, while remaining blind to the scores of each individual.

Measures and Procedure

Demographic, medical, accident-related and musical training characteristics were retrieved from each patient's medical file, and collected through questions during their hospitalization (Table 1). Consent to participate in the study was obtained when the patient's condition was medically stable, following resolution of post-traumatic amnesia. All evaluations were conducted by research assistants who were trained by a neuropsychologist. Extended Glasgow Outcome Scale assessments were done by the treatment team upon discharge from hospital (Levin et al., 2001). The Scale and Rhythm subtests of the MBEA along with a verbal short-term memory test were administered at each patient's bedside for a total duration of 25-30 minutes, with breaks between subtests as needed.

Scale and Rhythm tests of the Montreal Battery of Evaluation of Amusia (MBEA). These two subtests of musical perception were administered to evaluate whether the TBI patients had deficits following their injuries, using the total score for each subtest. The Rhythm test and Scale test are thought to tap relatively distinct abilities or processing components, with the Scale test measuring musical perception on the melodic dimension (varying sequences of pitch that are thought to be processed by a subsystem that specifies melodic contour and tonal functions), and the Rhythm test measuring musical perception on the temporal dimension (varying sequences of duration thought to be processed by a relatively independent subsystem in parallel to the processing of the melodic dimension; this subsystem treats the rhythmic structure and metric organization of music) (Peretz et al., 2003). The Scale and Rhythm subtests of the MBEA were chosen 1) to facilitate comparison with previous studies in chronic TBI patients, and 2) because acute TBI patients are easily fatigued and would likely have difficulty completing the entire MBEA battery. The Scale and Rhythm subtests were played at the patient's bedside through a wireless Bose SoundLink Color Bluetooth speaker II (Bose Corporation, Framingham, MA, USA) during a time in which patients were uninterrupted. The order of tests was counterbalanced across participants.

Each test lasted 10 minutes, and consisted of 2 practice trials, followed by 30 trials, and one catch trial. Feedback was limited to the practice trials. Each trial began with a warning tone, after which the patient was asked to compare a pair of musical stimuli for sameness. First, there was a target stimulus, followed by two seconds of silence, and then a comparison stimulus. There was an inter-stimulus interval of 5-seconds. In half of the trials, the Scale test contained one pitch that was altered to be out of scale, without changing the contour of the melody.

The Rhythm test consisted of the same melodies as the Scale test. However, in half of the trials, the rhythmic grouping of two of the tones was altered, while the meter and total number of sounds remained identical.

The MBEA has good sensitivity, with fewer than 80% of the participants not achieving perfect scores on the subtests. Test-retest reliability is also adequate (r = .75, p < .01), as is convergent validity, when compared with Gordon's Musical Aptitude Profile (r = .53, p < .001). Furthermore, it has been demonstrated to be useful in identifying music perception difficulties in populations with brain insult, such as stroke, resection of tissue in epilepsy, and the surgical clipping of an aneurysm (Peretz et al., 2003).

Digit Span. This is a subtest of the Wechsler Adult Intelligence Scale | Fourth Edition (WAIS-IV) (Wechsler, Coalson, & Raiford, 2008). Digit Span Forward is thought to measure short-term memory, or temporary storage of information. Patients were asked to repeat a sequence of digits in order that had been verbally presented by the research assistant, with the longest span calculated. The Digit Span has an internal consistency of α = .94 and a test re-test reliability of r = .74 (Lichtenberger & Kaufman, 2013).

Extended Glasgow Outcome Scale (GOSE). This widely-used scale measures functional outcomes after acquired brain injury by classifying patients into eight broad outcome categories, including death, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, and upper good recovery (Wilson, Pettigrew, & Teasdale, 1998).

Image acquisition

Computerized tomography (CT) scans were acquired from the radiology department of the Montreal General Hospital using a Toshiba scanner (Minato City, Tokyo, Japan). All CT images were reconstructed to 2.5 mm thick slices acquired in an axial orientation. Patients were scanned at the discretion of the attending emergency department physician, as per Canadian CT

Scan guidelines (Sharp et al., 2018), and each scan was independently reviewed by a neurosurgeon certified under the Royal College of Physicians and Surgeons of Canada.

Statistical analyses

To evaluate the performance of TBI patients versus controls on pitch and rhythm processing, a quasi-experimental, paired-samples t-test design was used in a sample of TBI patients who were age- and education- matched with normal controls as independent variables, and the Scale test and Rhythm test total scores as dependent variables. An alpha level of .05 was used for all analyses.

To determine whether there was a relationship between performance on the Scale and Rhythm tests of the MBEA, Pearson product-moment correlation coefficients were calculated.
To determine whether damage predominantly located in the right or left hemisphere was associated with the hemispheric lateralization of pitch and rhythm discrimination, two 2-tailed independent samples t-tests were used to compare patients with left hemisphere damage to those with right hemisphere damage. In both, the independent variable was injury location, and the dependent variable was total score on the Scale test and the Rhythm test.

To determine whether there was a relationship between performance on the Scale and Rhythm tests, and severity of brain injury, Pearson product-moment correlation coefficients were calculated.

To determine associations between performance on the Scale and Rhythm tests and verbal short-term memory tests (*Z* scores representing longest digit span forward), Pearson product-moment correlation coefficients were calculated.

All analyses were performed using SPSS 24.0.

Results

Data Integrity

During testing, there were 11 randomly missing values for Digit Span Forward (*n* = 31), and 6 randomly missing CT scan values (*n* = 36). There were no missing values for the other measures. There were no outliers in the sample. In the Scale and Rhythm tests, all variables of interest were normally distributed, with skewness values below three, and kurtosis values below 10 (Kline, 2009).

Comparison of music perception scores in TBI patients versus controls

Scale test. To test the hypothesis that TBI patients would have poorer perceptual skills compared with controls when judging musical input on the melodic dimension, the total score (/30) was calculated. TBI patients had significantly lower scores (*M* = 22.98, *SD* = 4.34) than controls (*M* = 26.88, *SD* = 1.70), indicating poorer pitch perception than that of controls, $t\ (41) = -5.42$, $p < .001$ (Figure 1). Forty-three percent of TBI patients (18/42) had Scale test scores below the cut-off of 22 as indicated in the MBEA (Peretz et al., 2003), compared with none of the healthy controls (0/42), indicating a deficit in pitch perception (Figure 2).

Rhythm test. To test the hypothesis that TBI patients have poorer perceptual skills compared with controls when judging musical input on the temporal dimension, the total Rhythm test score was calculated, and a two-tailed paired samples *t*-test conducted. TBI patients had significantly lower scores (*M* = 23.31, *SD* = 3.29) than controls (*M* = 26.69, *SD* = 2.28), indicating lower perceptual ability for rhythm than that of controls, $t\ (41) = -\ 5.43$, $p < .001$ (Figure 1). Forty percent of the TBI patients (17/42) had Rhythm test total scores that fell below the cut-off of 23 as indicated in the MBEA (Peretz et al., 2003), compared with only one of the healthy controls (1/42), indicating a deficit in rhythm perception (Figure 3). All patients and controls passed the catch trial for both subtests (Peretz et al., 2003).

The co-occurrence of pitch and rhythm deficits in acquired amusia

A moderate positive correlation was found between performance on the Scale test and the Rhythm test, r (40) = .61, $p \leq .001$. Thirty-one percent of the TBI patients (13/42) had co-occurring pitch and rhythm deficits (Table 2). In addition, nine patients had deficits exclusively in pitch, and three patients had deficits exclusively in rhythm.

Neuroimaging and performance on the Scale and Rhythm tests of the MBEA

Of the 36 patients who had CT scans performed, 18 demonstrated trauma-related brain abnormalities. Of these, two were classified according to the GCS score as severe, seven were moderate, and nine were mild complex. Group sizes were comparable with respect to lateralization (right, n = 6; left, n = 7; bilateral, n = 5)(Table 2). The data were normally distributed among sub-groups, and parametric tests were applied.

An independent samples t-test was applied to compare performance on the Scale test in TBI patients with injury involving the right hemisphere (right, bilateral) (M = 20.36, SD = 3.93) to those without predominant right hemisphere damage (left, no mass effect) (M = 23.92, SD = 4.13), t (34) = - 2.68, p = .011, d = 0.97, indicating that damage to the right hemisphere results in decreased pitch perception.

Performance on the Rhythm test was compared in TBI patients with injury involving the right hemisphere (right, bilateral) (M = 21.18, SD = 2.64) versus those without right hemisphere damage (left, no mass effect) (M = 24.04, SD = 3.45). Patients with right hemisphere damage performed worse on the Rhythm test, t (35) = - 2.45, p = .020, d = 0.93), indicating that damage to the right hemisphere decreases rhythm perception.

Finally, two-tailed independent samples t tests were performed to determine whether TBI patients with right hemisphere damage (*n* = 6) would perform more poorly than those with left hemisphere damage (n = 7) when bilateral cases (*n* = 5) were excluded. Results on the Scale test indicated that patients with right hemisphere damage (*M* = 20.50, *SD* = 5.21) performed worse than those with left hemisphere damage (*M* = 25.86, *SD* = 3.18), *t* (11) = - 2.28, *p* = .044, despite decreasing the sample size by excluding bilateral cases (Figure 4).

Results on the Rhythm test indicated that patients with right hemisphere damage (*M* = 20.50, *SD* = 2.81) also performed more poorly than those with left hemisphere damage (*M* = 24.71, *SD* = 2.29), *t* (11) = - 2.98, *p* = .012, again indicating that patients with right hemisphere damage had poorer music perception than patients with left hemisphere damage (Figure 4).

Severity of brain injury and music perception deficits

There was no correlation found between the GCS and the Scale test total score, *r* (40) = .12, *p* =.45, or the Rhythm test total score, *r* (40) = .26, *p* = .10.

Verbal short-term memory and music perception deficits

Longest Digit Span Forward. On the Digit Span Forward subtest, TBI patients scored in the low average range (*Z* = -1.01, *SD* = 0.67), with spans between four and seven digits, indicating a weakness in short-term memory. Three individuals had scores that were at least two standard deviations below average, indicating verbal STM deficits. See Table 2 for performance on a case-by-case basis.

The relationship between music perception scores and verbal short-term memory. Pearson product-moment correlation coefficients were calculated to determine if there was a relationship between performance on the Scale and Rhythm tests, and performance on verbal short-term memory tasks. A moderate positive correlation was found between longest Digit Span

Forward (*Z* = - 0.90, *SD* = 0.79), and performance on both the Scale test (*M* = 23.19, *SD* = 4.62) *r* (29) = .43, $p \leq .05$, and Rhythm test (*M* = 23.30, *SD* = 3.89) *r* (29) = .41, $p \leq .05$. There was no significant difference in performance on Digit Span Forward in patients with right (*M* = -.87, *SD* = .62) versus left (*M* = 1.00, *SD* = .82) hemisphere damage *t* (10) = .30, *p* = .767.

Pitch processing and verbal short-term memory. Fifty-eight percent of the TBI patients demonstrated either intact performance on both the Scale test and Digit Span Forward, or impaired performance on these two tests (*n* =18). Of the 42% that demonstrated deficits exclusively on one test or the other (*n* = 13), 12/13 demonstrated intact performance on Digit Span Forward coupled with impaired performance on the Scale test (Table 2).

Rhythm processing and verbal short-term memory. Sixty-one percent of the TBI patients demonstrated intact performance on the Rhythm test and Digit Span Forward, or impaired performance on these two tests (*n* =19). Of the 39% that demonstrated deficits exclusively on the Rhythm test or on Digit Span Forward (*n* = 12), 10/12 demonstrated intact performance on Digit Span coupled with impaired performance on the Rhythm test (Table 2).

Location of injury, music perception scores, and verbal STM scores. Scans were available for 15 patients who completed the Scale and Rhythm tests along with Digit Span Forward. Of these, six patients with damage involving right frontal regions had impaired performance on the Scale test and intact performance on Digit Span Forward, while one demonstrated deficits in neither. One patient who had lesions to the left inferior and prefrontal cortices had deficits on Digit Span Forward and intact performance on Scale test. Four out of six patients with injury to right or bilateral frontal regions had deficits on the Rhythm test and intact performance on the Digit Span test, while two patients had deficits in neither (Table 2).

Discussion

The present results indicate a high prevalence of music perception deficits resulting from acute TBI, particularly when the damage involves the right hemisphere. Pitch and rhythm deficits often co-occur, but are partially dissociable. Moreover, there is a partial dissociation between domain-general short-term memory and pitch and rhythm perception. This suggests that STM may fractionate into different network dynamics, depending on whether the cognitive task involves the processing of pitch, rhythm, or verbal information. We elaborate on each of these findings below.

Performance on the Scale and Rhythm subtests of the Montreal Battery of Evaluation of Amusia (MBEA)

In line with our prediction, a significant number of acute TBI patients demonstrated deficits in pitch and rhythm perception. Forty-three percent had pitch deficits, a prevalence ten times greater than in congenital amusia, which Peretz estimates only comprise 4.2% of the general population, when using the more lenient criteria of the Scale test alone (Peretz, 2016; Peretz & Vuvan, 2017). Similarly, 40% of the TBI patients demonstrated deficits on the Rhythm test. This was in contrast to age- and education- matched controls, none of whom had pitch deafness, and only one of whom had deficits in rhythm perception. There was no relationship between severity of brain injury and music perception performance, indicating that patients with mild TBI were also vulnerable to deficits in music perception.

The present results in acute TBI patients expand on results demonstrated in severe chronic TBI, in which pitch and rhythm deficits were identified in 42% and 52% of the patients, respectively (Léard-Schneider & Lévêque, 2020). Similar results were also found in a small population of mild chronic TBI patients (*n* =10), who were impaired on the Rhythm test compared to controls, and were marginally outperformed on the Scale test (p = .07) (Balzani et al., 2014), results that may have achieved significance in a larger sample size. Thus, acquired amusia following TBI may be longstanding based on the results of studies conducted in chronic TBI populations, which were collected between one year and 10 years post-TBI. It would be of interest to perform a longitudinal study comparing short- and long-term deficits in the same patients, in order to determine the recovery rate over time.

The relationship of pitch and rhythm processing in acquired amusia

As predicted, a significant number of TBI patients demonstrated co-occurring deficits in pitch and rhythm perception. In fact, 31% of acute TBI patients with pitch-deafness demonstrated comorbid rhythm processing deficits (Table 2). This builds on recent results obtained during the chronic phase of TBI, which indicate that 29% of patients have co-occurring pitch and rhythm deficits (Léard-Schneider & Lévêque, 2020). Our results are also in keeping with recent findings in congenital amusics that indicate co-occurring pitch and rhythm deficits (Lagrois & Peretz, 2019; Peretz et al., 2002). Finally, co-occurring deficits have been found in patients with acquired amusia following stroke (Sihvonen et al., 2016; Sihvonen et al., 2017; Sihvonen et al., 2019). The co-occurrence of pitch and rhythm deficits in acute and chronic TBI, stroke, and congenital amusia indicate a close link between pitch and rhythm processing that may point to shared neural networks. However, the co-occurrence of pitch and rhythm deficits may also be the result of communication deficits between separate processing components that contribute to the organization of pitch and temporal information (Peretz & Coltheart, 2003).

Given the pitch cues inherent in the Rhythm test of the MBEA, another question arises as to whether pitch processing deficits attenuate rhythm discrimination ability due to simultaneous processing demands, which may erroneously point to shared networks. This is known as the pitch interference hypothesis (Lagrois & Peretz, 2019). A previous study found support for this hypothesis by demonstrating that congenital amusics were able to perceive rhythm when pitch variations were removed (Foxton et al., 2006). However, the present study does not support the pitch interference hypothesis, as nine patients with impaired pitch perception had spared rhythm perception (Table 2). A recent study in congenital amusics also found that rhythm discrimination was spared in a number of individuals with pitch deafness (Lagrois & Peretz, 2019). Furthermore, when examining beat processing, these difficulties were present even without pitch cues, providing further support for pitch and rhythm deficits as distinct disorders, as beat processing and rhythm processing are closely associated (Lagrois & Peretz, 2019). Finally, the fact that 26% of the TBI patients with music processing deficits demonstrate selective impairment in pitch or rhythm indicates that there is some degree of neural specificity for the treatment of pitch versus rhythm.

Although it is clear that sequential patterns of melody and rhythm are integrated at some level of music processing (Peretz, 1990), little is known about the levels at which this occurs. Imaging studies identifying neural correlates for pitch and rhythm processing are sparse. However, one recent study illustrated the close connection between pitch and rhythm processing regions in the brain using voxel-based lesion-symptom mapping (VLSM) (Sihvonen et al., 2016). In a sample of 77 stroke patients, deficits on the Scale and Rhythm tests of the MBEA were both associated with right hemisphere lesions in the auditory cortex, Heschl's gyrus, basal ganglia (putamen, caudate, pallidum), and insula. Furthermore, recovery from acquired amusia was associated with smaller decreases in gray matter in the right temporal lobe for both rhythm and pitch. This indicates shared structures in the processing of rhythm and pitch. However, for pitch amusia, the decreases were observed posteriorly, and for rhythm deficits, anteriorly

(Sihvonen et al., 2017), indicating partial dissociation in the neuroanatomy underlying pitch and rhythm processing. In the present study, a total of 11 patients demonstrated a dissociation between pitch and rhythm processing (nine of whom had impaired pitch and preserved rhythm processing; and two of whom had impaired rhythm and preserved pitch processing).

In sum, the present results in acute TBI patients support a partly shared, partly dissociable network for the processing of pitch and rhythm. This has been proposed in other populations, such as congenital amusia (Lagrois & Peretz, 2019), stroke (Lagrois & Peretz, 2019; Sihvonen et al., 2016), and healthy individuals (Zatorre & Belin, 2001). For example, one study found evidence of anatomically distinct areas in the processing of spectral (tone spacing) versus temporal variations in the auditory cortex of healthy individuals (Zatorre & Belin, 2001). Future PET and fMRI studies may elucidate the overlap and independence of associated structures and network dynamics. This would expand our understanding of the nature of rhythm processing deficits, and how temporal and melodic dimensions may combine in music processing.

The lateralization of pitch and rhythm deficits

As predicted, patients with right hemisphere damage had greater deficits in pitch and rhythm perception than those with damage to the left hemisphere. To our knowledge, this has not been previously demonstrated in a group of acute TBI patients. However, the hemispheric lateralization has been demonstrated in other neurological populations, such as stroke (Rosslau et al., 2015; Särkämö et al., 2010; Sihvonen et al., 2016), and early single case studies, in which right hemisphere damage was associated with more severe pitch perception deficits in individuals with unilateral temporal lobe excisions (Zatorre, 1998), temporal lobectomy (Milner, 1962), and stroke (Terao et al., 2006). Right hemisphere damage was also associated with difficulty detecting rhythm violations (Fries & Swihart, 1990) (Fujii, 1990). Finally, our results provide supportive evidence for the predominantly right neural network underlying the processing of pitch and rhythm that has been observed in congenital amusia (Brown & Martinez, 2007; Gaab, Gaser, Zaehle, Jancke, & Schlaug, 2003; Liegeois-Chauvel et al., 1998; Peretz, 2016; Zatorre, Evans, & Meyer, 1994). Both pitch and rhythm activate a network of frontal and temporal areas in the right hemisphere (Sihvonen et al., 2016).

There is also evidence for interhemispheric involvement in music processing, with left lateralization of certain subsystems (Liegeois-Chauvel et al., 1998; Peretz, 2016; Schuppert, Munte, Wieringa, & Altenmuller, 2000; Sihvonen et al., 2019; Zatorre, 1998). Furthermore, acquired amusia is associated with interhemispheric connectivity damage originating in the corpus callosum and tapetum (Sihvonen et al., 2019). However, the normal perception of pitch and rhythm depends on functional connectivity between core structures in a distributed network of brain regions located mainly in the right hemisphere.

This connectivity may be disrupted in TBI patients who suffer from grey matter injury, and/or traumatic axonal injury, which is defined as the stretching, breaking, or twisting of neuron fibres (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013). Damage is commonly located in the frontal lobe, temporal lobe, and corpus callosum, according to studies using diffusion tensor imaging (DTI), a method optimized for detecting white matter injury (Hulkower et al., 2013). White matter tract damage may disrupt fronto-temporal networks connecting auditory regions to inferior frontal regions, which may underlie the maintenance of pitch in STM (Albouy et al., 2019; Hyde et al., 2006; Peretz, 2016). Indeed, in congenital amusics, anomalous processing has been identified in the arcuate fasciculus, a major white matter tract connecting the frontal and temporal regions (Peretz, 2016). Given the fact that the corpus callosum has white matter fibres through which interhemispheric auditory pathways run (Aboitiz, 1992), damage to this region may also contribute to anomalous processing.

Finally, it is possible that the scores of TBI patients in the present study in the context of left or right unilateral lesion do not only reflect an inability of the damaged region to analyze pitch or rhythm information, but also the inhibiting effects of contralateral homologous regions, which may undergo widespread structural changes as an adaptive part of functional reorganization. Support for this phenomenon is found in studies of stroke patients with aphasia (Heiss & Thiel, 2006). Currently, there is a lack of research examining this in TBI patients in the context of music processing, possibly due to the complicating factor of frequently diffuse injuries in this population, and the widespread functional networks involved in music processing. Future studies examining this process in the context of music perception and TBI would be warranted.

The relationship between music perception scores and verbal short-term memory

Pitch processing and verbal short-term memory. As hypothesized, a relationship between pitch perception and verbal short-term memory ability was found in 58% of the TBI patients (*n* = 18). These results suggest shared processing components between tonal and verbal material in short-term memory, which is in keeping with research studies conducted in other populations, such as normal healthy individuals (Schendel & Palmer, 2007), musicians (Chan et al., 1998; Talamini et al., 2017), individuals with congenital amusia (Schaal et al., 2015), and stroke (Särkämö et al., 2010). For example, one study demonstrated that recovery on amusia tests three months post-stroke was associated with the recovery of general-domain verbal memory (Särkämö et al., 2009).

However, in addition to these shared regions for pitch processing in STM, we provide evidence for at least partly distinct brain mechanisms for pitch and verbal material, as observed in 42% of the TBI patients. The majority of these patients (12/13) had impaired performance at pitch perception (which relies on pitch STM) (Peretz, 2016; Tillmann et al., 2009) with preserved verbal STM. To our knowledge, this is the first time that this dissociation is being demonstrated in TBI patients with pitch perception deficits. The results of partly shared and partly separate regions for pitch processing are in keeping with results found in stroke patients, some of whom demonstrated impairment only in pitch STM, some only in verbal STM, and some in both (Hirel et al., 2017). Our results in acute TBI patients expand on studies of individuals with congenital amusia, which have shown that those with a selective impairment in pitch processing have intact verbal STM (Albouy et al., 2019; Marin, Gingras, & Stewart, 2012; Williamson & Stewart, 2010).

To examine the origins of this dissociation, we turn to previous studies examining the contribution of low-level perceptual deficits (such as detection of pitch changes and directions, deviancies, and duration) to amusia. However, these deficits are thought to be a manifestation of amusia, as opposed to its functional root (Peretz, 2016; Särkämö et al., 2010). This is based on studies that indicate that while pitch is adequately processed in the amusic brain, it is not done in conscious awareness (Moreau, Jolicœur, & Peretz, 2013). Indeed, congenital amusics demonstrate pitch detection thresholds that are comparable to controls, pointing more to a deficit in STM for pitch, rather than low-level perceptual deficits (Tillmann et al., 2016). Furthermore, while certain studies report that pitch detection deficits in amusics decrease performance in tasks measuring pitch STM (Albouy et al., 2013; Tillmann et al., 2009; Williamson & Stewart, 2010), these results were based on amusics more accurately discriminating differences in comparison melodies with contour variations or larger pitch intervals, which was similar in controls (Tillmann et al., 2016). Therefore, it is reasonable to propose that the current results of our study point to altered dynamics in the recruitment of higher-order processing, such as pitch STM (Gosselin et al., 2009; Tillmann et al., 2016), rather than in low-level perceptual pitch deficits.

The altered neural dynamics associated with deficits in short-term memory for pitch are elucidated in a recent fMRI study by Albouy, Peretz, et al. (2019). Compared to controls, congenital amusics demonstrated 1) reduced activity in auditory regions that facilitate low-level sensory processing of fundamental musical elements such as pitch detection; and 2) a deficit in recruiting higher-level association areas, such as the right frontal IFG and DLPFC, key areas for maintaining pitch in short-term memory (Albouy et al., 2019). A study by Schaal (2015) also identified the role of the DLPFC in maintaining pitch in short-term memory, with findings that transcranial alternating current stimulation applied to the right DLPFC resulted in increased pitch memory in amusics (Schaal et al., 2015). Reduced connectivity between frontal and temporal regions in the right hemisphere is thought to disrupt feedback/feedforward systems that would normally combine low-level information about pitch and duration (Johnsrude, Penhune, & Zatorre, 2000; Liegeois-Chauvel et al., 1998; Peretz, 1990; Sihvonen et al., 2016; Tillmann et al., 2016; Zatorre, 1998) with higher order associative functions, such as short-term memory, awareness, and error correction (Brown & Martinez, 2007; Gaab et al., 2003; Peretz, 2016; Särkämö et al., 2010). Failure to integrate components of elemental musical features with higher-order processing could result in a deficit in an entire domain, such as music, while leaving another domain, such as verbal, intact (Brown & Martinez, 2007; Peretz, 2016).

Indeed, the present study demonstrates that damage to right frontal areas, which are fundamental to pitch processing in short-term memory, may cause deficits in pitch perception, while leaving verbal short-term memory intact. For example, five of six patients with damage involving right frontal regions had impaired pitch perception, and unimpaired verbal STM (Table

2). Based on the aforementioned studies, it is possible that these patients had a diminished capacity for recurrent processing between the right auditory region and the right frontal region due to disrupted connections. This would be expected to compromise pitch STM while leaving verbal STM intact, as the latter relies more heavily on left-lateralized structures (Buchsbaum & D'Esposito, 2008; Buchsbaum, Olsen, Koch, & Berman, 2005; Fiez et al., 1996; Ravizza, Delgado, Chein, Becker, & Fiez, 2004). Recent evidence demonstrates that that while verbal and tonal maintenance involves similar structures, network dynamics differ, such that recruitment of these structures is primarily left- lateralized for verbal maintenance, and right-lateralized for tonal maintenance (Albouy et al., 2019). Damage to these areas is the most significant predictor of severe acquired amusia (Sihvonen et al., 2017). Indeed, in the present study we observed that in contrast to the right-lateralized frontal injury accompanying the selective pitch deficit in six patients, there was one patient with lesions in the left inferior and prefrontal cortex who had intact pitch ability, with deficits in verbal STM.

It should be noted that the present study did not use analogous tasks to measure pitch and verbal STM. However, one study that used analogous tasks in individuals with congenital amusia demonstrated similar results: deficits in pitch STM, with preserved verbal STM (Williamson & Stewart, 2010). Therefore, there is a clear pattern of dissociation between pitch and verbal STM that mirrors the pattern of that found in congenital amusics. That is, decreased STM for pitch that does not touch STM for verbal information. In sum, the present study results indicate that there are both shared and distinct processing components between verbal and tonal material in STM in TBI patients.

Rhythm processing and verbal short-term memory. As hypothesized, a relationship between rhythm perception and verbal short-term memory was found in 61% of the TBI patients

(n = 19). Furthermore, similarly to pitch, the results demonstrate a dissociation between performance on rhythm discrimination and verbal short-term memory in 39% of the TBI patients, indicating partly separable subsystems. The majority of these patients (10/12) demonstrated impaired rhythm perception with preserved verbal short-term memory. Scans were available for six of these patients, five of whom also had co-occurring deficits in pitch perception. Four of the six patients demonstrated injury to right or bilateral frontal regions. This was expected, given the extensively overlapping lesion patterns for pitch and rhythm STM located in right frontal, temporal, subcortical structures, and insula (Jerde et al., 2011; Sihvonen et al., 2016). However, there are also differences in dynamics and structure between the neural networks treating pitch and rhythm. For example, rhythm deficits are associated with more significant lesions to the right dorsal-striatum than pitch deficits. Furthermore, while recovered pitch amusia is associated with a smaller grey matter volume decrease in the temporoparietal junction, rhythm amusia is associated with a smaller gray matter volume decrease in the inferior temporal pole (Sihvonen et al., 2017).

Finally, it is important to note that in the vast majority of cases of dissociation, verbal STM is preserved in the face of impaired musical STM, whether for pitch or rhythm. Of the individuals with verbal STM deficits, only one of 13 performed adequately on pitch perception, and only two of 12 individuals with verbal STM deficits performed adequately on rhythm perception, providing support for the notion that general-domain STM appears to be a fundamental component to both pitch and rhythm discrimination, and that it fractionates to treat musical versus verbal information.

Implications of acquired music perception deficits on music interventions following TBI

Certain studies indicate that more than half of individuals with congenital amusia do not enjoy music (McDonald & Stewart, 2008; Omigie et al., 2012), compared to only 6% of controls (Omigie et al., 2012), or no controls (McDonald & Stewart, 2008). They incorporated music less frequently into their everyday lives, and experienced fewer mood state changes when listening to music (McDonald & Stewart, 2008; Omigie et al., 2012). Thus, in TBI patients with music deficits, the goals of music therapy, which include altering mood state, increasing motivation for rehabilitation, and decreasing the stress response (Gilbertson & Aldridge, 2008), may not be met during the acute stage of recovery.

Thus, given the prevalence of pitch and rhythm disorders in the acute TBI population, and the fact that music listening can significantly contribute to quality of life (Ruud, 1997), it is important to include measures of music perception in cognitive follow-up after TBI. This is particularly important in patients with injury involving the right hemisphere, who would be expected to perform most poorly. The MBEA is free of cost, and results may inform patient counseling, and the tailoring of music rehabilitation programs to patients' individual needs. Screening for music perception would also help identify deficits in patients who are musicians, who may experience a direct impact on employment.

Limitations

There are several limitations to the present study. First, we did not use audiometry to measure the patients' hearing ability, due to time constraints in testing. However, patients who reported that they suffered from hearing deficits when questioned were excluded from the study. We also confirmed that the stimuli during the sample trials was audible, and hearing deficits were not noted in conversation.

Second, we used only the Scale and Rhythm subtests of the MBEA, as testing time in an acute care setting is limited due to patient fatigue, pain, and nausea. These two tests are thought to best represent the melodic and temporal dimension of music perception, with the Scale test identified as the most diagnostic subtest of amusia in the MBEA (Goulet, Moreau, Robitaille, & Peretz, 2012; Peretz, 2016; Peretz et al., 2008). It has been used alone to flag amusia cases in several studies (Balzani et al., 2014; Goulet et al., 2012; Särkämö et al., 2009). Furthermore, the combination of scale and rhythm subtests is thought to provide a reasonable estimate of overall music perception (Särkämö et al., 2009). However, certain researchers have suggested that using the cut-offs for these tests may result in a negatively skewed distribution and over-diagnosis of amusia cases (Henry & McAuley, 2010; Pfeifer & Hamann, 2015). It is important to acknowledge that the MBEA was created for clinical screening, rather than as a stand-alone diagnostic battery. It plays a critical role in the comprehensive evaluation for amusia, which includes tests of audiometry, cognitive assessments, and questionnaires. Nevertheless, this fact would likely not account for the significant number of cases of impaired music perception in the present findings, as a control group was used for comparison. Furthermore, there is abundant evidence of similar patterns of impaired music perception in other neurological populations that support the present findings (Milner, 1962; Rosslau et al., 2015; Särkämö et al., 2010; Sihvonen et al., 2016; Zatorre, 1998).

Third, CT scans, which detect damage on the millimeter (and sometimes sub-millimeter) level, may fail to detect damage in patients with mild brain injury, who often exhibit neuronal damage only at the micron and nanometer level (Bigler & Maxwell, 2011, 2012). While MRI provides more detailed views than CT, both methods are limited to detecting only the largest lesions (Bigler, 2015). Furthermore, CT and MRI are unable to directly identify injured axons

(Mac Donald, Dikranian, Bayly, Holtzman, & Brody, 2007; Silver, McAllister, Arciniegas, & American Psychiatric Association, 2019). Therefore, it is possible in the present study that even patients with no observable lesions on CT (n = 18) had undetected damage that contributed to their music perception deficits. Head CT, like the MBEA, is used as a screening tool to identify the presence of hemorrhage, rather than whether an individual has a TBI. Future studies using DTI in a larger sample size would allow for more accurate anatomical identification of brain injury. Examining damage to white matter tracts in TBI patients in clinical and research settings might further characterize the connectivity of neural networks involved in music processing. Ideally, longitudinal studies encompassing the acute and chronic phases of TBI would help to formulate more direct conclusions as to the effect of lesion location on music perception. Understanding the role of music perception and processing would enable the development of evidence-based rehabilitation protocols using music therapy in TBI, which is already being used, despite a lack of comprehensive understanding of neural networks.

Fourth, the fact that there was no relationship between injury severity and performance on the Scale and Rhythm tests may be attributable to the fact that post-traumatic amnesia is more common in TBI patients with severe injury, and precludes them from participating, resulting in an under-representation of this sub-population in this study.

Fifth, patients were matched with controls on education and age only, not on sex or years of musical training. Thus, the sex of the individuals in the present study is not equivalent between groups. Evidence for the influence of sex on music cognition is unknown, as studies examining sex differences in music cognition are sparse. However, two studies reported limited, if any significant differences between sexes in performance on tasks of pitch perception. For example, one study demonstrated differences in cerebellar activation patterns between adult males and females on a pitch memory task. However, this did not correspond to differences in scores between groups. Because performance differences could not explain activation differences, the authors concluded that the differing activation pattern between males and females may simply reflect different processing strategies (Gaab et al., 2003). A second study that examined the ability to distinguish between two tones found that females answered correctly 1% more frequently than males. However, it was unclear as to whether this difference was significant, as statistical analyses were not performed (Ingram, 2004). However, given the small percentage, it is unlikely. As for musical training, this information was not available for controls. However, the majority of TBI patients in the present study had fewer than three years of musical training, with only five patients reporting three or more years (see Table 1). It is unlikely that these five patients would significantly influence the results, given that 24 patients had fewer than three years of musical training. Importantly, the MBEA was created for people without musical training. Thus, the influence of musical training did not likely significantly influence results.

Conclusions

We have shown that patients with acute TBI have a high incidence of pitch and rhythm processing deficits that was previously under-recognized in this population. Pitch and rhythm deficits co-occur in TBI patients one third of the time, but occur separately two-thirds of the time. This suggests partly shared but dissociable neural networks for pitch and rhythm. Furthermore, pitch and rhythm processing are predominantly right lateralized, so that traumatic injury to right frontal and temporal areas is associated with these deficits. Finally, neural networks underlying the processing of verbal STM, pitch STM, and rhythm STM intersect, but are partly dissociable. We suggest that general domain short-term memory is recruited and combined with specific areas that process pitch, rhythm, and verbal material.

Further studies examining how music-processing deficits relate to other cognitive deficits, especially those involving the right hemisphere, would be useful. Morphometric or functional imaging studies in TBI patients with well-characterized deficits in the musical perception domain may better elucidate the functional and structural connectivity networks that underlie music processing. Longer follow up of these patients may demonstrate to what extent recovery is possible following acute TBI. Finally, evaluation of the frequency and characteristics of musical anhedonia in TBI patients may inform music therapy interventions.

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Table 1
Demographics and Accident History

Variable	
Age at injury (*M* ± *SD*)	51.1 ± 18.5
Sex	
Male	36 (86%)
Female	6 (14%)
Musical Training (*M* ± *SD*)	1.2 ± 2.6
< 3 years	24 (57%)
≥ 3 years	5 (12%)
Accident Variables	
TBI Etiology	
MVA	16 (38%)
Fall	15 (35%)
Assault	3 (7%)
Suicide attempt	2 (5%)
Sports	2 (5%)
Other	4 (9%)
TBI Severity	
mild	31 (74%)
moderate	8 (19%)
severe	3 (7%)
LOC	
No	14 (33%)
Yes	28 (67%)
PTA	
No	11 (26%)
Yes	31 (74%)
LOS (in days; *M* ± *SD*)	14.70 (9.36)
Delay to Testing (in days; M ± SD)	6.7 ± 4.6

Note. LOC = loss of consciousness; PTA = post-traumatic amnesia; LOS = length of stay.

Table 2

Individual patient characteristics, performance on the Scale and Rhythm tests of the MBEA, and the Digit Span Forward test of the WAIS-IV.

	Patient Characteristics					Tests		
	Age	Gender	Severity	Hemi	Description of Injury	Scale (Z)	Rhythm (Z)	Digit Span Fwd (Z)
P1	23	M	moderate		--	**-2.28**	-1.62	-0.09
P2	50	M	mild complex		no mass effect	1.25	0.57	-0.69
P3	63	F	mild		--	**-6.40**	-1.62	**-2.08**
P4	65	M	moderate	B	left holohemispheric SDH (20 mm); midline shift 10 mm; previous surgical resection of right temporal lobe in 1967.	**-4.64**	**-2.93**	--
P5	61	M	mild		no acute intracranial findings	-0.52	-1.62	--
P6	35	M	moderate	B	multiple small foci of hemorrhagic contusions in the white matter of pre-SMA and SMA of frontal lobes	**-2.87**	**-2.93**	-1.50
P7	37	M	mild		no acute intracranial findings	-1.69	**-3.81**	-1.50
P8	64	M	mild complex		no mass effect	0.66	0.57	-0.54
P9	62	M	mild		--	1.25	-0.74	--
P10	62	M	severe	L	holohemispheric SDH (27 mm), midline shift 6 mm left to right	0.07	0.14	0.23
P11	40	M	mild		no acute intracranial findings	-1.11	-1.62	--
P12	78	F	moderate	R	frontal lobe intraparenchymal hematoma (32 mm)	**-6.99**	**-3.37**	-1.00
P13	63	M	mild complex	B	SDH in right parietal lobe (15 mm) and left frontal lobe (13 mm).	**-5.22**	**-2.06**	--
P14	43	M	mild complex		no mass effect	0.66	0.57	0.17
P15	72	M	mild complex	R	hemorrhagic contusion in the pre-SMA of the right superior frontal gyrus (12 mm)	**-3.46**	**-3.81**	--
P16	17	M	mild complex		no mass effect	**-4.05**	-0.74	--
P17	73	M	mild complex		no mass effect	**-2.87**	-0.30	--
P18	55	M	mild complex		no mass effect	**-3.46**	**-2.06**	-1.31
P19	52	M	mild complex	R	right parietal (4 mm) and right temporal (3 mm) SDHs	-0.52	-1.62	-1.46

P20	71	M	moderate	R	frontal SDH (10 mm) and residual hypodensities in the temporal lobe, following evacuation for a holohemispheric SDH	**-4.64**	**-3.37**	-0.64
P21	43	M	severe	B	multiple small foci of hemorrhagic contusions involving the subcortical white matter of both frontal lobes	**-2.28**	**-2.06**	-0.67
P22	55	M	mild complex	L	hemorrhagic contusion in the parahippocampal formation (6 mm).	0.07	**-2.50**	-1.31
P23	44	M	mild		no acute intracranial findings	0.07	0.14	-1.50
P24	56	F	mild complex	L	hemorrhagic contusions in the inferior frontal and prefrontal cortex	0.07	0.57	**-2.08**
P25	60	M	mild complex	L	hemorrhagic contusion in the left frontoparietal area (8 mm)	1.25	-1.18	-0.54
P26	27	F	mild		--	**-3.46**	-1.18	--
P27	51	M	moderate	L	holospheric hematoma (9 mm) with left to right midline shift (3 mm)	-0.52	-1.18	-0.69
P28	58	M	moderate	R	hemorrhage in the pallidum and putamen (15 mm).	**-6.99**	**-3.37**	-1.31
P29	48	M	severe		--	**-4.64**	**-2.06**	-1.46
P30	87	F	mild complex		no mass effect	**-5.22**	**-2.93**	--
P31	33	F	mild		no acute intracranial findings	**-3.46**	**-4.25**	--
P32	18	F	mild		no acute intracranial findings	**-5.81**	**-3.37**	**-2.18**
P33	21	M	mild complex		no mass effect	-0.52	**-2.50**	-1.00
P34	26	M	mild		no acute intracranial findings	0.66	0.14	0.00
P35	20	F	mild		--	1.25	1.01	-1.00
P36	34	F	mild		no acute intracranial findings	-0.52	1.01	1.43
P37	65	M	mild complex		no mass effect	**-4.05**	-1.18	-0.57
P38	77	M	moderate	L	large holohemispheric mixed density subdural hematoma (13 mm) with left to right midline shift (9 mm)	**-4.64**	-1.18	-1.91
P39	56	M	mild complex	B	small frontal hemorrhagic contusions in the SMA (6 mm on right, and 7 mm on left)	**-4.64**	-0.30	-1.31
P40	52	M	mild complex	R	holohemispheric SDH (18 mm), right to left midline shift (7 mm)	0.07	-0.74	0.08
P41	84	M	mild complex		no mass effect	**-5.81**	-1.62	-0.85
P42	45	M	mild complex	L	inferior frontal SDH (4 mm)	-0.52	-0.74	-0.69

Note. P= patient; Age in years; M = male; F = female; L=left, R = right, B= bilateral; SDH = subdural hematoma, SMA= supplementary motor area.

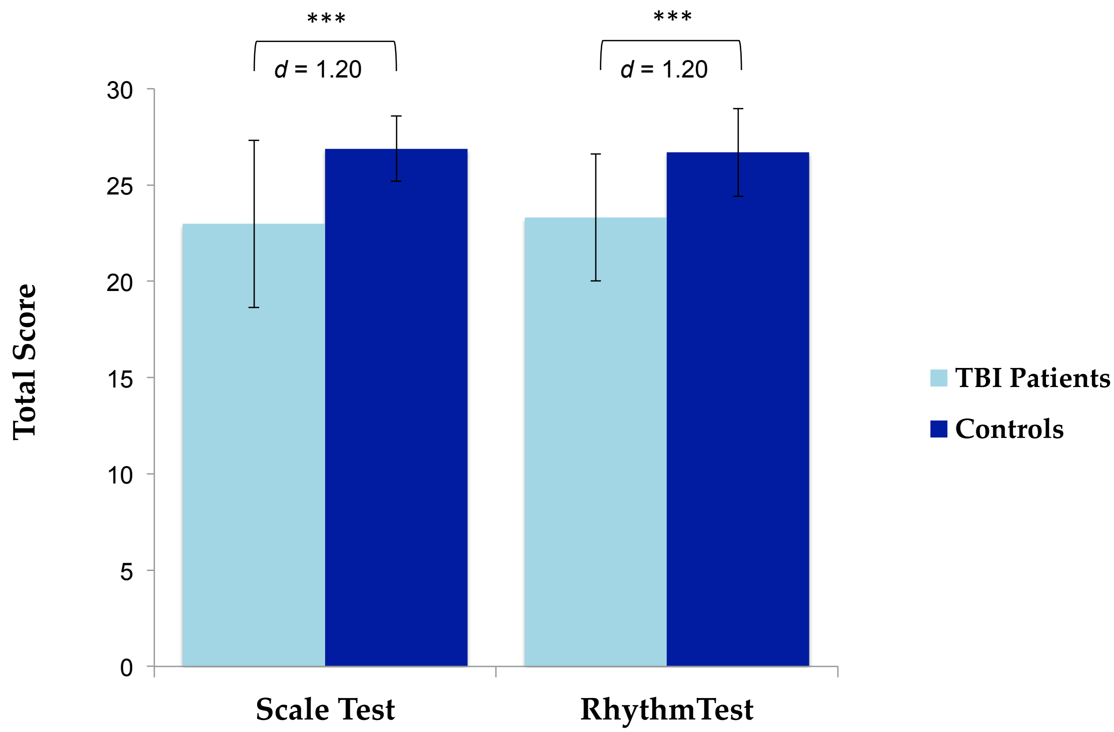

Figure 1. Mean scores and standard errors of TBI patients and matched controls. Controls performed significantly better than TBI patients on both the Scale test and the Rhythm Test. *** = $p \leq .001$

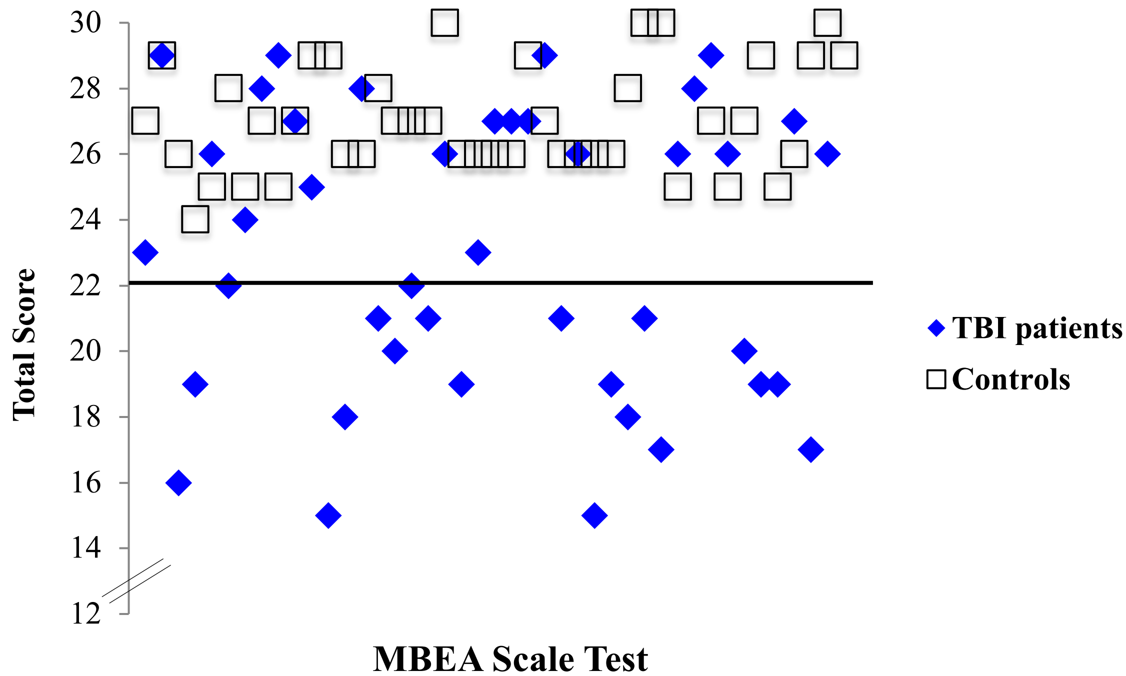

Figure 2. Individual scores for TBI patients and controls on the MBEA Scale test.
Note. The black line represents the cutoff score for this test, which corresponds to two standard deviations below the mean (Peretz, 2003).

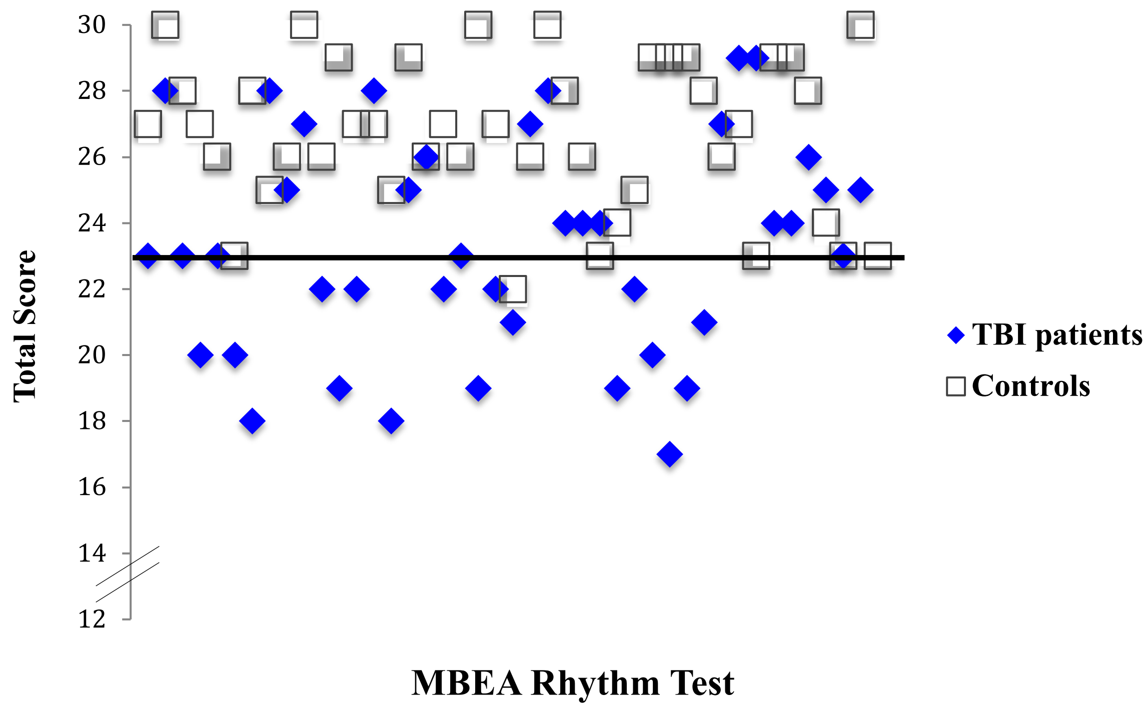

Figure 3. Individual scores for TBI patients and controls on the MBEA Rhythm test. *Note.* The black line represents the cutoff score for this test, which corresponds to two standard deviations below the mean (Peretz, 2003).

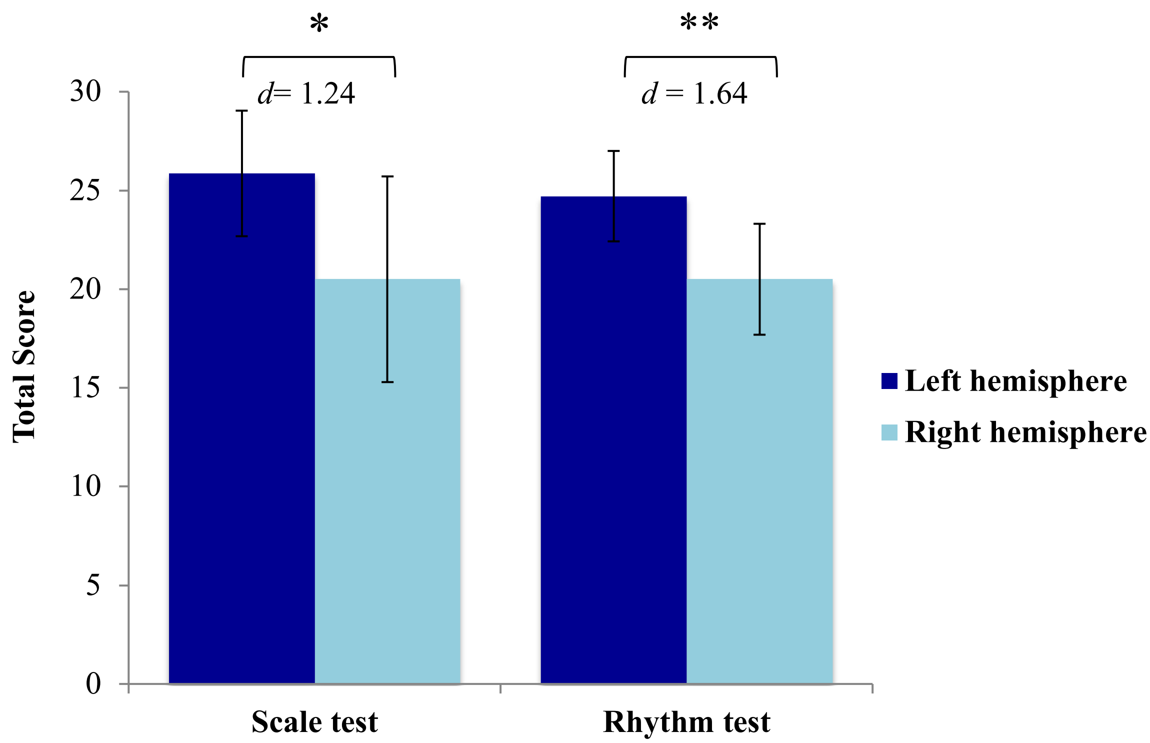

Figure 4. Mean values of total score in patients with injury located in the right hemisphere and left hemisphere on the Scale test and Rhythm test of the MBEA. Standard errors of the mean are represented by the error bar attached to each column. Patients with injury located in the right hemisphere performed more poorly on the Scale test than those with injury located in the left hemisphere. * = $p \leq .05$; ** = $p \leq .01$

CHAPTER III: Article 2

The Management of Agitation During Acute and Sub-acute Hospitalization for Traumatic Brain Injury

Kirsten Anderson[1], BA, Jehane Dagher[2], MD, Nathalie Gosselin[1], PhD, Simon Tinawi[2], MD, and Elaine de Guise[1,3], PhD

[1]Département de Psychologie, Université de Montréal, Montréal, QC, Canada

[2]Physical Medicine and Rehabilitation Service, McGill University Health Centre, Montreal, Quebec, Canada

[3]Neurology and Neurosurgery Department, McGill University Health Centre, Montreal, Quebec, Canada

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Abstract

Agitation is a state during the acute post-traumatic phase that is characterized by specific physical, cognitive and behavioral symptoms, such as motor hyperactivity, disorganized thinking, emotional instability, and aggression. Between 35 and 70% of traumatic brain injury (TBI) patients experience symptoms of agitation. Agitation behaviors pose safety threats to patients and caregivers, and preclude patients from rehabilitative treatment. Current management strategies include physical or pharmacological restraints, as well as environmental modifications. Physical restraints can result in physical injuries, and pharmacological restraints can cause drowsiness, confusion, and extrapyramidal effects. Environmental modifications, though often helpful, may be insufficient on their own. As such, a growing number of studies are examining novel non-pharmacological interventions for agitation in TBI patients.

The goal of the present chapter is to review the evidence for behavioral interventions for the management of TBI in acutely hospitalized patients, focusing specifically on recent literature from 2000-2015. The chapter will consist of four main sections: (i) Overview of agitation following TBI. This section will define agitation and its prevalence, the monitoring of agitation, antecedents to agitation, outcomes for patients with agitation, and agitation management using physical and pharmacological restraints. (ii) Managing the antecedents of agitation using environmental modifications. This section will examine interventions to minimize overstimulation in patients with agitation. (iii) Behavioral interventions for the management of agitation. This section will outline case studies and case series that use musical interventions, operational contingency management, occupational therapy, the Information Contingencies Awareness Relationship (ICAR) behavioral model for agitation management, and general therapeutic activities. (iv) Concluding remarks. This section will briefly summarize the overall

findings of current behavioral studies and conclude with recommendations for future directions of research.

Traumatic brain injury (TBI) is a significant health problem worldwide. In industrialized societies such as the United States, 500 cases are noted per 100,000 population each year (Saout et al., 2011). In fact, TBI is the leading cause of trauma-related death and disability (Tateno, Jorge, & Robinson, 2003). The number of people who survive TBI has increased in recent years due to advancements in emergency medical care (Brooks, Gabella, Hoffman, Sosin, & Whiteneck, 1997; Slifer & Amari, 2009). Surviving patients may show maladaptive behaviors in both the acute and chronic phase. As a result, the management of maladaptive behaviors is increasingly important, utilizing significant resources and contributing to the burden of care.

One of the most prevalent behavioral issues is agitation, a state in which motor hyperactivity, emotional lability and cognitive dysfunction can preclude patients from participating in rehabilitative care (Hufford, Williams, Malec, & Cravotta, 2012; Lequerica et al., 2007). Agitation is extremely common in the TBI population, affecting up to 96% of patients (Singh, Venkateshwara, Nair, Khan, & Saad, 2014). Despite the prevalence of maladaptive behaviors following TBI, there have been few studies into behavioral interventions that target agitation during acute care. Considering the fact that the major phase of cognitive recovery takes place during the first six months following injury (Lequerica et al., 2007), it is imperative to investigate solutions for the management of agitation during the acute and sub-acute phases of recovery.

One reason for the scarcity of studies on agitation in this population is undoubtedly the abundance of methodological and theoretical obstacles. These include: 1) a lack of consensus on the definition of agitation; 2) brain injuries are heterogeneous in brain distribution and severity, making randomized controlled studies difficult; 3) sedative medication administration is common during research studies that wish to determine whether a given intervention effectively reduces agitated behavior; 4) spontaneous healing can occur during this medically unstable period, making it difficult to determine if lowered agitation levels are due to the treatment or the natural course of healing; 5) it is difficult to control the hospital environment; for example, nursing care regimens, including bathing and feeding, may alter agitated symptoms, and confound behavior scores during intervention protocols; 6) studies must also control for concurrent rehabilitative treatments; and 7) the pathophysiological mechanisms underlying agitation are still not well-elucidated (Ducharme, 2000; Slifer & Amari, 2009). As a result, there is currently no consensus as to a standard of care for the management of agitation.

Currently, agitation management may be broadly grouped into three main categories: 1) the use of physical and pharmacological restraints, 2) management of the patient's environment, and 3) behavioral interventions. Although highly utilized, the use of physical restraints is not recommended unless other options have been exhausted (McNett, Sarver, & Wilczewski, 2012; Ponsford et al., 2014). The pharmacological approach may be helpful at diminishing maladaptive behaviors. However, in some cases it may not address the underlying cause of agitation, and often has undesirable side effects, such as drowsiness and confusion (Flanagan, Elovic, & Sandel, 2009). Minimizing environmental stimulation is helpful but may be insufficient in itself. Because each of these approaches falls short in adequately managing agitation, behavioral interventions have increasingly elicited the interest of researchers and clinicians. In addition, patient care has evolved to a more positive patient-focused approach (Slifer & Amari, 2009). The recognition of patients with TBI as heterogeneous, with varied combinations of neural, cognitive, somatic (e.g., other injures) and environmental factors, has encouraged clinicians and researchers to increasingly turn toward a multi-faceted approach that uses a combination of behavioral methods targeted to the individual (Nick Alderman, 2003; Flanagan et al., 2009).

The goal of the present paper is to explore in the current literature the evidence for behavioral interventions for the management of TBI. The paper will consist of four main sections: (i) Overview of agitation following TBI. This section will define agitation and its prevalence, the monitoring of agitation, antecedents to agitation, and outcomes for patients with agitation. (ii) Managing the antecedents of agitation using environmental modifications. This section will examine the use of physical and pharmacological restraints, as well as interventions to minimize overstimulation in patients with agitation. (iii) Behavioral interventions for the management of agitation. This section will outline case studies and case series that use musical interventions, operational contingency management, occupational therapy, the Intervention Contingencies Awareness Relationship (ICAR) behavioral model for agitation management, and general therapeutic activities. (iv) Concluding remarks. This section will briefly summarize the overall findings of current behavioral studies and conclude with recommendations for future directions of research.

Overview Of Agitation Following TBI

The Lack of a Consensus Definition of Agitation Following Traumatic Brain Injury

Agitation is a state during the acute post-traumatic phase that includes specific physical, cognitive, emotional and behavioral signs and symptoms. It is characterized by motor hyperactivity, disorganized thinking, emotional instability, and aggression. It is associated with widespread changes in neural network activity. Thus, many studies have recommended that agitation be conceptualized and treated in a global manner (Singh et al., 2014). Unfortunately, a consensus as to the precise definition of agitation following traumatic brain injury has not yet been established, as the cluster of behaviors that characterizes agitation also presents in a variety of other disorders. These include dementia, schizophrenia, certain mood disorders, and drug intoxication/withdrawal. The underlying pathophysiology of agitation remains unknown. In the article, “The Pathophysiology of Agitation,” Lindenmeyer (2000) stated that despite observed pathophysiological abnormalities noted in GABAergic, dopaminergic, and serotonergic systems, it has not been possible to identify distinct clinical features that correspond to these system abnormalities. As such, few studies have conceptualized agitation as a separate syndrome with specific underlying neurobiological mechanisms (Lindenmayer, 2000).

To complicate the definition further, certain medical conditions feature behaviors that overlap with those seen in agitation. For example, akathesia, or motor restlessness with a compulsion to move about, can occur after TBI. However, unlike agitation, it excludes cognitive or behavioral elements. Restlessness may, however, have a common neuropathogenesis to that of agitation (Sandel & Mysiw, 1996). Post-traumatic amnesia (PTA) is another condition whose symptoms overlap with those of agitation. Post-traumatic amnesia is a period of impaired cognition following traumatic brain injury in which the patient suffers anterograde amnesia (the inability to encode new information in memory, or to learn), disorientation, and sometimes agitation (Ponsford et al., 2014).

For the purposes of the current review, agitation will be defined globally, as a variation of delirium, usually occurring during the PTA period after a TBI, in which there may be any combination of 1) cognitive symptoms, such as reduced attention, decreased information processing ability, and disorientation; 2) behavioral symptoms, such as verbal outbursts, disinhibition, and uncooperativeness; 3) emotional symptoms, such as emotional lability, impulsivity, and explosive anger; and 4) physical symptoms, such as motor hyperactivity, and wandering. It also includes a score of 22 or greater on the Agitated Behavior Scale (ABS) (Corrigan, 1989). These behaviors must be differentiated from those attributable to a disorder other than traumatic brain injury. We also propose that the acute phase be defined as occurring during the first four weeks after TBI, subacute as persisting beyond the first four weeks or occurring during the first 4 months after TBI, and chronic as persisting beyond or occurring after the first 4 months after TBI.

Prevalence of Agitation Following TBI

While clinicians working with hospitalized TBI patients often observe agitation, the lack of a consensus on a precise definition contributes to wide variations in estimated prevalence. Other contributing factors include differences in measurement tools, and populations ranging in age and phases of rehabilitation (Wolffbrandt, Poulsen, Engberg, & Hornnes, 2013). The majority of reports fall within the 30-70% range, but the extremes vary from 8% to 96% (Lindenmayer, 2000; McNett et al., 2012; Ponsford et al., 2014; Saoût et al., 2011; Singh et al., 2014). Agitation typically lasts 1-14 days (McNett et al., 2012). However, in the literature, it is seldom specified whether this agitation period is considered to occur in the acute, sub-acute, or chronic phases. This poses a major problem in characterization, clinical diagnosis and appropriate management selection. More severely injured patients tend to experience greater agitation (Ponsford et al., 2014).

The Monitoring of Agitation

In clinical practice, it is recommended that agitation be diagnosed using an objective scale that quantifies a variety of agitated behaviors and indicates their severity (Duraski, 2011). Furthermore, during interventions, the ongoing monitoring of agitation is necessary, as agitation fluctuates, and therapies must be adjusted accordingly (Duraski, 2011). Despite this, patients with agitation are distinguished on the basis of a yes/no diagnosis, rather than quantifying the severity of agitation using an objective tool that is reliable and valid. (Bogner, Corrigan, Fugate, Mysiw, & Clinchot, 2001; Sandel & Mysiw, 1996). The ABS is often inconsistently administered to agitated, hospitalized TBI patients. The fact that there is inconsistent reassessment of patients' agitation levels, often on a mainly subjective basis without evaluation of severity, can result in inconsistent interventions, especially as different care-givers are involved over time. For example, in one study, 68.6% of agitated patients were prescribed medications on a long-term basis. Of these, 62.7% were prescribed "as needed." (Janzen, McIntyre, Meyer, Sequeira, & Teasell, 2014). Indeed, in this study, even when using the ABS, the scores did not match with the treatment administered, since clear guidelines were not available to caregivers. Use of objective scales may better guide the need for type, frequency and dosage of pharmaceutical interventions, and allow for better evaluation of the most effective medical care in a given patient, while avoiding detrimental interventions.

The most commonly used measure of agitated behavior may be the Agitated Behavior Scale (ABS). It was developed by John Corrigan in 1989 for the traumatic brain-injured population. Widely used, it has good internal consistency, inter-rater reliability, and concurrent validity (Corrigan, 1989). Corrigan defines agitation as an excess of one or more behaviors that occurs during an altered state of consciousness (Bogner & Corrigan, 1995), which for traumatic brain injured individuals, would include the period of PTA. A behavior is considered excessive relative to the amount that it interferes with functioning and cannot be inhibited. The total score can range from 14-56, and a score of 22 or greater is classified as agitation. There are three possible subscores that can be derived from this scale: emotional lability, disinhibition, and aggression. However, the total score is considered to be the most accurate measure of agitation (Corrigan, 1989; Corrigan & Bogner, 1994).

One drawback of using an agitation scale is that the cutoff score that distinguishes between behavior that is or is not agitated may overlook certain nuances of agitation. For example, a patient's behavior may fall below the cut-off score because psychomotor behaviors have diminished, while they still exhibit important behaviors of impulsiveness and lack of attention, both of which may continue to interfere with the rehabilitative process (Lequerica et al., 2007). Notwithstanding these limitations, the measurement of agitation using standardized scales still provides standardized indicators that can help guide pharmaceutical and behavioral treatment, and provide a valuable tool for research.

Physical and Cognitive Antecedents to Agitation

Psychomotor agitation is often a positive sign of recovery in patients emerging from coma (Corrigan & Mysiw, 1988; Reyes, Bhattacharyya, & Heller, 1981). However, it can also interfere with everyday functioning, and limit a patient's independence.

Physical deficits. TBI patients with fronto-temporal lesions may be particularly prone to agitated behaviors (Van der Naalt, Van Zomeren, Sluiter, & Minderhoud, 2000). In addition, health issues such as pain, infection and communication problems can lead to increased levels of agitation (Bogner et al., 2015; Duraski, 2011; Lombard & Zafonte, 2005). Finally, patients with premorbid history of dementia, or multiple medical or psychiatric diagnoses are at greater risk for agitated behaviors (Waszynski et al., 2013)

Cognitive deficits. Patients with traumatic brain injury often have attention and information processing deficits that make interpreting of their environment difficult. This can lead to agitation (Duraski, 2011; Nott, Chapparo, & Heard, 2008). During PTA, patients often have trouble learning new information. This is an antecedent to agitated behavior. Cognitive capacity is related to emotion regulation and problem solving style (Nott, Chapparo, & Heard, 2008). Difficulty in regulating emotions can make the difference between whether a problem is approached rationally with patience, or whether it is approached with frustration and impulsivity (Nott et al., 2008).

Outcomes for TBI Patients with Agitation

Agitation is associated with poorer Global Outcome Scores and Glasgow Coma Scale scores, as well as poorer cognitive and motor function (Ponsford et al., 2014). In addition, agitated patients usually have longer durations of PTA (McNett et al., 2012; Van der Naalt et al., 2000). Finally, agitation is associated with decreased functional outcome, as seen in longer hospital stays, interference with family dynamics, and prevention or delay of return to work and reintegration into the community (McNett et al., 2012; Park, Williams, & Lee, 2015; Ponsford et al., 2014; Van der Naalt et al., 2000). A study by McNett and colleagues (2012) demonstrated that the majority of agitated patients were discharged to acute brain rehabilitation units instead of going home. This indicates that they have more severe cognitive deficits, necessitating more time and resources in order to learn to manage activities of daily living.

Managing the Antecedents of Agitation Using Environmental Modifications

The prompt management of agitation-related behaviors may be necessary, especially when physically violent, self-harming, or verbally abusive behaviors pose a risk for the patient, his or her family, other patients or healthcare workers (Baker, 2001; Lequerica et al., 2007). The management of agitation currently falls into three broad categories of intervention: pharmacological and physical restraints, environmental antecedents, and behavioral interventions.

Pharmacological Restraints

Pharmacological management is often the treatment of choice in hospitalized agitated patients, owing in part to staff shortages and reduced inpatient stays (Janzen et al., 2014). At times, it is also the only effective means to calm an agitated patient. This is problematic, as the effects of specific medications on agitated behaviors in patients during the acute phase of recovery from TBI remains largely unknown (Beaulieu et al., 2008; Flanagan et al., 2009; Fleminger, Greenwood, & Oliver, 2006). The lack of standardized care guidelines for the pharmacologic management of agitation in TBI patients results in an inconsistent application of a panoply of medications (Sandel & Mysiw, 1996). In certain cases, polypharmaceutical management can lead to a vicious cycle in which agitation symptoms are aggravated from medication side effects and prolonged hospitalization, resulting in further use of sedative agents (Waszynski et al., 2013).

Although medications have proven useful at reducing agitated behaviors, they may negatively impact upon cognition, thus compromising functional recovery (Bogner et al., 2015; Flanagan et al., 2009). For example, during acute care, pharmacological management of agitation can have paradoxical effects, prolonging PTA and exacerbating confusion, disorientation, and drowsiness (Baker, 2001; Flanagan et al., 2009; Ponsford et al., 2014). Indeed, many researchers and clinicians assert that the sedative effect of medications may pacify the patient rather than treating the mechanism underlying the aggressive behavior. Furthermore, the deleterious effects of medications may manifest in prolonged cognitive issues after the patients' agitation has resolved. Prolonged sedation may also preclude patients from rehabilitation activities that are required for physical and cognitive recovery. To compound this problem, it has been proposed that TBI patients have heightened sensitivity to medications (Flanagan et al., 2009).

Neuroleptics, benzodiazepines, analgesics and anti-convulsants are regularly administered in this population for the management of maladaptive behaviors, pain or seizures. Neuroleptics such as haloperidol, which are commonly used, are correlated with poorer cognitive recovery and longer duration of PTA in TBI patients (Ponsford et al., 2014). Some investigators propose that clinicians limit the use of pharmacological approaches for the management of agitation. Rather, they should investigate and treat based on the underlying pathophysiology, and develop better standards of care (Beaulieu et al., 2008). Finally, the fact that cognitive functions mediate the relationship between agitation and outcome supports minimizing the use of medications in TBI patients (Bogner et al., 2015). Ultimately, a balance must be struck between safety issues and cognitive and functional recovery (McNett, 2012). Perhaps the most appropriate management would be to start by administering low doses or single agents, while monitoring and communicating the effectiveness of the medication using objective measures (Ponsford et al., 2014).

Physical Restraints

Physical restraints are not recommended as a first-line treatment for agitation. Common restraints include mitts, enclosed beds, and vests that restrict movement and prevent patients from eloping from the ward or harming themselves and others. Physical restraints are typically used after having exhausted other environmental and behavioral options. In a comprehensive review on the management of post-traumatic amnesia following traumatic brain injury, Ponsford and colleagues (2014) recommended that physical restraints be avoided, allowing the patient to move freely. Restraint use can result in serious injuries such as pressure sores, deep vein thrombosis and secondarily pulmonary embolism (Beaulieu et al., 2008; Bromberg & Vogel, 1996; Ponsford et al., 2014). Another contraindication for the use of restraints is that they may further aggravate agitation (Beaulieu et al., 2008; Duraski, 2011; McNett et al., 2012). As a result, the Joint Commission on Accreditation of Healthcare Organizations in 2005 introduced restrictions on the use of restraints (Duraski, 2011). U.S federal law also restricts their use (Amato, Salter, & Mion, 2006). Behavioral and environmental strategies can be effective and are preferred compared to physical restraints.

Managing the Antecedents of Agitation Using Environmental Modifications

It is recommended that the environmental stimulation be kept to a minimum, as it may produce arousal levels in the patient that exceed his or her cognitive processing capacity (Flanagan et al., 2009). Noise in the patient's room, including that generated by TV and radio, should be limited (Becker, 2012; Duraski, 2011; Figueiro et al., 2014). Adequate sleep is also important when managing agitation. Agitation may result from insufficient sleep in as many as 70% of TBI patients, (Makley et al., 2008). Therefore, strategies such as limiting light is recommended. In addition, avoiding naps and neurostimulants after 3 pm, as well as heavy meals before bed may also be of benefit (Duraski, 2011). The number of visitors may also be limited (Becker, 2012). Pain may be additionally managed with hot or cold packs, massage, and non-narcotic analgesics (Duraski, 2011). Unfortunately, budgets often don't allow patients to have private rooms. In addition, patient feeding and bathing routines, while essential, can increase agitation (Duraski, 2011).

The unit may be locked, with exit alarms installed, and a bed close to the floor, which may reduce the risk of injury and prevent eloping (Duraski, 2011; Ponsford et al., 2014; Slifer & Amari, 2009). It would also necessitate fewer sitters who provide constant observation. Consistency of treatment teams and schedules is helpful (Becker, 2012; Duraski, 2011). Patients may receive rehabilitative treatment in their room rather than relocating for therapy. Familiarizing materials may be of help in orienting patients (Baker, 2001). Finally, positive staff attitudes and strong therapeutic rapport are an important part of recovery (Becker, 2012). This includes frequent reassurance to agitated patients with PTA (Ponsford et al., 2014). It is important to calmly anticipate and de-escalate aggression (Becker, 2012).

Continuous Observation

Continuous observation is sometimes provided by nursing staff and assistants to ensure that the patient does not harm him or herself or others. However, evidence demonstrates that continuous observation may actually increase agitation (Waszynski et al., 2013). Patients have reported that they felt intruded upon. In addition, it is costly and time-consuming, and it can be difficult to anticipate the number of sitters required for a given shift. Sometimes, nursing staff must be reallocated from their regular duties to act as sitters, which may decrease the quality of care provided to other patients. Finally, sitters report boredom when being passive observers (Waszynski et al., 2013).

Behavioral Interventions for the Management of Agitation

Musical Interventions

Music therapy may be defined as, "a controlled use of music and its influence on the human being to aid in physiological, psychological, and emotional integration of an individual during treatment of an illness or disability" (Munro & Mount, 1978). In the therapeutic relationship, it may also facilitate social comunication (http://www.musictherapy.ca/fr/information/musicotherapie.html). Recent evidence indicates that musical interventions may be effective at reducing agitation in patients with TBI. Indeed, musical interventions may be of particular benefit for patients with severe TBI who have cognitive deficits that exceed their ability to participate in more cognitively demanding types of behavioral rehabilitation intervention that require task execution. It is well-established that music induces widespread neural changes in the brain that have been shown to positively affect cognition and emotion in healthy populations as well as in clinical populations (Magee et al., 2011; Moreno et al., 2011). In addition, a widespread activation of several neural networks has been observed in adults with reduced consciousness when listening to music. Music's far-reaching influence on neural activity may be promising for managing agitation in a heterogeneous population, such as traumatic brain-injured patients.

In one study, stroke patients who were exposed to music showed improved recovery of attention and verbal memory compared with listening to audiobooks (Särkämö et al., 2008). These improvements in the music group were also associated with greater recovery of grey matter volume in fronto-limbic areas (Särkämö et al., 2014). Preferred music may elevate mood and help regulate emotion, which could be of benefit in the agitated, brain-injured population (Castro et al., 2015). For example, the pleasurable feelings that arise when listening to music are associated with changes in activity of key structures in the limbic system that are involved in emotion interpretation, including the ventromedial prefrontal cortex, hippocampus, amygdala, ventral striatum, and caudate nucleus. These same areas are associated with motivation and reward behaviors (Blood & Zatorre, 2001; Koelsch & Skouras, 2014). Indeed, the network including the ventral striatum and frontotemporal cortical areas is believed to be modulated by the mesocorticolimbic dopamine reward system (Salimpoor et al., 2013; Zatorre, 2015).

Until recently, music interventions were discouraged in agitated PTA populations, as it was believed to be over-stimulating (Baker, 2001). Since radio and television are known antecedents to agitation, music listening seems counterintuitive for agitation management. There are few studies that explore the effects of music at reducing agitation in a TBI population. However, in both healthy and clinical populations, it has been well-demonstrated that music listening may assist in maintaining homeostasis by modifying the stress response (Chanda & Levitin, 2013; Gooding, Swezey, & Zwischenberger, 2012). For example, in one study, a single 30-minute music listening session altered sympathetic nervous system responses in mechanically ventilated patients, including decreased heart rate, blood pressure and respiratory rate (Lee, Chung, Chan, & Chan, 2005). Another study demonstrated that patients in a music listening group secreted lower levels of cortisol and required lower doses of propofol during surgery, compared with a control group (Koelsch et al., 2011). Some researchers caution that this effect is dependent upon the parameters of music listening (Hunter, Schellenberg, & Schimmack, 2010). For example, the tempo should not be too fast, as this can over-stimulate agitated patients. However, at reasonable volumes and tempos, it is proposed that music stimulates optimal levels of arousal, rather than overstimulation (Baker, 2001). Some researchers have proposed that in agitated patients, music may provide a predictable external structural framework for the appropriate release of agitated energy. This may manifest in more organized movements, such as tapping along to the rhythm (Baker, 2001; Bower, Catroppa, Grocke, & Shoemark, 2013). The repetitive structure in songs may also contribute to a lower cognitive load (Baker, 2001).

The predictability of a familiar song may also help patients with PTA to orient themselves in an unfamiliar and stressful environment. Preferred music induces positive mood and memories, further increasing their sense of orientation (Park et al., 2015). Familiar possessions may also function in this manner, facilitating meaningful interaction between patients and their environment (Baker, 2001). This may further decrease agitation.

The potential therapeutic use of music in managing agitation in TBI patients is supported by compelling evidence in other neurological populations with agitation, such as those with dementia. Indeed, there is ample evidence that music is effective at managing agitation in elderly patients with dementia (Gerdner, 2012; Sung & Chang, 2005; Tabloski, Mckinnon-Howe, & Remington, 1995; Vasionytė & Madison, 2013). For example, in home-dwelling patients with dementia, just two 30-minute sessions of preferred music listening per week for two weeks resulted in decreased agitation scores compared with controls (Park et al., 2015). Another study found that streaming music into the rooms of patients living in an assisted-living facility with Alzheimer-type dementia resulted in decreased levels of agitation and depression (Janata, 2012). Music therapy with a trained therapist was found to reduce agitation and limit increases in medication dose in patients in nursing homes with moderate to severe dementia (Ridder, Stige, Qvale, & Gold, 2013). Given the evidence for decreases in agitation during musical interventions in the dementia population, there is a growing interest in the application of musical interventions to patients with TBI over the last decade. The music listening studies reviewed in the following section can help further research using similar strategies in the TBI population.

Music Listening Interventions

A pioneering case-crossover study by Baker (2001) examined the effects of patients' preferred taped and live music on agitated behavior in 22 patients with PTA. Two sessions were held each day for 10-12 minutes in random order during six days, for a total of 12 sessions. Each patient received one music condition per day, with no condition used twice in a row. Thus, each condition (live, taped, no music) was administered a total of two times. ABS scores, which were performed at baseline and immediately following the intervention, were significantly lower after the musical conditions than the no music condition. Qualitatively, researchers observed that some patients replaced continuous inappropriate movements with more organized movements, such as tapping along with the music. Others stopped pacing, or paced in time. Following PTA, two thirds of the patients reported remembering the music and preferring when it was played live. Though both live and taped music are effective, music may have a stronger effect when combined with the live, social element of human interaction. However, the absence of a control condition in this study raises questions as to whether music itself was influencing agitation levels, or if patients were simply responding to the fact that there was an intervention. For example, there may have been differences in tempo between preferred music types among patients. There may also have been age differences that may in part have contributed to the fact that for some, classical music may be less familiar than for others.

Baker's study also demonstrated improvements in scores on the Westmead PTA scale, which measures orientation to person, place and time, as well as the ability to learn new information. Baker proposes that the improvements following the preferred music condition may be due to patients' familiarity with the music having created a familiar environment. Such an approach is recommended in the management of PTA (Ponsford, 1995). A familiar environment reduces anxiety and helps patients to interpret their surroundings. Indeed, de Guise and colleagues (2005) found that increasing familiarity with the environment resulted in a trend of shorter duration of PTA (de Guise, Leblanc, Feyz, Thomas, & Gosselin, 2005). In addition, a study by Willis & LaVigna (2003) found that agitated patients suffered an exacerbation of symptoms when surrounded by unfamiliar people.

Park, Williams & Lee (2015) had similar findings in their case-crossover design. They found that agitated patients (ABS score $\geq$ 22) with severe head injuries (GCS < 8) scored significantly lower on the ABS when listening to preferred music, compared with classical music or no music. There was a decrease in agitation only in the preferred music condition, and not in the classical listening condition. The areas of agitation most affected were the physical and cognitive aspects, especially impulsive and destructive behaviors. For example, similar to Baker's observations, several patients went from attempting to remove their mitts and repetitive hitting of the beds to tapping in time with the music. In this study, 14 patients participated in one three-hour intervention per day for three days. During the first hour, baseline data was collected and the ABS score was calculated. During the second hour, the patient was exposed to either preferred music or a classical music listening condition followed by the calculation of the second ABS score. After the third hour, during which no music was played, the third and last ABS score was calculated. The second day of the intervention was a washout period, followed by the musical intervention again on the final third day. These interventions were all done during normal daily nursing routines, including bathing and wound dressings. The authors suggest that the effects of musical interventions may actually depend on the type of music played, rather than the simple fact that there is an intervention.

Active Improvised Music Therapy Interventions

Active improvised music therapy involves creating a dialogue between therapist and patient, in which the patient is invited to engage in music playing. A new type of active music therapy has emerged, which is a modification of the creative music therapy approach often attributed to Nordoff and Robins. These authors proposed that every human being has an innate responsiveness to music, and that the parameters and structure inherent in music can enhance communication and change in the client, even those with severe cognitive deficits (Nordoff & Robbins, 1977). It should be noted that certain patients with amusia and other musical disorders may excepted from this assumption (Peretz, Champod, & Hyde, 2003). In any case, the active improvised music therapy is a variation of Nordoff and Robins' creative music therapy approach, in which the music therapist attempts to engage and evoke a response in patients with TBI with severely limited mobility and cognition, such as those in a coma, or other low awareness states. This is done by adapting tempo, dynamics, and volume according to observations of the patient's vital functions (respiratory rate, heart rate) and physical mobility (Formisano et al., 2001).

In a case series, Formisano and colleagues (2001) examined the effects of music in 34 severely injured agitated patients (GCS < 8; GOS < 3) during the first phases of coma recovery, 18 of which were TBI patients. Treatment took place three times per week for 20-40 minutes per session, depending on the patient's attention levels. The therapist varied dynamics and tempo according to each patient's respiration and heart rate. As patients began to participate, significantly lower psychomotor agitation was observed on a semi-quantitative scale. However, the authors did not specify what type of participation patients demonstrated, nor how agitation was specifically measured.

A similar case study implemented Bower, Catroppa, Grocke, & Shoemark's 2014 yielded inconclusive results when examining whether active music therapy served to decrease agitation. In this study, a 10 year-old girl with a severe TBI participated in 10 therapist-led sessions that lasted from 5-22 minutes each day. The tempo, volume and timbre of familiar songs was adapted to the child's breathing rate, in an effort to maximize her adaptive responsiveness. A qualitative rating of agitation was performed, as well as the ABS scale before, during, and after the intervention. The qualitative ratings demonstrated increased responsiveness. However, agitation scores were inconclusive. The authors cited poor inter-rater reliability as the contributing factor; the first rater had scoring patterns that resulted in findings of significantly decreased agitation, while the second rater did not. In addition, since the patient was nonverbal, this may have falsely lowered the ABS scores, which has as one of its items rapid, loud, or excessive talking.

Summary. Musical intervention studies to date indicate that the administration of music may not be contraindicated in the management of agitation in TBI patients, as previously thought. In three of four studies, music listening interventions resulted in decreases in agitation. The fourth study had inconclusive results. Musical interventions may reduce agitation. However, the lack of a nonmusical control condition makes it difficult to determine if effects are due to mood, arousal, or attention (Chanda & Levitin, 2013) and limits the conclusions that can be drawn. However, these initial findings are compelling. Furthermore, there have been multiple studies that have established the efficacy of musical interventions at decreasing agitation in patients with dementia. Therefore, it would be of benefit to further explore the effects of music on agitation in TBI using well-controlled studies investigating the efficacy of music as one component of the treatment regimen for patients with agitation.

Areas that could be further explored are what types of musical characteristics best decrease agitation. For example, whether the music is calm or stimulating, its tempo, and emotional valence may be examined. Another important question is whether interventions that are associated with reductions in agitation are dose-dependent. What is the optimal duration of the musical intervention required to decrease agitated behavior, and how long do the effects of musical interventions last? Additionally, , functional magnetic resonance imaging studies could investigate the activity of brain regions during music listening in TBI patients, allowing inferences to be drawn on the possible brain networks modulated by music during the agitation phase. Finally, the stress response could be investigated using quantitative measures such as measures of salivary cortisol, heart rate and respiration rate.

If future studies using larger sample sizes corroborate the finding that musical interventions decrease agitation in TBI patients, it could lead to decreased reliance on physical and pharmacological restraints. Furthermore, administering preferred music to patients is a low-risk, low-cost intervention that can involve families. It may even be effective in phases of recovery beyond the agitation phase, extending to rehabilitation.

Individualized Therapeutic Activities

Waszinski and colleagues (2013) evaluated whether offering patients individualized therapeutic activities during continuous observation would serve to alleviate their agitation. Activities included art activities (drawing, coloring, painting, knitting, craft kits), reading, (books, magazines), music (tapes) and games (playing cards, stuffed animals, puzzles, activity apron, picture communication board, “puffer” balls). Agitation scores on the ABS were greater before the intervention than after the intervention. However, in addition to TBI patients, this study included several other patient populations, such as those with dementia, delirium, alcohol withdrawal, and other psychiatric patients. The number of TBI patients was not specified. In addition, the authors indicated that seven of the patients in the study did not exhibit agitation before, during or after the intervention. Also, the fact that raters were not blind to the condition could have created bias when interpreting behavior. Finally, the study lacked a control condition, limiting the conclusions that can be drawn.

However, the fact that this study found that a range of activities, not just music, were effective at reducing agitation, is interesting. It raises an important question about music and art therapy studies: are the interventions beneficial due to the effects of the music or art itself, or the fact that the patient is being engaged in an intervention? Perhaps the type of intervention is not important. Similarly, in interventions involving an art or music therapist, to what extent is the therapeutic alliance itself important at reducing agitation? Again, well-controlled studies using clearly specified intervention groups with appropriate controls would be necessary in order to evaluate the efficacy of these various individualized therapies in agitation.

Operant Contingency Management Interventions

Behavioral therapy requires an in-depth knowledge of the environmental factors that contribute to the behavior of the patient (Ducharme, 2000). As such, these approaches are most useful in conjunction with environmental measures. Since 2000, a collaborative approach has been increasingly adopted, in which adaptive behaviors are encouraged in TBI patients (Giles, Baxter, & Manchester, 2013). These include positive operant contingency behavior programs, which have been referred to using several different terms in the literature, such as Positive Behavior Interventions and Supports (PBIS)(Ylvisaker et al., 2007) and intensive positive behavioral supports (Gardner, Bird, Maguire, Carreiro, & Abenaim, 2003). These similar procedures combine operant contingency with antecedent management to help patients adapt their behaviors to task performance.

Behavioral interventions are based in positive reinforcement (the provision of a desired item or event, including social approval, in response to a targeted behavior), and negative reinforcement (the withdrawal of an item or event that the person does not desire in response to a targeted behavior). The goal is to strengthen desired behaviors and alleviate undesirable behaviors. Punishment is not recommended as a way of managing behavior in TBI patients, as it is both ineffective and unethical (Ducharme, 2000; Slifer & Amari, 2009).

Slifer and Amari (2009) propose that operant contingency management interventions may be appropriate at all stages of TBI management, including at early stages. Operant contingency management interventions are thought to be most effective when used in combination with environmental antecedent management. For example, when environmental factors, including rehabilitative therapy, overwhelm a patients' cognitive capacity, they may become frustrated. Because of deficits in language and cognition, self- expression may manifest in maladaptive aggressive and verbal assaults in an attempt to modify the patient's environment and arousal level (Alderman, 2001; Ducharme, 2000) . When staff respond by acquiescing to these demands, it reinforces the maladaptive behavior (Alderman, 2001). However, carefully monitoring behavior using standardized measures such as the ABS, while adjusting therapeutic activities appropriately, can help the patient achieve optimal arousal levels and participation in adaptive activities. Introducing activities in incremental doses can help patients to learn coping strategies. For example, a patient with communication problems can be taught to use manual signs for simple requests. When staff emphasize positive behaviors, involvement in rehabilitative activity may increase and allow patients to behave in more adaptive ways (Slifer & Amari, 2009).

Behavioral Contracting

Most behavioral contracting research involves interventions with TBI patients months to years after their injury. However one case study by Hufford, Williams, Malek, and Cravotta (2012) demonstrated that behavioral contracting may also be effective at decreasing patient agitation just days after TBI. In their study, a 37 year-old man with a severe TBI demonstrated agitated symptoms. After being transferred to an acute inpatient rehabilitation facility, the agitation continued, and repeated administration of medication, as well as environmental and behavioral treatment failed. The patient denied his deficits and was non-compliant with rehabilitative treatment. He required restriction to a locked unit with one-on-one supervision.

Nine days post-injury, a written contract was drawn, in which specific positive behaviors were listed as expectations for the patient's discharge. From the moment the behavioral contract was signed, the patient cooperated, and his ABS scores decreased significantly. The authors concluded that behavioral contracting may be particularly useful in patients who have a low level of awareness of t their cognitive and functional deficits. They also stated that direct attempts to promote awareness in patients may be unnecessary. Rather, patients may only require specific directives for behavior along with the possibility of reaching a meaningful personal goal.

This approach of setting meaningful goals rather than coercing patients to behave is also supported by other research. For example, Medley (2010) found that patients who perceive their environment to be coercive are less compliant with rehabilitative activities.

Ownsworth (2006) also reported that confrontational feedback strategies can worsen the behavior of patients who are unable to accept injury-related deficits. Finally, Sohlberg & Mateer (2001) reported that patients can be taught how to use compensational strategies for their cognitive and functional deficits without overtly addressing their deficits.

Hufford, Williams, Malek, and Cravotta (2012) noted certain limitations in their case study. The decrease in the patient's agitated behavior could have been due to the delayed effect of medication administration, or spontaneous healing. The establishment of the contract between the staff and patient may have strengthened the therapeutic alliance, as positive behaviors were noted and encouraged. Still, this study offers a point of departure for further investigation.

Summary. The study cited in the current review suggests that there is some potential for success of operant contingency management programs at reducing agitation in TBI patients in acute care. In addition, there is evidence to support the efficacy of such programs in long-term care patients (Ylvisaker et al., 2007). However, further research is needed in both populations. Slifer & Amari (2009) recommend that studies would best be conducted in acute populations once methodologically stronger studies are completed in long-term care populations, as acute care populations pose a greater challenge.

The ICAR Model of Behavioral Management of Agitation

Prigatano et al., (2003) proposed the ICAR model that includes contingencies to guide the treatment of TBI patients using a comprehensive individual patient-tailored behavioral approach. The model consists of four elements: 1) *Information.* A neuropsychological exam can highlight deficits and strengths. This can help patients and families develop strategies to manage their condition and plan their next steps in care; 2) *Contingencies*. As described in the previous section on operant contingency management, a problem behavior is identified along with contingencies that would be most effective as motivators. Then maldaptive behavior is monitored, and the maintenance of more desirable behaviors is encouraged; 3) *Awareness*. There are several ways by which self-awareness may be improved. Prigitano outlines a non-confrontational method, in which the therapist and patient together monitor the patient's performance on certain tasks, identify strengths and weaknesses, and compare performance to previous performance by the patient as well as to performance of the same task by the therapist, as a gentle way of bringing awareness to the patient about his or her deficits. During this time, a therapeutic alliance is formed. A forum for discussion may be opened in which compensation strategies can be identified to improve performance, without emphasizing the deficit, which may help patients come to terms with their disability; and 4) *Relationship.* The working therapeutic alliance contributes to productivity. Prigitano states that the therapist must have a solid foundation in learning theory and psychodynamic principles, be able to identify brain-behavior disturbances, and deal with patients' existential crises. Importantly, these interventions are more applicable to chronic maladaptive behaviors managed in an outpatient setting, rather than the acute time-frame of post-TBI agitation.

Occupational Therapeutic Approach: The Perceive, Recall, Plan and Perform System Approach

As outlined in section one, the inability to acquire new information during post-traumatic amnesia is a known antecedent to agitation. Acquiring information processing strategies post-TBI is instrumental to adaptive behaviors. Nott, Chapparo, & Heard (2008) demonstrated that the Perceive, Recall, Plan, and Perform (PRPP) System approach appears to be more effective at improving information processing strategies in agitated patients with PTA than traditional occupational therapy methods (Nott et al., 2008).

The PRPP approach is an information-processing model that teaches patients to apply trained strategies to everyday tasks. When performing a task, they learn to "stop," or focus on acquiring the level of arousal necessary to complete the task; "sense," or focus on perceiving sensory information that is related to the task; "think" or consider the planning strategies they have learned in order to complete the task; and "do," or implementation of the plan. The therapist supports the patient's use of these strategies and retreats when the patient becomes capable of implementing them.

In an initial case study by Nott & Chapparo (2008), specific information processing problems were identified in an adult with severe agitation. His main deficits were in sensory processing, planning and attention. The PRPP approach was then applied, and the patient was assessed on performance of three tasks over a one-month period. The authors noted that the PRPP system approach is sensitive to information processing changes over short time intervals and could thus be used to reassess task performance in severely agitated adults during occupational therapy interventions. It is therefore useful at guiding occupational therapy interventions by categorizing processing errors under the four-stage information- processing model (Nott & Chapparo, 2008).

In a small case series, the same group investigated the application of the PRPP model in eight patients with agitation. Seven were TBI patients, and one patient had suffered a brain injury after hypoxia (Nott et al., 2008). Patients were classified as agitated based on stage IV or V on the Ranchos Los Amigos Scale. Daily therapy involved tasks of self-care, recreation, community integration and home management. A traditional occupational therapy intervention was alternated and compared with the PRPP system over a period of four weeks. There was a large to very large effect of the PRPP system on information processing capacity during task performance. Notably, the most severely agitated patient in the group did not show a significant decrease in agitation. However, his agitation scores demonstrated a trend toward improvement. The authors suggested that the intervention may need to be of longer duration in patients with more severe agitation in order to achieve the same results. Conversely, the results may suggest that the PRPP approach may simply be of limited utility in persons with greater dysfunction.

Summary. The Perceive, Recall, Plan, and Perform (PRPP) System approach may be better suited to improvements in information processing strategies than are traditional occupational therapeutic approaches. Given the fact that one of the antecedents to agitation is thought to be decreased cognitive capacity, this intervention, which provides strategies for managing cognitive impairment in agitated patients, may be of indirect benefit. Further investigation into this approach is necessary, focusing specifically on whether agitation scores decrease following the intervention using the ABS. However, no data as to the functional outcome in these patients was presented.

Non-Violent Crisis Intervention

Non-violent crisis intervention (NVCI) is a widely-marketed commercial program that involves the de-escalation of verbal and physical violence through techniques taught by NCI certified instructors to staff managing TBI patients (Beaulieu et al., 2008; Morrison & Love, 2003). The goal is to reduce reliance on physical and pharmacological restraints. Staff must learn to identify behaviors that are likely to escalate to aggression. Levels of escalation are specified, along with the appropriate intervention for each level. Staff must use verbal de-escalation to avoid an escalation of agitation to the point of physical aggression. Self-defense is also taught.

Beaulieu and colleagues (2008) examined the efficacy of the NVCI at decreasing levels of agitation in 222 patients hospitalized on the brain injury unit. Included were patients with TBI, neoplasms, encephalopathy, and hydrocephalus. They specifically examined whether there were decreases in the use of physical and pharmacological restraints and medication in these populations. Overall, the use of physical and pharmacological restraints did not progressively decline with the training of more staff in NCVI. However, it should be noted that there was no control group, so it is difficult to conclude without reservation that this treatment was efficient. In addition, it was not specified how many of these were TBI patients. Also, the ABS was only administered at the beginning of the study, rather than ongoing measurement at specified time points. This is problematic since later analysis on the effectiveness of reducing agitation relied primarily on staff behavior as an outcome variable. The authors noted the possibility that the training made staff more sensitive to the presence of agitated behaviors, thus resulting in greater use of restraints, since this was their habitual solution for agitation management.

Summary. There is currently no clear evidence for the efficacy of the NVCI program in the agitated TBI population. However, very few studies have been conducted. Future studies could include pre- and post- intervention measurements of agitation, which would provide a more objective measure of agitation.

Concluding Remarks

The majority of research studies on the treatment of agitation in hospitalized TBI populations recommend a multi-faceted approach to agitation management. This is necessary in order to address various cognitive, behavioral, emotional and physical deficits that underlie the agitated state following TBI. The most effective approach to managing agitation in TBI may be to combine the judicious use of pharmaceutical agents with the management of environmental antecedents and behavioral interventions appropriate to the specific causes underlying agitation. The literature into the behavioral management of agitation during the acute stages of hospitalization is sparse. However, there is preliminary evidence that demonstrates beneficial effects for three main types of behavioral approaches: musical interventions, occupational therapy interventions, and operational contingency management interventions.

Despite promising evidence that behavioral interventions may reduce agitation, the current studies have substantial methodological weaknesses, including lack of control groups and conditions. More rigorous research designs are required in order to improve generalizability and draw definitive conclusions. Unfortunately, due to the range of agitated behavior, inter-current administration of medications, and ongoing interruptions to interventions by necessary patient care regimens, rigorous controlled experimental studies are difficult to conduct during acute care. Random assignment into experimental and control groups is difficult due to the heterogeneity of brain injury and may also present an ethical dilemma in some cases. In addition, the heterogeneity of the TBI population necessitates individualized treatment during the phase of medical instability. As such, single case and case series designs still make an important contribution to this field (Nott et al., 2008; Ottenbacher, 1986; Slifer & Amari, 2009).

When considering future treatment applications in the agitated TBI population, a more systematic process is needed (Eisenberg, Im, Swift, & Flanagan, 2009). Currently, there is no consensus as to a standard of care for agitated patients (Janzen et al., 2014). The following improvements are proposed: 1) researchers must reach a consensus on the definition of agitation. This would increase research replicability, and contribute to more accurate measures of agitation prevalence; 2) many studies in the field lack detailed descriptions of the intervention employed, thus limiting interpretation and replicability. For example, in a music study, it may be important to specify the criteria for musical selection and which songs were used, as well as the measures used to determine musical preference; 3) studies should be furnished with greater detail of demographic and medical characteristics of the experimental and control groups. For example, details as to the length of time from injury to intervention, specific location of injury, and presence of any other significant injuries would all aid in the interpretation of the results and inform future research; 4) during patient interventions, the patient's agitation levels should be regularly monitored using a standardized measure that is valid and reliable, such as the ABS. In this manner, clinical interventions may be tailored to each patient's response. Clinicians could refer to the scale to help them precisely identify the point of balance between adequate stimulation to promote cognitive recovery, and overstimulation leading to agitation. This would reduce the chance of inappropriate interventions; 5) Follow-up studies investigating the patients' subjective experience of therapy would be of interest in providing the best possible interventions; and 6) Blind ratings of agitation by trained observers, in order to minimize ambiguity when interpreting results.

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CHAPTER IV: Article 3

The effects of preferred music, relaxing classical music, and waterfall sounds on agitation during acute hospitalization for acquired brain injury: a phase-II trial

Kirsten S. Anderson [1,2,3,*], Nathalie Gosselin [1,3], Abbas F. Sadikot [4],
Esther S. H. Kang [6] Benjamin Lo, Maude Laguë-Beauvais [4,5],
Judith Marcoux [4,5], Jehane Dagher, [2,5] and Elaine de Guise [1,2,8,*]

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Abstract

Agitation is a state characterized by motor hyperactivity, disorientation, emotional lability, and disinhibition. It is commonly observed during the acute phase of recovery from acquired brain injury (ABI), and requires management, as it poses safety risks to patients and caregivers. Chemical and physical restraints are common treatments, though both may have negative side effects. Few studies have explored non-pharmacological treatments for agitation in ABI patients. Two studies in TBI patients, and multiple findings in dementia populations indicate that preferred music decreases agitation. However, important methodological limitations have impeded the progression to larger controlled trials. Thus, this phase-II development-of-concept trial in ABI patients aimed to determine the practicality of applying a structured evaluation protocol for listening interventions in medically complex patients. Four ABI patients with moderate to severe TBI (n = 3) and middle cerebral artery stroke (n = 1) were exposed to preferred music, relaxing classical music, and a nonmusical control (waterfall). Agitation was measured with the Agitated Behavior Scale (ABS), and actigraphy, and the clinical course of these patients was described in detail. Decreases in agitation on the ABS were observed in two patients while listening to relaxing classical music and the nonmusical control. Preferred music did not affect agitation scores. However, certain patients expressed positive emotion and memories, along with displaying more organized movement, such as tapping along to the beat. Results are discussed in the context of current literature, and recommendations for a structured protocol are proposed based on an assessment of outcome measures, data collection, and scoring procedures.

Introduction

Agitation is a state during the acute post-traumatic phase that includes specific physical, cognitive, and behavioural symptoms. It is characterized by motor hyperactivity, disorganized thinking, emotional instability, and aggression (Bogner, Corrigan, Fugate, Mysiw, & Clinchot, 2001; Lombard & Zafonte, 2005; Van der Naalt, Van Zomeren, Sluiter, & Minderhoud, 2000). Agitation is well-recognized in the context of several neurological disorders, in patients undergoing intracranial surgery, dementia, stroke and traumatic brain injury (TBI) (Ojaghihaghighi, Vahdati, Mikaeilpour, & Ramouz, 2017; Särkämö & Soto, 2012; Sung & Chang, 2005). Agitation is extremely common in the TBI population. The majority of reports fall within the 30-70% range (Lindenmayer, 2000; McNett, Sarver, & Wilczewski, 2012; Ponsford et al., 2014; Saoût et al., 2011), but the extremes vary from 8% to 96% (Singh, Venkateshwara, Nair, Khan, & Saad, 2014). In hospitalized TBI patients, agitation typically lasts one to 14 days (McNett, Sarver, & Wilczewski, 2012), although these behaviours may persist for much longer in up to one quarter of patients (Baguley, Cooper, & Felmingham, 2006).

Despite the common presentation of agitation, there is little research on novel non-pharmacological interventions for acquired brain injured populations during acute care. At present, there are no approved therapies for the management of agitation, other than physical and chemical restraints. Physical restraints can be useful as a temporizing measure, but can lead to injury, deep vein thrombosis and pulmonary embolism, or pressure sores (Beaulieu et al., 2008; McNett et al., 2012). Chemical measures in the form of medications can also be helpful, but side effects include drowsiness, confusion, and extrapyramidal symptoms that may be detrimental to the patient (Battaglia, 2005; Laursen, Jensen, Bolwig, & Olsen, 2005). Therefore, effective systemic therapies represent a substantial unmet medical need.

Recent evidence demonstrates that music listening interventions significantly decrease agitated behaviour in dementia patients (Gaviola, Inder, Dilworth, Holliday, & Higgins, 2020; Harrison et al., 2021; Oteng, 2020; Särkämö et al., 2008; Schroeder et al., 2018; Sung & Chang, 2005). Furthermore, it is well established that music induces widespread changes in neural activity throughout brain regions implicated in cognition and motor function (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011; Särkämö & Soto, 2012). Music listening also positively affects mood and regulates emotion (North, Hargreaves, & O'Neill, 2000; Saarikallio, 2011), in part by activating limbic and paralimbic brain areas (Blood & Zatorre, 2001; Ferreri et al., 2019; Formisano et al., 2001; Hegde, 2014; Salimpoor et al., 2011; Salimpoor et al., 2013).

It is proposed that certain parameters contribute to the perception of music as “relaxing” (Bernardi et al., 2006). For example, tempos of 60-80 beats per minute (bpm), which are similar to the human heart rate, tend to be more relaxing than tempos that are too fast or slow (Elliott, Polman, & McGregor, 2011; Ho et al., 2011; Nilsson, 2009). Preferred music is proposed to be particularly effective, as allowing patients to select their own music is thought to bring a sense of personal control back to them, which promotes recovery and well being (Hole, Hirsch, Ball, & Meads, 2015). It is also proposed to have a particularly calming effect, as it helps orient TBI and dementia patients by creating a familiar environment through the induction of positive memories and emotions (Formisano et al., 2001; Park, Williams, & Lee, 2016; Sung & Chang, 2005), which reduces patient anxiety (Sung, Chang, & Lee, 2010) and promotes positive behaviours, such as smiling and humming to the music (Janelli, Kanski, & Wu, 2002).

There is ample evidence supporting the efficacy of preferred music at reducing agitation in dementia populations (Gerdner, 1997; Gerdner, 2000; Gerdner & Swanson, 1993; Harrison et al., 2021; Hicks-Moore & Robinson, 2008; Janata, 2012; Park & Park, 2019; Ragneskog, Asplund, Kihlgren, & Norberg, 2001; Schroeder et al., 2018; Scudamore et al., 2021; Sung, Chang, &

Abbey, 2006). However, to our knowledge, there are no studies examining the effectiveness of music interventions at treating agitation in a stroke population, and only two exploratory studies in a TBI population (Baker, 2001; Park et al., 2016). In a pioneering study, 22 patients with TBI demonstrated lower agitation scores during preferred music listening than without music (Baker, 2001). The second, a case-crossover design, demonstrated significant decreases in agitation in 14 patients during a preferred music condition compared to a classical music condition or no music during the acute phase of TBI (Park, Williams, & Lee, 2016). In both studies, qualitative observation indicated that some patients replaced disorganized motor behaviours, such as pacing and inappropriate movements, with organized movements, such as tapping along to the rhythm or pacing in time with the music (Baker, 2001; Park, Williams, & Lee, 2016).

While these two studies demonstrated the benefits of music at decreasing agitation in TBI patients, there were important methodological limitations. First, the lack of a nonmusical control condition limited the conclusions that can be drawn. Thus, it was impossible to determine whether these diminished agitation effects were in response to music, or if they were simply due to the masking of environmental noise. Second, they lacked the more objective measures of agitation such as motor changes measured using actigraphy. Third, during administration of the Agitated Behavior Scale (ABS), an observational tool that measures level of agitation (Corrigan, 1989), the observer was present in the room. It is therefore unclear if the decrease in agitation was due to the connection with the observer, or related to the music itself. Fourth, the raters were not blind to the listening condition, introducing possible bias. Therefore, it would be important to design studies that include appropriate controls, such as comparison of the effects of preferred music and relaxing classical music with a nonmusical control condition, use objective measures such as actigraphy, administer the intervention with as few caregivers in the room as possible, and use blinded raters of agitation.

Thus, the purpose of this phase II, development-of-concept pilot study (Dobkin, 2009) was 1) to determine the feasibility of applying measures of agitation during the acute phase of recovery from ABI during the exposure to preferred music, relaxing classical music, and a nonmusical control (waterfall sounds). The feasibility of the intervention was tested in two ABI groups; patients with acute stroke, and TBI. We hypothesized that during the acute phase of recovery from ABI, a preferred music listening intervention would be more effective at decreasing agitation than classical music, a non-musical control condition, or no music; and 2) to report in detail the clinical course of four agitated hospitalized ABI patients that participated in a structured evaluation protocol, focusing on: a) the effect of each listening condition on agitation as measured by ABS scores and actigraphy; and b) the challenges encountered in applying music interventions in medically complex patients. We aimed to determine how lessons learned based on these case studies may be applied to the design of a larger study to determine the efficacy of listening interventions as a non-invasive non-pharmacological intervention, addressing an important unmet medical need.

Method

Participants

Three TBI patients (ages 63, 67, and 79) who were hospitalized on the neurology and neurosurgery ward at the McGill University Health Centre-Montreal General Hospital (MUHC-MGH), and one patient (age 71) hospitalized on the stroke ward of the Montreal Neurological Institute (MNI) were included in this study (Table 1). The study was approved by the MUHC Research Ethics Board.

Inclusion criteria were as follows: The patient had a moderate to severe acute brain injury, defined as an initial Glasgow Coma Scale score (GCS) between 3 and 12, with 9 -12 indicating moderate injury, and 3-8 indicating severe injury. The patient had to be over the age of 18, and required hospitalization (Rowley & Fielding, 1991). Each patient was selected by a physician during the in-patient recovery phase, on the basis of agitated behaviour according to level 4 of the Rancho Los Amigos Scale (Gouvier, Blanton, LaPorte, & Nepomuceno, 1987). All patients had a family member who was able to complete the music preference questionnaire. They were able to understand English or French. Exclusion criteria consisted of patients who had severe orthopedic injury, spinal cord injury, those in the intensive care unit, or who were receiving intravenous narcotics for pain management, and those with a diagnosed hearing impairment, or who had notable deficits in conversation. Demographic, medical and neuropsychological status was retrieved from each patient's medical file during their hospitalization, including age, sex, language, education, work, and previous medical issues (neurological and psychiatric issues). Delay between the onset of accident and intervention was also computed.

Material and measures

Assessment of Personal Music Preference (Family Version)(Gerdner & Schoenfelder, 2010). This questionnaire included questions about preferred musical pieces, musical genres, and artists, and has been used in the context of dementia studies. From this list, the more soothing pieces were selected for administration at the patient's bedside.

Agitated Behavior Scale. This scale provides a total score for agitation by describing 14 different verbal and physical behaviours on a rating scale of 1 (absent) to 4 (present to an extreme degree), with a maximum score of 56. Scores above 21 indicate agitation (Corrigan, 1989). It is highly valid and reliable in a TBI population (Corrigan, 1989). Two raters who were blind to the condition used this scale to evaluate agitation when reviewing videotapes of the different listening interventions. Using Kripperndorf's alpha (Krippendorff, 2011), the intercoder reliability for this study was estimated to be α = 0. 81, or “almost perfect” (Landis & Koch, 1977; Landis & Koch, 1977).

Actigraphy. This is a non-invasive validated device (28 x 27 x10 mm) worn as a wristwatch that weighs 17 grams (Actical, Mini Mitter Co., Inc., Bend, OR). The Actical detects the magnitude of acceleration and deceleration associated with each movement, and records movement from 0.05 to 2.0 grams. Motion is digitally integrated from an electrical signal to determine the activity count for selected time epochs (Duclos et al., 2013; Grap, Borchers, Munro, Elswick, & Sessler, 2005).

Procedure

After consent was obtained by the research assistant, the music selection process for preferred music began with the patient’s relative completing the Assessment of Personal Music Preference (Family Version), in addition to discussing the patient’s musical preferences. When possible, this was verified with the patient. A 15-minute file of musical extracts was then created for each patient based on their favourite music (Table 2), using GarageBand ’11 Version 6.0.5 (428.5 When possible, pieces were selected for compatibility with a major mode, and tempos between 60 and 80 bpm (Nilsson, 2009; Ho et al., 2011). A 15-minute file of classical music extracts was also created by the researcher and was used in all the patients (Table 3). Each selected piece was selected for compatibility with a major mode, and with tempos between 60 and 80 bpm. Waterfall sounds were selected for the nonmusical control condition (Thoma et al., 2013). It was recognized that several control conditions may be used, such as continuous sound, audio books, and nature sounds. In stroke patients, audio books were found to be ineffective at reducing depression and confused mood when compared to preferred music (Särkämö et al., 2008). This may have been an appropriate control for certain studies. However, during post-traumatic amnesia, TBI patients often have impairments in perception and speech (Ponsford et al., 2014). Thus, in certain cases, conversation may exceed patients' cognitive processing capacity and increase their agitation in contrast with nature-based sounds. On the other hand, birdsong has been suggested to be similar to music with regards as to the pitch variations and rhythmic relationships (Baptista & Keister, 2005). Therefore it may not be appropriate for the present study. Waterfall sounds were chosen as the nonmusical control, based on a study by Galbrun & Ali (2013), in which paired comparisons were made between the sound of streams, fountains and waterfalls. Healthy participants preferred streams, then fountains, then waterfalls, in that order (Galbrun & Ali, 2013). Waterfalls may more closely resemble a neutral sound when compared with music and seemed to be a justified choice. We chose a heavy waterfall sound, as it may better mask background noise than light or intermittent waterfall sounds. Thus, a 15-minute file entitled "small multi-step waterfall 2" was created from the following website: https://www.zapsplat.com/page/6/?s=waterfall&post_type=music&sound-effect-category-id

The research assistant then determined the time of day that the patient was typically the most agitated, by observing each patient, and consulting with nurses on the ward. Thereafter, the patient's room was visited to fasten an actigraphy wristwatch to each wrist, in order to measure movement bilaterally. We exposed each patient to a 45-minute-long listening intervention once per day during times of active agitation, for a total of three interventions (either preferred, classical, or waterfall) on three separate days. Interventions occurred on different days and times of day, depending on the patient. However, most interventions occurred in the morning between 6:00 a.m. and 11:00 a.m, and the interventions did not interfere with meals, medication administration, visits with relatives, or medical care. On days that the patient's condition necessitated further medical interventions (surgery, worsening of systemic condition requiring ICU care), the study was interrupted. When the patient's agitation level was below the threshold agitation score required for the intervention on the ABS (< 22), data was not collected. The door to the room was closed when possible, and the TV and radio were off. A speaker was placed at the patient's bedside so that music could be played at a comfortable volume using an MP3 player. Each intervention included a 15-minute baseline condition (no auditory material presented)(See Figure 1). Then, one of three 15-minute listening conditions were presented: 1) A music condition in which researcher-chosen relaxing classical music was played in the room at a comfortable volume (MC); 2) A music condition in which the patient's preferred music was played in the room at a comfortable volume (MC); or 3) A non-musical control condition (NMC) in which the presented sound was a heavy waterfall resembling white noise. Finally, there was a 15-minute post-intervention condition in which no auditory material was presented. The order of listening conditions was counterbalanced. For example, for patient 1, either the preferred or classical music condition was presented during the first intervention, followed by the non-musical control condition during the second intervention, and the other music condition presented at the third intervention. For patient 2, the order of these interventions was reversed. If the patient asked that the music be turned off, the intervention was stopped for that day. When there were interruptions to testing for nursing care or because someone stopped in and spoke with a patient, an event marker was pushed on the device to mark the spot that it had occurred, and corresponding data was later removed from analysis.

Each intervention was video recorded, and all videos cut into three parts for each listening intervention, including the pre-intervention baseline "before" condition, the "during" listening condition, and the post-intervention "after" condition, for a total of 36 videos, or nine videos per patient. Adobe Premiere Pro CC (version 12.0) software was used for editing. Videos were assigned a random number, and viewed by two research assistants, who recorded observations as written notes. First, videos were scored without sound. The following day, all data was reviewed with sound added, to contextualize movement and verbalizations, including verbal complaints, intent to wander, repetitive and unnecessary calls for help, nonverbal vocalizations such as humming, and cooperation with care, corresponding to items 1, 2, 3, 4, 6, 8, 11, and 14 of the ABS, all of which require listening.

Statistical analyses

ABS. Two blinded raters viewed videos for each condition (before, during, after) of each intervention (preferred, classical, waterfall). The total score of the first rater and the second rater was computed for each 15-minute segment. The sum of the two scores was then divided by two to obtain a mean for each segment. Finally, the percent change was calculated from the baseline condition to the music condition for each intervention.

Actigraphy. Data were uploaded from the actigraph wristwatches to dedicated software (Actiware 5.0) and activity counts derived per 1-minute epoch. A separate activity count was summed for each 15-minute condition (before, during, after), resulting in three separate scores per listening intervention (preferred, relaxing classical, waterfall). Data corresponding to event markers in which nursing care interruptions occurred were removed from analysis. For each 15-minute condition, activity counts were summed for each wristwatch. Then, sums for the left and right wristwatch were added together, resulting in one score per condition.

To determine associations between the ABS total score and activity counts on actigraphy, a Pearson product-moment correlation coefficient and effect size (Cohen, 1992) was calculated

Results

Medical profile of each patient

Patient 1

History of the injury. Patient 1 was a 71 year-old woman who was active and fully independent before suffering a middle cerebral artery stroke. A CT scan indicated a right frontal intraparenchymal hematoma measuring 6.4 x 4.4 cm. Following one month of hospitalization, she was discharged to a rehabilitation centre. However, the following day, she was readmitted with a massive re-bleed extending from the right side of the brain's surface to the ventricles, and involving the entire deep matter of the second and third gyri, corresponding to the inferior frontal gyri, with significant mass effect. A right frontotemporoparietal craniectomy was performed.

Physical state at the time of testing. Patient 1 was confined to her bed, with a right-lateralized bone flap and swelling of her scalp. On her left side, she had hemiplegia, hemineglect, and neuropathic pain (tingling, pins and needles, numbness, pain on touch). She had a nasogastric feeding tube.

Cognitive state at the time of testing. She demonstrated post-stroke delirium, conversing with people who were not present during imagined scenarios. She was oriented to her name, but orientation to time and place fluctuated. She followed simple commands, but was unable to initiate tasks, and required maximum assistance in all her activities of daily living (ADLs). Due to her decreased learning potential, she was deemed by an occupational therapist to be unsuitable for rehabilitation.

Testing environment. All listening interventions were done at her bedside, in a private room, and with no physical restraints. Actigraphy was measured only on her right wrist, due to left hemiplegia.

Patient 2

History of the injury. Patient 2 was a 67 year-old man with a history of seizures and difficulty with balance. He fell from his own height at the geriatric centre where he had been living semi-autonomously for one month. A CT scan demonstrated an acute left frontotemporoparietal subdural hematoma measuring 17 mm in thickness, and multiple hyperdense foci in keeping with cortical hemorrhagic contusions and subarachnoid hemorrhages in the right frontal, temporal, and parietal lobes. He also had a chronic 9 mm right holohemispheric subdural hematoma, for which he had undergone a right parietal craniotomy four months prior to evaluation. He worked part-time until six months before his accident.

Physical state and medications at the time of testing. Patient 2 required total care in all ADLs. He communicated his needs with a tracheostomy speaking valve, had a percutaneous endoscopic gastrostomy (PEG), and required oxygen delivered via face mask. Psychoactive medications included hydromorphone (1 mg every 4 hours, by subcutaneous injection) and quetiapine (25 mg daily, per os).

Cognitive state at the time of testing. Patient 2's neuropsychological report indicated that he was unable to participate adequately in a quantitative neuropsychological evaluation. However, significant difficulties were observed by the neuropsychologist that suggested executive dysfunction, including cognitive and behavioural perseverations, word-finding difficulties, and the inability to initiate tasks. He also demonstrated poor insight, psychomotor slowing, and rapid fatigue. His ability to orient to person, place, and time fluctuated. He communicated by nodding his head, raising his eyebrows, and occasionally forming short sentences in a laborious manner.

Testing environment. Patient 2 had a private room. All listening interventions were done at his bedside. He wore mitten restraints and loose wrist restraints during all listening conditions.

Patient 3

History of the injury. Patient 3 was a 63 year-old man who was active and fully independent at the time of his accident. He suffered a TBI after a probable electrocution and fall of 12 feet from the roof of his house onto a wooden platform below. His CT scan demonstrated diffuse axonal injury with a moderate sized hemorrhagic focus in the splenium of the corpus callosum on the right, as well as bilateral hemorrhagic contusions at the base of the frontal lobes, scattered subarachnoid hemorrhages, bilateral subdural fluid collections, and a temporal bone fracture. His brain hemorrhages were treated without surgery. He also had fractures of the left clavicule and scapula, fractures of the left first through eighth ribs, and a left pneumothorax that required insertion of a chest tube.

Physical state and medications at the time of testing. Patient 3 required total care in all ADLs. He had a PEG. Psychoactive medications included hydromorphone (1 mg three times daily by subcutaneous injection), donepezil (10 mg daily per os), and quetiapine (25 mg once daily per os).

Cognitive state at the time of testing. He scored 6/30 on the MoCA, indicating severe cognitive impairment. He had difficulty with visuospatial functions, planning and organizing, working memory, verbal fluency, mental abstraction, and word finding difficulties. He was disoriented to the date, or place.

Testing environment. Patient 3 shared a room with three other patients. All listening interventions were done at his bedside. He wore a Pinel belt throughout the listening interventions. He also had different combinations of physical restraints on different days, as detailed below.

Patient 4

History of the injury. Patient 4 was a 79 year-old man who was active and fully independent at the time of his accident. He was hit by car going 60 km/hr while cycling without a helmet. He suffered a polytrauma, with diffuse brain injury, including multicompartmental bleeds of intraventricular, intraparenchymal, and subarachnoid, and subdural regions on MRI. This included bilateral frontotemporal subdural hematoma measuring 7 mm in thickness, with mild mass effect on the frontal lobes of both sides, intraventricular hemorrhages in the posterior lateral ventricles measuring 2.7 cm x .8 cm x 1 cm at the right measuring 3 cm x .5 cm at the left, and foci of frontotemporoparietooccipital subarachnoid hemorrhages over both cortical cerebral convexities. He also sustained several orthopedic injuries, including multiple rib and facial fractures, right zygomatic facial fractures, facial lacerations, a left pneumothorax, left pleural effusion, right pulmonary contusions, and a right adrenal contusion.

Physical state and medications at the time of testing. Patient 4 required total care in all ADLs. He had a PEG. He demonstrated spontaneous movements of both legs and arms, and his eyes were closed for the most part. Psychoactive medications included hydromorphone (0.5 mg eight times daily, per os), and quetiapine (25 mg once daily, per os).

Cognitive state at the time of testing. He was able to state “yes” or “no” in response to questions about his immediate needs, though infrequently. Thus, it was reported that his state of consciousness was insufficient to carry out a neuropsychological examination. He was oriented to name and place, but not time.

Testing environment. Patient 4 shared a room with three other patients. All listening interventions were done at his bedside. He wore a Pinel belt throughout the listening interventions. However, he had different combinations of physical restraints on different days, as detailed below.

Listening Interventions

Quantitative measures for the Preferred music condition

Agitated Behavior Scale (ABS). ABS total scores indicated that the patients' agitation scores were unchanged during the preferred music condition. Preferred music did not have an appreciable effect on agitation scores, with only a 9% decrease in Patient 4, and no exacerbation in Patients 1 (-5%), 2 (-4%), and 3 (-5%). (Figure 2). The residual after-effects varied between patients.

Actigraphy. Individual activity counts during the preferred music listening condition indicated that agitation did not increase in any of the patients, and appeared to decrease in Patient 2, who nodded off to sleep momentarily. Agitation increased in Patient 3 following nursing care. Patient 4 also had an increase in agitation, during loud talking between a nurse and another patient in his room (Figure 3) Disruptions to testing were excluded from the analysis.

Qualitative observations for the preferred music listening condition

Before the music was introduced, Patient 1 was mildly agitated. She fidgeted, folded and patted down her blankets, rubbed her leg, and called out occasionally for loved ones. When preferred music was introduced, she smiled upon hearing each song, and spontaneously redirected wandering thoughts back to the music. She verbalized about a delirious scenario in which she conversed with her son about taking him to a concert. Her movements were organized, and she conducted and nodded in time, and sang along. Of the three interventions (relaxing classical, preferred, and waterfall), Patient 1 appeared to focus on and enjoy preferred music the most, listening intently. Her body was calm with less leg movement. She thanked the researcher for the music. When the music was removed, she resumed rearranging the blankets constantly. Her mood remained positive for the first five minutes, as her verbalizations centered around the songs. However, her complaints and poor mood began to reappear after five minutes, with increased physical agitation, and loud speech. She called out for her physiotherapist, complained of being cold, and searched for her blanket.

Patient 2's agitation remained fairly consistent throughout conditions, indicating mild agitation. However, during the music condition, he seemed to relax enough to nod off a bit, and his actigraphy demonstrated slightly lower activity counts.

Patient 3 wore a Pinel belt and wrist restraints. The noise from the nursing station fed into his paranoid delusions. His sense of distress appeared to increase across the three conditions, with the most substantial increases observed after receiving nursing care, interacting with people, and during loud background noise. The music, which was happy, contrasted his mood. He commented, "it's a nice song but I haven't seen my wife for 25 minutes."

Patient 4 was consistently restless, with leg slung over side and speaking indecipherably to people who weren't present. He opened his eyes only occasionally. When his preferred music was introduced, he continued to be physically restless, but appeared to be pausing to listen. His vocalizations decreased and he became more organized, singing the words to the choruses. When asked if he liked the music, he responded, "yes." However, his physical agitation remained constant, with increases when loud talking was occurring in his room between a nurse and another patient.

Quantitative measures for the Relaxing Classical Music Condition

ABS. Total scores during relaxing classical music listening showed no increase in agitation in any of the patients. Overall, classical music was the most beneficial of the three interventions (relaxing classical, preferred, and waterfall), with decreases in agitation observed in Patients 1 (-31%) and 2 (-14%), and no exacerbation of agitation in Patients 3 (+3%) and 4 (-4%) (Figure 4). The residual after-effects varied between patients, with only one patient showing a significant decrease (Patient 1) and others showing a return to at or above their baseline at the "before" level.

Actigraphy. Activity counts indicated that agitation decreased in three patients while listening to classical music (Patients 1, 3, and 4), followed by a return to baseline after the intervention (Figure 5). In Patient 2, there was no change during classical music listening, but activity decreased compared to baseline following the intervention. However, the validity of results is uncertain in these patients, as actigraphy only measured arm movements, whereas certain demonstrated restlessness primarily through excessive leg movement. In addition, the listening condition was stopped and restarted due to interruptions for nursing care.

Qualitative Observations

Patient 1 demonstrated significant anxiety and emotional lability, consistently yelling, raising her head to look toward the door, calling out for loved ones, fidgeting with blankets, and complaining of isolation. When classical music was introduced, she lay back on her pillow, stopped yelling, and decreased her fidgeting. She quietly talked or moved her lips silently. She commented that the music was relaxing. After the music was removed, she remained calmer, with no vocalizations. However, her physical restlessness continually increased.

Patient 2 attempted to remove his gloves, waved his hands, looked toward the door, and vocalized. When classical music was introduced, his hand waving decreased, and he appeared to be listening to the music. His facial expression was calm. He yelled intermittently, and when the classical music was almost finished, began looking toward the door again. Once the music was turned off, he became very agitated. He removed his gloves and oxygen, and was uncooperative with nursing care.

Patient 3 was consistently restless, pulling at his feeding tube and attempting to remove his Pinel belt. He was not wearing wrist restraints or soft mitts. He also fiddled with his bed, removed the Actical wristwatch, and stated urgently his intent to leave. The condition was stopped and restarted after he agreed to wear the Actical wristwatch. He fixated on the nursing station outside his room, and whistled loudly with both hands in his mouth to get the attention of healthcare workers and passersby. He removed his bed sheets and again removed the Actical wristwatches, and both wrist restraints and wristwatches were added during the music listening condition. He said he was thankful for the music, but no changes in agitation were noted. His agitation was predominantly verbal, calling out, and lifting his head to look around. He struggled against his restraints while verbalizing ongoing plans involving delirious scenarios. The fact that the condition was stopped and restarted twice makes its validity questionable. Wrist restraints added partway through the "during" condition likely contributed to decreased agitation on actigraphy. He also mainly moved his head and verbalized, rather than moving his hands, where actigraphy wristwatches were placed.

Patient 4 wore a Pinel belt and gloves throughout the intervention. He demonstrated intermittent periods of restlessness (forcefully kicking the footboard of his bed, slinging his leg over the side rail, waving his hands, pulling at restraints, tapping his hands on his legs), and self-stimulating behaviours (monotone humming, jittering) alternating with calm. Patient 4's level of agitation appeared to decrease slightly during the classical music listening condition.

Quantitative measures for the nonmusical control (waterfall)

ABS. Total scores for each individual indicated that during the nonmusical control condition (heavy waterfall), agitation decreased in patients 1 and 2 in a similar manner to that of classical music (-13% and -26% respectively). It did not affect agitation levels in Patient 3 (+2%). Patient 4's agitation increased (+29%) (Figure 6). The residual after-effects varied, with two patients showing a decrease compared to baseline and during music, and two showing virtually no change.

Actigraphy. Individual activity counts indicated that agitation increased in Patient 4 during the non-musical control (heavy waterfall) condition (Figure 7). On the other hand, activity counts decreased in three patients (Patients 1- 3) indicating a decrease in agitation. The "after period" was characterized by persistent calm in patients 1-4, and persistent agitated motor activity in patient four.

Qualitative Observations

Patient 1 was highly agitated, rocking, rubbing her leg, and yelling constantly, complaining of pain, and crying for loved ones, demonstrating significant emotional lability. When the waterfall was introduced, she stopped vocalizing for short periods, and appeared to be listening. However, after 12 minutes, she stated, "I am sick of the waterfall, I don't know if I can listen to this." The intervention was therefore discontinued. She leaned back on the bed, with a peaceful facial expression. She stopped vocalizing, and there were moments of complete stillness without fidgeting.

Patient 2's agitation decreased across conditions as he appeared to grow increasingly drowsy.

Patient 3 wore a Pinel belt, wrist restraints, and soft mitts throughout all conditions. His agitated behaviour remained steady, and he seemed indifferent to the waterfall, commenting that it was "ok." He had paranoid delusions, engaging in imaginary conversations, calling out, attempting to remove his gloves, and speaking of leaving his bed. He engaged in conversation with an orderly who was tending to another patient.

Patient 4 wore a Pinel belt and wrist restraints. Before the waterfall sound was introduced, he mumbled to himself, jiggled his body, and rearranged his blankets in a non-purposeful manner. His restlessness fluctuated during the intervention. Patient 4's agitation increased when listening to the waterfall both in physical movement, and vocalizing. It reminded him of the bathroom, and he complained of having to relieve himself. This continued throughout the 15 minutes after, although his verbalizations decreased, relative to the waterfall condition

Correlations between ABS scores and activity counts on actigraphy

To determine associations between the ABS total score and activity counts on actigraphy, for each video (n = 36), a Pearson product-moment correlation coefficient was calculated. A moderate positive correlation was found between the ABS total score (M = 28.19, SD = 5.63), and activity counts (M = - 3744.92, SD = 210.17), r (34) = .351, p = .036. A moderate positive correlation was also found when summing only the physical components (items 6-10) of the ABS (M = 12.53, SD = 3.92), and relating them to actigraphy counts, r (34) = .443, p = .015 (Figure 8)

Discussion

This Phase-II pilot study, exemplified by a case series of four acutely hospitalized TBI and stroke patients, demonstrated decreases in agitation during the classical music and nonmusical control conditions (heavy waterfall) in two of four patients. In contrast with our hypothesis, agitation did not decrease in the preferred music listening condition. However, there was evidence of positive memories and emotion in addition to more organized movement, such as tapping along to the beat (for more detailed interpretation, refer to the general discussion of the present thesis). Finally, there was a moderate positive correlation between scores on the ABS and Actigraphy, such that the higher the ABS score, the greater the number of movements on actigraphy. In the first section of the discussion, we present our results in the context of a clinical review of previous studies. In the second section, we discuss the practicality of delivering and measuring outcomes of the intervention, and suggest how a structured protocol might be applied to a larger group of patients based on lessons learned in this development-of-concept study.

Section 1: Music Listening Interventions

Relaxing classical music listening versus preferred music listening

The finding that classical music was more effective than preferred music at decreasing agitation in ABI patients contrasts findings in the two previous studies performed in TBI patients to date (Baker, 2001; Park, Williams, & Lee, 2016). For example, a recent case crossover study of 14 TBI patients demonstrated that preferred music decreased scores on the ABS, while classical music did not (Park, Williams, & Lee, 2016). Since four of the 14 patients included in the classical music listening sample had scores below the cutoff of 22 on the ABS at the time that music was introduced, it is possible that they were not actively agitated (Park, 2010). When excluding those four patients and viewing the data on a case-by-case basis, a sizeable minority (30%) of the remaining 10 patients demonstrated decreases in agitation on the ABS during the classical listening intervention. This more complex picture is in keeping with our findings, in which two of four patients demonstrated decreased agitation during the classical music intervention. Furthermore, in the Park study, only six of 14 patients qualified as agitated (ABS score >21) at the time that preferred music was introduced (Park, 2010). If the eight patients who were not actively agitated at the time of the intervention had been excluded, it is unclear whether the results would have reached significance. Furthermore, group analyses may have overlooked the complexity of individual differences within the sample.

It is unclear as to why preferred music failed to decrease agitation in our patients, given ample evidence supporting its use in dementia studies (Baker, 2001; Gerdner, 2000; Harrison et al., 2021; Janata, 2012; Sánchez et al., 2016; Scudamore et al., 2021), and TBI patients (Baker, 2001; Park et al., 2016). One explanation is that certain selections of the preferred music in the present study were not between 60 and 80 beats per minute for all patients, which is considered optimal for reducing the stress response, as it is similar to the human heart rate, (Ho et al., 2011). In fact some pieces reached 147 beats per minute, and others fluctuated in tempo. Another explanation is that it may be due to the fact that some interventions in the present study were not delivered prior to peak agitation, which has been proposed to maximize efficacy in individuals with dementia (Gerdner, 2000). This is challenging to coordinate in medically unstable TBI patients in acute care, whose testing times must occur outside of daily visits from hospital staff, friends, and family, as well as sedative administration.

In keeping with previous studies in TBI patients (Baker, 2001; Park et al., 2016), some patients demonstrated positive behaviours in response to preferred music. This included replacing disorganized movement (picking, rocking, non-purposeful movement) with organized movement (tapping along, swaying to the beat, and conducting to the music), and replacing negative verbalizations (unwarranted requests for help, complaining, or verbalizing the intent to wander) with positive verbalizations (singing, talking softly, and reminiscing on good memories). Preferred music is thought to improve orientation by providing a familiar environment for patients with post-traumatic amnesia (Baker, 2001; Gerdner, 2000). In the present study, Patient 4, who had his eyes closed and vocalized incoherently, opened his eyes intermittently and sang along to his preferred music, though he remained restless. Certain patients expressed positive memories and gratitude for their preferred music. Thus, while patients' agitation did not decrease on the ABS, their behaviours and feedback indicated a positive response.

This was also the case in a recent study by Huber (2021), in which positive behaviours were observed despite unchanged agitation scores in individuals with dementia (Huber et al., 2021). Furthermore, a recent meta-analysis demonstrated that the implementation of at least five sessions of music-based therapeutic interventions reduced depression, while having little effect on agitated behaviour (Van der Steen et al., 2018). While preferred music activates brain regions associated with reward, emotion, and arousal on positron emission tomography (PET)(Blood & Zatorre, 2001), the brain network underlying agitated behaviour is not well defined. Thus, it is currently unclear how the modulation of reward-related pathways might influence agitation in different populations.

Our findings of decreased agitation during relaxing classical music listening support similar findings in several dementia studies (Gerdner, 1997; Gerdner, 2000; Heim, Nair, Mowbray, & Tavender, 2003; Hicks-Moore & Robinson, 2008; Ragneskog et al., 2001; Tabloski, Mckinnon-Howe, & Remington, 1995). Similar to the dementia studies, our patients were older adults, who tend to have a greater affiliation with classical music (Götting, 2021). Thus, it is unclear whether a sample consisting of young adults would respond as favourably. Importantly, all tempos in the relaxing classical music intervention were between 60 and 80 bpm. Tempos quicker than this are associated with increases in heart rate, respiration rate, blood pressure, and an increased skin conductance (Bernardi, Porta, & Sleight, 2006; Zimny & Weidenfeller, 1963; Finn & Fancourt, 2018). Given that tempo may be one of the most important factors influencing the stress response (Björkman, Karlsson, Lundberg, & Frisman, 2013), manipulating the stress response through tempo, which is easier to do using researcher-chosen music, may be more effective than using preferred music in certain patients.

Finally, although the optimal duration for music listening interventions has not been established, some previous studies have demonstrated that just 10 -12 minutes is effective (Baker, 2001; Tabloski, Mckinnon-Howe, & Remington, 1995). Further research is needed in order to determine optimal exposure times to listening interventions. Longer listening conditions and performing multiple trials at separate times may be effective and might also help to adjust response variability. However, this may be more feasible in a chronic population, since the medically acute population evolves rapidly.

The effects of a nonmusical control (waterfall) on agitation

Agitation decreased during the waterfall intervention in patients 1 and 2. There is evidence that white noise may decrease the stress response in healthy adults (Kim & Kim, 2017). Furthermore, numerous studies indicate that in environments in which there is already background noise, white noise may enhance comfort by blocking certain frequencies (Lu, Huang, & Lin, 2020). For example, white noise decreases the intelligibility of speech (Vassie & Richardson, 2017), which was noted to exacerbate agitation in the present study. Irrelevant background speech is processed automatically, which interrupts semantic processing in healthy adults (Marsh, Hughes, & Jones, 2008). In TBI patients, who are already confused and disoriented, continuous waterfall sound, like white noise, may provide relief from the increased cognitive demand that environmental speech noise imposes on them, which may decrease agitation.

However, not all patients tolerated waterfall sounds. For example, despite a decreased agitation response (-13%) in Patient 1, she requested that the intervention be ended a couple of minutes early, stating that she couldn't listen anymore. Patient 4 demonstrated an increase in agitation (+29%), with verbalizations indicating the need to relieve his bladder. This may have been related to the lower frequency water sounds that were faintly audible within the heavy waterfall stimulus. It is recommended that future studies consider using white noise without water sounds, which may confuse some patients in post-traumatic amnesia.

Clinical impact of the listening interventions

An important question to ask is whether the listening interventions had a noticeably meaningful effect on the daily life of patients and their caregivers. In the context of the present study, two of the patients whose ABS scores decreased or stopped their frequent, repetitive, loud vocalizations. This was meaningful because it provided a more restful environment for the agitated patient, hospitalized patients in neighbouring rooms, and staff. Due to limitations associated with the short-term nature of our intervention, we only measured the clinical impact using the ABS and qualitative observation. Alternative research designs could examine other meaningful change, such as whether PRN medication administration and use of restraints decreases. Another measure of clinical impact would be an increase in cooperative behaviour measured by participation in rehabilitative therapy.

Individualized responses to listening interventions

Individual differences in response to listening interventions may in part reflect heterogeneity of injury. Dementia studies report individual differences in response to music based on mental health and dementia type (Garrido, Stevens, Chang, Dunne, & Perz, 2018; Hsieh, Hornberger, Piguet, & Hodges, 2011). For example, feasible music selection in neurological populations may vary according to specific pathology types and how these impact upon music processing (Sihvonen et al., 2017; Vanstone & Cuddy, 2009). Future research might clarify which patients derive the greatest benefits from music listening based on specific neuropathological profiles.

Patient 1, who suffered a middle cerebral artery stroke, responded favourably to all three listening conditions. Functional neuroimaging studies in healthy participants have found that music listening is associated with increased blood flow in the middle cerebral artery, which regulates and maintains blood flow (called cerebral autoregulation) to a variety of brain regions (Meyer, Spray, Fairlie, & Uomini, 2014). Impaired cerebral autoregulation may exacerbate secondary injury, and is associated with poorer outcome (Armstead, 2016; Czosnyka & Miller, 2014). Thus, it is reasonable to suppose that by therapeutically manipulating autoregulation, recovery may be promoted (Czosnyka & Miller, 2014). In a randomized controlled trial of patients with middle cerebral artery stroke, two months of 1-2 hour daily music listening was associated with enhanced cognitive recovery and improved mood, compared with audiobooks (Särkämö et al., 2008).

Finally, Patients 3 and 4 did not respond to any of the listening interventions with decreased agitation scores. These patients, for whom testing was performed within one month of injury, may have been under more severe acute stress than patients 1 and 2, who were already 2.5 months post injury. Neuroinflammatory processes peak in the first few weeks after injury (Algattas & Huang, 2013), and significant improvements in function and cognition occur within two to six weeks of injury in patients with severe traumatic and non-traumatic brain injury (Oujamaa et al., 2017). Further advancement is needed in order to consider the appropriate application of music at different stages of recovery.

There were also differences between patients in terms of testing environment. Disruptions to testing in Patients 3 and 4 occurred that were associated with nursing care, having shared rooms, and being in a central location next to the nursing station. For example, conversations emanating from the nursing station, and from individuals visiting other patients in the room visibly distracted these patients and increased their agitation. Although the intervention was discontinued and restarted after the disruption was finished, the effects of the disruption may have lingered. This made it difficult to determine whether the lack of decreased agitation observed across listening conditions in Patients 3 and 4 was due to imperviousness to the intervention, or disrupted testing.

Section 2: Feasibility of the intervention

Evaluation of data outcome measures

The ABS is essential, as it is the only measure that quantifies both verbal and physical symptoms of agitation. It also contextualizes the behaviour in the patient's environment, which is essential in this population.

Actigraphy was complementary to the ABS, as the two correlated moderately well. The fact that it provides a more objective measure of physical agitation that can be quantified as a continuous variable decreases the risk of inter-rater bias and allows for comparison of different studies if used in a standardized fashion. It is relatively easy to use, and cost-effective devices are increasingly available. It is therefore a useful adjunct to the ABS, with the following caveats: 1) actigraphy lacks the capacity to monitor the environment of the patient. For example, if a patient's agitation shifts from being predominantly physical to verbal during the intervention, it may be mistaken as decreased agitation, and lack agreement with the ABS, which provides a more comprehensive assessment of agitation. Similarly, if physical restraints are applied partway through the intervention, the decreased movement may falsely be attributed to reduced agitation in response to the listening intervention; and 2) greater agreement would likely be achieved by placing devices on all four limbs rather than just the wrists, as some patients' agitation is observed primarily in their legs. Thus, use of both the ABS and actigraphy is recommended in future studies.

Neurophysiologic measures of arousal, such as changes in heart rate and skin conductance, are potentially useful measures of the autonomic stress response (Aghaie et al., 2014; de Witte, Spruit, van Hooren, Moonen, & Stams, 2020; Léonard, Desaulniers-Simon, Tat, De Beaumont, & Gosselin, 2021; Maseda et al., 2018; Saadatmand et al., 2013; Sakamoto, Ando, & Tsutou, 2013) that might facilitate interpretation of how the stress response relates to agitation and responsiveness to music. However, these measures require further validation in this population.

Finally, qualitative observations are a necessary adjunct to the ABS, as they allow for more accurate interpretation of movement and verbalizations. Thus, it may be useful to add a more refined qualitative measure that ascertains intensity and valence of affective responses, as individual differences in mood may contribute to the efficacy of music listening interventions (Garrido et al., 2018). Facial electromyography, which uses electrodes to record the movement of facial muscles, would be too invasive in this population. Therefore, facial expression might be coded from video footage using the Facial Action Coding System, an automated system that has shown efficacy in dementia populations (Garrido et al., 2018; Girard, Cohn, Jeni, Sayette, & De la Torre, 2015). This measure is compatible with using silent video footage.

Feasibility of data collection

Testing was sporadic, as agitation varied hour to hour in many patients. Furthermore, in order to minimize contamination of outcomes, testing times were coordinated outside of medication administration and multiple daily visits from physicians, nurses, physiotherapists, cleaning staff, volunteers, friends, and relatives. However, this did not eliminate occasional disruptions from passersby, who would respond to patients' calls for assistance. Disruptions also occurred when patients removed their actigraphy wristwatches, breathing tubes, and feeding tubes during heightened confusion. To adapt to the small testing windows, the total duration originally planned for each intervention was cut by half, from 1.5 hours to 45 minutes. Although it was difficult to arrive in times of active agitation, testing was facilitated by a nurse that notified the researcher during periods of active agitation in flagged patients. It is important to note that data corresponding to disruptions was removed from the analysis, which was a strength of the present study that differed from previous studies that continued testing throughout nursing regimens, increasing the risk of contaminating results.

Evaluation of scoring procedures

Use of video recordings for data collection, and blinding observers to outcome. Using video recordings was a strength of the present study. First, it allowed the research assistant to leave the room during the intervention, which was essential to preventing sharp increases in agitation associated with patients' attempts to interact. This is in keeping with previous studies that report that continuous observation increases agitation (Waszynski et al., 2013). Second, video recordings allowed for more than one rater, and partial blinding to the condition. It was impossible to fully blind raters to intervention type, as patients were intolerant to headphones, which necessitated the use of a portable speaker at their bedside. However, this is the first study in TBI patients to achieve partial blinding by first rating silent videos of randomly ordered conditions and intervention types, and then re-rating with sound to clarify items requiring auditory information. This is crucial to reducing confirmation bias (Karanicolas, Farrokhyar, & Bhandari, 2010). Thus, it was an important strength of the present study design.

Limitations

One limitation of the present study is that we were unable to evaluate patients for music perception deficits, as they had post-traumatic amnesia. It would have been interesting to have evaluated patients for music perception ability once their PTA had resolved. When looking to previous studies in patients with middle cerebral artery stroke, we see that music perception deficits are common (Särkämö, 2009; 2010), which may be similar in a TBI population. Furthermore, case studies in individuals with acquired amusia demonstrate that certain individuals experience a decrease in the ability to enjoy music (Griffiths et al., 1997; Johannes, Jöbges, Dengler, & Münte; Peretz et al., 1994; Picirilli, Sciarma, & Luzzi, 2000; Satoh et al., 2016). However, in some individuals, music enjoyment is spared (Peretz & Gagnon, 1999; Schuppert, Münte, Wieringa, & Altenmuller, 2000). In the present study, Patient 1, whose agitation decreased during the interventions, commented that she enjoyed the music despite suffering damage to the deep matter underlying the second and third gyri of the right inferior frontal lobe, a region critical to the processing of pitch, rhythm, and recognition of familiar music (Sihvonen, 2018; Peretz, 2016; Peretz, Brattico, Järvenpää, & Tervaniemi, 2009). Future studies may wait until the patient has recovered from PTA and then evaluate music perception. Future group studies systematically examining music enjoyment in patients with acquired brain injury might also provide important insights into how this population experiences music, which would inform treatment with music interventions.

Another limitation of the present study was that our sample consisted exclusively of older adults. Thus, it is unclear as to whether results would have differed in a younger population. However, evidence indicates that music perception abilities tend to be preserved across the lifetime (Lagrois, Peretz, & Zendel, 2018; Halpern et al.,1995; Halpern and Bartlett, 2002). On the other hand, certain patients in the present study had pre-existing conditions such as Alzheimer's disease, which are far more likely to occur with advanced age. This makes it difficult to parse out the separate contributions of the different disease processes. However, the precise pathophysiological mechanisms underlying agitation are unclear and vary from individual to individual. Thus, treatments are symptom-driven, and successful strategies vary between patients (Ringman & Schnieder, 2019). Irrespective of age, It has been demonstrated that music regulates arousal and cognition by modulating catecholamines (dela Pena 2018; Bogner, 2015; Salimpoor et al., 2011), which likely contributes to the efficacy of music during listening interventions. Furthermore, a similar study conducted in a younger population of TBI patients demonstrated that preferred and relaxing music listening interventions were effective at decreasing agitation (Park, 2016). Thus, whether the study was performed in an older or younger population with comorbidities such as dementia, it would not change the hypothesis that music listening may decrease agitation levels. However, the magnitude of change may be modulated with age, something that merits further investigation.

It should be noted that while comorbid conditions may complicate the interpretation of results, a predominance of older adults would be expected in most samples of moderate to severe TBI patients. For example, in Quebec between 2013 and 2016, 4362 individuals aged 55 and over were admitted to hospital for moderate to severe head injury compared to only 1727 individuals under the age of 55 (National Institute of Excellence in Health and Social Services of Quebec, 2019). Nevertheless, future studies with a larger patient sample might ensure a broader age range. Another limitation was that the preferred music was not in the optimal range of 60-80 beats per minute for two of four patients. Future studies comparing classical and preferred music should attempt to include preferred songs within the 60-80 beat per minute range whenever possible, in order to parse out the influence of tempo versus familiarity.

Conclusion

The present results indicate that classical music and heavy waterfall sounds may be effective at decreasing agitation. If larger clinical trials confirmed these findings, using classical music or white noise to decrease agitation would have certain advantages over preferred music. Standardized recordings would ensure consistency across studies, allowing for clearer conclusions to be drawn. Furthermore, eliminating the need for individual music compilations is practical for clinical nursing staff and caregivers, who may be unfamiliar with music software, or have limited time. However, there may be no "one size fits all" listening intervention for reducing agitation. Preferred music may reorient patients and create a familiar environment. Classical music at optimal tempos may reduce the stress response. White noise may be most effective at blocking background noise on noisy hospital wards. Thus, further exploration of different types of listening interventions in patients with different pathological profiles is warranted in future studies.

In summary, this phase-II multiple case series pilot study justifies a larger phase II multi-centre trial in order to recruit a sufficient number of patients to warrant group analyses and determine the generalizability of listening interventions across sites. Based on the lessons learned in the present study, we recommend that patients with shared rooms be excluded, in order to minimize disruptions to testing. Trials would benefit by close collaboration with nurses on the ward, who could send an alert to an on-call research assistant in moments that flagged patients are agitated. The ABS would ideally be used in conjunction with actigraphy, to provide a continuous measure of physical agitation that may be standardized across studies. However, it is recommended that a device be used on both wrists and ankles, as the type of restlessness varies between patients. An autonomic measure, such as heart rate variability, would add important information about the stress response for interpretation of outcomes. Video recordings of interventions is recommended in order to enable the researcher to leave the room during testing to avoid influencing outcomes, and to achieve the partial blinding of raters. Interruptions to testing should result in discontinuation of the intervention and resumption the following day. Implementing these recommendations would minimize the contamination of outcomes, and encourage replicability. If future studies confirm the efficacy of listening interventions in larger controlled trials, listening interventions may serve as an adjunct treatment to physical and chemical restraints during acute care, which would meet an important medical need.

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Table 1

Demographic and Medical History

	Age	Gender	TBI Severity	Laterality of injury	Delay to Testing (days)	Language	Education	Previous Medical Issues
Patient 1	71	female	severe	right	81	English	university	anxiety, hypertension
Patient 2	63	male	moderate	bilateral	111	English	grade 10	hypertension, bipolar disorder, atrial fibrillation, epilepsy, diabetes
Patient 3	67	male	moderate	bilateral	22	French	college	coronary artery bypass graft surgery, spinal disc degenerative disease with stenosis; recent diagnosis of Alzheimer's disease
Patient 4	79	male	severe	bilateral	28	French	university	osteoporosis, glaucoma, chronic obstructive pulmonary disease

Table 2

Preferred Music Selections for Each Patient

	Patient 1	Patient 2	Patient 3	Patient 4
Selection 1	Hallelujah by K.D. Lang (57 bpm)	Is This Love by Bob Marley and the Wailers (61 bpm)	Only Time by Enya (92 bpm)	Choral Music - Personal Recording of Patient Four's choir (50 bpm)
Selection 2	Bridge Over Troubled Water by Simon and Garfunkel (82 bpm)	No Woman No Cry by Bob Marley and the Wailers (66 bpm)	In the Morning Light by Yanni (110 bpm)	Hallelujah by Leonard Cohen (54 bpm)
Selection 3	Tchaikovsky: Nutcracker Suite, Op. 71a-3 Waltz of the Flowers by Wiener Philharmoniker (66 bpm)	Three Little Birds by Bob Marley and the Wailers (73 bpm)	Love Theme from St Elmos Fire by David Foster (124 bpm)	If It Be Your Will by the Webb Sisters (63 bpm)
Selection 4	Tchaikovsky: Nutcracker Suite, Op. 71a-Dance of the Sugarplum Fairy by Arthur Fiedler (130 bpm)	Zimbabwe by Bob Marley and the Wailers (62 bpm)	Easy by the Commodores (133 bpm)	Träumeri (Dreaming) by André Rieu (54 bpm)
Selection 5	Swan Lake (Suite), Op. 20a by Royal Philharmonic Orchestra (80 and 106 bpm)			

Table 3

Classical Music Selection for all Patients

	Composer	Piece	Performed by	Tempo (bpm)
Selection 1	Johann Pachabel	Canon in D Major	Gravid Musikk for Barn I Magen	76
Selection 2	Franz Schubert	String Quintet in C Major, D. 956 2. Adagio	Takacs String Quartet	63
Selection 3	Johann Sebastian Bach	Air on G String from Orchestral Suite No. 3 in D Major	Eduardo Marturet	68

Pre-intervention baseline (no listening condition)	Listening condition (MC of classical or preferred music, or NMC of waterfall)	Post-intervention (no listening condition)

15 minutes	15 minutes	15 minutes

Figure 1. Model of the Order of Listening Conditions and Baselines. Sessions began with a pre-intervention baseline condition lasting 15 minutes, followed by a 15-minute listening condition in which either 1) researcher-chosen classical music or the patient's preferred music was introduced or 2) a non-musical condition was introduced. Finally, there was a post-intervention 15-minute condition in which no listening condition was presented. Actigraphy and the Agitated Behavior Scale was used to measure agitated behaviors for the baseline, listening, and post-intervention conditions.

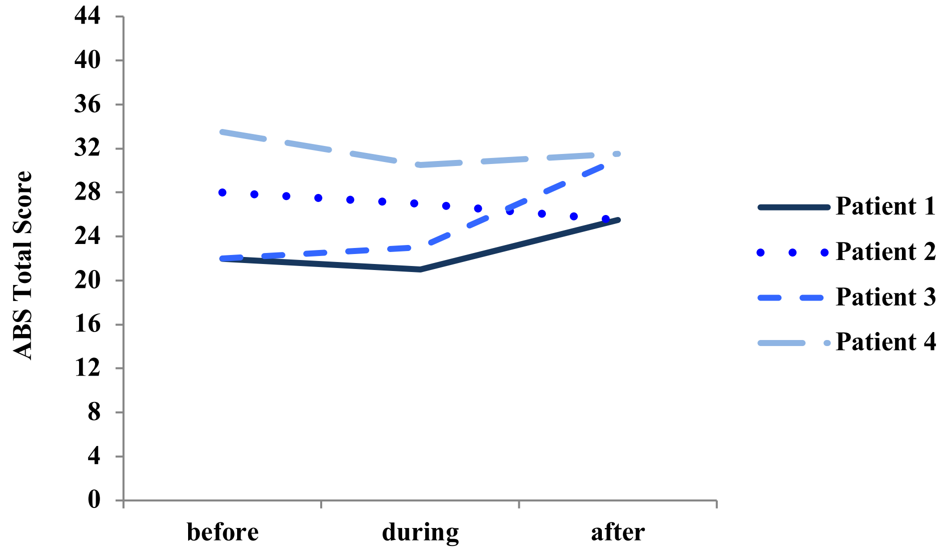

Figure 2. Agitated Behavior Scale (ABS) total score for each condition during the preferred music listening intervention

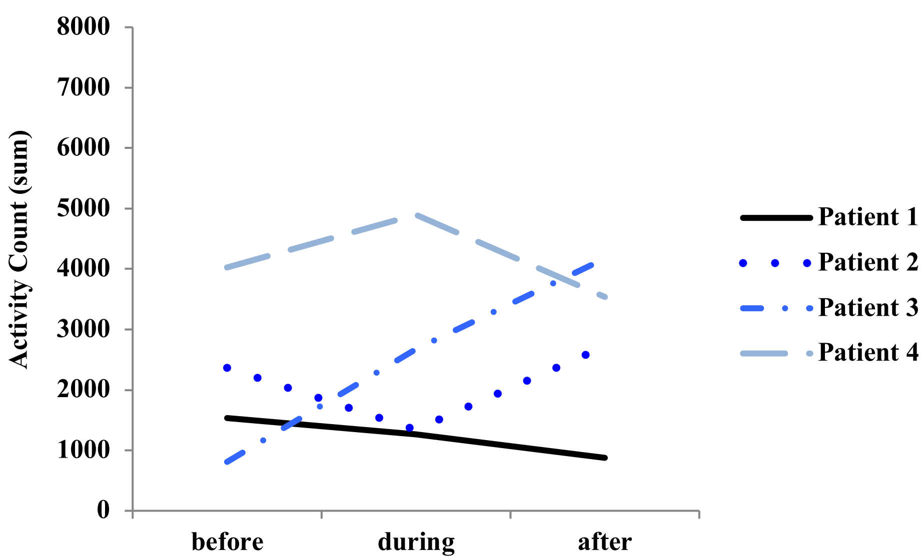

Figure 3. Sum of activity counts for each condition during the preferred music listening intervention

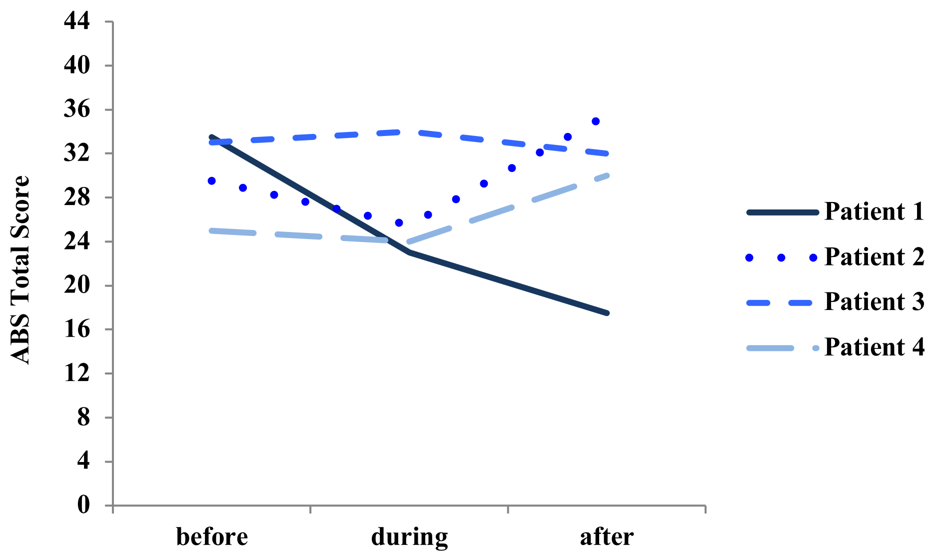

Figure 4. Agitated Behavior Scale (ABS) total score for each condition during the relaxing classical music listening intervention

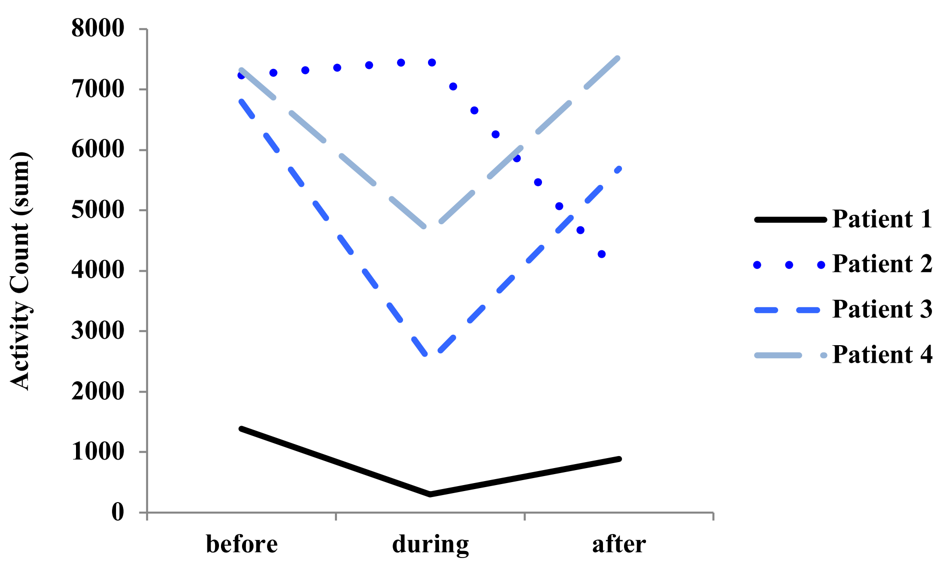

Figure 5. Sum of activity counts for each condition during the relaxing classical music listening intervention.

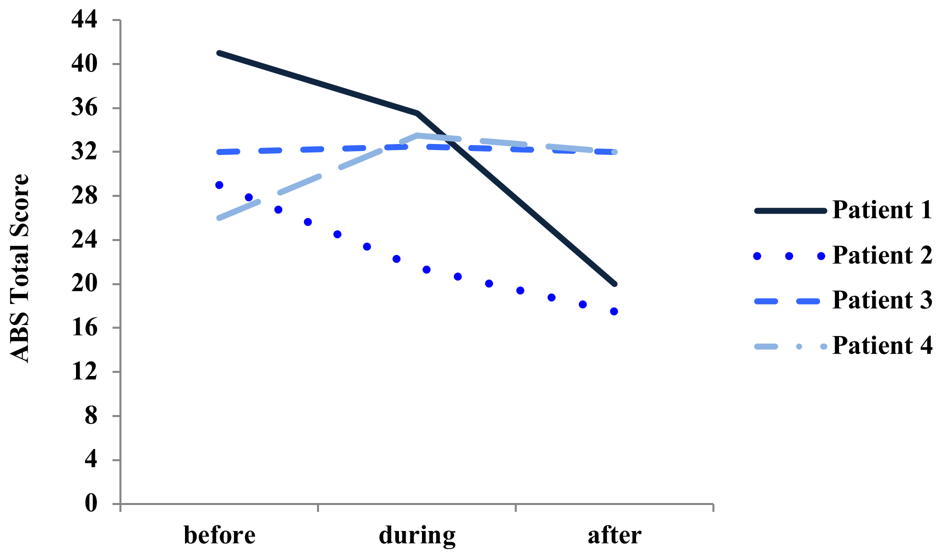

Figure 6. Agitated Behavior Scale (ABS) total score for each condition during the non-musical control (waterfall) intervention.

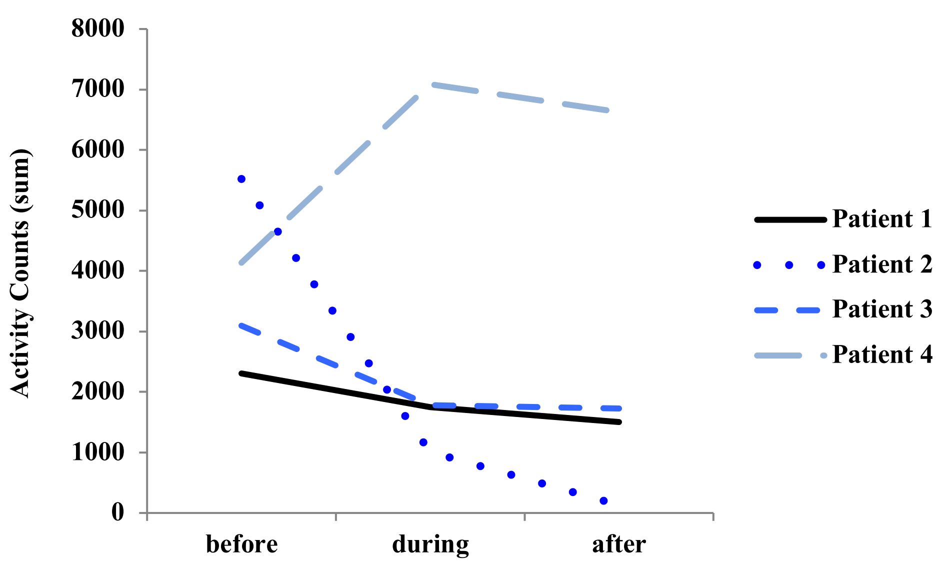

Figure 7. Sum of activity counts for each condition during the non-musical control (waterfall) intervention.

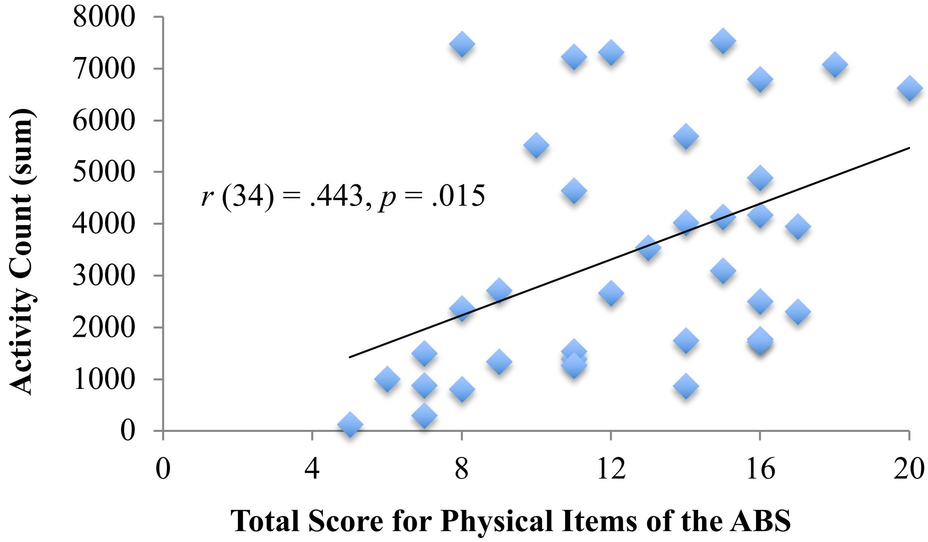

Figure 8. Individual scores for patients depicting the relationship between scores on the physical agitation items on the ABS (Items 6-10), and activity counts on actigraphy. Patients with greater physical agitation scores on the ABS tended to have higher activity counts on actigraphy.

CHAPTER V: General Discussion

Review of the Aims of the Thesis

Agitation is a common behavior encountered following moderate and severe TBI and other forms of brain injury (Bogner et al., 2001). Agitation comprises multiple manifestations, including motor hyperactivity, and cognitive impairments such as disorientation, emotional lability, and disinhibition (Bogner et al., 2001; Williamson et al., 2019). Given the variability in efficacy and side effects of current pharmacological management or physical restraints, there is an urgent need for the development and validation of complementary methods for agitation (Luauté, Plantier, Wiart, & Tell, 2016; Williamson et al., 2019). Evidence suggests that music listening has beneficial cognitive, physical, emotional, and behavioral effects that are associated with widespread neural changes (Chanda & Levitin, 2013; Särkämö & Sihvonen, 2018; Sihvonen et al., 2017). Music listening interventions may be an important complementary strategy in TBI patients (Baker, 2001; Park et al., 2016). Limited evidence suggests that music interventions may be effective at reducing agitation in TBI patients (Baker, 2001; Park et al., 2016). Thus, the development of music listening interventions as a potential therapy in TBI would be enhanced by improved knowledge of the impact of TBI on music processing. Further development requires evaluation of the efficacy of non-pharmacological behavioral interventions in agitated patients following common acute brain injuries such as TBI or stroke. Due to the complexity of the clinical state and hospital environment of these patients, it is important to identify and address methodological challenges that may be encountered in validating the efficacy of music listening interventions in patients suffering from agitation during the acute phase of brain injury.

Thus, the overarching goals of the present thesis were: 1) to determine if TBI patients have music processing deficits in the acute care setting (Anderson et al., 2021); 2) to perform a non-systematic review of non-pharmacological behavioural interventions in the management of agitated behaviour in TBI patients in the acute and sub-acute care setting (Article 2, Anderson, et. al., 2016); and 3) to examine the feasibility of music listening interventions in acutely agitated hospitalized patients in the context of two common conditions, TBI and stroke. To this end, we conducted a phase-II, development-of-concept case series study to determine how the efficacy of music listening may be evaluated in a group of acutely agitated hospitalized patients with acute brain injury (ABI) from TBI or stroke (Article 3, Anderson et. al., manuscript in preparation).

Synthesis of Results

Pitch and Rhythm Perception and Verbal Short-Term Memory in Acute Traumatic Brain Injury (Study 1)

Music perception deficits are common in Acute Traumatic Brain Injury (ABI) following stroke (Peretz, 1990; Särkämö et al., 2009; Sihvonen et al., 2016; Sihvonen et al., 2017; Steinke et al., 2001), aneurysm clipping (Liegeois-Chauvel et al., 1998; McChesney-Atkins et al., 2003; Sihvonen et al., 2019; Zatorre, 1985, 1988), and epilepsy surgery (Ayotte et al., 2000; Peretz, 1996; Peretz et al., 1994). However, few studies have examined music perception deficits following acute TBI, resulting in an under-appreciation of the problem in this population. To our knowledge, no study to date has examined associations between music perception deficits and regional brain abnormalities on brain imaging. Furthermore, little is known about the relationship between impaired music perception and deficits in verbal short-term memory that are common following TBI, and which are proposed to be supported by a distinct neural network to that used for the processing of tonal information (Albouy et al., 2019).

Our first study helped characterize the nature of music processing deficits in TBI (Anderson et al., 2021). As main findings, our work 1) established a high prevalence of music perception deficits in TBI patients during the acute phase of recovery; 2) demonstrated a relationship between injury to frontal and temporal regions of the right hemisphere and deficits in music processing related to pitch and rhythm; 3) revealed a partial dissociation in pitch and rhythm processing in TBI patients, suggesting partly shared and partly dissociable neural networks underlying these aspects of music processing; and 4) demonstrated that networks underlying the processing of verbal short-term memory, pitch short-term memory, and rhythm short-term memory in TBI patients are also partly shared and partly dissociable (Anderson et al., 2021).

The Management of Agitation in Traumatic Brain Injury Patients During Acute and Sub-Acute Hospitalization (Study 2)

Our second major objective was to provide a non-systematic review of the current management of agitated behaviour, with a focus on evaluating the evidence for behavioural interventions. We offered an overview of agitated behaviour and its management in acutely hospitalized TBI patients, highlighting the need for a multifaceted approach to address the range of physical, emotional, behavioural, and cognitive deficits following TBI (Alderman, 2003; Ducharme, 2000; Flanagan, Elovic, & Sandel, 2009; Slifer & Amari, 2009). We found a lack of consensus on the standard of care for agitation, due in part to the fact that the pathophysiological mechanisms of agitation are poorly elucidated (Alderman, 2003; Slifer & Amari, 2009). Treatment generally consists of environmental modifications, pharmacological management, and the use of physical restraints, the latter two of which have important side effects (Ponsford et al., 2014). Thus, there is an urgent need for validated behavioural interventions to complement current approaches to the management of agitation. We found that there is a paucity of controlled studies that examine and validate the behavioural management of agitation. Initial evidence suggests certain behavioural interventions may be effective, including music interventions (Baker, 2001; Nott, Chapparo, & Heard, 2008; Park et al., 2016), occupational therapy interventions (Nott et al., 2008), and operant contingency management interventions that encourage adaptive behaviour through positive and negative reinforcement (Hufford, Williams, Malec, & Cravotta, 2012; Ylvisaker et al., 2007). Music interventions may be of particular benefit in moderate to severe TBI patients, whose cognitive deficits often preclude them from participating in more demanding forms of rehabilitation that require the execution of specific tasks (Lequerica et al., 2007). We outlined numerous methodological limitations in validating behavioural agitation studies in work published so far. These included heterogeneity of injury, ability to integrate the therapy with ongoing medical treatment plans, and challenges of validating interventions in acute care such as necessary interruptions for nursing care, medical tests, or visits from family members. These practical challenges are compounded by the lack of detailed reporting of methodology, which poses an obstacle to critical evaluation. The lack of appropriate non-musical control conditions was also noted. We recognized that due to the individualized treatment common in the acute phase of agitation, case reports and case series studies are an important means of incremental study of a difficult problem. However, the substantial methodological limitations present in behavioural studies was acknowledged and we proposed recommendations for a more systematic approach to this line of research.

The effects of preferred music, relaxing classical music, and waterfall sounds on agitation during acute hospitalization for acquired brain injury: a phase-II trial (Study 3)

Our objective in Study 3 was to conduct a phase-II, development-of-concept case series study to determine the feasibility of using a music intervention in agitated brain injured patients in the setting of acute care. We designed a rigorous protocol to compare the effects of preferred music, relaxing classical music, and waterfall sounds on agitation. We tested our protocol on four patients with acquired brain injury patients including TBI ($n = 3$) and stroke ($n = 1$). Outcomes were measured using the Agitated Behaviour Scale (ABS), and actigraphy, a quantitative measure of kinetic motor behavior at the upper limbs. We found that the protocol was readily applicable in all four patients, and we were able to identify potential methodological challenges to address the design of a future study that includes a larger number of patients. We found that agitation levels decreased for two patients while listening to both relaxing classical music and a waterfall. Although agitation levels did not decrease for preferred music, there was an increase in more organized behaviours, such as tapping and singing along. There was a moderate positive correlation between scores on the ABS and actigraphy-based counts of activity, suggesting that both qualitative observational scales and more quantitative measures that provide a continuous variable would be useful practical endpoints for evaluation of therapy for agitation. Outcomes were interpreted in the context of a highly variable literature that suffers from inadequate study design and lack of appropriate music intervention-related controls. In addition, we performed a critical assessment of outcome measures, data collection, and scoring procedures. Based on our experience, we proposed recommendations for design of a practical structured protocol that can be applied in studies for validating music interventions in larger groups of hospitalized patients who suffer from agitation after acquired brain injury.

The following sections examine music perception in TBI patients and how these findings may guide music listening interventions for agitation. We also explore the effects of music on the arousal and stress responses that are important components of agitation, and the relationship of music to mechanisms of emotion and reward as applied to agitated patients. We then discuss the possible importance and practical challenges of providing a "locus of control" by using musical choice. We also address how various parameters of music may modify the precursors to agitation through the responses we observed in our patients. Finally, based on our experience in designing and implementing the music intervention protocol in acute TBI patients, we propose recommendations for critical design elements to be included in listening interventions, and in the design of future trials. We conclude by discussing the overall thesis in the context of strengths and limitations, clinical implications, and future directions.

The Potential Impact of Music Perception Deficits on Music Listening Interventions

The goals of music therapy are to promote relaxation by decreasing the stress response, encouraging motivation in rehabilitation activities, and altering mood states

(Gilbertson & Aldridge, 2008). An important consideration in the application of music listening interventions to TBI patients is the potential music processing deficits related to TBI that may act as modulators or impediments to the intervention.

Our findings in Study 1 demonstrated music processing deficits in nearly half of the TBI patients in our sample. To date, no group studies have systematically investigated music enjoyment in TBI patients with music perception deficits. Thus, we look to case studies in ABI patients with disorders of music listening (Griffiths et al., 1997; Johannes, Jöbges, Dengler, & Münte, 1998; Peretz, 1996; Peretz & Coltheart, 2003; Peretz et al., 1994; Piccirilli, Sciarma, & Luzzi, 2000; Satoh et al., 2016; Satoh, Nakase, Nagata, & Tomimoto, 2011; Satoh et al., 2005), as well as a group study in ABI patients (Belfi, Evans, Heskje, Bruss, & Tranel, 2017), and group studies in congenital amusics (McDonald & Stewart, 2008; Omigie et al., 2012), to determine how individuals with music processing deficits might experience music. It is evident that there are a number of individuals with music processing deficits who also report a diminished ability to enjoy music (Griffiths et al., 1997; Johannes et al., 1998; Peretz et al., 1994; Piccirilli et al., 2000; Satoh et al., 2016; Satoh et al., 2011), and /or to recognize familiar music (Johannes et al., 1998; Peretz et al., 1994). For example, individuals have stated that following their injury, music sounded empty or dull (Satoh et al., 2016; Satoh et al., 2011), that the notes all sounded the same and elicited an unpleasant feeling (Piccirilli et al., 2000), or that singers sounded like they were talking or shouting (Peretz et al., 1994; Piccirilli et al., 2000). This disturbed some individuals, who were avid music lovers before their injury (Griffiths et al., 1997; Piccirilli et al., 2000). Conversely, individuals with music processing deficits may have spared ability to enjoy music (Peretz & Gagnon, 1999; Schuppert, Münte, Wieringa, & Altenmüller, 2000).

Two group studies have systematically characterized music engagement and appreciation in individuals with congenital amusia (McDonald & Stewart, 2008; Omigie et al., 2012). These studies indicate that over 50% of individuals with congenital amusia do not enjoy music, compared with only 6% of controls (Omigie et al., 2012), or no controls (McDonald & Stewart, 2008). Congenital amusics experience fewer changes in affective state when listening to music, listen to music three times less often than controls, and have less tolerance for imposed music than controls (McDonald & Stewart, 2008). Thus, these individuals might be expected to be less tolerant of researcher-imposed music than those without music processing deficits. Indeed of music listening, one individual stated "[I have experienced] just a sort of irritable rage..." Another expressed difficulty when hearing music at a party or a special occasion: "I find it very hard to stay in the room...I find it makes my ears and head hurt and so avoid those situations at all costs" (Omigie et al., 2012).

On the other hand, a sizeable subpopulation of congenital amusics engage in music to a similar degree to that of controls**,** and scores on the Montreal Battery for Evaluation of Amusia (MBEA)(Peretz, Champod, & Hyde, 2003) do not account for who engages in and appreciates music, and who does not (Omigie et al., 2012). Indeed, insofar as increased agitation levels might be related to an intolerance to music listening interventions, our findings in Study 3 suggest that music was well-tolerated, as none of the patients demonstrated increased agitation. In fact, decreases in agitation were observed in certain patients, with two patients even commenting that they enjoyed the music. Thus, music interventions are not necessarily contraindicated in TBI populations, even those with moderate to severe injury who are at elevated risk of music processing deficits. The enjoyment of music in certain patients with TBI suggests either: 1) that these particular TBI patients do not have significant music processing deficits despite extensive brain injury. Indeed, one patient in Study 3 sang along in tune, indicating that his pitch discrimination may still be intact; or 2) that despite music processing deficits, TBI patients are able to benefit from and enjoy music. Indeed, studies indicate that a substantial sub-population of congenital amusics reports enjoyment when listening to music despite music perception deficits on the MBEA (McDonald & Stewart, 2008; Omigie et al., 2012). Several factors may account for this preservation of musical enjoyment.

First, individuals who have deficits on the MBEA, which measures explicit pitch perception, may still retain implicit knowledge of music structure. This is supported by fMRI and EEG studies which demonstrate that congenital amusics perceive pitch deviations below conscious awareness (Braun et al., 2008; Hyde, Zatorre, & Peretz, 2011; Peretz, Brattico, Järvenpää, & Tervaniemi, 2009). Thus, they may be capable of generating predictions as to what comes next in the musical piece, which is thought to underlie musical reward (Zatorre, 2018), as further discussed below.

Second, despite pitch impairments, certain individuals with amusia may still retain sufficient rhythm perception, allowing them to derive some benefit from music listening (Omigie et al., 2012). This is plausible based on our findings that 26 percent of the TBI patients had intact rhythm perception despite impaired pitch perception. A similar phenomenon was demonstrated in certain individuals in a recent study of congenital amusics (Lagrois & Peretz, 2019). Indeed, individuals with pitch deficits may still benefit from the modulation of arousal through the rhythmic dimension of music (Omigie et al., 2012). For example, there is ample evidence that slower tempos reduce the stress response, while quicker tempos increase it (Bernardi et al., 2009; Bottiroli, Rosi, Russo, Vecchi, & Cavallini, 2014; Elliott et al., 2011; Gerra et al., 1998; Karageorghis & Priest, 2012; Khalfa, Bella, Roy, Peretz, & Lupien, 2003). This may explain why many congenital amusics report that they listen to music to relax or increase energy levels, rather than listening to music for the emotional experience. This contrasts with individuals without amusia who tend to listen to music to enhance or alter mood or emotion (Juslin & Sloboda, 2001).

In sum, it is important not to overlook the high proportion of TBI patients with music perception deficits when planning music listening interventions. Besides auditory sensory deficits related to skull base injury that must be excluded as was the case in our study, it is possible that music perception deficits may alter the response of the music listening intervention in moderate to severe TBI patients. Given the fact that individuals with music perception deficits seem to use music more often for its tempo than for its motivational effect, prioritizing the selection of music on the basis of tempo may optimize outcome, rather than selecting it based solely on patient preference.

Conversely, there are also case studies of patients with severe music perception impairment who still enjoy music (Peretz, Gagnon, & Bouchard, 1998). In a recent group study of 78 patients with ABI, Belfi and colleagues concluded that musical anhedonia was rare in this population (Belfi et al., 2017; Matthews, Chang, De May, Engstrom, & Miller, 2009; Peretz et al., 1998). However, they did not verify whether the handful of patients they identified with musical anhedonia had music perception deficits, making it difficult to draw conclusions as to whether this played a role in their ability to engage with and enjoy music. The authors also selected only patients with focal injury, which may differ from the diffuse injury commonly observed in moderate to severe TBI. The study was also conducted in chronic patients (defined as at least 3 months post-injury), and it has not been determined if music anhedonia may be more prevalent during the acute phase of TBI, and gradually resolve with recovery.

Future longitudinal studies could extend our study to the recovery phase, by determining whether TBI patients show music perception deficits at three months and six months post-injury, and by associating these results with their appreciation and use of music through experience sampling. Retrospective comparisons of perceived changes in music listening habits before and after the injury may also be examined. Together, these results may help clarify the contribution of music perception deficits to the outcome of music listening interventions in TBI patients.

In sum, music perception, while influential in the enjoyment of music listening, is not the sole determinant. Indeed, music perception constitutes just one factor in the individual response to music interventions. Enjoyment of music in the context of ABI is likely mediated by clinical factors, such as injury characteristics, premorbid conditions, and cognitive deficits; individual factors, such as the role that music played in the individual's life before the accident, culture, personality type, and musical training; and characteristics of the music listening intervention, such as music type, measures used, and duration of the intervention (Särkämö & Sihvonen, 2018). Ultimately, the efficacy of music interventions on agitation is inter-related with autonomic and arousal responses, and a wide variety of cognitive factors, including impacts on the reward system (Särkämö & Sihvonen, 2018). In order to further understand the possible contributions of different parameters of music to the reduction of agitation, it is necessary to explore biological and cognitive factors associated with agitation in ABI.

Precursors to agitation

As outlined in Study 2, precursors to agitation in ABI may include pain, infection and sepsis, adverse treatment effects, metabolic abnormalities or drug withdrawal (Rahmani et al., 2021). These may be compounded by cognitive deficits that include disorientation, decreased attention and language or memory deficits that may all exacerbate agitation (Luauté et al., 2016; Williamson et al., 2019). Importantly, patients with acute brain injury often have a heightened stress response that increases levels of stress hormones such as cortisol and catecholamines that increase sympathetic drive (Bales, Wagner, Kline, & Dixon, 2009; Hamill, Woolf, McDonald, Lee, & Kelly, 1987; Wagner et al., 2011).

The Effects of Music on Arousal and the Stress Response: Entrainment in Music Listening Interventions

Mammalian autonomic nervous system responses to stress are well studied, including in the context of TBI (Kaur & Sharma, 2018). Music is an environmental stimulus that may assist in maintaining homeostasis by modulating the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, both of which regulate the stress response (Chanda & Levitin, 2013; Thoma et al., 2013). It is a mystery as to why music, a sequence of tones, elicits such intense pleasurable responses (Salimpoor, Benovoy, Longo, Cooperstock, & Zatorre, 2009). However, it is proposed that the autonomic nervous system and limbic related structures participate in primal responses to the psychoacoustic features of music, such as tempo, pitch, rhythm, and volume, which appear relevant to survival (Juslin, 2013). For example, a rapidly advancing predator might quicken the rhythm of its steps, which would require an arousal response and focused attention (Gabrielsson and Lindstrom, 2010, Juslin, 2013; Kiss & Linnell, 2021). Thus, manipulating the acoustic features of music, such as loudness and tempo, may modulate the sympathetic nervous system response (Bernardi et al., 2006). The external rhythm found in music induces entrainment in the listener's brain activity, and is often observed in brainstem-mediated autonomic responses such as altered heart rate, respiratory patterns, blood pressure, and skin conductance, which are also associated with pleasurable responses (Chapados & Levitin, 2008; Juslin, 2013; Loui, 2021; Tichko, Kim, Large, & Loui, 2020; Trost et al., 2014). Indeed, music with fast tempos and high volumes stimulates a faster heart rate, while slower tempos and lower volumes may in turn reduce it (Bernardi et al., 2006; Bottiroli et al., 2014). The fact that we observed decreases in agitation in certain patients during relaxing classical music listening compared to preferred music in Study 3 may be partly attributable to the fact that classical music was played at optimal tempos of 60 to 80 beats per minute, while preferred music tempos fluctuated, and reached 147 beats per minute in certain pieces. This supports previous literature that suggests that the parameters of music, such as tempo, may be more important than music preference in reducing agitation and the stress response (Bernardi et al., 2006; Finn & Fancourt, 2018).

Music is also thought to induce social entrainment (Hobeika et al., 2021; Juslin, 2013; Koelsch, 2014; Trost et al., 2014). Music emerged spontaneously in human societies over 40,000 years ago (Conard, Malina, & Münzel, 2009), and likely served the adaptive function of increasing social cohesion though attachment-related emotions, which is central to human survival (Koelsch, 2014; Peretz & Zatore, 2001). Keeping this in mind, the music intervention in Study 3 may be interpreted in a broader context as a survival response designed to seek social contact in the face of injury. One commonality across patients in Study 3 was the consistent search for social contact during periods of heightened agitation. Given that music evokes attachment-related emotion (Juslin, 2013; Schäfer, Saarikallio, & Eerola, 2020), it may provide a source of company for the solitary listener (Schäfer et al., 2020), by evoking a sense of presence and empathy with the emotional states of the performer (Overy & Molnar-Szakacs, 2009; Wallmark, Deblieck, & Iacoboni, 2018). The musical intervention may also evoke a powerful nostalgic reminiscence that connects the listener to people from the past (Barrett et al., 2010; Garrido & Davidson, 2019; Schäfer et al., 2020; Wildschut, Sedikides, Routledge, Arndt, & Cordaro, 2010). In Study 3, one patient who often complained of being alone responded to her preferred music from the Nutcracker Suite by incorporating it into a delusion of a pleasant shared experience with her son. As she conducted along, she stated, as if to him, “I want to take you to the ballet at Christmas time. I want you to listen to it now so that you get to know it, and then you’ll recognize it when we go; it’s more fun that way.” The level of motor entrainment of an individual can be monitored through observations of spontaneous singing or tapping in time (Ghilain et al., 2020). One patient who had previously sung in a choir consistently mumbled incoherently to himself, yet each time he heard the chorus to his favorite song, he sang along with clear speech. Thus, listening to preferred music elicited more entrainment behaviours than relaxing classical music. The full extent of the application of music to increase feelings of social contact has not been explored. Given the social and evolutionary associations that individuals inherently have with music (Huron, 2001), it may be a worthy path of exploration in future studies, especially in the ABI population, for whom we observed that basic social contacts such as sitters were often lacking due to inadequate resources.

Agitation and Music–Evoked Mechanisms of Emotion and Reward

Autonomic nervous system-related mechanisms that are related to arousal and agitation are also intricately connected to the reward system (Trost et al., 2014). Functional imaging studies using fMRI and PET demonstrate that music listening activates a broad brain network that overlaps with reward-related areas involved in primary (e.g. food, and sex) and secondary reward (e.g. power, and money) processes that are essential for survival (Blood & Zatorre, 2001). This music-evoked emotion network encompasses the dopaminergic ventral tegmental area, the nucleus accumbens, amygdala, hippocampus, cingulate, and prefrontal cortex, as well as the limbic and auditory thalamus, and cortical auditory areas such as Heschl's gyrus (Blood & Zatorre, 2001; Koelsch, 2014; Koelsch, Fritz, DY, Muller, & Friederici, 2006; Salimpoor et al., 2011). These music reward network structures receive powerful modulatory influences from the ascending dopaminergic system that originates in the midbrain and regulates motivation and goal-directed behaviours (Chanda & Levitin, 2013; Mohebi et al., 2019). Anticipation of reward is crucial to applying predictions to future events based on past experience (Dayan & Berridge, 2014). During music listening, a dissonant note may be startling, because we encode the properties of sound, and based on inherent knowledge of musical structure and sound patterns of the music, generate predictions about what comes next in the musical piece (Zatorre, 2018; Zatorre & Salimpoor, 2013). Preferred music may generate more intense pleasurable responses than unfamiliar music. However, music need not always be preferred or even familiar to generate expectancies based on musical structure in order to elicit a positive emotional response or behaviour (Brown, Martinez, & Parsons, 2004). When music is consonant and pleasurable, dopamine is released in the nucleus accumbens in amounts proportional to the intensity of the pleasurable emotional response (Blood & Zatorre, 2001; Zatorre, 2018).

Ascending dopaminergic and noradrenergic systems originating respectively in the midbrain and pons modulate widespread cortical and subcortical areas, with a range of cognitive and emotional effects (Chanda & Levitin, 2013). For example, due to its implication in multiple systems, dopamine release in one area may elicit motivation behaviour, while in another, it may enhance attention (Kiss & Linnell, 2021) or memory (Chanda & Levitin, 2013; Ferreri et al., 2021). Agitation in acute brain injury associated is associated with high sympathetic drive and widespread brain dysfunction with lack of attention (Flanagan et al., 2009; Ganau et al., 2018; Williamson et al., 2019), and it is possible that music-evoked activation of cortical and subcortical structures may reduce agitation by enhancing parasympathetic responses and improving deficits in attention.

Indeed, some work even suggests that activation of specific brain areas by music listening may even lead to structural alterations that may be beneficial for mood and concentration (Baylan, Swann-Price, Peryer, & Quinn, 2016; Särkämö et al., 2014). For example, a longitudinal, voxel-based morphometry study examined the neuroplastic effects of music listening and associated cognitive gains in stroke patients (Särkämö et al., 2014). The study compared grey matter volume (GMV) in groups listening to preferred music, audiobooks, or no listening condition during the 6-month recovery period. The music group demonstrated greater increases in GMV in specific frontolimbic networks associated with the processing of music and reward, including bilateral superior frontal gyri and limbic areas, such as the left ventral/subgenual anterior cingulate cortex, as well as the ventral striatum. Furthermore, these GMV increases were associated with improved verbal memory, focused attention, and language skills. The fronto-limbic music reward areas associated with grey matter increases in this study overlap with regions associated with agitation. For example, the restlessness of agitation is attributed in part to damage in the limbic ventral striatum, which regulates mood and pleasure, and promotes arousal. The ventral striatum is well-connected to the prefrontal cortex and hippocampal formation, providing a basis for the dysregulation of emotion and cognitive ability (Lindenmayer, 2000; Luauté et al., 2016). Therefore, music interventions that activate these limbic networks may promote the resolution of agitation by enhancing activity in limbic networks that decrease anxiety and improve concentration. They may also contribute to long-term plastic changes that may ultimately reduce the tendency to agitation following the acute phase of injury. Similar longitudinal studies could be conducted in TBI patients, comparing GMV and cognitive functions at baseline and six months, with the added measure of agitation in acute and chronic phases. By measuring grey matter volume, cognitive abilities, and agitation levels, it may be possible to determine whether the resolution of agitation coincides with cognitive improvements and increases in grey matter volume in similar regions associated with musical reward. If so, we would have evidence that music has neurorehabilitative effects in severe TBI patients, some of whom live with chronic agitation, and who might benefit from music interventions to complement their medication regimes.

Interestingly, Study 3 included a patient who had suffered a massive middle cerebral artery territory hemorrhage in the right hemisphere that resulted in damage involving the deep matter underlying the second and third frontal gyri of the inferior frontal region. This region includes the dorsolateral prefrontal cortex, an area crucial to attention and working memory (Petrides, 1991, 2000). Damage to the inferior frontal cortex is also associated with disinhibited behaviour, aggression, and dysphoric bipolar states that characterize the agitation syndrome (Kim, 2002; Rolls, Hornak, Wade, & McGrath, 1994; Tateno, Jorge, & Robinson, 2004). The stroke may have also resulted in disrupted connections to the orbitofrontal cortex, a region implicated in adapting to social situations (Rolls et al., 1994). Individuals with damage to the inferior and orbito-frontal cortices perseverate on certain behaviours, even when they are followed by negative consequences (Rolls et al., 1994), and these may contribute to persistent long-term tendencies to agitation and other maladaptive responses.

Before music was introduced, this stroke patient was emotionally labile, with loud crying spells punctuated by brief pauses of apparent insight during which she mused out loud that her behaviour was “upsetting others” and expressed bewilderment that she was unable to modify it. During relaxing classical music listening, the yelling was replaced by quiet musings, and she lay back on her pillow, commenting that the music was relaxing. Her agitated behaviour resumed shortly after the music stopped, indicating further that the intervention itself was effective. Keeping track of a melody over time requires attention and working memory (Särkämö & Sihvonen, 2018), with expected engagement of the dorsolateral prefrontal cortex (Petrides, 1991, 2000).

Since the DLPFC and its associated subcortical network are richly supplied by dopamine, other monoamines and their receptors (Cools & D'Esposito, 2011), it follows that they may be modulated by the monoaminergic circuitry of reward. Given the decrease in agitation, and the fact that the agitated behaviour recommenced shortly after the music stopped, one possible explanation is that the music intervention may have enhanced dopaminergic transmission at the level of the frontal cortex and ventral striatum (Salimpoor et al., 2011), resulting in more focused attention (Zatorre & Salimpoor, 2013).

The fact that music is able to modulate the release of dopamine in reward-related subcortical and cortical areas that may also be part of the network for agitation raises the question of whether a pharmacological approach may not eventually be combined with a music intervention to help agitated patients. Interestingly, catecholamine modulators are currently used in the clinic for agitated patients (e.g. methylphenidate, propranolol) (Williamson et al., 2019). How these drugs interact with music in modulation of agitated behaviours remains an open question for further investigation.

The Use of Music to Supplement the Pharmacological Management of Agitation

As outlined in Study 2, the impaired cognitive state is an important modulator of the tendency to agitation. It therefore follows that sedative agents such as antipsychotics and hypnotics/anxiolytics, although useful in the acute situation where the patient may harm him/herself or others, are detrimental to behavior and cognitive recovery in the longer-term (Bogner et al., 2015; Luauté et al., 2016; Williamson et al., 2019). Prior to resorting to pharmacological management, it is recommended that non-pharmacological management be used when possible (Luauté et. al., 2016). Brain systems that are modulated by music listening are also the target of some pharmacological agents used for management of agitation. For example, methylphenidate acts on ascending monoamine systems with increased activity of dopamine and noradrenaline in the basal ganglia and prefrontal cortex (dela Peña, Shen, & Shi, 2018), resulting in improved attention and memory, thereby decreasing hyperactivity and agitation (Bogner et al., 2015). While the mechanism of the action of music is likely distinct from these drugs, its action on monoaminergic systems may enhance cognition with fewer deleterious side effects. Indeed, preferred music listening is associated with decreased agitation and use of antipsychotics and anxiolytics in nursing home patients with dementia (Thomas et al., 2017), and in inpatient psychiatric patients (Scudamore et al., 2021).

Furthermore, there is convincing evidence for the beneficial effects of music listening on the stimulation of endogenous opioids during the consummatory phase of music-evoked reward (Chanda & Levitin, 2013; Goldstein, 1980). A meta-analysis by Hole (2015) cited sufficient evidence to recommend that all patients in post-operative care be exposed to music (Hole et al., 2015). Since pain induces and aggravates agitation, future studies in TBI patients might examine whether the application of music listening interventions results not only in decreased agitation, but also a decrease in the pain response, with decreased need for opiate analgesics. As an anecdotal observation from

Study 3, one patient who continually complained of neuropathic pain stopped complaining entirely during relaxing classical music listening. Addition of pain scales to future music intervention studies in agitated patients may therefore be useful.

It is possible that the type of music listening intervention may need to be individualized to each patient's medical and rehabilitative needs (Garrido et al., 2018). For example, it appears that acoustic features target cognitive functions differentially. Studies in healthy individuals have demonstrated that faster tempos and major modes stimulate improvements in processing speed (Bottiroli et al., 2014; Schellenberg, 2012; Thompson, Schellenberg, & Husain, 2001), while episodic memory may improve with slower tempos and lower valence (Bottiroli et al., 2014). In future work it would therefore be important to systematically investigate the effects of specific parameters of music, such as pitch, rhythm, and tempo, on the stress response and agitation in patients with traumatic brain injury, in order to better parse out the contributions of different acoustic features to the modulation of arousal and reward mechanisms.

When managing agitation in TBI patients pharmacologically, determining the course of treatment is based on target symptoms in the context of concurrent treatment for co-existing conditions (for e.g. anxiety, epilepsy, sepsis, hemodynamic instability, pain). Physicians also take into account the possibility of collateral biological effects in the context of the patient's personal and present condition (Luauté et al., 2016). Music intervention design elements may require similar personalized considerations in order to determine which type of music is best suited to the needs of individual patients. Appropriate selection may also take into account the individual's personal history, such as music perception deficits, past musical experience, and culture. Finally, affording patients a sense of control over their treatment is associated with better responses (Hole, Hirsch, Ball, & Meads, 2015; Knappe, 2009), so allowing some control over musical preference may eventually be validated.

Future Directions: Towards a "Gold Standard" for Music Listening Interventions?

In the preceding sections, as well as in Study 3, we highlighted that both preferred or unfamiliar pleasant music can modulate the reward pathway and the stress response, which in turn affects cognition (Blood & Zatorre, 2001; Sihvonen et al., 2017) and agitation levels (Gaviola et al., 2020; Park et al., 2016; Singh, Chakraborty, Jha, Haider, & Chandra, 2013; Tsoi et al., 2018). Thus, as demonstrated in Study 3, relaxing classical music is effective at modulating these systems in a manner that may reduce agitation. However, if preferred music at optimal tempos were chosen, the application of preferred music would be expected to have certain advantages over unpreferred music. Preferred music may modulate the stress response, in part by modulating the reward system and dopamine release (Blood & Zatorre, 2001). Individuals respond more intensely to self-chosen music than randomly chosen music, and this may be especially important for patients who feel powerless and have a sense of low control, or "external" locus of control (Kesavayuth, Poyago-Theotoky, & Zikos, 2020; Lefcourt, 1991), which is typical following TBI. Patient- centered health approaches focus on active listening and providing care on their own terms as much as possible. This implies providing choices in treatments designed to reduce the stress response (Seeman & Seeman, 1983). Thus, asking patients to choose their own music for listening interventions shifts the external locus of control to an internal locus, which may enhance the beneficial effects of music listening interventions on well-being and recovery (Knappe & Pinquart, 2009). For example, a meta-analysis of studies conducted in post-operative patients who were allowed to choose music from either personal choice or a playlist demonstrated modest reductions in pain, use of analgesias, and anxiety compared to when they had no choice (Hole et al., 2015; Liljeström, Juslin, & Västfjäll, 2013). Choosing their own music was associated with enhanced well-being and recovery (Hole et al., 2015; Knappe & Pinquart, 2009). Preferred music may more effectively engage the listener (Finn & Fancourt, 2018), drawing his or her attention from the novel hospital environment to a more familiar one, and further decreasing agitation (Baker, 2001; Park et al., 2016).

With this in mind, preferred music at optimal tempos would likely optimize interventions. However, as we have observed, not all patients have preferred music at optimal tempos. Several procedures may help address this problem. For example, an effort should be made to obtain specific pieces and artists that patients prefer, and the choice confirmed directly with patients that are able to communicate, thus promoting an internal locus of control. In cases in which patients do not have preferred music at optimal tempos between 60 and 80 bpm (Chang, Huang, Lin, & Lin, 2010; Ho et al., 2011; Nilsson, 2009), or the quantity of preferred music at optimal tempos is insufficient to fill the entire listening condition, the researcher may present a playlist to the family that is exhaustive and features music in optimal tempos that span a variety of musical genres and artists. In this manner, preferred music listening could be evaluated in this population while avoiding rapid tempos that stimulate the stress response (Bernardi et al., 2006).

Finally, it is important to address the benefits that the nonmusical control waterfall condition had on agitation in certain cases in Study 3. Waterfall sounds may be preferable to music in patients with shared noisy rooms, as the continuous noise of the heavy waterfall may more effectively drown out background noise than music in a manner similar to that of white noise. Furthermore, recent studies demonstrate that white noise may improve cognitive function in healthy adults, including attention, working memory, long-term memory, executive functions, processing speed (Haka et al., 2009; Lu et al., 2020), and sleep quality (Kim & Kim, 2017). In newborns, white noise is associated with reduced pain scores and less crying time (Karakoç & Türker, 2014). Given that cognitive, pain, and sleep difficulties are commonly observed after TBI and are associated with increased agitation (Barr et al., 2013; Ganau et al., 2018), it is plausible that listening to white noise may decrease agitation and enhance cognitive rehabilitation in neurological populations. However, it is essential to note that of the three conditions in Study 3, the music conditions were tolerated by all four patients, while white noise was only tolerated by two of four patients. Thus, as with all types of listening intervention, it is important that the patient be monitored for signs of distress when introducing a new condition.

Limitations of the Present Thesis

There were several limitations that are worth highlighting. First, TBI patients have heterogeneous injuries, treatments, and comorbid medical conditions that may influence the outcome of a behavioral intervention study and confound interpretation of results. For example, medication administration, sleep deprivation, injury-related pain, apathy, depression, and other forms of stress may have influenced outcomes. Furthermore, the busy hospital environment (e.g. phones ringing, nurses conversing with other patients, cleaning staff, and visitors) may disrupt testing. In Study 1, disruptions were minimized by choosing testing times in which patients were calm with no visitors present, and placing a notice at the door during the intervention. Thus, the results of Study 1 were likely not impacted upon significantly by changes in the environment. However, Study 3 required longer testing sessions, which elevated the risk of disruption. This issue was also noted in a similar study in hospitalized TBI patients, and identified as a possible influence on results (Park et al., 2016). Thus, we excluded data corresponding to periods of interruptions, which may be considered a strength of the present work.

Second, in Study 1 we opted to administer only one test of domain general cognitive function in order to keep testing duration to a minimum and decrease the potential influences of fatigue, pain, and interruptions to testing on outcome. We chose verbal short-term memory because it has been related to the MBEA Scale and Rhythm tests in studies conducted in other populations, making it ideal for contextualizing our results. However, the structural and functional damage caused by a TBI commonly results in domain-general cognitive deficits, which might be expected to impact upon performance on the MBEA (Särkämö et. al., 2009; 2010). For example, focusing on detection of the deviant tone in each melody requires sustained attention and error detection, and determining whether melodies are similar or different from one another requires certain executive functions such as decision-making (Särkämö et al., 2009). Future studies in TBI patients might investigate the various contributions of other domain general cognitive function deficits on music perception deficits.

Third, we did not use audiometry due to testing constraints. Instead, we verified with patients that they had no hearing deficits, consulted their medical file, and ensured that patients could hear the sample stimuli at a comfortable volume. Furthermore, hearing deficits were not observed during conversation. However audiometry might have detected deficits that were overlooked, especially since TBI patients can have sensory auditory deficits with skull base fractures.

Fourth, we used scores from age- and gender-matched individuals included in the database of the MBEA. There were no scores available for Digit Span Forward. It would have been preferable to have conducted an evaluation of verbal short-term memory in a hospitalized age- and sex-matched control group with orthopedic injuries.

The main limitation of Study 2 was that it was not a systematic review. Our study was rather meant to be informative, and not an exhaustive review of all the literature. This allowed for a more in-depth summary of each of several behavioural intervention studies that may otherwise have been excluded.

Study 3 had several limitations. First, it was a case series study, which limits the conclusions that can be drawn about efficacy and statistical significance. On the other hand, the case series approach is better suited to reporting qualitative and unexpected observations that may be excluded in a large scale controlled trial. This allowed us to better evaluate practical obstacles that should be addressed in a larger resource intensive study. Second, the preferred music of certain patients had tempos that fluctuated or were much more rapid than the optimal tempos of 60-80 bpm, which may have reduced the beneficial effect of the music on the stress response, and therefore on agitation. Finding enough preferred music at optimal tempos is a common methodological obstacle. A previous study in TBI patients noted that the tempos of preferred music selections in patients who responded less favourably were rapid (Park, 2010). As stated earlier, this might be mitigated with a supplemental preferred music playlist consisting of pieces at optimal tempos.

Third, we may have missed important response variability by exposing patients to each condition only once. However, rather than repeat conditions twice or more, we opted to limit exposure to once per condition, as testing time may be cut short due to the resolution of agitation, or to the transfer of patients to other services as their medical needs evolve. In future studies, repeated exposures would likely be possible using only one music condition rather than two, along with the nonmusical control.

Fourth, the optimal duration for music listening interventions has not been established. Thus, it is possible that we would have obtained different results with longer exposure times to each listening condition. Some previous studies have demonstrated that just 10 -12 minutes is effective (Baker, 2001; Tabloski et al., 1995). However, further research is needed in order to determine optimal exposure times to listening interventions.

Strengths and clinical implications of the present thesis

A major strength of this thesis is the relevance of the questions addressed by our studies. Development of alternative approaches to the management of agitation is a major unmet medical need in hospitalized patients with acute brain injury. The studies in the present thesis introduced methodology that may alleviate common issues that plague many music intervention studies conducted in neurological populations, including: 1) methods to reduce bias when rating agitation, such as the cutting and random ordering of videotaped conditions; 2) the removal of data collected during disruptions; 3) the demonstration of an efficacious complementary objective measure of physical agitation in TBI patients that promotes standardization across studies; and 4) the presentation of a viable nonmusical control condition in TBI patients.

The present thesis identified the high proportion of TBI patients with music perception deficits. Based on past studies of individuals with music perception deficits, this would be expected to impact upon the ability of a subpopulation of patients to engage in and appreciate music. Considering the widespread use of music, these findings do not only apply to musicians, whose livelihood depends on their perceptual ability; they apply to non-musicians as well, who may find decreased benefit from music listening post-injury, which may decrease their quality of life (Ruud, 1997). It may also be of clinical use to individuals implementing music interventions in this population, allowing for a better understanding of the mechanism underlying failure to respond to treatment.

The fact that there appear to be shared processing components between verbal and tonal material in TBI patients may be used in clinical practice in the following manner: patients with poor verbal short-term memory scores at assessment may be flagged as being at elevated risk of music deficits, and offered an evaluation of music perception if the patient feels this would be of benefit. Currently, there is little support offered to assist individuals for whom decreased music engagement and appreciation has an important impact on quality of life. This thesis allows for an important first step in identifying individuals with music listening disorders after TBI. It may allow for patients who previously "fell between the cracks" due to this invisible disability to receive supportive follow-up as they re-integrate into their social and professional lives. Future studies identifying typical recovery trajectories may help inform patients in order to better manage their expectations. Finally, our work opens the door to future research into brain mechanisms of music perception and evaluation of the pattern of recovery from such deficits following TBI.

Another important contribution of the present work is the highlighting of methodological caveats that exist in most music intervention studies in neurological patients, along with detailed recommendations for a structured approach to future music interventions.

Strengths of Study 2 include the fact that it focused specifically on a critical review of present knowledge of behavioural interventions for the management of agitation in TBI patients, a subject that has received inadequate attention given its clinical impact. The study allowed for a much needed critical review of the benefits and drawbacks of a diverse group of non-pharmacological interventions. We found that these types of intervention, while much needed, are in urgent need for a more systematic approach beyond case and case series studies, with a critical examination of feasibility in acute care and efficacy in complex patient groups.

Many studies in clinical populations do not sufficiently recognize that the main goal of pilot studies is to report the feasibility of conducting larger trials, rather than reporting statistical significance that provides evidence of efficacy (Thabane et al., 2010). The result is a literature predominantly consisting of small pilot studies with unclear methodology, making comparison between studies difficult (Sihvonen et al., 2017; Sung & Chang, 2005). In a paper outlining future directions for pilot studies, it is pointed out that researchers often underemphasize data that doesn't comply with the expectations of the study. Positive statistically significant results are highlighted, and limitations understated or left unreported (Dobkin, 2009). The result is exaggerated treatment effects (Samson et al., 2015). To compound this problem, underpowered studies often use group analyses in this population that is necessarily heterogeneous, rather than reporting detailed results in biologically relevant subgroups. Thus, negative results and the complex clinical pictures that characterize heterogeneous neurological populations do not emerge, in part related to the "drawer effect". To progress from pilot studies to large-scale multi-centre randomized clinical trials during the acute phase of recovery, caveats must be systematically reviewed and negative results reported (Dobkin, 2009). In Gilbertson's words, "the precipitous leap from a few studies to systematic reviews has ignored the necessary stages in between that will provide suitable material for review" (Gilbertson & Aldridge, 2008).

The Path Forward

Musicologists, neuroscientists and clinicians require coherent aims for measuring how individuals respond to music in health and in specific pathological conditions. In complex disease states, it is especially important to design a well-thought-out methodological foundation prior to the evaluation of a potential therapy. Music intervention studies should therefore provide detailed descriptions of the etiology of brain injury, specific location of injury, other comorbid injuries and conditions, medications administered, and cognitive test results. In addition, studies should include details of the patient's testing environment (ie. shared or private room, restraints applied), delays in testing, measures used to determine musical preference, specific song compilations and their tempos, how the intervention was delivered (eg. speakers vs headphones), and individual agitated behaviour scale scores in addition to group analyses. Furthermore, limitations of the intervention, including interruptions, must be explicit, and information provided on how these potential confounds were managed in data analysis. The goal in validating an intervention in complex patient groups is therefore to consolidate lessons learned in previous studies to optimize future research. In this manner, replicability would be promoted, and the methodological flaws observed in music intervention trials performed in clinical populations would be reduced. These incremental studies may eventually lead to useful translation of validated music interventions from research to clinical practice.

Well-documented and systematically executed underpowered stage II trials should be successively staged to determine the most effective delivery of musical interventions (Dobkin, 2009). Components of the intervention, such as number of sessions, duration of delivery, types of listening conditions, and treatment effects can be evaluated and optimized from one study to the next, so that each study acts as a stepping-stone to large controlled trials. Clinical experience should also be drawn on to define what constitutes a clinically meaningful effect (Leon, Davis, & Kraemer, 2011).

Finally, there is a need for studies that integrate behavioural measures such as the ABS and actigraphy with structural and functional imaging in ABI patients, including as CT, SPECT, PET and MRI, as well as measures of sympathetic arousal, such as heart rate, skin conductance, oxygen saturation and blood levels of catecholamines or stress hormones (Sihvonen et al., 2017).

Conclusion

The families and nursing staff of patients with TBI often ask whether agitated patients should listen to music during acute care. Indeed, technologically sophisticated beds in hospital often incorporate a musical selection. The answer to this valid question is complex, and needs to be parsed out by combining multi-disciplinary findings in basic and clinical neuroscience and musicology. To this end, the present thesis demonstrated that music interventions applied to a small sample of moderate and severe TBI patients were feasible and well-tolerated. Agitation even decreased in certain cases, providing initial evidence for a beneficial effect of music interventions. However, we also determined that a significant proportion of patients have music perception deficits following TBI which might be expected to impact upon music listening engagement and appreciation in certain individuals. Thus, the present thesis provides important observations that will inform larger scale trials of music interventions for agitation in acute brain injury patients, addressing an important unmet medical need.

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APPENDIX: Article 4

Detecting Migraine in Patients with Mild Traumatic Brain Injury Using Three Different Headache measures

Kirsten Anderson, B.A[1], Simon Tinawi, M.D[2], Julie Lamoureux, M.D[3], Mitra Feyz M.Sc. PS[4], Elaine de Guise Ph.D.[1,5]

1. Département de Psychologie, Université de Montréal, Montréal, QC, Canada
2. Physical Medicine and Rehabilitation Service, McGill University Health Centre, Montreal, Quebec, Canada.
3. Social and Preventive Medicine Department, University of Montreal, Montreal, Quebec, Canada.
4. Traumatic Brain Injury Program, McGill University Health Centre, Montreal, Quebec, Canada
5. Neurology and Neurosurgery Department, McGill University Health Centre, Montreal, Quebec, Canada.

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Abstract

Post-traumatic migraine may represent an important subtype of headache among the traumatic brain injury (TBI) population, and is associated with increased recovery times. However, it is underdiagnosed in patients with mild traumatic brain injury (mTBI). This study examined the effectiveness of the self-administered Nine-Item Screener (Nine-Item Screener-SA), the Headache Impact Test- 6 (HIT-6™) the 3-Item Migraine Screener, and the Rivermead Post-Concussion Questionnaire (RPQ) at discriminating between mTBI patients with (n = 23) and without (n = 20) migraines. The Nine-Item Screener demonstrated significant differences between migraine patients with and without migraine on nearly every question, especially on Question 9 (disability), sensitivity: 0.95, specificity: 0.65 (95% CI, 0.64 – 0.90). The HIT-6™ demonstrated significant differences between migraine and no migraine patients on disability and pain severity, with disability having a sensitivity of 0.70, specificity: 0.75 (95% CI, 0.54 – 0.83). Only question three of the 3-Item ID Migraine Screener (photosensitivity) showed significant differences between migraine and no migraine patients, sensitivity: 0.84, specificity: 0.55 (CI, 0.52 – 0.82). The RPQ did not reveal greater symptoms in migraine patients compared with those without. Among headache measures, the Nine-Item Screener-SA best differentiated between mTBI patients with and without migraine. Disability may best identify migraine sufferers among the TBI population.

Keywords: post-traumatic headache, migraine, disability, mild traumatic brain injury, concussion

Post-traumatic headaches (PTH) are common in the TBI population, with a prevalence ranging from 30-90% depending on the type of measurement instrument administered to patients (Alves, Macciocchi, & Barth, 1993). Post-traumatic headaches may persist long after the TBI, with 18% to 22% of PTH sufferers still experiencing symptoms one year later (Lew et al., 2006). Approximately 75% of the 1.7 million patients with traumatic head injuries in the United States (annual) are classified as mild (Monteith & Borsook, 2014). Post-traumatic headaches in this population may be the major cause of persistent disability. The frequency of different headache types after TBI can be quite variable in different studies. An important reason underlying this variability may be differences in the measurement instruments used to classify them. Several widely used and well-validated tests have been designed to measure the specific characteristics of headache and headache-related disability, including the Headache Disorders, 2nd Edition (ICHD-II), the Nine-Item Screener (Lipton et al., 2003), the Headache Impact Test™ (HIT-6™) (Kosinski et al., 2003), and the Three-item ID Migraine Screener (King, Crawford, Wenden, Moss, & Wade, 1995). Few studies have examined the efficacy of these tests in distinguishing between mild TBI patients with and without migraines.

Classification of PTH types is useful for both research and treatment. Post-traumatic headaches are classified as secondary headaches. However, they have no clear defining features that distinguish them from primary headaches other than their close temporal relationship with the TBI. As such, primary headache questionnaires that distinguish headache types according to duration, frequency and character of pain, are often applied to PTH (Lucas, Hoffman, Bell, Walker, & Dikmen, 2012). A significant number of post-traumatic headaches fall into the category of the migraine phenotype, when using the International Classification of Headache Disorders, edition 2 (ICHD-II) (DiTommaso et al., 2014; Lucas et al., 2012). Post-traumatic migraines can lead to significant disability, even following mild TBI (Kontos et al., 2013).

Using the primary headache criteria, migraine headaches are defined as moderate to severe headaches, that may be accompanied by systemic problems such as nausea and vomiting, pain worsening with activity, and photo-sensitivity (Monteith & Borsook, 2014). Migraines can also disturb cognitive function, vestibular function, emotional state, and social interactions. Thus, they may be debilitating and impede patients' recovery from TBI (Monteith & Borsook, 2014).

An accurate diagnosis of post-traumatic migraines is essential for proper treatment. The management of headache necessitates the use of analgesics such as acetaminophen and ibuprofen, whereas migraine sufferers are often prescribed anti-nausea medications and preventive or abortive treatments, such as triptans (DiTommaso et al., 2014; Lucas, 2011). Unfortunately, a substantial proportion of the mild TBI population does not receive adequate management for their migraines. This may due to inadequate classification (DiTommaso et al., 2014), or failure to seek medical attention. In spite of the known diversity of primary headache types, 70% of patients with mild TBIs rely solely on over-the-counter non-specific medications such as acetaminophen and non-steroidal anti-inflammatories to treat their headache symptoms (DiTommaso et al., 2014). Amongst post-traumatic migraine sufferers, only 26% experience symptom relief (DiTommaso et al., 2014). Preventive treatment can lead to attacks that are less severe and shorter in duration (Lucas, 2011). Furthermore, excessive use of over-the-counter analgesics may provoke medication-overuse headache (DiTommaso et al., 2014; Tepper, 2012; Watanabe, Bell, Walker, & Schomer, 2012). This can lead to further management challenges and poorer functional outcome (Watanabe et al., 2012).

Post-traumatic migraine sufferers are reported to have longer recovery times from mild TBI than other PTH patients (Kontos et al., 2013; Lau, Lovell, Collins, & Pardini, 2009; Mihalik et al., 2013). In one study, patients suffering from post-traumatic migraines demonstrated a 7.3 times greater risk for extended recovery time than non-migraine TBI patients (Kontos et al., 2013). Disability is a key factor in planning level of care based on the patient's work and family obligations.

The goal of the present study is to determine which of the commonly used headache questionnaires best detects migraines in a population of mild TBI patients. We compared the sensitivity and specificity of the Nine-Item Screener, the HIT-6™, and the Three-item ID Migraine Screener at detecting and distinguishing patients with migraines from those without migraines in a mild TBI population. By focusing on these commonly used, well-validated tests, this work aims to better characterize the usefulness of different headache inventories in the TBI population, and may serve as an important basis for diagnostic classification for research and treatment purposes.

Materials and Method

Participants

Forty-three patients with mild traumatic brain injury were seen at the outpatient clinic at the McGill University Health Centre - Montreal General Hospital (MUHC-MGH) between September 1, 2012 and August 1, 2013 and consecutively enrolled in the present study. The patients had recently sustained a head trauma, and were diagnosed with an mTBI by a physician who used WHO Task Force Criteria (Carroll et al., 2004), which includes at least one of the following symptoms: post traumatic amnesia of less than 24 hours, loss of consciousness of up to 30 minutes, seizure, focal signs, disorientation or scans demonstrating intracranial lesions that do not require surgery. The etiology of injury was varied (Table 1). This study was approved by the MUHC-MGH research ethics board.

Pre-trauma socio demographic characteristics, clinical variables, and accident variables. Data was collected from the TBI program database maintained at the MUHC-MGH. Accident etiology and duration of post-traumatic amnesia was examined, as well as gender, and history of headaches and migraines (Table 1). Migraine patients included those with (n = 3) and without (n = 20) aura.

Procedure

Self-report questionnaires were administered to patients before the medical evaluation, an average of 43.24 days (SD = ± 29.96) post-TBI. Next, a physician specializing in rehabilitative medicine performed a migraine assessment based on 2004 ICHD-II criteria for migraine (Olesen, 2005), the HIT-6, family history of headache, cervical sprain, childhood motion sickness, and food intolerance. He then conducted a neurological examination.

Measures

Headache Disorders, 2nd Edition (ICHD-II): Nine-Item Screener. (Lipton et al., 2003)**.** In the present study, this widely accepted physician-administered questionnaire was self-administered by patients. It is based on IHS criteria and consists of nine yes or no questions that serve to identify and categorize headaches into a hierarchical system. The questions help characterize pain and aura. They also help identify nausea, light and sound sensitivity, and functional impairment. The sum of positive answers is calculated to obtain a total score.

The Headache Impact Test™ (HIT-6™) (Kosinski et al., 2003). This self-report questionnaire can be used as both a screening tool, and a way of measuring changes in headache impact. It consists of six questions that are designed to measure the impact that headaches have on the patient's normal function in social situations, at work, home, and school. Items are on a rating scale of 1-5 that includes never, rarely, sometimes, very often and always. Scores of 50 or higher indicate that the patient requires medical attention.

Three-item ID Migraine Screener (Lipton et al., 2003). This self-report questionnaire consists of three yes or no items and can be used as a screening tool in a primary care setting to identify headaches, nausea, light sensitivity and functional impairment.

The Rivermead Post-Concussion Symptoms Questionnaire (King et al., 1995). This self-report questionnaire measures the severity of cognitive, emotional and somatic symptoms in TBI patients. It consists of 16 questions on a rating scale including 0 (not experienced at all), 1 (no more of a problem), 2 (a mild problem) 3 (a moderate problem) and 4 (a severe problem). If at least three symptoms are present at three months, the patient is considered to have Post-Concussion Syndrome.(Ingebrigtsen, Waterloo, Marup-Jensen, Attner, & Romner, 1998)

Results

Data Integrity

Three patients did not complete the HIT-6™ questionnaire. There were no values missing for the Nine-Item Screener. Two or three values were missing on the 3-Item ID Migraine Screener, depending on the question, due to incomplete information provided by patients.

Descriptive Statistics

Twenty of the forty-three mild TBI patients suffered migraines, according to ICHD-II classification. Ages ranged from 26 to 63 with an average of 44.8 years (*SD* =18.3). Approximately half (51.2%) of the patients were female. There were no statistically significant differences between the migraine and no migraine groups in terms of previous TBIs, cervical sprains, duration of post-traumatic amnesia, and length of stay (Table 1). Groups also did not differ significantly on psychiatric problems, education, or alcohol and drug abuse. Finally, no significant differences were found between groups on food intolerance and motion sickness.

Headache Test Results

Headache Disorders, 2nd Edition (ICHD-II): Nine-Item Screener-SA (Lipton et al., 2003). Chi-square tests were used to compare scores between the migraine group and the no migraine group on each question. There was a higher frequency of migraine symptoms and lower functioning in the migraine group compared with that of the no migraine group on all questions except number four (Table 2). To evaluate the validity of the Nine-Item Screener as a predictor of migraine headaches in the mild TBI population, sensitivity and specificity were examined. Item nine was the most predictive (Table 3). Finally, since each item of the Nine-Item Screener-SA reflects only the absence/presence of symptoms, an overall score was calculated to compare the migraine group to the no migraine group. The mean number of symptoms in the group with migraines was 7.60 (*SD* = 1.60), with a median of 5 and a range of 0 to 9. The group without migraines had a mean of 4.2 (*SD* = 3.1), with a median of 8 and a range of 3 to 9. The distribution was not normal, therefore the non-parametric Wilcoxon rank sum test was used. Migraine patients reported significantly more symptoms than those without migraines, $z = 3.78$, $p < .001$ (Figure 1). The sensitivity of the total score was 90.0% and the specificity was 69.9%, while question 9 had a sensitivity of 95.0% and a specificity of 65.2%, indicating that this question alone has almost as much validity as the overall score.

The Headache Impact Test (HIT-6™) (Kosinski et al., 2003). The HIT-6™ total score was compared in the migraine group versus the no migraine group using a two-tailed independent samples t-test. There were marginally significant differences between the migraine group ($M = 2.60$; $SD = 0.70$) and the non-migraine group ($M = 2.10$; $SD = 1.00$), $t\ (38) = 3.82$; $p = .076$. Chi-square tests were then performed on specific questions to determine whether migraine symptoms and functional problems in daily life were more frequently experienced by migraine patients than the no migraine group. Migraine patients reported a statistically significant higher frequency of symptoms than non-migraine patients on item one, χ^2 (4, N = 40) = 11.47, p = .022. To evaluate the validity of the HIT-6™ as a predictor of migraine headaches in the mTBI population, the sensitivity and specificity was evaluated. At a cut-off of "very often," item one had a sensitivity of 70% and a specificity of 75%. Migraine patients also demonstrated a higher frequency of symptoms on the second question, χ^2 (4, N = 40) = 9.57, p = .048. Item two had a sensitivity of 60% and a specificity of 70%. There was no statistically significant difference between groups on the last four questions (Table 4).

The 3- Item ID Migraine Screener (Lipton et al., 2003). Chi-square tests were used to compare scores between the migraine group and the no migraine group on eachquestion. Item 2, light sensitivity, was the only item that revealed statistically significant differences between the migraine and no migraine groups χ^2 (1, N = 41) = 6.60; p = .010 (sensitivity = 84.2%; specificity = 54.6%). This item was also the only one with good predictive power (sensitivity = 84.2% ; specificity = 54.6%; Table 5).

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ). (King et al., 1995). The RPQ total score was compared between patients with and without migraine, using a two-tailed independent samples t-test. No statistically significant differences were found between the migraine group (M = 33.40; SD = 13.08) and the non-migraine group (M = 32.52; SD = 17.77), t (38) = .18; p = .859.

Discussion

To our knowledge, previous studies have not examined the effectiveness of different headache tests at detecting migraine in a mild TBI population. Therefore, the main purpose of this study was to determine which headache tests among the Nine-Item Screener-SA, the HIT-6™, and the 3-Item ID Migraine Screener would best differentiate between mild TBI patients with and without migraines. Results on the Nine-Item Screener and the HIT-6™ demonstrated that migraine patients experienced more disability than non-migraine patients. Across headache inventories, the items that best detected differences between TBI patients with and without migraines were pain severity, disability and photosensitivity, with migraine patients reporting greater levels of each. The headache test that best differentiated between migraine patients and non-migraine patients was the Nine-Item Screener, which demonstrated differences on nearly every item. The HIT-6™ and the 3-Item ID Migraine Screener appeared to be less sensitive for this purpose. The RPQ did not demonstrate higher scores among migraine patients.

Post-traumatic migraine has been identified as an important subtype of headache among the TBI population due to the compounded cognitive and physical disability associated with this diagnosis (Monteith & Borsook, 2014). Functional disability is also high in migraine sufferers in the general population. Indeed, one study reported that 75% of migraineurs felt they required complete bed rest and suffered severe disability during a migraine (Lipton, Stewart, Diamond, Diamond, & Reed, 2001). Furthermore, Kontos and colleagues found that migraine patients' scores on computerized neurocognitive tests reflected slower reaction times and poorer visual and verbal memory than scores of TBI patients with headache only, or no headache (Kontos et al., 2013). The same study also demonstrated higher scores during recovery from head injury, especially on tests sensitive to cognitive, emotional, sleep, and somatic problems, indicating a greater level of disability amongst migraineurs (Kontos et al., 2013).

Diagnostic Migraine Screeners

Nine-Item Screener-SA. All Nine-Item Screener items except question 4 indicated that post-traumatic migraine sufferers experienced proportionately more symptoms than non-migraine patients. These included pain severity, unilateral location, throbbing, nausea, symptoms of aura, photo- and phonosensitivity, and functional impairment. Question 9, which evaluates functional impairment due to headache during the last three months, was the strongest predictor of migraines. Furthermore, it demonstrated nearly as much sensitivity and specificity as the overall score. The present results therefore suggest that greater functional impairment may be the cardinal symptom that most distinguishes migraine patients from non-migraine patients in the mild TBI population. Future studies could evaluate the efficacy of administering this question alone, for more rapid diagnosis.

Migraine and non-migraine groups did not differ on Question 4, indicating that the effect of physical exertion on migraine symptoms may not be as important as pain characteristics, and autonomic effects.

The 9-Item Screener-SA differentiated migraine sufferers from non-migraine sufferers on eight of nine items, and demonstrated high sensitivity and specificity in an mTBI population. Indeed, it was comparable to the extensive physician diagnosis in the present study, which was based on several headache measures in addition to the Gold Standard ICHD-II diagnosis, family and personal medical history, and a neurological exam. This suggests that it could serve as a stand-alone diagnosis for classifying migraine headaches in a mTBI population, in both clinical and research designs. If the 9-Item Screener-SA is equally accurate at detecting migraine, this could reduce physician workload and improve the efficacy of healthcare delivery. However, these results must be interpreted with caution. More detailed physician examinations may lower the incidence of false positives that would threaten patient safety. For example, a patient presenting with migraine-type pain may require a more thorough consultation to differentiate migraine from a hematoma or cervical sprain. Misdiagnosing the latter as migraine is a significant safety risk that would also be costly as well, both to the healthcare system, and the patient.

3-Item ID Migraine Screener. Only light sensitivity differed between migraine patients and non-migraine patients, with migraine sufferers experiencing greater sensitivity. Few studies have examined photosensitivity in TBI populations. Bohnen et al. suggested that photosensitivity in TBI patients may be due to inadequate inhibition of sensory processing by the orbitofrontal cortex in subcortical and posterior areas of the brain (Bohnen, Twijnstra, Wijnen, & Jolles, 1991). However the present study suggests that migraine in a TBI population may play a more important role in photosensitivity than previously acknowledged. In cases where TBI does not directly injure the visual pathways, photosensitivity may not exist as a function of post-concussive syndrome. Rather, it may be a function of post-traumatic migraine. Migraine history before TBI is also believed to be a risk factor for developing light sensitivity after injury (Chrisman, Rivara, Schiff, Zhou, & Comstock, 2013). Interestingly, in our population, there were no significant differences in headache history between migraine patients and those without migraines.

Lastly, Lipton et al. determined that the Nine-Item Screener did not have any more sensitivity or specificity for detecting migraines in the general population than the 3-Item ID Migraine Screener (Lipton et al., 2003). In contrast, the present results indicate that the Nine-Item Screener inventory has the best positive predictive value and the best differentiation of migraine patients, even over that of the 3 Item ID Migraine Screener, when evaluating a mild TBI population.

Headache Impact Measure

HIT-6™. Similar to results on the Nine-Item Screener, the HIT-6™ demonstrated that migraine patients suffered the greatest pain and functional limitations. Migraine and non-migraine patients did not differ on questions three through six, which examine cognitive and emotional aspects such as concentration, fatigue, and irritability. One possible explanation is that these symptoms overlap with those of post-concussion syndrome, a common condition in the TBI population (Bigler, 2008). This is supported by the fact that there were no significant differences in groups on the RPQ.

Interestingly, the findings of the present study contrast with those of Kontos and colleagues, who demonstrated cognitive differences between PTH patients with and without migraines. This difference may have been due to the latter group's use of objective measures to investigate cognitive constructs that were more specifically defined (Kontos et al., 2013). We used self-report measures, which may have been more vulnerable to response changeability. Furthermore, their study focused exclusively on sports concussions, while ours included patients who had been in motor vehicle accidents, which are often associated with more complex traumas, and require more medications for conditions, such as pain, that may decrease cognitive ability independent of headaches. This could obscure subtle differences in cognitive function between migraine and non-migraine groups.

Post-Concussive Symptoms

Rivermead Post-Concussive Symptoms Questionnaire (RPQ). The lack of significant differences found between groups on the RPQ demonstrates that administering this questionnaire alone may result in failure to distinguish migraine headaches from other post-concussion symptoms in mTBI patients. The RPQ is an inventory of post-concussive symptoms, including headaches, irritability, difficulty concentrating, phono- and photosensitivity, nausea and vomiting. Previous studies have demonstrated that mTBI patients suffering from migraines often don't receive the treatments they require (DiTommaso et al., 2014).

One limitation of the current study was the exclusion of asymptomatic patients who were seen in the emergency department without further referral to a clinic. The small sample size may also limit generalizability. In addition, among possible triggers for migraine, only motion sickness and food intolerance were examined. Other factors that trigger migraines could be explored in future studies. Finally, headaches were recalled by patients retrospectively. A daily headache log may have reduced any possible bias or memory deficits in patients' self-reports.

Conclusion

The present study demonstrated that the Nine-Item Screener may be the best inventory at detecting migraine headaches in a mild TBI population. Furthermore, the 9-Item Screener, when self-administered, appears to be equally accurate at identifying migraine patients as an extensive physician-administered diagnosis based on the 2004 ICHD-II criteria for migraine (Olesen, 2005), the HIT-6, family history of headache, cervical sprain, childhood motion sickness, and food intolerance. However, the physician-administered assessment may still be instrumental in differentiating between migraines and other important types of headache. The current study also suggests that administering the RPQ alone may result in an oversight of the contribution of migraine headaches to post-concussion symptoms in mTBI patients.

Our work contributes to a sparse literature comparing the ability of different measures of headache to detect migraine in a TBI population. This is an important contribution, since migraine-specific disability may be related to protracted recovery from mild TBI, and in the present study, items measuring pain severity, photosensitivity and disability on the Nine-Item Screener, the HIT-6™ and the 3-Item ID Migraine Screener may best differentiate migraine sufferers from non-migraine sufferers. It is not yet known whether it is appropriate to generalize these results to all mTBI patients with migraine. However, the findings from this study could contribute to a more standardized approach to classifying migraine headaches in a TBI population, for the optimization of clinical and research designs. Further research is necessary to better classify post-traumatic headache types and conduct more effective research on the contribution of migraine to disability. Migraine-targeted treatments could help increase functional outcome, and reduce healthcare costs related to protracted recovery times from traumatic brain injury.

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Table 1

Demographics and previous medical history

Variable	Frequency (%)
Total number of patients	43
Age at injury ($M \pm SD$)	44.8 ± 18.3
Male	48.8
Female	51.2
Medical history	
History	
Previous migraines	
No	31 (79%)
Yes	8 (21%)
Chronic headaches	
No	21(55%)
Yes	17 (45%)
Motion sickness	
No	25 (86%)
Yes	4 (14%)
Food intolerance	
No	26 (90%)
Yes	3 (10%)
ICHD-II Diagnosis	
Migraines	
No	23 (53%)
Yes	20 (47%)
Accident variables	
TBI etiology	
Fall	16 (38%)
MVA	8 (19%)
MVA (pedestrian or cyclist)	3 (7%)
Assault	3 (7%)
Suicide attempt	3 (7%)
Sports	8 (19%)
Other	1 (2%)
LOC	
No	22 (59%)
Yes	15 (41%)
Duration PTA	
None	14 (38%)
< 5 min	3 (8%)
5-10 min	3 (8%)
10-15 min	2 (5%)

15-30 min	2 (5%)
30-60 min	5 (14%)
60+ min	8 (22%)

Note. ICHD-II = Inteernational Classification of Headache Disorders, Edition 2; MVA = motor vehicle accident; LOC = loss of consciousness; PTA = post-traumatic amnesia.

Table 2

Comparison of headache symptoms in migraine and no migraine groups on the nine-item screener

Item	Overall (%)	Migraine (%)	No migraine (%)	Chi-square test	*p*-value
**Q1	48.8	70.0	30.4	6.70	.010
**Q2	67.4	90.0	47.8	8.67	.003
**Q3	81.4	100	65.2	8.55	.003
Q4	69.8	80.0	60.9	1.86	.173
*Q5	42.9	60.0	27.3	4.58	.032
**Q6	44.2	70.0	21.7	10.10	.001
**Q7	76.7	95.0	60.9	6.98	.008
**Q8	83.7	100	69.6	7.27	.008
***Q9	62.8	95.0	34.8	16.60	< .001

Chi-square tests demonstrated that migraine patients had significantly more symptoms and lower functioning that the no migraine group on all questions except number four.
* $p < .05$
** $p < .01$
*** $p < .001$

Table 3

Sensitivity and specificity of the nine-item screener in patients with and without migraine

Item	Sensitivity (%)	Specificity (%)	95% CI AUC
1. Pain is worse on just one side	70	69.6	0.54- 0.83
2. Pain is pulsing, pounding or throbbing	90	52.2	0.56 - 0.85
3. Pain is moderate or severe	100	34.8	0.52 - 0.81
4. Pain is made worse by activities such as walking or climbing stairs	80	39.1	0.44 - 0.75
5. You feel nauseated or sick to your stomach	60	72.7	0.50 - 0.80
6. You see spots, stars, zigzag lines, or gray area for several minutes or more before or during your headaches	70	78.3	0.59 - 0.87
7. Light bothers you (a lot more than when you do not have headaches)	95	39.1	0.52 - 0.81
8. Sound bothers you (a lot more than when you do not have headaches)	100	30.4	0.49 - 0.79
9. Functional impairment due ot headache in the last three months	95	65.2	0.64 – 0.90

Note. *N* = 43

Table 4

Comparison of Headache Impact Symptoms in Migraine and No Migraine Groups on the HIT-6™

Item	Chi-Square Test	p-value (%)
*1. When you have headaches, how often is the pain severe?	11.47	0.022
*2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?	9.57	0.048
3. When you have a headache, how often do you wish you could lie down?	2.51	0.642
4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?	6.02	0.198
5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?	8.04	0.09
6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?	5.01	0.286

Table 5

Sensitivity and Specificity of the 3-Item ID Migraine Screener in Patients with and without Migraine

Item	Sensitivity (%)	Specificity (%)	95% CI AUC
Limiting Activities	79.0	36.4	0.42 - 0.74
Talking to Physician	73.7	33.3	0.36 - 0.69
Lipton 1: Nausea	63.2	45.5	0.37 - 0.69
Lipton 2: Light Sensitivity	84.2	54.6	0.52 - 0.82
Lipton 3: limited for ≥ one day	84.2	40.9	0.47 - 0.78

Note. $N = 41$

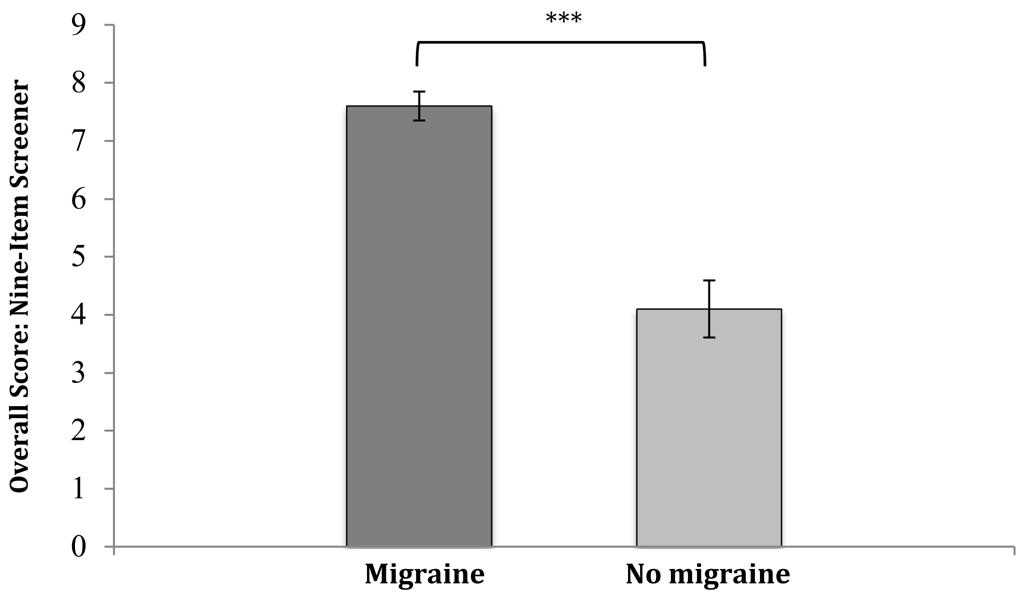

Figure 1. Mean values of migraine scores for migraine and no migraine patients on the Nine-Item Screener. Standard errors of the mean are represented in the figure by the error bar attached to each column.

*** $p < .001$