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MUSIC THERAPY IN THE COGNITIVE AND NEURAL REHABILITATION OF TRAUMATIC BRAIN INJURY

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DOCTORAL DISSERTATION

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“The most sensitive musical instrument
is the human soul.”

~ Arvo Pärt

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ABSTRACT

Traumatic brain injury (TBI) is a highly common and debilitating health condition that can have lifelong cognitive, emotional, and physical consequences. Importantly, many TBI survivors come from young age groups, which further raises the individual, societal and economic burden of the condition and the need for effective rehabilitation methods to support the independent functioning and quality of life of the patients. Due to their prevalence and impact on everyday life, executive functioning (EF) deficits are often viewed as the core cognitive symptoms of TBI and challenging for rehabilitation. Music is a versatile and motivating activity that engages many cognitive, motor, and emotional functions and large-scale brain networks, making it a promising tool for neurological rehabilitation. Importantly, given that musical training has been found to enhance EF and recruitment of the cognitive control network in behavioural and neuroimaging studies of healthy individuals, music-based interventions could provide an effective way to rehabilitate EF deficits in TBI patients. However, the rehabilitative effects of music in TBI are still largely unknown.

The aim of this thesis was to explore the efficacy of neurological music therapy in the rehabilitation of moderate and severe TBI. The thesis includes three studies based on a cross-over randomized controlled trial (RCT), in which forty participants with TBI (time since injury < 2 years) were randomized into two groups (AB/BA) to receive a 3-month neurological music therapy intervention either during the first (AB, n = 20) or second (BA, n = 20) half of a 6-month follow-up period. Neuropsychological and motor testing, questionnaires, and structural and functional magnetic resonance imaging (MRI) were performed at baseline and at the 3-month and 6-month stage. Additionally, follow-up questionnaires and subjective feedback from the intervention were obtained at 18-month stage. Thirty-nine subjects who participated in baseline measurement were included in an intention-to treat analysis of the efficacy of the intervention.

Results from Study I showed that in the neuropsychological testing general EF (as indicated by the Frontal Assessment Battery) and set shifting ability (as indicated by the Number-Letter Task) improved more in the AB group than in the BA group over the first 3-month period, and the effect on general EF was maintained in the 6-month follow-up. Voxel-based morphometry analysis of the structural MRI data indicated that gray matter volume in the right inferior frontal gyrus increased significantly in both groups during the intervention versus control period, which also correlated with cognitive improvement in set shifting ability.

Findings from Study II reporting the questionnaire data showed that the Behavioural Regulation Index of the Behaviour Rating Inventory of Executive Function (BRIEF-A) improved more in the AB than BA group from baseline to 3-month stage, and the effect was maintained in the 6-month follow-up. No changes in mood or quality of life questionnaires were observed. However, a qualitative content analysis of the feedback questionnaires revealed that many participants experienced the intervention as helpful in terms of emotional well-being and activity.

Finally, Study III explored functional connectivity patterns using resting-state functional MRI and revealed that music therapy increased the coupling between the frontoparietal and dorsal-attentional networks as well as between these networks and primary sensory networks. By contrast, the default mode network was less connected with sensory networks after the intervention. Similarly, there was a shift towards a less connected state within the frontoparietal and salience networks, which are typically hyperconnected following TBI. Furthermore, improvement in EF was correlated with resting-state functional connectivity changes within the frontoparietal network and between the default mode and sensorimotor networks.

All in all, these results suggest that neurological music therapy enhances EF skills, including general EF, set shifting ability and behavioral self-regulation, after TBI and that these gains are linked to specific volumetric and functional neuroplastic changes in the brain. These novel findings give support to the use of music therapy in rehabilitation of moderate and severe traumatic brain injury.

TIIVISTELMÄ

Traumaattinen aivovaurio on varsin yleinen toimintakykyä alentava vamma, joka voi aiheuttaa elinikäisiä kognitiivisia, emotionaalisia ja fyysisiä oireita. Koska suuri osa vammautuneista on iältään nuoria, ovat aivovammojen vaikutukset yksilölle, yhteiskunnalle ja taloudelle merkittävät. Tehokkaille, toimintakykyä ja elämänlaatua tukeville kuntoutusmuodoille on suuri tarve. Aivovammasta seuraavat toiminnanohjauksen ongelmat ovat varsin yleisiä, ja niillä on suuri vaikutus potilaiden päivittäiseen selviytymiseen, minkä vuoksi niitä voidaan pitää aivovamman kognitiivisina ydinoireina. Musiikki on monimuotoinen ja motivoiva toiminto, joka aktivoi useita kognitiivisia, motorisia ja emotionaalisia aivoverkostoja, mikä tekee siitä lupaavan hoitomuodon neurologisessa kuntoutuksessa. Tutkimukset ovat myös osoittaneet, että musiikin harjoittelu parantaa toiminnanohjaustaitoja sekä vahvistaa aivoissa kognitiivisten toimintojen säätelyverkoston toimintaa terveillä henkilöillä, minkä vuoksi musiikkipohjainen kuntoutus voisi tukea toiminnanohjaustaitoja myös aivovamman jälkeen. Musiikin vaikuttavuutta aivovammakuntoutuksessa on kuitenkin toistaiseksi selvitetty varsin vähän.

Tässä väitöskirjassa tutkitaan neurologisen musiikkiterapian vaikuttavuutta keskivaikeiden ja vaikeiden aivovammojen hoidossa. Väitöskirja koostuu kolmesta osatutkimuksesta, jotka perustuvat satunnaistettuun kontrolloituun tutkimukseen. Tähän tutkimukseen rekrytointiin 40 potilasta, joiden vammautumisesta oli kulunut alle 2 vuotta ja heidät satunnaistettiin kahteen ryhmään AB/BA. Ensimmäinen ryhmä (AB, n = 20) sai neurologista musiikkiterapiaa 6 kuukauden seurantajakson alkupuoliskolla (3 kk) ja toinen ryhmä (BA, n = 20) sai intervention seurantajakson jälkimmäisellä puoliskolla. Mittaukset, mukaan lukien neuropsykologiset ja motoriset testaukset, kyselylomakkeet sekä strukturaalinen ja funktionaalinen magneettikuvaus, suoritettiin alussa, 3 kuukauden ja 6 kuukauden kohdalla. Lisäksi seurantakyselyt ja subjektiivista kokemusta kartoittava palautekysely kerättiin 18 kuukauden kohdalla. 39 tutkittavaa, jotka osallistuivat alkumittaukseen, otettiin mukaan hoitoaikeen mukaiseen (intention-to-treat) analyysiin.

Tutkimuksen I tulokset osoittavat, että yleiset toiminnanohjaustaidot (Frontal Assessment Battery -testistöllä arvioituna) sekä erityisesti kognitiivisen prosessoinnin joustavuus (Number-Letter Task -testillä testattuna) paranivat AB-ryhmässä BA-ryhmään verrattuna seurantajakson alkupuoliskolla ja positiivinen vaikutus yleisiin toiminnanohjaustaitoihin säilyi vielä 6 kuukauden seurannassa. Myös harmaan aineen volyymi oikealla alemmalla otsolohkopoimulla kasvoi merkittävästi molemmissa ryhmissä interventiojaksolla verrattuna kontrollijaksoon. Tämä harmaan aineen lisääntyminen korreloi kognitiivisen suorituksen kanssa prosessoinnin joustavuutta vaativassa tehtävässä.

Tutkimuksessa II, jossa raportoidaan kyselylomakkeiden tulokset, osoitetaan että itse raportoitu käyttäytymisen säätely Behaviour Rating Inventory of Executive Function (BRIEF-A) mittarissa kohentui enemmän AB- kuin BA-ryhmässä ensimmäisen kolmen kuukauden seurannan aikana ja saavutettu taso säilyi vielä 6 kuukauden seurannassa. Merkittäviä muutoksia mielialassa tai elämänlaadussa ei musiikkiterapiajaksoon liittyen havaittu. Palautteen laadullinen sisältöanalyysi kuitenkin toi esiin, että useat osallistujat kokivat terapian tukevan emotionaalista hyvinvointiaan ja aktiivisuuttaan.

Tutkimuksessa III selvitettiin aivojen toiminnallisissa verkostoissa musiikkiterapian vaikutuksesta tapahtuneita muutoksia, joita mitattiin lepotilaverkostojen toiminnallisella magneettikuvauksella. Tulokset osoittavat, että yhteydet frontoparietaalisen verkoston ja dorsaalisen tarkkaavuusverkoston verkoston välillä, sekä näiden verkostojen ja primaaristen sensoristen verkostojen välillä vahvistuivat. Sitä vastoin oletustilaverkoston (default mode network) yhteydet sensorisiin verkostoihin vähenivät musiikkiterapian jälkeen. Samoin frontoparietaalisessa verkostossa ja olennaisen tunnistavassa hermoverkossa (salience network), joissa nähdään usein aivovamman seurauksena yliaktiivisuutta, tapahtui yhteyksien rauhoittumista. Muutokset toiminnanohjaustaidoissa korreloivat frontoparietaalisen verkoston sisällä sekä oletustilaverkoston ja sensorimotoristen verkkojen välillä tapahtuviin funktionaalisten muutosten kanssa.

Kokonaisuudessaan nämä tulokset osoittavat, että aivovamman jälkeen musiikkiterapia kohentaa toiminnanohjaustaitoja mukaan lukien yleistä toiminnanohjausta, kognitiivisen prosessoinnin joustavuutta sekä käyttäytymisen säätelyä ja nämä muutokset ovat yhteydessä aivojen rakenteellisiin ja toiminnallisiin neuroplastisiin muutoksiin. Nämä uudet tulokset tukevat musiikkiterapian hyödyntämistä keskivaikeiden ja vaikeiden aivovammojen kuntoutuksessa.

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**Noelia Martinez-Molina and Sini-Tuuli Siponkoski contributed equally to the work (shared 1st authorship).*

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ABBREVIATIONS

ANOVA	Analysis of variance
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult version
CER	Cerebellar network
DAI	Diffuse axonal injury
DAN	Dorsal attention network
DMN	Default mode network
DTI	Diffuse tensor imaging
EF	Executive functioning
FAB	Frontal Assessment Battery
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional MRI
FMT	Functionally-Oriented Music Therapy
FPN	Fronto-parietal network
FWE	Family-wise error
GCS	Glasgow Coma Scale
GMV	Grey matter volume
GOSE	Glasgow Outcome Scale Extended
ICA	Independent component analysis
IFG	Inferior frontal gyrus
INS	Insula
ITT	Intention-to-treat
LAN	Language network
LMM	Linear mixed model
MAR	Missing at random
MOFC	Medial orbitofrontal cortex
MRI	Magnetic resonance imaging
MST	Music supported therapy
NLT	Number-Letter Task
NMT	Neurologic music therapy
PP	Per protocol
PTA	Posttraumatic amnesia
PTSD	Posttraumatic stress disorder
RCT	Randomized controlled trial
ROI	Region of interest
R2R	ROI-to-ROI
rsFC	Resting-state functional connectivity
rsMRI	Resting-state magnetic resonance imaging
RSNs	Resting-state networks
SAL	Salience network
SART	Sustained Attention to Response Task

SBC	Seed-based connectivity
SD	Standard deviation
SM	Sensimotor network
sMRI	Structural magnet resonance imaging
TBI	Traumatic brain injury
TP1	Time point 1 (baseline)
TP2	Time point 2 (3-month stage)
TP3	Time point 3 (6-month stage)
TP4	Time point 4 (18-month stage)
VBM	Voxel-based morphometry
VIS	Visual network
QoL	Quality of life
QOLIBRI	Quality of Life after Brain Injury

1 INTRODUCTION

1.1 TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a major cause of disability across all ages. Over 50 million people have a TBI each year worldwide. (Maas et al., 2017). Importantly, a high percentage of TBI survivors are from young age groups (<25 years) and the injury often has a profound effect on their future lives (Maas et al., 2017; Peeters et al., 2015). Particularly severe and moderate injuries can cause lifelong impairments, which extend from physical symptoms and fatigue to cognitive, emotional and behavioral impairments (Cantor et al., 2013; Dikmen et al., 2013; Hoofien et al., 2001; Langlois et al., 2006).

TBI is defined as an alteration of brain functioning, or other evidence of brain pathology, caused by external force (Menon et al., 2010). The leading causes of TBI are falls and traffic accidents (Peeters et al., 2015). Traditionally, the severity level of TBI has been classified to range from mild and moderate to severe, based on the initial clinical information. However, there are currently no refined, universal criteria for this classification (Maas et al., 2017). Glasgow Coma Scale (GCS), which describes the level of consciousness, is currently the most used approach although it has some considerable limitations, including the effect of confounding factors such as sedation to the evaluation (Maas et al., 2017). Additionally, the use of posttraumatic amnesia (PTA), alteration of consciousness/mental state and presence of brain imaging findings as a basis of evaluation have also been suggested (Department of Veterans Affairs, 2016). Severe TBI has a high mortality rate (30-40%) and a substantial risk for unfavorable outcome (Maas et al., 2017; Rosenfeld et al., 2012). Long-term consequences have been recognized also in a marked proportion of cases primarily classified as moderate or mild (Stocchetti & Zanier, 2016; Yamamoto et al., 2018).

1.1.1. COGNITIVE, BEHAVIORAL, AND EMOTIONAL SYMPTOMS OF TBI

Clinical manifestations of TBI depend on a variety of factors, including the type, intensity, direction, and duration of the external forces impacting the brain (Maas et al., 2017). Typically, TBI leads both to focal and diffuse injuries, which disrupt the functioning of the frontal lobes and give rise to cognitive, behavioral, and emotional symptoms linked to TBI (Cicerone et al., 2006; Stuss et al., 2011). Mental fatigue is common, and it can exacerbate the consequences of neuropsychological deficits (Azouvi et al., 2017).

Cognitive impairments vary across patients, but most deficits are in the domains of attention, memory, communication, and executive functioning (EF), which require integration of information processing across spatially distinct brain regions (Burgess et al., 2017; Ham et al., 2012; Maas et al., 2017; Sharp et al., 2014; Stuss et al., 2011). Given their clinical importance and profound effect on daily lives of the patients, the executive dysfunctions are often viewed as a core symptom of TBI. EF is a broad umbrella term referring to “high-level” cognitive processes that enable individuals to regulate their thoughts and actions during goal-directed behaviour (Friedman & Miyake, 2017). There is no consensus on the exact definition of the term, but various cognitive processes such as set shifting (switching from one task to another), inhibition (avoiding a dominant or prepotent response), and updating (continuously updating the contents of working memory) have been proposed as key components of EF (Friedman & Miyake, 2017). Additionally, a broader view integrating the regulation of emotions and social behaviour into the concept of EF has been suggested (Chan et al., 2008). According to this view, EF is divided into so called “hot” elements including for example decision making involving emotional and personal interpretation, and more traditional “cold” elements, which cover purely cognitive processes, such as planning and problem solving (Chan et al., 2008). Overall, EF seems to be central in integrating and appraising the environment in terms of cognitive, emotional and social significance (Wood & Worthington, 2017). On the level of everyday life, executive dysfunction typically appears in novel situations when it is not possible to rely on routines (Gilbert & Burgess, 2008) and can manifest itself as problems of planning, organizing, and prioritizing, lack of flexibility and impaired concept formation (Wood & Worthington, 2017). Impulsive behavior, problems of decision making, poor judgement and inability to learn from experience are also common behavioral consequences (Wood & Worthington, 2017).

Emotional symptoms are common after TBI, and the risk for developing psychiatric disorders, such as depression, anxiety, bipolar disorder, post-traumatic stress disorder (PTSD) and psychotic disorders, after TBI is twofold compared to healthy controls (Yeh et al., 2020). Biological factors, such as the involvement of the prefrontal cortex and other limbic and paralimbic structures, likely play an important role in mood disorders after TBI (Jorge et al., 2003). Additionally, prior psychiatric history and lack of social support are associated with higher risk and medium to high-level intensity rehabilitation with lower risk for developing psychiatric problems after TBI (Jorge et al., 2003; Yeh et al., 2020). Interestingly, it has been suggested that different coping strategies used by TBI patients may be modulated by their EF skills (Krpan et al., 2007), emphasizing the importance of supporting cognitive recovery in the treatment and prevention of emotional problems after TBI.

1.1.2. TBI AS A PROCESS OF NEURODEGENERATION AND RESTORATION

The pathological changes caused by TBI can be classified into primary and secondary injuries. Primary injuries are directly caused by the external forces and secondary injuries are the body's response to this, evolving over time. Most of the secondary injuries take place soon after the initial accident, but some processes can endure even for lifetime (Maas et al., 2017). TBI patients are in fact affected by neural "polypathology", including white matter degradation, neuronal loss, protein misfolding and persistent neuroinflammation (Stocchetti & Zanier, 2016). Accumulating evidence supports the view that the initial injury caused by TBI is followed over time by gradual loss of brain volume (atrophy), which can be quantified using volumetric MRI measures and has been associated with diffuse axonal injury (DAI) (Ding et al., 2008). In the chronic phase of moderate and severe TBI, the regions with gray matter volume (GMV) reductions have been detected in the frontal, temporal, occipital, and insular cortices, whereas white matter volume (WMV) loss has been observed in the corpus callosum, corona radiata, internal capsule, and brainstem (Cole et al., 2018). Importantly, also protective neurorestorative events, including neurogenesis, gliogenesis, angiogenesis, synaptic plasticity, and axonal sprouting, take place particularly during the first months after injury and have been linked to cognitive and motor recovery (Stocchetti & Zanier, 2016). On the behavioral level, a recovery plateau in cognitive recovery is typically reached within 6-18 months after the injury (Ruttan et al., 2018).

In summary, there is accumulating evidence that outcomes after TBI may change in the direction of both further recovery and progressive worsening (Stocchetti & Zanier, 2016). It has also been suggested that the neural changes taking place after TBI could be mediated by post-injury environmental factors, with cognitive disuse and environmental impoverishment contributing to poor recovery and negative neuroplasticity changes and environmental enrichment contributing to better recovery and positive neuroplasticity changes (de la Tremblaye et al., 2019; Miller et al., 2013; Tomaszczyk et al., 2014). This idea comes originally from animal research into environmental enrichment (Hebb, 1947), and it has also been applied in explaining cognitive decline in older adults as a result of self-reinforcing spiral of negative brain plasticity (Mahncke et al., 2006). Importantly, this view emphasizes the potential of rehabilitation in treatment of TBI in the acute phase and prevention of cognitive decline after TBI in the chronic stage.

1.1.3. TBI AS A PROBLEM OF NEURAL CONNECTIVITY

The pathological changes caused by TBI can be categorized into focal and diffuse injuries. Typical manifestations of the focal injuries include for example frontal and temporal contusions and hematomas (McGinn & Polvischock, 2016). Diffuse injuries are more scattered and can occur at numerous brain sites involving grey and white matter (McGinn & Polvischock, 2016). There are different pathological processes behind the changes linked to DAI, including axonal swelling/disconnection, and other damages to axonal populations leading to destructive and degradative processes (McGinn &

Polvischock, 2016). All in all, these changes lead to network/circuit dysfunction, which is characteristic of TBI across all severity levels. The development of advanced brain imaging techniques has allowed detailed study of these changes. Microstructural axonal injuries can be detected with diffusion tensor imaging (DTI), which explores structural connectivity in white matter pathways (Xiao et al., 2015). In turn, functional connectivity between different brain regions can be investigated with fMRI by exploring resting-state functional connectivity (rsFC), which is characterized by task-free spontaneous fluctuations in brain activity that occur synchronously across spatially distant regions (Hutchinson & Everling, 2012). These fluctuations are spatially organized into different resting-state networks (RSNs), which have different functional roles (Smith et al., 2009). The functional connectivity within these networks also reflect underlying changes in structural connectivity produced by DAI (Sharp et al., 2014).

rsFC studies of TBI patients have revealed both increases and decreases in network connectivity, including the default mode (DMN) and salience (SAL) networks as well as multiple sensory and cognitive networks across the spectrum of injury severity (Hillary et al., 2011b; Mayer et al., 2011; Sharp et al., 2011; Shumskaya et al., 2012; Stevens et al., 2012; Stevens et al., 2012; Vakhtin et al., 2013). In several cases, these abnormalities correlated with post-concussive symptoms (Hillary et al., 2011b; Stevens et al., 2012) and cognitive impairment (Zhou et al., 2012), suggesting that they are closely linked to functional recovery after TBI.

Despite the complex abnormalities of interactions within and between RSNs following TBI, it is possible to identify some distinctive patterns. Within networks, reduced rsFC between the nodes of the DMN predicts attentional impairment (Bonnelle et al., 2012). The temporal coordination between networks, which is important for efficient high-level cognitive function, has also shown consistent abnormalities after TBI. According to an influential model of cognitive control (Sharp et al., 2010), the switching from automatic to controlled behavior is mediated by the interaction between the SAL and DMN networks, including deactivation of the DMN when directing attention to unexpected external events. Indeed, TBI patients exhibit a failure to appropriately deactivate the DMN, which is associated with impaired response inhibition to a stop signal (Bonnelle et al., 2012).

The paradoxical yet well-documented finding that functional connectivity may increase secondary to TBI (Bharath et al., 2015; Hillary, et al., 2011a; Hillary et al., 2011b; Mayer et al., 2011; Sharp et al., 2011; Hillary et al., 2014; Iraji et al., 2015; Johnson et al., 2012) has given rise to the “hyperconnectivity” hypothesis to explain the evolution of brain network reorganization after neurological disruption (Hillary & Grafman, 2017). Although this hyperconnected state may be adaptive in the short term by reestablishing network communication through network hubs, Hillary and Grafman (2017) have argued that it may also have negative consequences due to the chronic enhancement of brain resource utilization and increased metabolic stress. In support of this view, abnormal functional connectivity has been associated with increased self-reported fatigue, which is a highly common and debilitating symptom after TBI (Nordin et al., 2016; Ramage et al., 2019). Over a longer period of time, this hyperconnectivity may even lead to late pathological complications, including Alzheimer's disease (Mortimer et al., 1991; Nemetz et al., 1999), where amyloid beta deposition has been linked to the neurodegeneration of posterior DMN hubs with high metabolic rate (Buckner et al., 2009; Myers et al., 2014; Vlassenko et al., 2010).

1.1.4. TRADITIONAL APPROACHES TO TBI REHABILITATION

Rehabilitation after TBI is a complex process and must be adjusted individually to meet the needs of the patient (Maas et al., 2017). Time since injury, nature of TBI, premorbid functioning and level of social support along with injury severity are all important background factors contributing to the planning of rehabilitation. Receiving appropriate information and follow-up are often sufficient after milder injuries, whilst more intensive rehabilitation after moderate and severe injuries is needed (Turner-Stokes et al., 2015). Right timing and sufficient intensity of the treatment play an important role (Turner-Stokes et al., 2015). There is a lack of randomized controlled trials (RCTs) in TBI rehabilitation, partly due to the complexity and length of the process and ethical considerations (Maas, 2017). Given the diversity of the consequences of TBI, a comprehensive, holistic approach to rehabilitation delivered by a multidisciplinary team in close interaction with the patient and family is considered most fruitful (Cicerone et al., 2019; Maas et al., 2017). Traditionally, these therapies include neuropsychological/cognitive rehabilitation in addition to physical, occupational and speech therapy. Main challenges in the rehabilitation process typically arise from the core symptoms of TBI; fatigue may limit possibilities for intensive training, and deficits in EF may result in problems of initiation and motivation and reduce the patient's ability to transfer activities to daily life (Marin & Wilkosz, 2005).

1.2 MUSIC AS A REHABILITATION TOOL

Given the substantial burden caused by TBI on individual survivors, their families, and the whole society, new effective rehabilitation methods are urgently needed. Considering the heterogeneous and complex nature of TBI, there is a need especially for motivating rehabilitation tools that are able to address multiple deficits simultaneously, especially targeting EF. Compared to more traditional approaches, music combines cognitive, motor, emotional and social elements in a unique fashion and provides a multimodal approach in itself. Importantly, music is intrinsically motivating because it is recruits the brains reward system (Blood & Zatorre, 2001; Koelsch, 2014; Zatorre &

Salimpoor, 2013), which supports initiation and commitment to therapy. Moreover, music aids in regulating arousal and vigilance (Greene et al., 2010, Särkämö & Soto, 2012) and may therefore be beneficial for TBI patients with fatigue. Unlike other therapies, which often focus mainly on the problems brought by the injury and relearning of lost abilities, music therapy centers on positive action and learning of new skills. Although both approaches are needed, music therapy can be an empowering experience and serve as a counterbalance in the recovery process.

1.2.1 MUSIC IN THE BRAIN

Music is a very complex and rich stimulus, which has been an important part of all known cultures throughout history and is therefore an inherently human activity. We have a natural interest and a well-developed set of skills for processing music, starting already from infancy (Zatorre et al., 2005). Music is interesting from the point of view of neuroscience due to its' diverse demands on the brain. Mere music listening leads to widespread brain activations in the healthy brain (for a review, see Särkämö et al., 2013): First, the acoustic signal from the inner ear is transferred to the brain stem for initial analysis of basic features of the sound, and further to the thalamus and the primary auditory cortex where more detailed analysis of the acoustic elements, such as frequency, pitch, sound level, temporal variation, motion, and spatial location, takes place. Additionally, the activation is simultaneously spread to limbic areas, including the amygdala and the medial orbitofrontal cortex, which are linked to the emotional experience induced by music. Upon the initial coding and perception, music listening leads to more complex cognitive, motor, and emotional processes in the brain. Importantly, keeping track of music requires attention and working memory and activates the prefrontal cortex (Zatorre et al., 1994; Janata et al., 2002). Familiar music also activates long-term memory systems, including the hippocampus (Janata, 2009; Platel et al., 2003). Rhythm perception requires the recruitment of sensory-motor networks of the brain, including areas in the cerebellum, basal ganglia and motor somatosensory cortices (Grahn & Rowe, 2009; Zatorre et al., 2007). Listening to emotionally touching and particularly chill-evoking music engages deep limbic and paralimbic areas and particularly the dopaminergic pleasure or reward network (Blood & Zatorre, 2001; Koelsch, 2010).

Active music making by instrument playing or singing leads to further activation of the brain, requiring the precise timing, sequencing and spatial organization of actions coordinated by the cerebellum, basal ganglia, premotor and supplementary motor areas, and prefrontal cortical regions (Zatorre et al., 2007). Several studies have shown that musical training is associated with structural and functional changes in the brain (e.g., Habibi et al., 2018; Hyde et al., 2009). Although these effects are more fundamental when the training starts early in life and is long-lasting (Vaquero et al., 2015, 2020), positive effects of musical training on brain plasticity have been detected even in late adulthood (Bugos et al., 2006; Guo et al., 2021). Importantly, behavioural and neuroimaging studies in healthy individuals have revealed that musical training enhances EF and the recruitment of the cognitive control network (Bugos et al., 2007; Carpentier et al., 2016; Habibi et al., 2018; Jasche et al, 2018; Moradzadeh et al., 2015; Moreno et al., 2011; Putkinen et al., 2015; Sachs et al., 2017; Strong et al., 2019; Zuk et al., 2014), raising the question of whether music-based interventions could have similar positive effects on the executive dysfunction experienced by TBI patients.

1.2.2 MUSIC IN NEUROLOGICAL REHABILITATION

The evidence supporting the positive effects of music interventions on cognitive functions continues to accumulate; for example, daily music listening can enhance attention and verbal memory after stroke (Särkämö et al., 2008). Music also holds the potential to support motor functions in neurological disorders. Playing-based music interventions, such as Music-Supported Therapy (MST) have been shown to enhance fine and gross motor skills and also promote auditory and motor neuroplasticity in chronic stroke patients (Amengual et al.., 2013; Bradt et al., 2010; Ripollés et al., 2016; Rodriguez-Fornells et al,2012; Rojo et al., 2011; Schneider et al., 2010). Importantly, some of these studies suggest that experience-dependent plasticity driven by musical training could also take place in patients with brain injury at the chronic stage. Although these studies have been conducted with stroke patients, a similar process could potentially take place after TBI and requires further investigation. In addition, music-based interventions have previously shown to enhance mood and quality of life (QoL) in patients with neurological disorders (Raglio et al., 2015; Särkämö et al., 2008). Collectively, this evidence suggests that music therapy holds much potential in the rehabilitation of cognitive, motor, and emotional deficits after TBI in a rich, motivating, and versatile way.

1.2.3 MUSIC AND TBI

To date, most of the music rehabilitation studies conducted with neurological patients have concentrated on other patient groups, particularly stroke patients (Magee et al., 2017). The effects of music-based interventions after TBI have been largely unexplored and the use of controlled research paradigms has been rare.

In early stages of recovery after TBI when patients are in a minimally conscious or comatose state, studies have shown that music-based interventions can support awareness and arousal and decrease agitation (Baker, 2001; Formisano et al., 2001; Froutan et al., 2020). At later recovery stages, only few studies have evaluated the efficacy of music-based interventions on cognitive recovery using a pure sample of TBI patients. Thaut and colleagues reported positive intervention effects of neurologic music therapy (NMT) on EF (mental flexibility) in a quasi-experimental study (n = 31) (Thaut et al., 2009). Lynch and LaGlasse conducted a small-scale feasibility study on Musical Executive Function Training (MEFT) on EF in persons with brain injury (n = 14) (Lynch & LaGasse, 2016). A trend toward enhancement of mental flexibility was detected, although these findings were not significant. In a more recent study, Vik et al. (2018) reported results from a piano training intervention on mild TBI patients (n = 7) and healthy participants (n = 11) compared to group of healthy controls (n = 12). They found improvement in verbal memory performance after the piano training in both intervention groups compared to control condition. The Cochrane review on music interventions for acquired brain injury (Magee et al., 2017) additionally mentions two small-scale randomized controlled trials by Pool (2012) and Mueller (2013) with acquired brain injury samples, also including participants with TBI. The study of Mueller exploring the effect of NMT on endogenous task shifting (n = 15) yielded inconclusive results. Pool found positive effects of NMT on sustained attention, memory recall as well as emotional functioning (n = 10). All the studies mentioned above relied on neuropsychological test performance to demonstrate the cognitive effects of music therapy. Therefore, a complementary, more ecologically valid assessment of intervention effects at the level of daily living is still lacking (Gioia & Isquith, 2004).

There are some studies mapping the effects of music on emotional wellbeing, QoL, and social functioning after TBI. However, the sample sizes are relatively small and no randomized controlled trials (RCT) targeting the TBI population alone have been reported. All of the studies focusing on the effects of music-based interventions exclusively on TBI report some positive effects on mood and emotional well-being: Thaut et al. reported positive effects of NMT on self-reported mood and self-efficacy (n = 31) (Thaut et al., 2009), Guetin et al. found significant short-term improvement in mood and reduction in anxiety and depression symptoms followed by individual music therapy in institutionalized TBI patients (n = 13), (Guetin et al., 2009) and Baker et al. (n = 4) described positive long-term changes in various mood states after a song singing programme (Baker et al., 2005; Baker & Wigram, 2004).

Studies using more heterogeneous samples, including patients with different neurological illnesses, have revealed a similar pattern of results. Baker et al. (2019) found that a song writing intervention significantly improved life satisfaction (RCT with acquired brain injury or spinal cord injury, n = 47) (Baker et al., 2019), and their earlier study (Baker et al., 2015) suggested that a song-writing program could support emotional adjustment after injury (acquired brain injury including TBI or spinal cord injury, n = 10) (Baker et al., 2015). Nayak et al. (2000), who implemented a group-based music therapy intervention (4-10 sessions) including instrumental improvisation and playing together in acute rehabilitation setting, reported a trend towards improvement in self- and family-reported mood following a music therapy intervention (stroke and TBI, n = 18). Furthermore, the intervention group showed a significant improvement in the family members' assessment of the participants' social interaction. Magee & Davidson (2002) reported significant difference in pre- and post-music therapy intervention (2 individual music therapy sessions) regarding various mood states (composed-anxious, energetic- tired, agreeable-hostile) in a single-subject design (TBI, multiple sclerosis, stroke or anoxia, n = 14) and Pool (TBI and stroke, n = 10) also found significant effect of NMT on various emotional needs, including feeling confident, productive/useful, supported, valued, part of a group, and enjoyment (Pool, 2012). Roddy et al. (2020) have further explored the feasibility of a song-writing intervention with neurological patients in a descriptive case series study, particularly from the point of view of self concept (TBI and stroke, n = 5). The study revealed a link between the functional progress and gains in self-concept and subjective wellbeing of the participants, which support the use of individualized songwriting with neurological patients.

All in all, the results from previous studies suggest that music could support both cognitive recovery, social functioning, and emotional adjustment after TBI. However, the evidence is limited by the lack of RCTs and the fact that most studies have been conducted using small and often heterogeneous samples, including also other types of brain injuries than TBI. This is understandable considering the challenges in recruiting study participants. Nevertheless, a more detailed picture of the efficacy of music-based interventions after TBI is clearly needed. The characteristics of both the injury and sociodemographic variables are different between for example survivors of stroke and TBI patients (Feigin et al., 2010; Kunz et al., 2010). Therefore, the circumstances and goals of the rehabilitation also differ from each other. TBI often leads to life-long disabilities in young people, causing considerable challenges in their daily lives and affecting their personal and vocational choices.

When evaluating the effects of the treatment, a multilevel approach should be adopted, assessing cognitive recovery, and functioning on the level of daily life and social activities, in addition to emotional adjustment. Furthermore, aside from using objective measures to evaluate the person's level of functioning, it is paramount to also explore subjective rehabilitation experiences. This can lead to a better understanding of motivational factors that enhance engagement and the rehabilitation process as a result (Prigatano, 2011; Teasdale et al., 1997).

2 AIMS OF THE STUDY

This thesis explores the efficacy of neurological music therapy in TBI rehabilitation from different behavioral and neural perspectives.

Study I aimed to examine the effects of the music therapy on cognitive and neural recovery using neuropsychological tests and structural MRI. We hypothesized that music therapy would enhance EF and induce structural neuroplastic changes, especially in prefrontal brain regions that have been associated with EF.

Study II aimed to map the subjective experience of the intervention effectiveness regarding cognitive, behavioral, and emotional outcome by using questionnaire data and qualitative feedback from the patients and caregivers. We hypothesized that effects of music therapy on EF would be detected on the level of everyday life functioning. Additionally, we hypothesized that the intervention would support mood and QoL of the patients.

Study III aimed to investigate changes in functional connectivity linked to the intervention by using resting-state functional MRI. We hypothesized that neurological music therapy would enhance coordinated activity between attention and executive function (DAN, FPN) supporting networks and sensory networks that are engaged during the music therapy, and that the intervention would elicit reduced connectivity of nodes within the SAL, DMN and FPN networks as a sign of reduced hypoconnectivity.

3 METHODS

3.1 STUDY DESIGN

Forty TBI patients from the Helsinki and Uusimaa area were recruited through the Brain Injury Clinic of the Helsinki University Central Hospital (HUCH), Validia Rehabilitation Helsinki, and the Department of Neurology of Lohja hospital during 2014-2017 to this RCT (trial number: NCT01956136). The inclusion criteria were: 1) diagnosed (ICD-10) TBI fulfilling the criteria of at least moderate severity (Glasgow Coma Scale: ≤ 12 p and/or posttraumatic amnesia (PTA) ≥ 24 hours); (Traumatic brain injury: Current guidelines, 2008) 2) time since injury ≤ 24 months at the time of recruitment; 3) cognitive symptoms caused by TBI (attention, executive function, memory); 4) no previous neurological or severe psychiatric illnesses or substance abuse; 5) age 16-60 years; 6) native Finnish speaking or bilingual with sufficient communication skills in Finnish; 7) living in the Helsinki-Uusimaa area; and; 8) understanding the purpose of the study and being able to give an informed consent. Clinical and sociodemographic characteristics of the patients are presented in Table 1 in the Results section.

No power analysis was conducted due to the exploratory nature of the study; there are no previous studies on similar music interventions in this particular patient population that would provide a reliable reference for effect size evaluations. Our sample size target (n = 40) was set in order to gather a representative sample within a reasonable time window. The trial was conducted according to the Declaration of Helsinki and was consistent with good clinical practice and the applicable regulatory requirements. The trial protocol was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (reference number 338/13/03/00/2012), and all participants signed an informed consent.

The study was a cross-over RCT with a 6-month follow-up period. Upon recruitment, subjects were randomly assigned to one of two groups, AB (n = 20) and BA (n = 20). Randomization was performed using an online random number generator (https://www.random.org/) by a person not involved in patient recruitment or assessments. To ensure steady allocation to both groups across the trial, the randomization was done in batches of two consecutive patients. The randomization was stratified for lesion laterality (left / right / bilateral). During the first three months, the AB group received neurological music therapy in addition to standard care whereas the BA group received only standard care, which included different combinations of physiotherapy, occupational therapy, neuropsychological rehabilitation, or speech therapy, depending on the individual rehabilitation plan of the patient. During the second 3-month period, the BA group received the music therapy intervention and standard care and the AB group received only standard care.

Measurements, including neuropsychological tests, MRI scans and questionnaires, were administered at time point 1 (TP1) and follow-up measurements were conducted at the 3-month cross-over point (TP2) and at the 6-month completion point (TP3). At the final 18-month follow-up (TP4, one year after completion of the 6-month study period), all participants were once again contacted to complete the questionnaires and a subjective evaluation of the music therapy. The research personnel conducting the behavioural tests and MRI scans was blinded regarding the group allocation of the participants. The subjects and their caregivers were informed about the blinding procedure and were instructed to discuss therapy-related issues only with the music therapists.

The flow chart of the included TBI patients is shown in Figure 1. During 2014-2017, 4994 TBI patients were screened for eligibility, 190 met the inclusion criteria, and 40 were randomized to the AB and BA groups. Of these, one participant dropped out before the baseline measurements, two participants dropped out before TP2, and another three participants dropped out before TP3. The drop-outs were mainly due to lack of energy and motivation. All of the drop-outs (n=6) occurred in the BA group which was likely linked to the long waiting period before the intervention. Of these, only one occurred during the music therapy intervention, the remaining five took place before the onset of the intervention. Compared to the rest of the BA group, the subjects who dropped out had lower education level, longer posttraumatic amnesia, and worse injury outcome according to Glasgow Outcome Scale Extended (GOSE). MRI was not possible to perform in 8 participants due to contraindications or technical difficulties during the scanning.

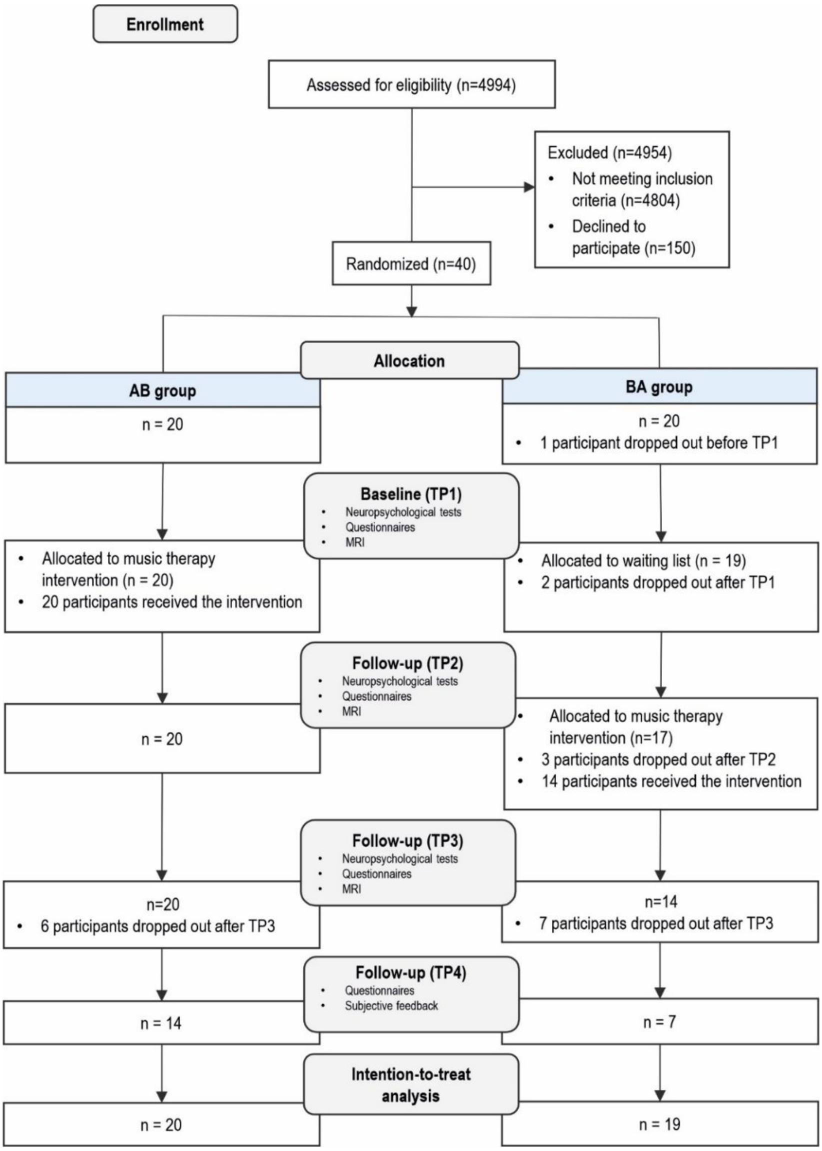

Figure 1. Flow chart outlining the design and progress of the trial.

3.2 INTERVENTION

The neurological music therapy intervention was targeted primarily for the (i) rehabilitation of cognitive deficits, especially of executive function, attention, and working memory, with a secondary goal of enhancing (ii) mood and emotional adjustment and (iii) upper extremity motor functions. The intervention model was adapted from two existing music therapy methods: Functionally-Oriented Music Therapy (FMT) (https://www.fmt-metoden.se/fmtsiteng/index.html) and Music-Supported Training (MST) method, which have both been applied in stroke rehabilitation (Schneider et al., 2010; Rodriguez-Fornells at al., 2012; Schneider et al., 2007). Since the music therapy literature covering TBI is scarce, methods proven efficient in other neurological patient groups were utilized in planning of the intervention and were modified using the existing scientific knowledge and clinical experience in TBI rehabilitation. Importantly, the intervention required no previous musical experience and was adaptable to different types of TBI patients depending on the level of injury.

The intervention consisted of 20 individual therapy sessions (2 times/week, 60 min/session) held by a trained music therapist at Validia Rehabilitation Helsinki. Each session included three modules (20 min each): (i) rhythmical training, (ii) structured cognitive-motor training, and (iii) assisted music playing (Figure 2). *Rhythmical training* involved playing sequences of musical rhythms and coordinated bimanual movements using hands on a djembe drum and on one’s own body (e.g., drumming knees and shoulders). *Structured cognitive-motor training* involved playing musical exercises on a drum set with varying levels of movement elements and composition of drum pads and drumsticks, accompanied with piano by the therapist. *Assisted music playing* comprised of learning to play the participant’s own favorite songs on the piano with the help of the therapist and using Figure Notes (https://www.figurenotes.org/ what-is-figurenotes), a special musical notation system utilizing colours and shapes originally developed in Finland, which makes music playing easily accessible without prior musical education. During all training, the therapist provided a visual and auditory model, and the participants were encouraged to make their own observations of their playing. When the participants were able to produce a certain rhythmical entity or melody, the therapist would add musical accompaniment. Emphasis was on musical, non-linguistic communication, in which the auditory feedback from the therapist was essential. Additionally, playing familiar songs on the piano using Figure Notes, provided an intuitive, direct form of feedback for the participants.

The training was increasing in complexity in all areas, and the difficulty level was adjusted for each participant according to a clear protocol. Importantly, the intervention did not require prior musical training, and the difficulty level of the exercises was initially adjusted and increased in a stepwise manner within and across the sessions to meet the skill level and progression of the individual participant. In addition, musical improvisation was included in all modules and encouraged throughout the therapy to provide a means of emotional expression. This was implemented through encouraging the participant to create individual playing styles and techniques of drumming and creating own rhythms in drum playing and melodies in piano playing, while the therapist provided a safe background through playing e.g., beat or chord progression. The therapist also adjusted the accompaniment to the musical ideas expressed by the participant to reinforce and validate them. The participants took part in choosing their favorite music for the sessions and on the level of performance, adjusted dynamics, tempo, and rhythm according to their individual style. All in all, the training performed during the intervention tapped into a number of executive (action planning and monitoring, inhibitory control, shifting), attentional (focused attention, spatial attention, vigilance), and working memory (updating) as well as motor (motor control, eye-movement coordination) and emotional (affect regulation, emotional expression) functions.

Figure 2. The three modules of the music therapy intervention.

3.3 BEHAVIORAL OUTCOME MEASURES

3.3.1 NEUROPSYCHOLOGICAL TESTS

During the recruiting process, both the Glasgow Outcome Scale Extended (GOSE) (Wilson et al., 1998) and the Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI) (Wilde et al., 2010) were administered in order to obtain information of the overall symptoms and current functional outcome after TBI. The effects of the intervention were evaluated by using neuropsychological and motor test batteries and structural MRI, administered at three time points (TP1, TP2, and TP3). The neuropsychological assessments were conducted by a licensed psychologist and each testing session lasted approximately 2 hours. Motor testing was performed by a physiotherapist / occupational therapist and it took approximately 45 minutes. All behavioral testing sessions took place at Validia Rehabilitation Helsinki in a quiet test room. The participants had the opportunity to take a short break during the sessions if needed.

Our primary outcome measure in the cognitive test battery was change in performance on the Frontal Assessment Battery (FAB) (Dubois et al., 2000). FAB measures different aspects of frontal lobe functions. It consists of six subtests exploring conceptualization (similarities subtest), mental flexibility (lexical fluency), motor programming (Luria's fist-edge-palm test), sensitivity to interference (conflicting instructions), inhibitory control (go-no go task), and environmental autonomy (prehension behaviour). FAB has previously been shown to be sensitive to TBI-related cognitive changes and it has a good test-retest reliability (Rojas et al., 2019; Nakaaki et al., 2007). The FAB total score (percentage correct) formed the composite score of EF, as the measure is designed to assess global EF and it is applicable through various severity levels of TBI.

Other cognitive and motor tests were defined as secondary outcome measures. Cognitive tests included computerized tests of EF and sustained attention, as well as measures of reasoning and verbal memory. Parallel versions of memory tests were used in different time points to minimize practice effects. The computerized tests of EF were chosen to reflect different aspects of EF (set shifting, updating, inhibition) defined by Miyake et al. (2000). They were regarded as secondary measures since they reflect more narrow aspects of EF compared to the FAB.

Set shifting was assessed by the Number-Letter Task (NLT) (Martin et al., 2012). In this computerized test, a number-letter combination appeared in one of two squares (top/bottom) in the centre of the screen and the subject was instructed to make a decision either based on the number or the letter by pressing one of two buttons. The task was divided into three blocks, each preceded by a short practice phase. In the first block (32 trials), all of the stimuli appeared in the top box and the task was to determine whether the number was odd or even. In the second block (32 trials), all of the stimuli appeared in the bottom box and the task was to determine whether the letter was a vowel or a consonant. In the third block, the stimuli randomly appeared in either of the squares, and the subject had to respond accordingly (make a decision based on the number if in the top square and based on the letter if in the bottom square). The third block had 32 switch trials (target different from the previous trial) and 48 non-switch trials (target same as in the previous trial). Switching costs for both reaction times and error percentages were calculated by comparing performance on switching and non-switching trials in the third block.

Updating was assessed by using a computerized Auditory N-back Task (Pallesen, 2010). The stimuli in this task consisted of three chords varying in their pitch (low/medium/high). The task was to determine if the stimulus was same/different compared to the previous stimulus (1-back) or the stimulus before that (2-back) by pressing one of two buttons. The task was divided into 4 blocks of 25 trials (two 1-back blocks and two 2-back blocks). The 1-back blocks were presented first, followed by the 2-back blocks. A short practice phase preceded both conditions.

Inhibition was assessed with the Simon Task (Martin et al., 2012; Simon, 1967). In this computerized task, a blue or a red square appeared either on the left or the right side of the screen. The instruction was to press the right button each time a red square appeared and the left button each time a blue square appeared, irrespective of which side the square was presented on. On congruent trials, the response button was on the same side as the square; on incongruent trials, it was on the opposite side. There were 100 trials (50 congruent, 50 incongruent). The Simon effect was calculated by comparing congruent and incongruent trials, reflecting the cost of irrelevant spatial information on reaction time and number of errors. A short practice phase preceded the task.

Sustained attention was assessed by using the Sustained Attention to Response Task (SART) (Robertson et al. 1997). In this computerized task, digits ranging from 1 to 9 are presented on a screen in a random order. Each digit was presented for 149 ms, followed by a 900-ms mask. The task was to respond to every other digit except digit "3" by pressing a response button. The original SART task consists of 225 digits, of which 25 digits are targets (3). For the purpose of this study, we created a version of the test with 450 digits including 50 targets (length approximately 8.6 min), in order to better detect TBI-related problems of sustaining attention over a long period of time. A short practice phase preceded the task. Both omissions and commissions in the SART were included in the analysis, since together they provide a more complete picture on the performance, reflecting inhibition errors as well as lapses of attention (Johnson et al., 2007). We also analyzed vigilance decrement during the task by comparing error rates and reaction times during the first and second halves of the task (Whyte et al., 1995).

For the other secondary outcome measures, which consisted of standard clinical tests, we formed composite scores of individual test measures (mean percentage of correct answers in all the measures included) to pool data and reduce the number of variables. Reasoning was assessed by using the Similarities and Block design subtests of the Wechsler Adult Intelligence Scale IV (Wechsler, 2008). Verbal memory was assessed by using the Word Lists I and II subtests of the Wechsler Memory Scale III (WMS-III) (Wechsler, 1997) and the Digit Span subtest of WAIS-IV (Wechsler, 2008).

3.3.2 MOTOR TESTS

Motor tests were used to evaluate fine and gross motor functioning, dexterity, and coordination of the upper limbs. These skills were assessed with the Box and Block test (Mathiowetz et al., 1985), the Action Research Arm Test (Lyle et al., 1981), and the Purdue Peg Board Test (Tiffin et al., 1948; Buddenberg et al., 2000).

3.3.3 QUESTIONNAIRES

3.3.3.1 Measures of executive function (EF), mood and quality of life (QoL)

As we were mainly interested in the intervention effects in EF, we defined Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A) as our primary questionnaire outcome measure (Roth et al., 2005). This questionnaire was given to the TBI patient (self-report version) and their caregiver (informant-report versions) to assess possible changes in EF. BRIEF-A is a 75-item scale that consists of nine subscales: Inhibit, Shift, Emotional control, Self-monitor, Initiate, Working memory, Plan/Organize, Task Monitor and Organization of materials. A three-point scale is used for rating and a higher score indicates more problems. In the original measure, the subscales form two indices (Behavioral Regulation Index and Metacognition Index) which together form the Global Executive Composite Index. However, later research has suggested a three-factor model (Egeland et al., 2010). Donders & Strong (2016) studied the factor structure of BRIEF-A in TBI patients and found that the three-factor structure was particularly well fitting to the self-report data. Even the updated version of the questionnaire for children (BRIEF-2) has adopted this new factor structure (Jacobson et al., 2020). In the current study, we utilized three indices: Behavioral Regulation Index (comprising the Inhibit and Self-monitor scales), Emotional Regulation Index (comprising the Shift and Emotional control scales) and Metacognition Index (comprising the remaining scales). These indices together formed the Global Executive Composite Index.

The subjective experience of mood and QoL was assessed with questionnaires filled out by the TBI patient. The Beck Depression Inventory II (BDI-II) was used to evaluate the presence of depressive symptoms, with higher scores indicating more severe depression (Beck et al., 1996). Health-related QoL was assessed using the Quality of Life after Brain Injury (QOLIBRI), which is specifically designed for TBI patients (von Steinbüchel et al., 2010a; von Steinbüchel et al., 2010b; Siponkoski et al., 2013). The QOLIBRI consists of six scales: Cognition, Self, Daily Life & Autonomy, Social Relationships, Emotions, and Physical. The total score indicates the level of life satisfaction on a percentage scale.

3.3.3.2 Subjective experience of the therapy

At the 18-month timeframe (12 months after the initial 6-month study period), a questionnaire about the experienced benefits of the rehabilitation was sent to the TBI patients and their caregivers, along with the other measures (see above). The questionnaire included both a numeric rating (1-10) and an open-ended question inquiring the benefits of the music therapy intervention in the following domains: overall, cognitive, motor, emotional and quality of life (*How beneficial has the music therapy been for your / your relative's overall recovery / mood / quality of life / cognitive functioning (e.g. concentration, memory) / motor functioning (e.g. hand movements)? What benefits have you noticed?*) The aim of the questionnaire was to collect complementary information in a short and structured fashion along with the other questionnaires, according to the preset hypothesis. Additionally, ratings of the current musical activities and their intensity during the past 12 months were collected.

3.3.4 DATA ANALYSIS

3.3.4.1 Intention-to-treat analysis

Statistical analyses of the behavioural data were performed using SPSS (version 25) (IBM Corporation, 2017). In order to control possible bias introduced by missing data, an intention-to-treat (ITT) analysis was performed on the dataset of subjects who participated in the baseline measurement [neuropsychological data: n=39 (AB: n=20, BA: n=19); questionnaire data: n=38 (AB: n=20; BA: n=18)].

First, sporadic missing values from questionnaires were imputed by using the individual mean of the subscale based on the participant's other answers at the same measurement point. Missing observations were imputed from TP1 and TP2 using multiple imputation, which is considered to be a reliable method when handling data missing under various missingness mechanisms (van Ginkel et al., 2020). We found that there was a significant relationship between background variables (belonging to BA-group/delayed treatment start, longer PTA and worse injury outcome, lower education level) and missing values. Because the absolute amount of missing data was relatively small and most important cases were identified, we conclude that missing value structure was missing at random (MAR). Twenty parallel datasets, which is generally considered to be a sufficient number to reduce sampling variability from the imputation process, were created using fully conditional specification imputation method (Sterne et al., 2009; Huque et al., 2018). Due to the large amount of data, the imputation was carried out separately for 1) neuropsychological test data; 2) patient questionnaire data; 3) caregiver questionnaire data. All demographic and clinical background variables (see Table 1) in addition to group allocation and outcome variables were included in the model as predictors; categorical variables were included using dummycoding. Additionally in the caregiver data, characteristics describing the relationship of the caregiver and TBI patient were included as predictors in the model.

Linear mixed model analyses (LMM) were conducted for the multiply imputed data. The model included main effects and interaction between group (AB/BA) and time points. Random intercept model, which is a special case of the more general LMM framework, was used to account for the within subject variation. These analyses were performed using the method described by van Ginkel and Kroonenberg (2014), which involves reformulation of the ANOVA model as a regression model using effect coding of the predictors and applying existing combination rules for regression models in order to pool the F-tests. This procedure is equivalent to a repeated measures (mixed-model) ANOVA. Effect sizes were calculated based on the observed data using repeated measures ANOVA, because the LMM procedure does not produce ηp^2 values.

The main Group x Time interaction analyses were conducted between TP1 and TP2, because of the potential interfering carry-over effect in the AB group over TP2-TP3. However, TP1-TP2 provides a clear comparison between the intervention and control conditions. Significant findings were further assessed by conducting a within-subject repeated measures analysis (LMM/ANOVA) over the three time points separately for both groups to assess the possible longitudinal intervention effects. At TP4, 9 TBI patients had dropped out from the AB group, which is why longitudinal analysis was no longer conducted on this sample.

Finally, relationships between the significant findings from the neuropsychological tests and the questionnaire outcomes were explored with Pearson correlation analyses. Change scores over the intervention period (TP1-TP2 for AB, TP2-TP3 for BA) determined by ANOVA / MLL were used for these analyses. Additionally, the relationship with questionnaire outcome and mood as measured by BDI-II was assessed with Pearson correlation.

3.3.4.2 Per-protocol analysis

Given the uncertainty involved in performing data imputation in a relatively small sample like ours, we also performed a per-protocol (PP) analyses to verify the results from ITT analysis in a smaller dataset of subjects who adhered to the study protocol and participated in all measurements (White et al., 2012). One participant in the BA group reported having practiced piano intensively (3 hours/week), with both piano lessons and independent training at home, between TP1-TP2 and was therefore excluded from the PP analysis. In the neuropsychological data the sample size was 25 (AB: 16, BA: 9) because participation in all MRI-measurements were used as a criterion. In the questionnaire sample, which was reported separately, only participation in this part of the study was used as a criterion, leading to sample size of 35 (AB: 20, BA: 15). The PP analysis was limited to the outcome measures that yielded significant findings in the ITT analysis to assess their sensitivity.

3.3.4.3 Analysis of the subjective rehabilitation experiences

The subjective evaluations of the TBI patients (n = 20) and the caregivers (n = 14) regarding the benefits of the music therapy in different domains were compared with each other using paired sample t-tests. A repeated measures ANOVA was conducted across different domains to see if some of the values differed significantly from the other. This analysis was carried out separately for TBI patients and caregivers. A pairwise comparison using FDR-correction was conducted to determine which areas were experienced as more or less beneficial.

In the 18-month follow-up questionnaire, the TBI patients and the caregivers were asked to give written feedback regarding the experienced benefits of the intervention in five domains: Overall rehabilitation, Cognition, Motor, Mood, and QoL. The inquiry letters were sent by and returned to the two psychologists who conducted the neuropsychological assessments. The feedback was analyzed using a directed qualitative content analysis approach, since we had a clear theoretical hypothesis of the expected benefits of the intervention (effects on cognitive, motor, and emotional recovery) (Assarroudi et al., 2018). The method included coding answers into categories by developing a formative categorization matrix. Along with deriving pre-existing categories based on prior research, we also aimed to recognize new, emerging categories. First, the question regarding overall benefits of the therapy was analyzed by categorizing the answers into preset categories: Cognitive, Motor, Mood, QoL, Other benefits, and Overall no benefit. Since the answers in Mood and QoL were largely overlapping in the entire dataset, these were combined into one theme called Mood / QoL. In the next step of the analysis, the goal was to find more specific underlying categories within the large themes. At that point, we combined all the answers given to different questions into one categorizing matrix. In cases where the participant had mentioned a topic that would thematically best belong to another section, the answer was coded according to the content. All the themes mentioned in the Overall section were integrated into the other sections (Cognitive, Motor, Mood / QoL, Other benefits). Several themes could be coded from one participant’s answer. However, if the same participant produced answers belonging to the same category in answers to different questions (e.g., Overall and Cognitive), only one was considered in the final quantification. Rare answers were classified into categories “other positive”. “No experienced benefit” was reported when the participant did not experience benefit or was unsure of it. One answer was discarded because it was not legible.

The answers belonging to certain themes were quantified and the data was managed using SPSS (Vaismoradi et al., 2013). No feedback was gathered from the participants regarding the coding and interpretation because the analysis concentrated on the manifest content of the data and was anchored in the verbatim expression of the participants.

3.4 MRI DATA ACQUISITION

Patients underwent structural MRI (sMRI) and resting-state functional (rs-fMRI) scanning using an 8-channel SENSE head coil, in a 3T Philips Achieva MRI scanner (Philips Medical Systems) of the HUS Helsinki Medical Imaging Center at HUCH. In sMRI, high-resolution T1-3D images were obtained using a magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE sequence). Twenty-five patients completed the scanning sessions in the three time points (sMRI AB: n = 16, BA: n = 9; rs-fMRI AB: n = 15, BA: n = 8). Only patients with T1 images from TP1-TP2-TP3 were included in the analysis. Focal brain lesions were detected in 12 TBI patients. In rs-fMRI, images were acquired with a T2*-weighted image sequence. During the rs-fMRI acquisition, the patients were instructed to remain still, eyes open to a fixation cross to ensure vigilance.

3.5 MRI DATA PREPROCESSING

Data were preprocessed using a standard voxel-based morphometry (VBM) pipeline in Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, University College London) running under Matlab Release 2017a (VBM data) and Matlab Release 2018b (connectivity data) (The MathWorks, Inc., Natick, MA, US). As the presence of lesions may influence the normalization algorithm, cost function masks (CFM) were defined for the 12 patients with focal brain lesions to achieve optimal normalization with no post-registration lesion shrinkage or out-of-brain distortion (Brett et al., 2001). For the rs-fMRI -data we used denoising to minimize the variability due to white matter and cerebrospinal fluid signals, realignment parameters and motion outlier scanseffects.

3.6 VOXEL-BASED MORPHOMETRY (VBM)

Voxel-wise statistical analyses were performed in SPM12. Individual smoothed GM and WM images were entered into a second-level analysis using a Group (AB/BA) x Time (TP1/TP2/TP3) mixed-model ANOVA. Six different Group (AB>BA, BA>AB) x Time (TP2>TP1, TP3>TP2, TP3>TP1) interactions were calculated and a conjunction analysis was performed between AB>BA x TP2>TP1 and BA>AB x TP3>TP2 contrasts. Results are reported at a whole-brain uncorrected $p < 0.001$ threshold at the voxel level with a cluster extent of 50 contiguous voxels. The GMV values for the effect size were obtained from the peak coordinates of the right IFG cluster with the highest T value in each contrast. We performed a conjunction analysis in SPM (conjunction null) to assess the voxels with significantly different grey matter volume during the intervention period in the AB and BA groups.

After confirming a significant Group x Time interaction, we carried out other second-level analyses by pooling data from AB and BA groups: (i) before and after the intervention period using one-sample t-test (AB: TP2>TP1 & BA: TP3>TP2) and (ii) before and after the intervention vs. control period using a paired t test (AB: TP2>TP1 & BA: TP3>TP2 vs. AB: TP3>TP2 & BA: TP2>TP1). Additional individual smoothed GM and WM images were calculated as the difference between the two time points in the intervention and control periods (AB group: intervention: TP2-TP1 and control: TP3-TP2; vice versa for the BA group) to perform these analyses. Results are reported at a whole-brain uncorrected $p < 0.001$ threshold at the voxel level with a cluster extent of 50 contiguous voxels and an FWE-corrected $p < 0.05$ threshold at the cluster level. The GMV values for the effect size were obtained from the peak coordinates of the right IFG cluster with the highest T value in the intervention versus control contrast. In all second-level analyses, the intracranial volume (ICV) of each patient was entered as a nuisance covariate to account for inter-individual variability.

To examine brain-behaviour correlations, we performed a region-of-interest (ROI) analysis with all significant clusters in the IFG from the pairwise comparison and computed the mean value of the individual smoothed GM and WM difference images for the control and intervention periods for each group. Bivariate correlations using two-tailed Pearson's r tests were calculated between these values and individual scores from the behavioural measures that showed a significant effect in the pairwise comparisons (switching cost error rate in the NLT) separately for the intervention and control periods.

3.7 FUNCTIONAL CONNECTIVITY ANALYSIS

3.7.1 CONNECTIVITY PATTERN ANALYSIS WITHIN AND BETWEEN LARGE-SCALE NETWORKS AND LONGITUDINAL ANALYSIS OF SEED-BASED CONNECTIVITY

To further understand functional connectivity (FC) changes induced by the neurological music therapy from the perspective of large-scale networks, we used the 8 resting-state networks (RSNs) comprising 32 regions of interests (ROIs) or nodes in the CONN toolbox (https://www.nitrc.org/projects/conn), which are derived from an independent component analysis (ICA) of 498 subjects from the Human Connectome Project (Nieto-Castanon, 2020). The 8

RSNs included default mode (DMN), salience (SAL), frontoparietal (FPN), dorsal attention (DAN), sensorimotor (SM), language (LAN), visual (VIS), and cerebellar (CER) networks. All of these networks have been widely reported in the rs-fMRI literature. We identified changes in both between-network and within-network connectivity from those networks that have shown alterations after TBI (Sharp et al., 2014) or are associated with EF, memory, and attention, which are the most commonly affected cognitive domains in TBI patients (Sharp et al., 2014; Burgess & Stuss, 2017; Ham & Sharp, 2012; Stuss, 2011). In particular, we selected nodes from the DMN, SAL, FPN, and DAN networks to examine the FC within their nodes and between their nodes and all the RSN included in the CONN toolbox.

Based on the findings from our VBM analysis, we selected the statistically significant clusters in the right IFG from the intervention period analysis to assess their seed-based connectivity in resting state, because it was the only region to significantly correlate with therapy-induced EF improvement. The seeds included two clusters in the right IFG pars triangularis in standard space that were imported into the CONN toolbox to compute seed-to-voxel functional connectivity.

All group-level analyses were carried out in the CONN toolbox using the General Linear Model framework. In the ROI-to-ROI (R2R) analysis, we calculated Group x Time interactions (AB > BA × TP2 > TP1; BA > AB × TP3 > TP2) using a mixed-model ANOVA. To increase the statistical power, we also performed a paired T-test pooling data across groups (pre- and post-intervention effect for the AB and BA groups; AB: T2 > TP1; BA: TP3 > TP2). Furthermore, a paired t-test was performed during the control period (AB: T3 > TP2; BA: TP2 > TP1) to ensure that the changes in rsFC were specifically caused by the intervention. For the within-networks analysis, we examined the R2R connectivity of the ROIs within each of the selected four RSNs (DMN, SAL, FPN, and DAN). For the between-network analysis, we examined the connectivity between the ROIs of each of these RSNs (DMN, SAL, FPN, and DAN) with every other RSN included in the CONN toolbox.

In the SBC analysis, we performed a paired t-test post-intervention rsFC as the seeds were derived from two right IFG clusters obtained during the intervention period in the previous VBM analysis. For the AB group, the beta maps fromTP1 were entered as the pre-intervention condition and the beta maps from TP2 were entered as the post-intervention condition. For the BA group, the beta maps from TP2 were entered as the pre-intervention condition and the beta maps from TP3 were entered as the post-intervention condition. As in the R2R analysis, we additionally performed a paired t-test during the control period. The statistical parametric maps obtained were corrected for multiple comparisons based on Gaussian Random Field Theory (Worsley et al., 1996). The maps were first thresholded using a “height” threshold of $p < 0.001$ and the resulting clusters thresholded with a cluster-level False Discovery Rate- (FDR-) corrected p value of <0.05 (Chumbley et al., 2010).

3.7.2 RESTING-STATE FUNCTIONAL CONNECTIVITY AND COGNITIVE PERFORMANCE

We investigated the link between rsFC and cognitive performance improvements after therapy. To do so we performed Pearson's bivariate correlation analyses between, on one hand, ROI-to-ROI (R2R) FC changes (found significant in the main analyses), and on the other hand, neuropsychological tests measuring general EF (FAB total score), set shifting (NLT switching cost errors), and the Self-Monitor and Inhibition subscales of BRIEF-A, which together comprise the Behavioral Regulation index. The chosen performance measures were those which showed a statistically significant improvement after the music therapy. We used the increment between pre- and post-intervention for the correlation with the within-network FPN connectivity results and the increment between timepoints 1 and 2 for the between-network DMN connectivity results.

4 RESULTS

4.1 CHARACTERISTICS OF THE PARTICIPANTS

Background information regarding sociodemographic and clinical factors and musical experience is presented in Table 1. The only significant difference between the groups was detected in the deviation on causes leading to injury (p = 0.022). However, this difference was not considered to be of clinical importance, particularly because the traffic-related injuries involving higher energy and possibly a different recovery trajectory were evenly divided between the two groups. The amount of other rehabilitation (standard care) did not differ between the groups (Table 2). Also, the amount of received music therapy sessions was comparable between the groups: the subjects who participated in the intervention received a mean of 17.1 (standard deviation [SD] = 5.9) sessions of individual music therapy in the AB group and 17.6 (SD= 5.2) sessions in the BA group.

Table 1. Demographic, Clinical, and Musical Background Information, t = independent sample t-test; X^2 = chi square test; F = Fisher's exact test.

Demographic information	**All**	**AB**	**BA**	**Difference between groups (p)**
Age m (sd)	41.3 (13.3)	41.6 (14.7)	40.9 (12.0)	0.871 (t)
Gender (female / male)	16 / 23	10 / 10	6 / 13	0.242 (X^2)
Handedness (right/left/both)	37 / 1 / 1	19 / 0 / 1	18 / 1 / 0	1.000(F)
Education in years m (sd)	14.6 (3.2)	14.73 (2.8)	14.6 (3.6)	0.867 (t)
Clinical information				
GCS m (sd)	11.8 (4.2)	12.3 (3.6)	11.2 (4.7)	0.613 (U)
PTA classification[a] m (sd)	2.1 (1.1)	1.9 (1.1)	2.3 (1.0)	0.280 (t)
Cause of injury (traffic-related / fall / other)	16 / 15 / 8	8 / 11 / 1	8 / 4 / 7	0.022 (F)
Time since injury (months) m (sd)	8.9 (6.4)	8.6 (6.7)	9.2 (6.3)	0.772 (t)
Lesion laterality[b] (left / right / both)	7 / 2 / 26	4 / 1 / 14	3 / 1 / 12	1.0 (F)
Contusion[b] (yes / no)	23 / 15	13 / 6	10 / 9	0.508 (X^2)
DAI[b] (yes / no)	21 / 17	9 / 10	12 / 7	0.515 (X^2)
Hemorrages, bleeds or ischemic injury[b] (yes / no)	24 / 14	10 / 9	14 / 5	0.179 (X^2)
GOSE[c] m (sd)	5.2 (1.2)	5.0 (1.5)	5.5 (0.9)	0.192 (t)
NOS-TBI[d] m (sd)	2.0 (2.5)	2.2 (2.4)	1.8 (2.7)	0.385 (U)
BDI-II m[e] (sd)	14.2 (8.9)	15.8 (10.5)	12.3 (6.6)	0.229 (t)
Musical background				
Instrument playing (yes / no)	25 / 12	14 / 6	11 / 6	0.732 (X^2)
Years of playing m (sd)	4.2 (8.4)	4.8 (10.3)	3.5 (5.4)	0.613 (U)
Singing (yes / no)	17 / 20	11 / 9	6 / 11	0.231 (X^2)
Years of singing m (sd)	4.7 (9.9)	6.7 (12.7)	2.6 (5.3)	0.369 (U)
Dancing (yes / no)	20 / 17	12 / 8	7 / 10	0.254 (X^2)
Years of dancing m (sd)	6.1 (10.8)	6.3 (10.6)	5.8 (11.4)	0.546 (U)

[a] 1=mild (< 24 hours); 2=moderate (1-7 days); 3=severe (>7days); 4=very severe (>4 week); [b] Based on MRI-findings, [c] Glasgow Outcome Scale Extended; [d] Neurological Outcome Scale for TBI, [e] Beck Depression Inventory II.

Table 2. Amount of standard care rehabilitation in hours (60 min). In addition to traditional TBI therapies, four of the participants received some other therapy (e.g. psychotherapy), which were included in the overall sum of rehabilitation. The comparisons were conducted using Mann-Whitney U-test due to skewness of the data.

	Group	Physiotherapy	Occupational therapy	Neuropsychological rehabilitation	Speech therapy	Sum
T1	AB	11.9 (26.7)	5.2 (17.2)	11.4 (19.7)	4.4 (17.2)	33.9 (78.2)
	BA	16.3 (29.0)	8.4 (17.6)	10.8 (14.2)	10.8 (14.2)	40.5 (63.4)
p		0.490	0.589	0.452	0.502	0.415
T2	AB	3.8 (4.4)	2.2 (5.1)	2.5 (3.8)	0.8 (2.3)	9.3 (12.4)
	BA	3.2 (7.2)	2.1 (6.9)	2.9 (3.8)	3.2 (8.4)	11.0 (22.7)
p		0.290	0.873	0.896	0.837	0.630
T3	AB	2.2 (3.9)	0.5 (1.7)	3.0 (3.2)	0.4 (1.6)	6.2 (8.3)
	BA	1.7 (3.9)	1.1 (2.5)	1.5 (3.2)	0.0 (0.0)	4.2 (6.8)
p		0.711	0.711	0.187	0.824	0.334
Intervention period	AB	3.8 (4.4)	1.7 (3.8)	2.5 (3.8)	0.8 (2.3)	9.3 (12.4)
	BA	1.7 (3.9)	1.1 (2.5)	1.5 (3.2)	0.0 (0.0)	4.2 (6.8)
p		0.208	0.906	0.332	0.654	0.226
Control period	AB	2.2 (3.9)	0.5 (1.7)	3.0 (3.2)	0.4 (1.6)	6.2 (8.3)
	BA	3.2 (7.2)	2.1 (6.9)	2.9 (3.8)	3.2 (8.4)	11.0 (22.7)
p		0.970	0.720	0.799	0.681	0.911

4.2 EFFECTS OF MUSIC THERAPY ON NEUROPSYCHOLOGICAL TEST PERFORMANCE (STUDY I)

Intention-to-treat analyses. Following the ITT protocol, we first performed multiple imputation (see Methods section) to replace missing values for dropped-out patients and then carried out LMM in the whole sample (n = 39) with Time (TP1/TP2) as a within-subject factor and Group (AB/BA) as a between-subject factor for all the behavioral outcome measures to assess the short term (pre-post) effects of music therapy compared with standard care.

For the primary outcome (EF measured by FAB composite score), these analysis yielded a significant Time x Group interaction ($F_{1,29} = 4.374$, $p = 0.045$, $\eta p^2 = 0.093$), indicating a greater improvement in EF in the AB group than in the BA group (Figure 3A). For the secondary outcomes, set shifting (switching cost errors in the NLT) showed a significant Time x Group interaction ($F_{1,67} = 4.798$, $p = 0.032$, $\eta p^2 = 0.112$), with a larger reduction in switching cost error rate in the AB group than in the BA group (Figure 3B). There were no other significant Time x Group interactions. All of the LMM results between time-points 1–2 using the complete dataset are presented in Table 3.

To assess if the positive effects of music therapy on EF and set shifting were (i) maintained in the AB group longitudinally and (ii) seen also in the BA group after their intervention period, we performed repeated-measures ANOVA for the AB group and LMM for the BA group with Time (TP1/TP2/TP3) as a within-subject factor. In the AB group, there was significant Time main effect for EF ($F_{1,25} = 9.258$, $p = 0.003$, $\eta p^2 = 0.328$) but not for set shifting ($F_{2,38} = 1.854$, $p = 0.171$, $\eta p^2 = 0.089$). Bonferroni-corrected pairwise contrasts indicated that EF performance improved in the AB group from TP1 to TP2 ($p = 0.043$) and from TP1 to TP3 ($p = 0.003$), but not from TP2 to TP3 ($p = 0.990$), indicating that the EF enhancement was maintained longitudinally. Within the BA group, there was no significant main effect of time in FAB ($F_{2,28} = 0.498$, $p = 0.952$, $\eta p^2 = 0.016$) or switching cost ($F_{2,42} = 0.805$, $p = 0.453$, $\eta p^2 = 0.043$).

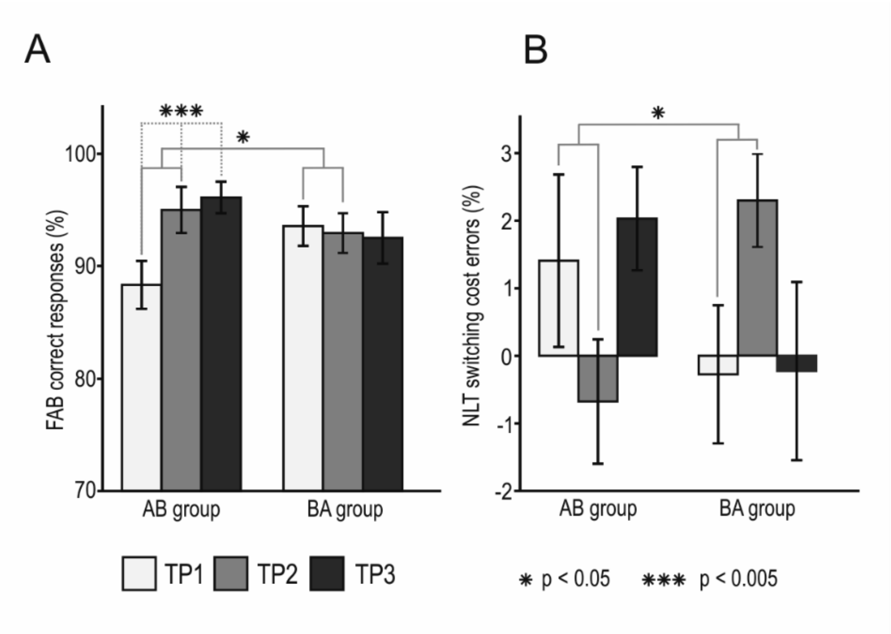

Figure 3. Behavioral test results from the Intention-to-treat (ITT) analysis. Frontal Assessment Battery (FAB) score and Number-Letter Task (NLT) switching cost error. The bar plots (mean ± SEM) show changes in test scores over the three time points (TP) presented group-wise (AB/BA) from the imputed dataset (depicting the mean of 20 imputations). Significant Time x Group interactions are shown with solid grey lines and significant within-group Time main effects are shown with dashed grey lines.

Table 3. Linear mixed model analysis (LMM) results between time points 1-2 using the complete dataset (n=39).

	Group	T1 (baseline) m (sd)	T2 (3-month) m (sd)	Baseline differences (p)	F	Δ T1–T2 (p)
Indices						
Executive function[a]	AB	88.3 (9.5)	95.0 (9.2)	.068 (t)	4.374	**0.045***
	BA	93.6 (7.7)	93.07 (7.7)			
Reasoning[b]	AB	68.3 (10.3)	72.0 (10.1)	.865 (t)	0.039	0.845
	BA	68.6 (15.1)	70.6 (14.5)			
Verbal memory[c]	AB	58.2 (14.0)	60.8 (10.9)	.899 (t)	0.964	0.359
	BA	57.7 (12.1)	60.5 (13.0)			
Motor performance[d]	AB	54.4 (10.0)	56.6 (10.4)	.198 (t)	0.074	0.789
	BA	54.2 (5.9)	56.2 (7.3)			
Computerized EF/attention tests						
N-back effect reaction time (ms)	AB	432.9 (409.7)	314.4 (316.8)	.542 (t)	0.462	0.501
	BA	364.3 (266.7)	304.0 (191.7)			
N-back effect error rate (percent)	AB	14.2 (8.8)	13.8 (8.5)	.832 (t)	0.479	0.492
	BA	15.0 (12.9)	17.9 (10.3)			
NLT switching cost reaction time (ms)	AB	379.3 (273.5)	443.7 (260.5)	.882 (t)	0.864	0.359
	BA	390.2 (167.1)	375.1 (149.8)			
NLT switching cost error rate (percent)	AB	1.4 (5.7)	-0.7 (4.1)	.314 (t)	4.798	**0.032***
	BA	-0.3 (4.5)	2.3 (3.0)			
Simon effect reaction time (ms)	AB	58.0 (42.9)	46.6 (53.3)	.609 (t)	0.076	0.782
	BA	63.8 (26.0)	56.8 (40.1)			
Simon effect error rate (percent)	AB	0.5 (1.3)	1.8 (2.5)	.068 (t)	1.895	0.182
	BA	1.5 (1.9)	1.1 (2.1)			
SART reaction time (ms)	AB	424.4 (97.5)	423.4 (94.8)	.466 (t)	0.347	0.560
	BA	399.9 (109.3)	382.3 (86.5)			
SART error and miss rate (percent)	AB	9.7 (11.0)	7.0 (9.5)	.243 (t)	1.370	0.255
	BA	6.6 (3.9)	6.1 (4.5)			
SART[e] vigilance decrement (percent)	AB	-0.2 (4.6)	0.5 (3.7)	.822 (t)	0.642	0.430
	BA	-0.5 (3.6)	-0.9 (3.0)			

Means and standard deviations are based on means of the imputed datasets. The indices represent Executive function[a] (Frontal Assessment Battery), Reasoning[b] (WAIS-IV Similarities and Block Design), Verbal memory[c] (WMS-III word lists and WAIS-IV digit span) and motor performance[d] (Box and block, ARAT, Purdue Peg Board) as the overall percentage of correct answers. SART vigilance decrement[e] reflects the change in error percent over the lengthened 8.6 min task (error percent during 1st half – error percent during 2nd half); a positive number reflects decrease in errors towards the end and a negative number reflects an increase in errors. The baseline differences have been evaluated using independent samples t-test (t) or Mann Whitney U-test (U).

Per-protocol analyses. We also performed PP analyses to verify that the ITT results on EF and set shifting (see above) were evident also in the sample of 25 patients who had full behavioral and structural MRI (sMRI) data from all three time-points and adhered to the study protocol. In the PP analyses, we performed mixed-model ANOVAs to test the short-term effects of the intervention versus control periods during the first (Time: TP1/TP2 x Group: AB/BA) and the second (Time: TP2/TP3 x Group: AB/BA) study phase. In EF, there was a significant Time x Group interaction from TP1 to TP2 ($F_{1,23} = 5.86$, $p = 0.024$, $\eta p^2 = 0.203$) but not from TP2 to TP3 ($F_{1,23} = 0.18$, $p = 0.673$, $\eta p^2 = 0.008$). In a within-subject (TP1/TP2/TP3) repeated measures ANOVA, there was a significant Time effect in the AB group ($F_{1.3,20.0} = 12.66$, $p = 0.001$, $\eta p^2 = 0.458$) but not in the BA group ($F_{2,16} = 0.04$, $p = 0.960$, $\eta p^2 = 0.005$). Bonferroni-corrected post hoc tests showed that EF performance improved in the AB group from TP1 to TP2 ($p = 0.010$) and from TP1 to TP3 ($p = 0.003$) but did not change from TP2 to TP3 ($p = 1.000$). In set shifting, the Time x Group interaction was approaching significance both from TP1 to TP2 ($F_{1,23} = 3.13$, $p = 0.090$, $\eta p^2 = 0.120$) and fromTP2 to TP3 ($F_{1,23} = 4.24$, $p = 0.051$, $\eta p^2 = 0.156$), indicating that in both groups' performance improved (reduced switching cost errors) during the intervention period and declined (increased errors) during the control period. Pooling the data across groups, this was further analyzed with a paired t-test comparing the change scores of the intervention period (AB: TP2-TP1 & BA: TP3-TP2) and control period (AB: TP3-TP2 & BA: TP2-TP1), which showed that set shifting was significantly enhanced after the intervention compared with the control period ($t_{24} = 2.49$, $p = 0.020$).

In summary, these results showed that general EF (as indicated by the Frontal Assessment Battery [FAB]) and set shifting improved more in the AB group than in the BA group over the first 3-month period and the effect ongeneral EF was maintained in the 6-month follow-up.

4.3 EFFECTS OF MUSIC THERAPY ON EXPERIENCED COGNITIVE FUNCTIONING, MOOD AND QOL (STUDY II)

Following the intention-to-treat (ITT) protocol, we first performed multiple imputation as described in the Methods section. The linear mixed model (LMM) analysis were carried out using the whole sample ($n = 38$) with Time (TP1/TP2) as a within-subject factor and Group (AB/BA) as a between-subject factor for the questionnaire data to assess the short-term (pre–post) effects of music therapy compared with standard care.

A significant Time x Group interaction was found in the self-reported BRIEF-A Behavioral Regulation Index (BRI; $F_{1,33}= 5.16$, $p = 0.030$, $\eta p^2 = 0.078$). All results from the Time x Group LMM analysis are presented in Table 4. The AB group showed a significant improvement as indicated by lowering of the BRI score compared to the BA group between TP1 and TP2. The development of the scores between TP1-TP3 is presented in Figure 4. No significant interactions were found in the other BRIEF-A indices or in the other questionnaires (BDI-II, QOLIBRI).

To evaluate the stability of the BRI treatment effect, we conducted repeated measures LMM group-wise (separately for AB and BA groups) over the three time points for the BRI measure. A significant change in the AB group was detected ($F_{2,36} = 5.17$, p = 0.011). The pairwise comparisons revealed that the BRI ratings improved between TP1 and TP2 (p = 0.002) and between TP1 and TP3 (p = 0.020), but not between TP2 and TP3 (p = 0.439) in the AB group. Both significant comparisons survived after the False Discovery Rate (FDR) correction (Glickman et al., 2014; Haynes, 2013), which indicate that the intervention effect was maintained over the 6-month follow-up period. The change within BA group did not reach significance ($F_{2,31}$= 1.34, p = 0.275). Additionally, to assess the changes in BRI related to the intervention in both groups combined, we conducted a paired sample t-test to compare performance before and after intervention (between TP1 and TP2 for AB, between TP2 and TP3 for BA), which yielded a significant result [$t_{39} = 2.50$, p = 0.012]. To test the sensitivity of the ITT analysis, we performed a per-protocol (PP) analysis for the BRI scores, which showed significant findings in the LMM, using the original non-imputed data set. Although the Time x Group interaction in repeated measures ANOVA did not reach significance ($F_{1,32}$= 2.79, p = 0.104, $\eta p^2 = 0.80$), the longitudinal within-group analyses revealed a significant main effect of time in the AB group ($F_{1,22}$= 6.45, p = 0.014, ηp^2 = 0.26) with a similar pattern of results in the pairwise FDR-corrected comparisons as in the main ITT analysis (TP1 vs.TP2: p = 0.007, TP1 vs. TP3: p = 0.026, TP2 vs.TP3: p = 0.934). We also conducted the paired samples t-tests before and after the intervention using the PP sample of the BRI scores. For the AB and BA groups combined, the result was again significant [t_{30} = 2.25, p = 0.032].

To examine the relationship between the BRI scores and our previous main results from cognitive tests measuring different aspects of EF (FAB, Number-Letter Task), we conducted Pearson correlations between the intervention period change scores (AB: TP1-TP2, BA: TP2-TP3) of these measures. No significant correlations were found. Additionally, we examined the correlation between BRI and BDI-II in a similar fashion to explore the relationship between self-reported EF and emotional wellbeing. A significant positive correlation was found between these measures (r = 0.484, p = 0.004) during the intervention period, but not during the control period (r = 0.163, p = 0.358).

In summary, these results showed that the self reported Behavioural Regulation Index of the Behaviour Rating Inventory of Executive Function (BRIEF-A) improved more in the AB than BA group from baseline to 3-month stage and the effect was maintained in the 6-month follow-up.

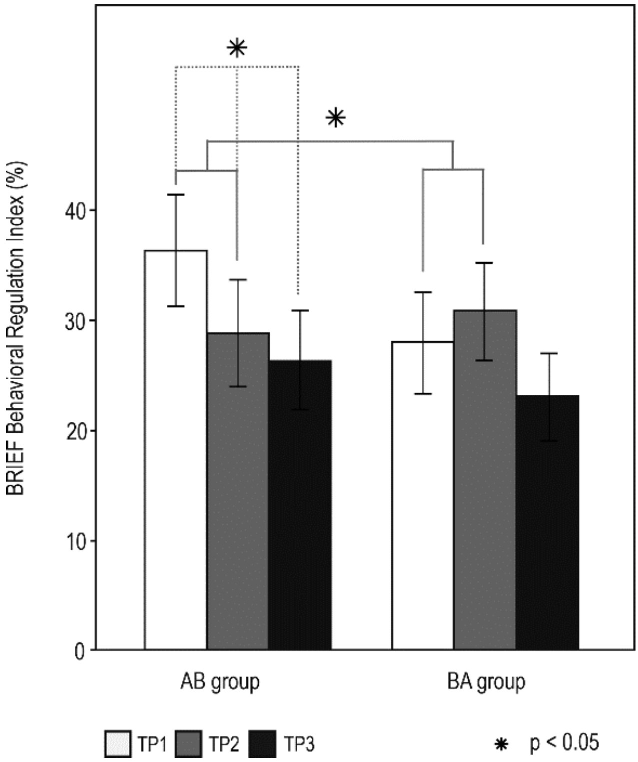

Figure 4. Results from the intention-to-treat (ITT) analysis BRIEF-A Behavioral Regulation Index. The bar plots (mean ± SEM) show changes in test scores over TP1-TP3 presented group-wise (AB/BA) from the imputed data set (depicting the mean of 20 imputations). Significant Time × Group interaction is shown with solid gray line and significant within-group Time main effects are shown with dashed gray lines. SEM, standard error of the mean.

Table 4. Linear mixed model analysis (LMM) results between time points 1-2 using the complete dataset (TBI patients: n=38, caregivers: n=33).

	Group	T1 (baseline) m (sd)	T2 (3-month) m (sd)	Baseline differences (p)	F value	Δ T1 – T2 (p)
BRIEF-A self-report						
Global Executive Composite Score	AB	41.8 (23.4)	38.1 (22.2)	.281	1.112	0.299
	BA	34.45 (18.2)	35.0 (18.8)			
Behavioral Regulation Index	AB	36.3 (22.6)	28.8 (21.8)	.231	5.162	**0.030***
	BA	28.0 (19.5)	30.8 (18.8)			
Emotional Regulation Index	AB	42.2 (25.3)	40.5 (25.7)	.257	1.126	0.296
	BA	33.5 (21.5)	37.6 (25.1)			
Metacognition Index	AB	43.5 (23.9)	40.4 (24.2)	.393	.112	0.740
	BA	37.1 (19.2)	35.4 (18.2)			
BRIEF-A informant						
Global Executive Composite Score	AB	45.6 (20.7)	41.0 (21.4)	.083	.673	0.419
	BA	32.1 (22.5)	31.3 (20.7)			
Behavioral Regulation Index	AB	36.9 (23.6)	33.6 (21.3)	.271	.044	0.836
	BA	28.1 (21.0)	25.9 (18.7)			
Emotional Regulation Index	AB	50.0 (22.4)	46.3 (23.1)	.124	.713	0.406
	BA	36.5 (26.9)	38.2 (21.5)			
Metacognition Index	AB	46.8 (21.6)	41.5 (22.8)	.060	.821	0.373
	BA	31.7 (22.8)	30.5 (22.2)			
Emotional and QOL measures						
BDI-II	AB	25.1 (16.7)	22.9 (17.7)	.221	.194	0.663
	BA	19.5 (10.4)	18.4 (9.8)			
QOLIBRI	AB	56.5 (17.8)	62.0 (18.3)	.143	.473	0.407
	BA	65.1 (18.1)	67.8 (16.1)			

Means and standard deviations are based on means of the imputed datasets. All of the results are presented in percentages compared to the maximum score. The baseline differences have been evaluated using independent samples t-test (t).

4.4 SUBJECTIVE EXPERIENCE OF THE REHABILITATION (STUDY II)

4.4.1 QUANTITATIVE RESULTS

The numeric ratings of the subjective experience regarding different domains of the intervention are presented in Table 5. The only domain in which the ratings of the TBI patients and the caregivers differed significantly was Motor: TBI patients experienced more benefits in motor functioning than the caregivers. Of note, the caregivers' ratings were significantly higher than 5.5 ($p \leq 0.05$) in all domains except in Motor. The repeated measures ANOVA revealed that there were significant differences between the evaluations of different domains both in the answers of the TBI patients ($F_{2,42} = 6.24$, $p = 0.002$, $\eta p^2 = 0.269$) and the caregivers ($F_{2,23} = 9.43$, $p =.001$, $\eta p^2 = 0.440$). The pairwise comparisons showed that the only domains differing from each other in self-report after were Cognitive and Mood ($p = 0.003$) and Cognitive and Overall recovery ($p = 0.009$). The Emotional benefits were evaluated as most beneficial and Cognitive as least beneficial. Caregiver responses demonstrated significant differences between the Motor domain, which received the lowest rating, compared to Overall benefits ($p = 0.006$), Mood ($p = 0.002$) and QoL ($p = 0.001$) domains, which received high ratings. Additionally, Cognitive benefits were rated significantly lower than in the Overall ($p = 0.011$) and Emotional ($p = 0.012$) domains. All of the above-mentioned findings survived after FDR-correction.

In summary, these results showed that the patients' and caregivers' evaluations were well in line with each other in all domains except Motor domain. Emotional benefits were emphasized both in the patients' and caregivers' ratings.

Table 5. Subjective evaluations regarding the efficacy of the intervention in five different domains, as rated by the TBI patients and caregivers. A numeric scale 1 – 10 (no benefit – very beneficial) was applied. The differences between the estimates of caregivers and TBI patients have been assessed using paired sample t-test.

Domain	***Likert ratings***				
	TBI patients	Caregivers	Difference		
	Mean (sd)		t	df	p
Overall	8.2 (1.6)	8.3 (1.5)	-.25	13	.807
Cognitive	6.9 (1.8)	7.1 (1.9)	-1.42	13	.179
Motor	7.9 (1.7)	5.5 (2.5)	3.16	12	**.008**
Mood	8.5 (1.5)	8.7 (1.3)	.31	13	.765
QoL	7.9 (1.4)	8.2 (1.3)	1.59	12	.139

4.4.2 QUALITATIVE FEEDBACK

Findings from the qualitative data regarding the experienced benefits for the TBI patients are presented in Figure 5. In the open-ended question covering overall benefits of the therapy, the Mood and QoL benefits were clearly emphasized (Figure 5A). In a more detailed analysis, the most common answers belonging to the Mood and QoL theme tapped into elevated mood and meaningful activity (Figure 5B). The descriptions of elevated mood varied from reduced feeling of depression to feelings of joy, which was mentioned by several participants. One TBI patient phrased her answer to the question regarding the effects of the therapy on her QoL: "*Particularly joy*". These feelings were closely linked to positive emotional experiences induced by music and increased enthusiasm for musical activities. Other mood-related topics mentioned were emotional regulation, enhanced level of energy, feelings of competence, self-awareness, and positive mindset. The comments tapping into emotional regulation included experiences of ability to detach from negative feelings and fear, handle stress/anxiety, and control impulsive behavior.

Within the Cognitive domain, positive effects were mostly experienced in attention and concentration, while some benefits were also described in memory and learning (Figure 5C). The answers falling into the Other positive category were mostly general comments on enhanced cognitive functioning. The subcategories belonging to Motor benefits are presented in Figure 5D. Enhancement in manual functioning was the most commonly mentioned topic, but improvements in gross and fine motor functioning were also endorsed. Finally, answers that did not clearly belong to any of the preset themes are presented in Figure 5E. Comments on enjoying and rediscovering music in one's life were included in this category together with mentions of social contacts. Although many of these comments were mentioned in the Mood and QoL sections, they could not be purely thematically integrated under these themes and seemed to form an entity of their own.

At a group level, no significant increase was found in the frequency of instrument playing, music listening or singing activity at T4 compared to the intensity of musical activities two years prior injury. However, many patients reported that the therapy helped and inspired them to start musical activities again after their injury, which provided meaningful activity, social contacts, and positive experiences. One caregiver of a young TBI patient described that the therapy was "very meaningful" for the patient, and particularly getting a piano of her own had "changed the course of her entire life". One year after the intervention, she was still active in bands and was composing music of her own. Some patients also reported adopting music listening to their daily routines, which helped them to concentrate and enhanced their cognitive and motor functioning.

In summary, these results showed that benefits in emotional wellbeing and QoL were emphasized in the subjective feedback of the patients and caregivers. In addition, answers related to increased activity in daily life and particularly involvement in musical activities after the therapy were pronounced.

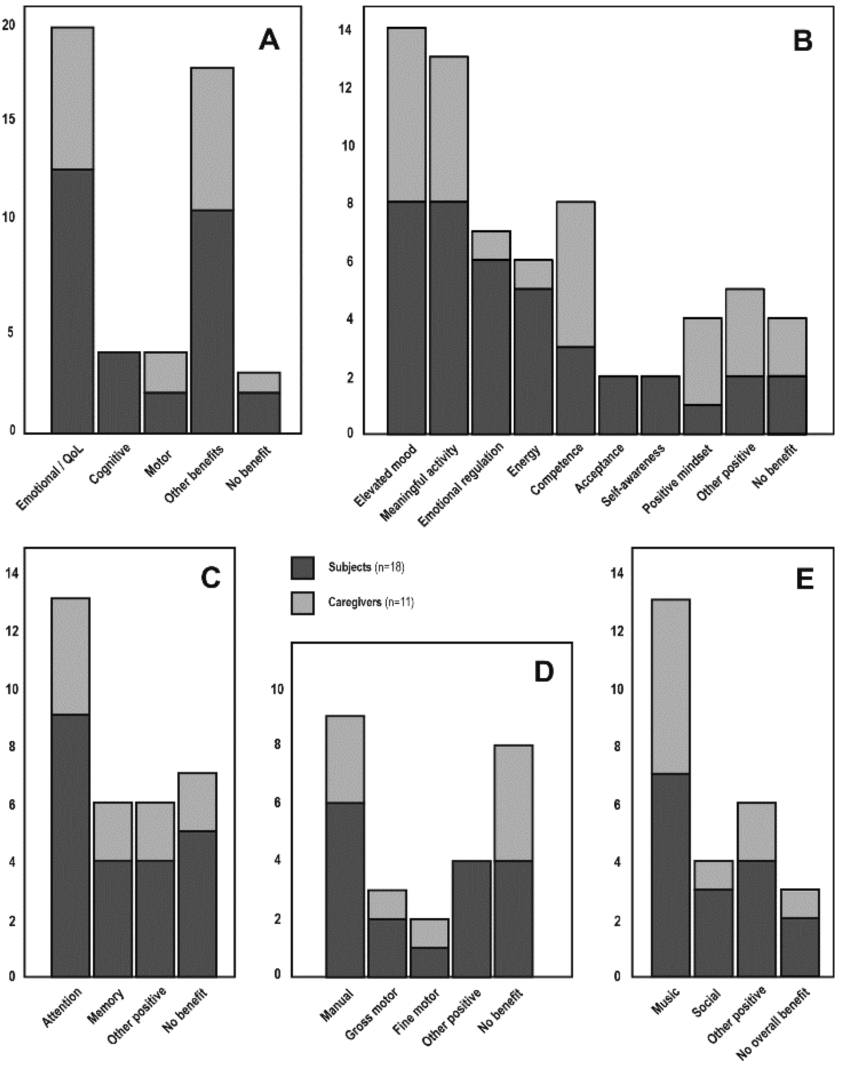

Figure 5. Findings from the qualitative content analysis presenting the amount of subjects' and caregivers' answers belonging to different categories (A) presents overall benefits as categorized into preset themes. B-E depict quantification of all answers across the sample belonging to the following themes: (B) Mood and Quality of life, (C) Cognitive; (D) Motor (E) Other benefits. Only one mention belonging to the same category per subject/caregiver was taken in account in the quantification.

4.5 EFFECTS OF MUSIC THERAPY ON GREY MATTER VOLUME (VBM RESULTS, STUDY I)

In the VBM data, we first examined the Time x Group interactions with a mixed-model ANOVA. Whole-brain analyses were performed for the AB>BA x TP2>TP1 interaction and for the BA>AB x TP3>TP2 interaction to assess changes in GMV in the group undergoing the music therapy compared with the group receiving only standard care. At a threshold of $p < 0.001$ voxel-level uncorrected and k=50 voxels cluster size, both interactions yielded common clusters in the right inferior frontal gyrus (IFG, triangular part), right middle frontal gyrus (MFG), left cerebellum, and left fusiform gyrus, with additional clusters observed variably in either interaction in other frontal, temporal, parietal, and cingulate regions (Figure 6A,B). A conjunction analysis (Figure 6C) across both interactions revealed a region of overlap specifically in the right IFG encompassing 152 voxels, indicating that this area showed the strongest GMV changes in both groups during the intervention versus control period. Notably, in a within-subject (TP1/TP2/TP3) repeated-measures ANOVA, there were no significant TP3>TP2 effects in the AB group or TP2>TP1 effects in the BA group, indicating that GMV did not change during the control period.

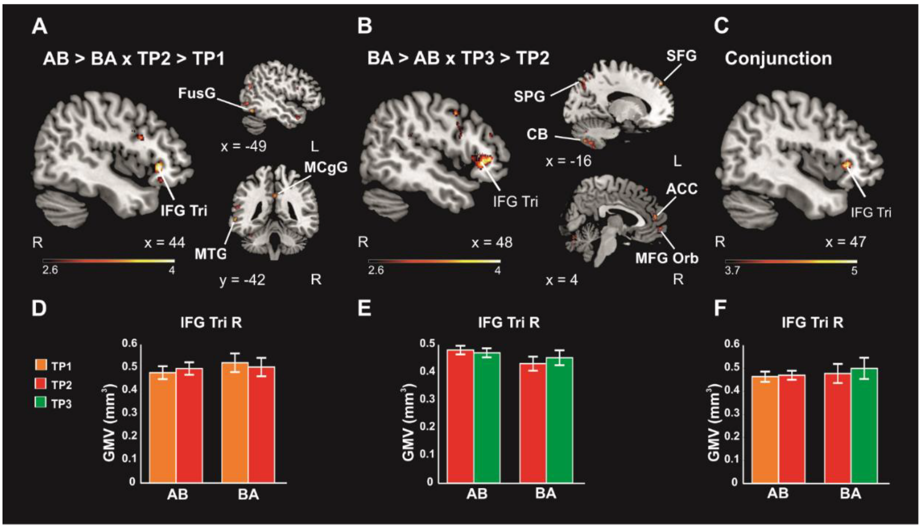

Figure 6. VBM results from the mixed-model ANOVA including 25 TBI patients and three time points (TP). (A) Group (AB>BA) x Time (TP2>TP1) interaction in grey matter volume (GMV). (B) Group (BA>AB) x Time (TP3>TP2) interaction in GMV. (C) Conjunction analysis between (A) and (B) in GMV. (D, E, F) Bar plots (mean ± SEM) for GMV from the local maxima in the right IFG Tri cluster in (A), (B) and (C) contrasts, respectively. The results are reported in MNI coordinates and at an uncorrected $p < 0.005$ threshold at the voxel level for visualization purposes. IFG Tri: inferior frontal gyrus triangular part, FusG: fusiform gyrus, MCgG: middle cingulate gyrus, MTG: middle temporal gyrus, SFG: superior frontal gyrus, SPG: superior parietal gyrus, CB: cerebellum lobule 8, ACC: anterior cingulate gyrus, MFG Orb: middle frontal gyrus orbital part. L: left, R: right.

Unfortunately, none of the contrasts reported above survived a FWE correction, most likely due to the small size of the sample and the individual variability in TBI neuropathology. To increase the statistical power of the analyses, we then pooled the data from the AB and BA groups together (n = 25) and compared GMV changes (i) before and after the intervention period using a one-sample t test (AB: TP2>TP1 & BA: TP3>TP2) and (ii) before and after the intervention versus control period using a paired t test (AB: TP2>TP1 & BA: TP3>TP2 vs. AB: TP3>TP2 & BA: TP2>TP1). In both of these analyses, the largest and most significant ($p < 0.05$ at FWE-corrected at cluster-level) GMV change occurred again in the right IFG (see Figure 7A). Other, less significant ($p < 0.001$ uncorrected and k=50 voxels cluster size) clusters also showing GMV increases during the intervention versus control period were in the left insula, right MFG, left IFG orbital part, medial orbitofrontal gyrus, left middle temporal gyrus, left cingulate cortex, and left cerebellum. Finally, using the pooled sample, we performed a bivariate correlation (Pearson, two-tailed) analysis between the pre-post intervention and control period changes in GMV in the right IFG and in set shifting performance (NLT switching cost error rate). This correlation was significant only in the intervention period (r=-0.41, r2 = 0.17, p = 0.043; Figure 7B), indicating that the enhancement in set shifting ability induced by the music therapy was associated with structural neuroplasticity in the right IFG.

In summary, VBM analysis of the structural MRI data indicated that GMV in the right IFG increased significantly in both groups during the intervention versus control period. This change also correlated with cognitive improvement in set shifting.

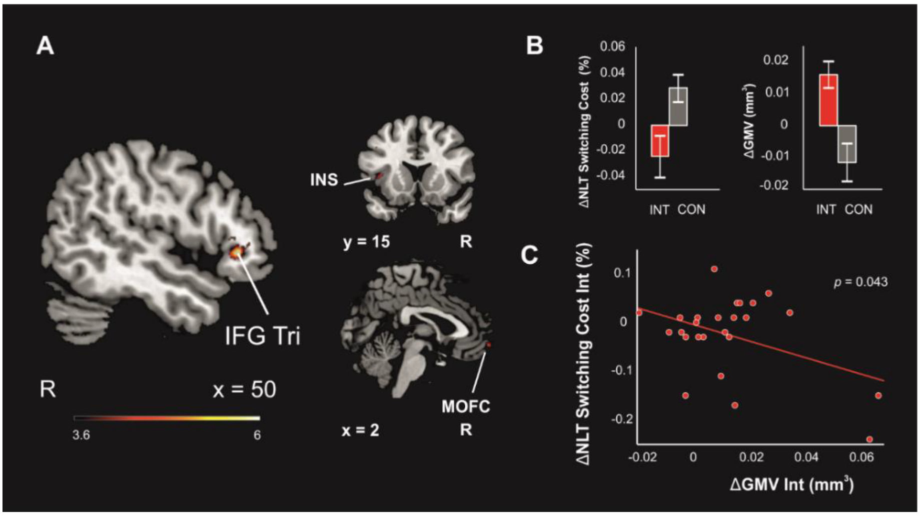

Figure 7. Changes during the intervention vs. control period pooled across groups in 25 TBI patients. (A) VBM results from the intervention vs. control comparison (AB: TP2>TP1 & BA: TP3>TP2 vs. AB: TP3>TP2 & BA: TP2>TP1). The results are reported in MNI coordinates and at an uncorrected $p < 0.001$ threshold at the voxel level. The right IFG Tri cluster shown survived a $p < 0.05$ FWE-corrected threshold at the cluster level. (B) Bar plots (mean ± SEM) for the number-letter task switching cost score (errors, %) change (left) and the GMV change (mm^3) from the local maxima in the right IFG Tri cluster shown in (A) (right) during the intervention (INT) and control (CON) periods. (C) Pearson correlation between changes in the number-letter task switching cost (errors, %) and in the GMV of the right IFG Tri cluster from (A) during the intervention period. IFG Tri: inferior frontal gyrus triangular part, INS: insula, MOFC: medial orbitofrontal gyrus. R: right.

4.6 EFFECTS OF MUSIC THERAPY ON FUNCTIONAL CONNECTIVITY (STUDY III)

4.6.1 BETWEEN-NETWORK AND WITHIN-NETWORK RESTING-STATE FUNCTIONAL CONNECTIVITY

To investigate the positive effect of the neurological music therapy on the coordinated activity between large-scale resting-state networks (RSNs) that are important for high-level cognitive function, we performed a ROI-to-ROI (R2R) analysis focusing primarily on the frontoparietal (FPN), dorsal attention (DAN), salience (SAL), and default mode (DMN) networks as source ROIs. When comparing the AB and BA groups at baseline, we did not find any difference in the inter-network connectivity between the nodes of the FPN, DAN, SAL, and DMN networks and every other node from the RSNs included in the CONN toolbox. Figure 8 shows the results of the between-network connectivity for these four RSNs, in a paired *T*-test of pre- versus post-intervention pooling together data from AB and BA groups (Figures 8A-8C) and in the Group x Time (AB > BA × TP2 > TP1) interaction (Figure 8D) with $p < 0.05$ FDR-corrected at the seed level. In the pre- versus post-intervention comparison, we found that the FPN increased its temporal coupling with the sensorimotor (SM) and DAN after the neurological music therapy.

Likewise, when the DAN was used as a source, we observed increased between-network connectivity with several nodes of the visual (VIS) network induced by the intervention. In particular, the left lateral prefrontal cortex node of the FPN increased its functional connectivity with the right lateral sensorimotor node of the SM network (Figure 8A) and the right intraparietal node of the DAN network (Figure 8B). In addition, the latter was also highly connected with the left visual occipital and left and right visual lateral nodes of the VIS network (Figure 8C). By contrast, in the AB > BA × TP2 > TP1 interaction, we found that the spontaneous fluctuations between the medial prefrontal cortex node of the DMN network and the superior sensorimotor node from the SM network were less coordinated after the intervention (Figure 8D). We did not find any change in the between-network connectivity for the BA > AB × TP3 > TP2 interaction.

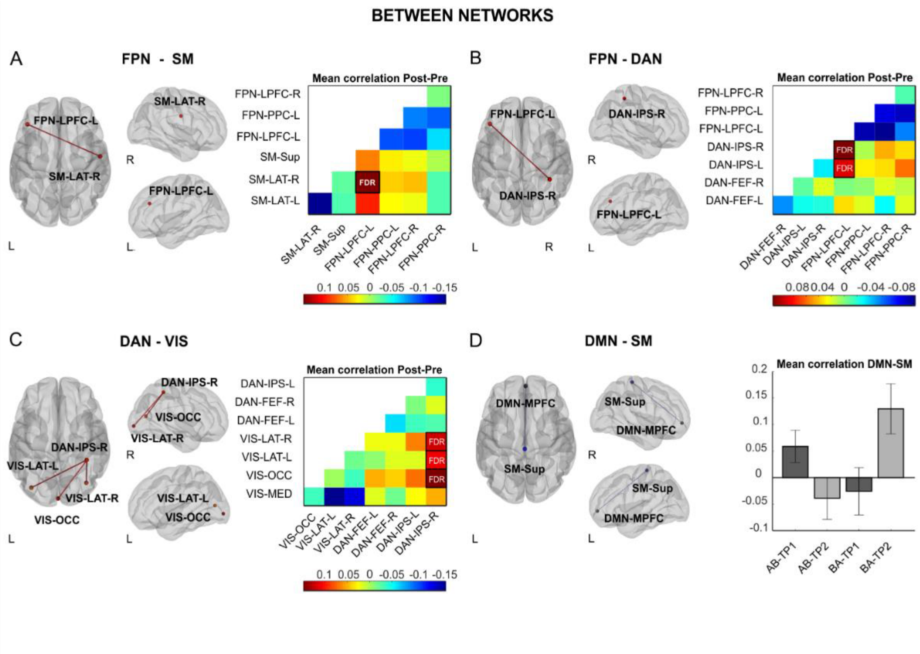

Figure 8. Changes in between-network connectivity induced by the neurological music therapy intervention. Nodes are overlaid on a rendered semitransparent brain generated using CONN. Connectivity matrices display the mean post- minus pre-intervention (a–c) Fisher-transformed Z-score correlation values for each node. The bar plots (d) show the effect size of the AB>BA and TP2>TP1 interaction represented by the Fisher-transformed Z-score correlation values for each node. FPN: frontoparietal; SM: sensorimotor; DAN: dorsal attention; VIS: visual; DMN: default mode network; FEF: frontal eye field; IPS: intraparietal sulcus; LPFC: lateral prefrontal cortex; LAT: lateral; MED: medial; MPFC: medial prefrontal cortex; OCC: occipital; PCC: posterior cingulate cortex; PPC: posterior parietal cortex; Sup: superior; R: right; L: left.

Next, we compared the connectivity within networks (Figure 9). In this case, only the pre- versus post-intervention comparison pooling together the AB and BA groups yielded significant results with $p < 0.05$ FDR-corrected at the seed level. The FPN and SAL networks showed a reduction in the functional connectivity between several of their constituent nodes. Specifically, the left lateral prefrontal cortex node exhibited less coupling with its contralateral counterpart and with the left posterior parietal cortex node (Figure 9A). Similarly, within the SAL network, the left supramarginal gyrus node showed a decreased coupling with its contralateral counterpart and with the right anterior insula node (Figure 9B).

In summary, the results showed that neurological music therapy increased the coupling between the FPN and DAN as well as between these networks and primary sensory networks. By contrast, the DMN was less connected with sensory networks after the intervention. Similarly, there was a shift towards a less connected state within the FPN and SAL networks, which are typically hyperconnected following TBI.

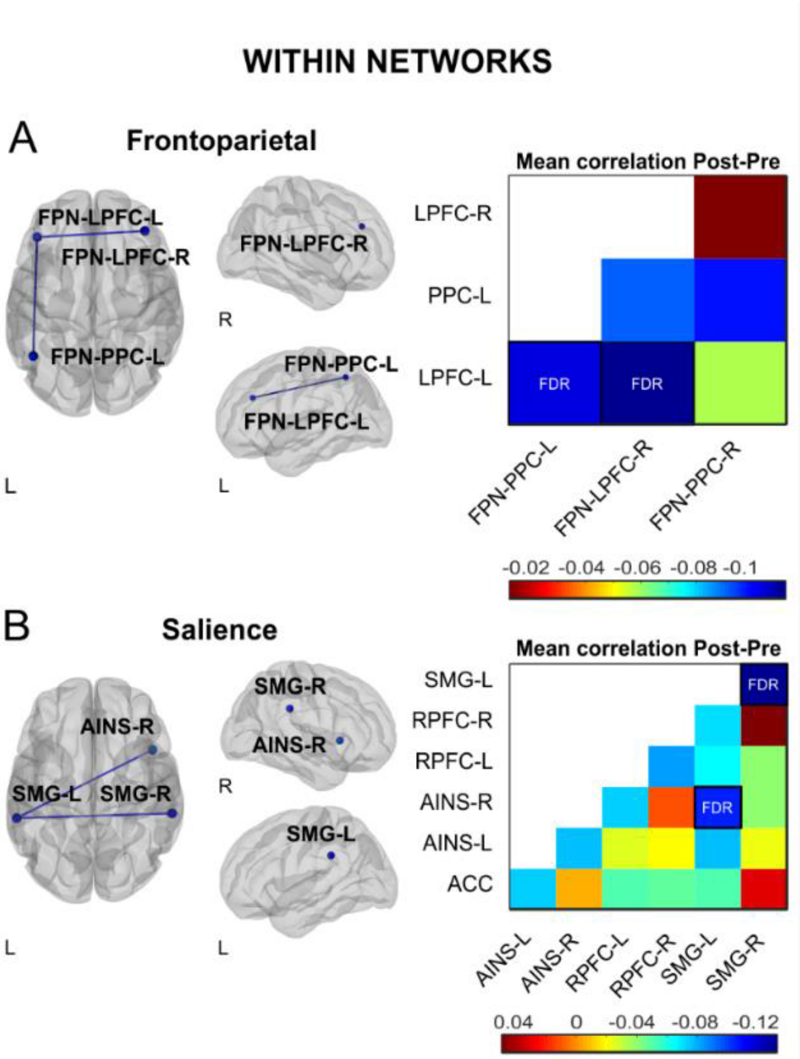

Figure 9. Changes in within-network connectivity induced by the neurological music therapy intervention. Nodes are overlaid on a rendered semitransparent brain generated using CONN. Connectivity matrices display the mean post- minus pre-intervention Fisher-transformed Z-score correlation values for each node. AINS: anterior insula; IPS: intraparietal sulcus; LAT: lateral; LPFC: lateral prefrontal cortex; MPFC: medial prefrontal cortex; OCC: occipital; PPC: posterior parietal cortex; RPFC: rostral prefrontal cortex; SMG: supramarginal gyrus; Sup: superior; R: right; L: left.

4.6.2 CORRELATION BETWEEN EF AND RESTING-STATE FUNCTIONAL CONNECTIVITY

Next, we investigated how the changes in RSNs induced by the neurological music therapy were associated with the parallel improvement in cognitive function, specifically in general EF (FAB score), set shifting (NLT switching cost errors), and self-reported executive deficits (BRIEF-A Self-Monitor and Inhibition subscales from the Behavioral Regulation Index). We found statistically significant associations between the therapy-induced cognitive improvement and within-network and between-network changes in RSNs after the intervention (Figure 10). Decreased within-network FC in the left and right lateral prefrontal cortex nodes of the FPN correlated significantly with decreased BRIEF-A Self-Monitor scores ($r = 0.485$, $p = 0.013$, FDR-adjusted $p = 0.039$, Figure 10(a), left) and showed marginal trend with increased FAB scores ($r = -0.372$, $p = 0{:}040$, FDR-adjusted $p = 0.060$, Figure 10(a), right). Decreased between-network FC between the DMN (medial prefrontal cortex node) and the SM (superior sensorimotor cortex node) networks correlated significantly with increased FAB scores ($r = -0.559$, $p = 0.003$, FDR-adjusted $p = 0.009$, Figure 10(b), left) and showed a marginally significant trend with decreased NLT switching cost errors ($r = 0.347$, $p = 0.052$, FDR-adjusted $p = 0.078$, Figure 10(b), right). There were no other significant correlations. Together, these results indicate that those patients who showed a larger reduction in connectivity within the FPN network and between the DMN and SM networks after training, exhibited greater improvement in general EF (higher FAB scores) and set shifting ability (less NLT errors), as well as greater reduction in executive deficits in self-monitoring (smaller BRIEF-A Self-Monitor scores). Thus, network-specific patterns of functional connectivity induced by the music-based intervention were associated with improvement in EF.

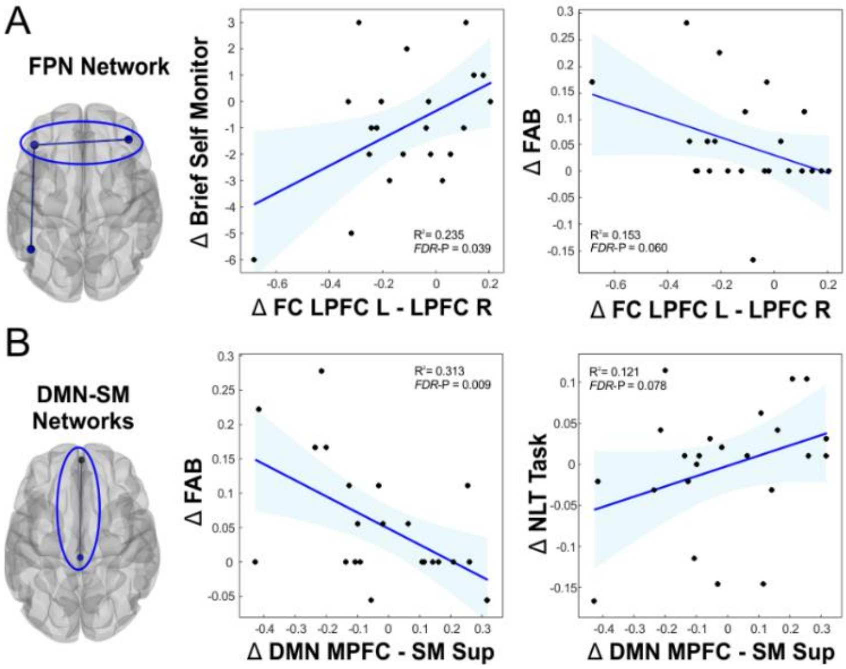

Figure 10. Within- and between-network functional connectivity changes associated with cognitive recovery induced by the neurological music therapy intervention. (a) The behavior and functional connectivity values are derived from the pre-post intervention comparison, which was significant for the within-network connectivity changes in the FPN. (b) The behavior and functional connectivity values are derived from the AB>BA and TP2>TP1 interaction, which was significant for the network connectivity changes between the DMN and SM network. The scatter plots represent the bivariate Pearson correlation and shaded areas represent the 95% CI prediction bounds. FPN: frontoparietal; DMN: default mode network; SM: sensorimotor; MPFC: medial prefrontal cortex; LPFC: lateral prefrontal cortex; Sup: superior; R: right; L: left.

4.6.3 SEED-BASED RESTING-STATE FUNCTIONAL CONNECTIVITY

Previously, using voxel-based morphometry (VBM), we found that GMV in the right inferior frontal gyrus (IFG) increased significantly in both groups during the intervention period and that this was positively correlated with enhanced set shifting ability. To examine the changes in resting-state functional connectivity (rsFC) associated with this increase in GMV, we performed seed-based connectivity (SBC) using as seeds the two clusters in the right IFG that resulted from our VBM analysis. In the SBC analysis (results shown in Figure 11), a paired T-test of pre- versus post-intervention rsFC (pooling together the AB and BA groups) revealed that during the intervention period the right IFG increased its connectivity with the right inferior parietal lobule (peak voxel $x = 38$, $y = -46$, $z = 48$; $T = 4:95$; Figure 11A and the left Rolandic operculum (peak voxel $x = -54$, $y = -2$, $z = 4$; $T = 6.07$; Figure 11(b)) with $p < 0.05$ after FDR-correction at cluster level. There were no other significant clusters.

In summary, in the seed-based connectivity analysis, the right IFG showed increased rsFC with the right inferior parietal and left frontoparietal (Rolandic operculum) regions.

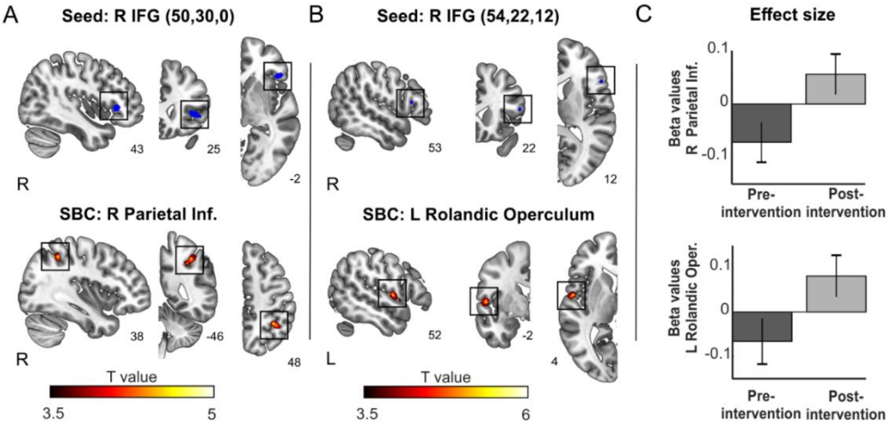

Figure 11. Changes in seed-based connectivity induced by the neurological music therapy intervention. (a) Top: R IFG mask used as seed with peak coordinates x = 50, y = 30, and y = 0, overlaid on the Montreal Neurological Institute (MNI) template; bottom: statistical map showing the $p < 0.05$ FDR-corrected cluster in the R parietal Inf. (b) Top: R IFG mask used as a seed with peak coordinates x = 54, y = 22, and y = 12, overlaid on the MNI template; bottom: statistical map showing the $p < 0.05$ FDR-corrected cluster in the L Rolandic Operculum. (c) Effect size plots displaying the functional connectivity (mean beta values) of each significant cluster in the pre-intervention relative to the postintervention period. IFG: Inferior Frontal Gyrus; Parietal Inf.: inferior parietal lobule; R: right; L: left.

5 DISCUSSION

The three studies presented here explored the efficacy of neurological music therapy in TBI rehabilitation from different perspectives. Study I revealed the impact of the intervention on cognitive functioning, particularly EF, based on neuropsychological test findings. An impact of the therapy was detected in general EF and in set shifting ability. Study II expanded these findings in an ecologically valid way to everyday life using questionnaire data, revealing that the participants experienced enhancement in behavioral regulation. Additionally, the changes in grey matter volume using VBM (Study I) and resting-state functional connectivity using rsfMRI (Study III) and their correlations with behavioral findings were explored to assess the neural correlates. A subjective view of the patients is presented through complementary, qualitative data (Study II). In this discussion central findings and their implications on clinical practices and future research will be addressed.

5.1. MUSIC THERAPY SUPPORTS EF AFTER TBI: EVIDENCE FROM NEUROPSYCHOLOGICAL PERFORMANCE

The behavioral findings in this study consistently confirmed an intervention effect of music therapy in EF, which is in line with the hypothesis. We detected both enhancement in cognitive test performance [general EF performance (FAB) and set shifting ability (NLT)]. Furthermore, the effects found in general EF and behavioral regulation were maintained in the 6-month follow-up.

The results of the neuropsychological tests are in line with previous TBI music intervention studies (Lynch & LaGlasse, 2016; Thaut et al., 2009; Vik et al., 2018). Thaut et al. (2009) reported an immediate positive effect of a single session on neurological music therapy on mental flexibility (indicated by the Trail Making Test), which nicely fits together with our result on the enhanced task set shifting performance. Compared to the recent study by Vik et al. (2018), our results converge on showing an effect of the music intervention on cognitive performance, albeit on different measures: Vik et al. found an effect on verbal learning (indicated by the California Verbal Learning Test) whereas we did not observe any effects on verbal memory or working memory updating. This could be due to characteristics of the sample and intervention; in the Vik et al. study, the patients had mild TBI and the intervention focused more on learning to play new songs which likely targets memory functions more than our intervention.

The enhancement of general EF observed in the AB group over the intervention period and in the 6-month post-intervention follow-up is in line with accumulating research evidence pointing towards transfer effects from musical skills to EF, which has been observed particularly in healthy children and adolescents (Carpentier et al., 2016; Habibi et al., 2015; Jaschke et al., 2018; Moradzadeg et al., Moreno et al., 2011; Putkinen et al., 2015; Sachs et al., 2017; 2015; Zuk et al., 2014). However, these effects have been reported in all age groups, including musically naïve adults (Bugos et al., 2007), indicating that EF is malleable to musical training throughout the lifespan. A possible mechanism behind these transfer effects is that musical activities require high-level cognitive skills, particularly EF, attention, and working memory, which enable us to focus on, maintain, and manipulate musical information and which are subserved especially by a network of frontal brain regions (D'Souza et al., 2018; Hannon et al., 2007). The neural networks recruited during musical activities are therefore likely shared with other cognitive processes. In our study, the observed effects of musical training on general EF endured over the 3-month post-intervention follow-up period, pointing to long-lasting positive cognitive effects of the therapy. However, as some patients in the AB group, being motivated and inspired by the intervention, reported having continued musical activities on a regular basis on their own after the intervention period, this longitudinal result may partly reflect the continued practice.

Our finding regarding the task set shifting is supported by previous evidence from Thaut et al. (2009), who reported an immediate positive effect of a single session of neurological music therapy on mental flexibility (indicated by the Trail Making Test). In our study, the set shifting abilities improved during the intervention period, but the effect was no longer detected after the follow-up period. When comparing change in both groups (AB+BA) during intervention and control period, a pattern of deterioration of performance was detected during the control period. Our results suggest that in this more difficult and cognitively demanding EF task (switching), there appears to be a trend towards weakening and music therapy can temporarily reverse this course to a positive direction. These findings are well in line with previous studies showing that the time course of the TBI recovery process is complex, and both cognitive enhancement and deterioration can take place (Himanen et al., 2006; Rabinowitz et al., 2018; Vasquez et al., 2018). However, determining the long-term rehabilitation effect on set switching would require a larger study with a different design and a longer intervention and follow-up periods.

The observed link between enhanced set shifting and the music intervention is intuitively appealing and supported by evidence from studies of musical expertise: playing music requires reacting flexibly to surrounding stimuli depending on the context, particularly when playing together with others. Studies in healthy subjects have shown that musical training is associated with better set shifting ability (Moradzadeh et al., 2015; Bugos et al., 2007; Zuk et al., 2014; D'Souza et al., 2018; Hanna-Pladdy et al., 2011), although some studies have not found this effect (Slevc et al., 2016; Bialystok

& DePape, 2009). Interestingly, since the shifting task was visual in nature (although linguistic strategies were likely used as well), the results point to modality-general effects of music, which is supported by previous studies (Slevc et al., 2016; Rodriguez et al., 2013). However, it should also be borne in mind that even if music in itself is an auditory stimulus, playing an instrument requires additionally integration of visuospatial and somatosensory information, which could lead to modality-specific training effects in these areas as well.

5.2. SUBJECTIVELY EXPERIENCED ENHANCEMENT OF EF

The questionnaire results revealed improvement in the self-reported BRIEF-A Behavioral Regulation Index, which measures subjective experience of EF on the level of daily life performance and social interactions. These findings increase the ecological validity of our study and are in line with results from neuropsychological test performance.

It is perhaps not surprising that this intervention effect was found in the domain of behavioral regulation, since the music therapy consisted mainly of instrument playing in close interaction with the therapist. Monitoring for one's own behavior lies at the very core of learning to play an instrument. In a cross-sectional study investigating amateur musicians, Jentzsch et al. (2014) found that compared to non-musicians, instrumental musicians are better able to detect conflicts and errors as indicated by systematic increase in the amplitude of the error-related negativity and the N200 in EEG. Furthermore, high levels of musical training were associated with more efficient and less reactive responses after experience of conflict and errors. Based on their findings, the authors suggest that playing a musical instrument could improve the ability to monitor behavior and adjust responses effectively when needed. It is intuitively appealing to think that these skills could be transferred to social situations, which also require sensitive online monitoring of one's own and other people's actions and rapid accommodation. Moreover, this effect could be emphasized when instrument playing includes interaction with other players. Rhythmic interpersonal coordination involves complex cognitive, motor, social and psychological factors, which form a microcosm of human social interaction (Keller et al., 2014). All these elements make music therapy an ideal platform to practice behavioral regulation in a social context.

An interesting question arising from the questionnaire findings is why the intervention effect on behavioral regulation was not detected in the BRIEF-A caregiver reports. The caregivers were overall very close to the patients and participated actively in their daily lives. On the other hand, important evidence that the EF skills actually improved during the music therapy intervention, comes from the neuropsychological test performance. In the qualitative feedback, TBI patients also reported experiences of becoming better at inhibiting impulsive behavior and having an enhanced understanding of their injury after the intervention. One possible explanation for this discrepancy is that the problems of EF are typically manifested in novel situations (Gilbert & Burgess, 2008). In everyday life, which is mostly shared with close relatives, routines often prevail and situations presenting a challenge for the EF skills occur less often.

Interestingly, we found that changes in everyday EF functioning were not directly connected to enhanced neuropsychological test performance. One explanation for this is that the reported cognitive tests and questionnaires measure different aspects of EF. Previous research has shown that correlations between neuropsychological test results and BRIEF-A / BRIEF are weak, while the measure correlates strongly with emotional distress (Lovstad et al., 2012; Vriezen & Pigott, 2002). EF is not a unified construct. The neuropsychological tests typically measure the "cold" components of EF, which refer to purely cognitive and logically based processes such as planning and problem solving, whereas the BRIEF has reported to tap more into the "hot" components, covering more emotional and motivational aspects of the EF (Lovstad et al., 2012). Therefore, it could be concluded that the music therapy intervention affected several domains of the EF, which may be partially independent of each other. Another possible explanation is that the performance-based neuropsychological tests measure optimal/maximal performance, while the ratings describe typical performance of the patients (Toplak et al., 2013).

5.3. MOOD, QOL AND MOTOR PERFORMANCE AFTER THE INTERVENTION

Contrary to our expectations, we did not find any effect of the intervention on mood or QoL of the TBI patients measured by quantitative questionnaires (BDI-II, QOLIBRI). The results also diverge both from previous literature, where most studies report positive changes in mood following music therapy in patients after TBI (Guetin et al., 2009; Magee & Davidson, 2002; Nayak et al., 2000; Thaut et al., 2009; Wheeler et al., 2003) and the qualitative feedback analyzed in this study.

One possible explanation is that our model of music therapy, which was particularly targeted at cognitive training, did not result in emotional benefits on a group level. Possibly, a therapy form concentrating more on emotional expression and adjustment could potentially show clearer benefits in mood and QoL. Additionally, the result could be related to the properties of the assessment instruments. Although BDI-II has been acknowledged as a valid screening instrument for depression in TBI patients, some concerns have been expressed about the possibility that symptoms of TBI are very similar and overlapping with somatic symptoms of depression, measured by the BDI-II (Green et al., 2001; Homaifar et al., 2009). Moreover, the participants were all in a relatively early stage of their recovery (6-24 months post injury), which entailed many major life changes, such as returning to work or applying for retirement, that coincided with the intervention period. Therefore, due to the small sample size and confounding factors, no definite conclusions can be drawn about the effects of music therapy on mood and QoL, particularly as the previous literature and the findings from our own qualitative data indicate at least some positive effects on emotional well-being. Interestingly, in support of this we found a significant correlation between the mood (BDI-II) and behavioral regulation (BRI) during the intervention period, which indicates that the change in BRIEF-A could actually be linked to emotional adjustment.

We also explored the motor performance, particularly upper-extremity motor functions, in this RCT. The music intervention was not associated with any gains in motor functions. This may be due to the fact that the intervention was primarily geared towards cognitive rehabilitation. Additionally, the inclusion criteria were designed to select participants with cognitive but not motor deficits, which is why motor problems were underrepresented in the current sample.

5.4. SUBJECTIVE EXPERIENCE OF THE MUSIC THERAPY

In the qualitative feedback, most of the participants' answers in fact emphasized the emotional and QoL benefits. Experience of elevated mood and the importance of having meaningful activity emerged as central themes. The findings are contradictory with the above-mentioned objective measures (BDI-II, QOLIBRI), which highlights the importance of subjective reports as a complementary source of information. Additionally, TBI patients experienced least benefit in the cognitive domain, which is surprising because the evidence from this RCT points to an intervention effect specifically on EF. However, it should also be borne in mind that in addition to methodological differences, the quantitative and qualitative samples differ in size and they were gathered at different time points. The 18-month follow-up and qualitative data were presumably somewhat selective due to the large dropout rate at that point. It is likely that most of the answers were received from the TBI patients and the caregivers who experienced the intervention as beneficial. On the other hand, enhancement in high-level cognitive skills such as EF can be difficult to detect or evaluate subjectively. Most of the cognitive changes reported in the qualitative feedback were in the domains of attention and memory, which are relatively concrete and easy to notice.

In spite of the limitations, the subjective feedback provided an important insight into the experience of music therapy from the subjective point of view. The ratings revealed that the TBI patients and their caregivers perceived the benefits across various areas in a similar fashion. The only area showing discrepancy between the ratings was the motor domain. One possible explanation for this is that the motor benefits were more subjectively experienced and perhaps not as visible to caregivers, because motor disorders were very mild in this sample. It is also possible that these functions were mostly addressed during the therapy sessions, where the progression was clear to the patients but not perceived by the caregivers.

The qualitative feedback was also in line with our findings regarding behavioral regulation, as some of the TBI patients reported for example enhanced impulse control. Overall, several participants mentioned using music as an aid in regulating emotions and stress. This is again in line with previous research showing that emotional regulation is one of the most important reasons for musical engagement across the lifespan (Saarikallio, 2011; Saarikallio & Erkkilä, 2007). Another common trait in the qualitative answers was emphasis on positive experiences and inspiration linked to musical activities, which formed an independent category of answers. These reports emphasize how the unique ability of music to engage the brain's reward system and to bring positive emotions has a great value in and of itself. Many participants also reported continuing musical activities after the therapy and adopting music as part of their daily lives.

Overall, the qualitative feedback revealed that many TBI patients experienced positive effects on their emotional well-being on an individual level. These individual reports also have a significance, and they can afford additional information easily lost in group-level analysis. In addition to the fact that music-based interventions are suitable for most TBI patients, they can have even a profound and life-changing effect for some individuals. Recognizing particularly these persons during the recovery process after TBI is of great importance as it can help in targeting and tailoring music therapy to meet individual needs and optimize treatment efficacy. It is also important to note that many of the participants had a musical background. It is possible that these individuals are more likely to attach to the therapy and continue musical activities in their daily lives.

5.5. MUSIC THERAPY IN REVERSING NEGATIVE NEURAL PROCESSES AFTER TBI

In the VBM analyses, we found that GMV in the right inferior frontal gyrus (IFG, in particular its foremost triangular part) increased significantly in both the AB and BA groups during the music intervention period, both when the groups were compared to each other across time (contrasts AB>BA x TP2>TP1 and BA>AB x TP3>TP2) and when pooled and compared to the control period. Moreover, in contrast with the increase in the GMV during the intervention period, a decrease in volume was detected during the control period in both groups. This finding is well in line with previous research describing progressive volume loss associated with TBI (Bendlin et al., Farbota et al., 2012; Sharp et al., 2014; 2008; Sidaros et al., 2009), which has been detected particularly WMV but also GMV in widespread areas and has been associated with DAI (Graham et al., 2020). Specifically, reduction in GMV has previously been documented in frontal, temporal and insular cortices (Cole et al., 2018). Our results show that neurological music therapy can reverse this negative trend in a specific frontal area and highlight the importance of environmental factors after the injury.

The fact that the intervention effect was detected mainly in the right IFG, is supported by evidence from fMRI studies in healthy subjects showing that right IFG has an important role in monitoring and sequencing of auditory information and musical syntactic processing (Bianco et al., Cheung et al., 2018; 2016; Koelsch et al., 2005; Tillman et al., 2006) as well as structural MRI studies showing that the cortical thickness and volume of this region is enhanced by musical training (Bermudez, 2009) whereas musical deficits (amusia) are linked to abnormalities in the same area (Albouy et al., 2013; Hyde et al., 2007; Hyde et al., 2006; Hyde et al., 2011). Importantly, we also found that greater GMV in the right IFG correlated with better performance in the set shifting task (NLT), which is consistent with the role of the right IFG in mental set shifting and with recent evidence showing that musical training reduces switching costs and can contribute to increased efficiency in mental set shifting (Oh et al., 2014; Habibi et al., 2018).

5.6. MUSIC THERAPY IN OPTIMIZING BRAIN CONNECTIVITY AFTER TBI

The resting-state functional connectivity (rsFC) methods were used to examine brain network chances induced by the music therapy intervention. Our analysis revealed that music therapy strengthened network connectivity between FPN and DAN, and between these networks and the sensorimotor (SM) and visual (VIS) networks, respectively. In contrast, the music therapy intervention reduced the connectivity between the nodes of DMN and SM network. The within-network connectivity revealed specific nodes of the FPN and SAL wherein coupling decreased in the pre- versus post-intervention comparison. Importantly, the decrease in the FPN and DMN-SM connectivity was paralleled by cognitive improvement in executive function (EF). Finally, using a seed-based connectivity analysis, we demonstrated that the right inferior frontal gyrus (IFG), in which we previously observed increased grey matter volume (GMV) induced by the music therapy intervention, showed high connectivity with left frontal and right parietal regions, implicated in music processing (for a review see Särkämö et al., 2016).

rsFC is still relatively rarely used a biomarker for intervention effects in TBI patients, and to our knowledge only two previous studies have utilized it to explore the effects of music-based interventions after TBI. First, Bitan et al., (2018) reported an interesting case study of an aphasic TBI patient receiving a melody-based intervention. Along with improvement in language production, they observed increase in connectivity between right frontal areas (inferior frontal gyrus triangular and opercular part) and regions involved in speech motor control (bilateral supplementary motor area and left insula) during the treatment period, and within the right frontal language areas. Despite the different goal in rehabilitation (language improvement), it is interesting that the same area, namely the right IFG, was detected in this study. Second, Vik et al. (2019) reported both fMRI findings in their piano intervention study for mild TBI patients. After the intervention, the patients showed several functional changes in the orbitofrontal cortex (OFC). Although compared to our findings, the results showed different connectivity patterns, Vik et al. also reported both increase and decrease in rsFC. Along with our findings, this gives further support to the idea that music can be utilized in balancing and optimizing network functioning after TBI through reducing harmful hyperconnectivity based on the hyperconnectivity hypothesis. An interesting question arising from this data is whether music therapy could in fact help in reducing and managing TBI-related fatigue, since this has previously been linked to a hyperconnected state (Ramage et al., 2019). The current study does not provide direct answer to this because we did not measure fatigue.

5.7. METHODOLOGICAL STRENGTHS AND LIMITATIONS OF THE STUDY

This RCT is to our knowledge the first randomized controlled study mapping the cognitive, motor, and neural effects of neurological music therapy after TBI, which is why it can be viewed as pioneering. Measures of this study were chosen to capture the important aspects of functional recovery after TBI in a detailed manner. In addition to the controlled study design, strengths include the use of a novel music therapy intervention, which was specifically developed for TBI patients. The intervention included three different modules (rhythmical training, structured cognitive-motor training, assisted music playing) and one overreaching component across modules (musical improvisation). The advantage was that the intervention was flexible and individually adjustable to answer the differing rehabilitation needs of the TBI patients who represent a heterogeneous group. This makes our findings generalizable to a wide range of TBI patients with varying degrees of cognitive impairment. Time since injury was limited in our sample to a maximum of two years after injury, which is why the efficacy of the treatment in TBI patients injured outside this time window is yet to be explored.

While the cognitive and neuroimaging results of the study are promising, the study does have some limitations. First, the relatively small sample size (39 patients in the behavioral analyses, 25 in the VBM analyses and 23 in the rsFC analyses) reduces the statistical power. This is a challenging patient population, and finding suitable participants that met the original inclusion criteria was highly demanding. For this reason, we were in fact forced to loosen the inclusion criteria regarding the time from injury, now covering two years after injury compared to the initially planned 6 months. This means that some of our patients may already have passed the most optimal neurobiological time window for cognitive and motor recovery (Kleim et al., 2008; Ruttan et al., 2008). However, previous studies in chronic stroke patients suggest that music-based rehabilitation can induce neuroplastic changes associated with motor recovery in the chronic phase of the recovery (Amengual et al., 2013; Ripollés et al., 2016). These findings indirectly suggest that experience-dependent plasticity driven by musical training could also take place in patients with brain injury at the chronic stage. Importantly, understanding the long-term effects of TBI and providing continuing support in the chronic phase has been recognized as an important health care goal (Maas et al., 2017), which is understandable considering the process-like nature of TBI. Further research is still needed to explore the efficacy of neurological music therapy in later stages in TBI.

In the current study, the small sample size prevents a fine-grained analysis of what are the differences and commonalities in the patterns of neural changes and cognitive recovery at the acute, subacute and chronic stages. Thus, we are not able to disentangle the effect of spontaneous remission processes occurring at the acute and subacute stages compared to the chronic stage. Future longitudinal studies with a stratification of patients by time since injury would be warranted to explicitly test whether the cognitive and neuroplastic changes induced by the music therapy differ between the acute/subacute and chronic stages (Amengual et al., 2013, 2014; Ripolles et al., 2016). Second, the design of the study (cross-over RCT with two groups) precludes comparing the efficacy of the music therapy to another control intervention and determining its long-term impact. The cross-over design was chosen for practical reasons, to minimize drop-outs that would be expected in a standard care-only control group, especially in the TBI population. However, because of the possible intervention carry-over effects in the AB group after the treatment, we were compelled to focus our main analyses between the first two measurements. In addition to this, the high drop-out rate in the BA group led to the fact that no reliable conclusions could be drawn from the effectiveness of music therapy in this group. We did not detect any changes in the general EF within the BA group in the imputed data set. However, only 13/20 (65%) of the patients completed the study to their post-intervention time point (TP3). The drop-outs were due to lack of motivation and energy to continue participation, which are common in the TBI population (Cantor et al., 2013; Marin & Wilkosz, 2005) and were likely linked to the long waiting period before receiving the intervention in the present study. In future, a larger three-arm parallel-group RCT with music therapy, another (control) therapy, and no intervention arms, as well as a longitudinal post-intervention follow-up for all groups would be warranted. The use of the cross-over design should perhaps be avoided if the follow-up period is very long and could affect motivation of the waiting-list group.

Third, although the complexity of the music therapy intervention is a strength, it is also a limitation because discerning how each of the therapy components contributed to the observed effects of the intervention is impossible. Fourth, the rsFC approach to study changes in large-scale networks relied on a widely used set of nodes for ROI-2-ROI analyses derived from the Human Connectome Project (Nieto-Castanon et al., 2020). However, other atlases could have been more sensible to detect results in rsFC after the music therapy. Finally, limitations of the qualitative data include structured formulation of the questionnaire and the late stage at which the subjective reports were gathered (18 months). The questionnaire was formed to inquire for certain outcomes, which could have led to a treatment expectancy effect, particularly in the numeric ratings. The aim of the questionnaire was to compare and investigate differences within the domains, and it should not be considered as a proof of an intervention effect. More extensive qualitative research exploring this question is beyond the scope of this study. The late stage at which the subjective feedback was gathered, clearly affected the drop-out rate as all participants could no longer be reached. On the other hand, the subject reports from this long-term follow-up consolidate our findings, because benefits from the intervention were still experienced over one year after the end of therapy. Many of the previously reported studies have focused on short-term benefits from the therapy, although long-term recovery and the profound changes obtained in everyday lives of the TBI patients are crucial in evaluating the utility and cost-effectiveness of the intervention. Our follow-up data suggests that at least some individuals gain long-term benefits from the intervention, which can lead to changes in daily routines and activities and support both cognitive and emotional well-being, long after the active music therapy intervention has ended.

5.8. CONCLUSIONS AND CLINICAL CONSIDERATIONS

Together these three studies show that neurological music therapy has a positive effect on frontal functions and neuroplasticity after TBI. Following the intervention, improvement was found in general EF (as measured by the Frontal Assessment Battery), set shifting ability (as measured by the Number Letter Task) and self-reported behavioral regulation (as measured by BRIEF-A Behavioral Regulation Index). In support of this, neuroplastic changes were revealing that the intervention effect was coupled with the increase of GMV specifically in the right IFG, which also correlated with the observed improvement in the set shifting. Moreover, the rsMRI results showed that neurological music therapy induces changes in the brain’s resting state functional connectivity, which taken together might be interpreted as a shift from a hyperconnected state to a connectivity state where efficient communication is maintained without a compensatory mechanism.

The improvement of EF induced by the music intervention is an important clinical finding considering the commonness of executive dysfunction in the TBI population and its highly debilitating effect on functional outcome (Spitz et al., 2012; Struchen et al., 2008). Problems in EF and set shifting are seen in everyday life as dysfunctional action patterns characterized by poor flexibility and perseveration tendencies and they can negatively affect the patients' ability to participate in various domains of life including work, education, and social interaction. Given that the incidence of TBI is high particularly in young age groups, investing in rehabilitation that supports cognitive and functional independence bears fruit far in the future both for the individual and the society.

The evidence from this study supports the use of neurological music therapy in the early phase (first two years) of recovery after moderate and severe injuries. The effectiveness of the treatment in mild injuries and more chronic stages after TBI still needs to be further investigated. Previous research suggests that the most effective approach to TBI rehabilitation is multidisciplinary holistic rehabilitation (Maas et al., 2017). The current findings imply that integrating music therapy in this process could enhance the outcome and support the overall recovery. Importantly, music therapy is applicable for nearly all patients regardless of their previous musical experience, as long as they enjoy music and find it meaningful.

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