Effects of Music Training on Cortical Plasticity:

Cognitive Rehabilitation of Patients with Traumatic Brain Injury

Berit Marie Dykesteen Vik

Thesis for the degree of Doctor Philosophiae (dr. philos.)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

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Date of defense: 10.05.2022

Year: 2022

Title: Effects of Music Training on Cortical Plasticity:

Name: Berit Marie Dykesteen Vik

Print: Skipnes Kommunikasjon / University of Bergen

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SCIENTIFIC ENVIRONMENT

This thesis is an independent scientific work with no financial or supervisory support. The fMRI scanning sessions of participants in the study were funded by BeRG-AP (Bergen Research Group on Auditory Perception), Department of Biological and Medical Psychology, Bergen fMRI Group, University of Bergen.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Professor Karsten Specht and Professor Geir Olve Skeie, who gave me an opportunity to carry out my study in the field of music and neuroscience. Without the generosity of these two distinguished scholars, who gave me access to the academic environment at the Department of Biological and Medical Psychology, University of Bergen, and the Department of Neurology, Haukeland University Hospital, Bergen, I would not have been able to complete my doctoral thesis. Despite being a guest, I always felt welcome in the two departments. Thank you for the use of the MR scanning machine and for the use of an office in the Neurology Department during assessment of the participants who took part in the study. I would also like to thank both of you for your contribution to two of my papers, and for your contributions to our scientific discussions, always with a positive attitude.

I would also like to thank radiographers Roger Brandon, Turid Randa, Eva Øksnes and Trond Øvreaas at the Department of Radiology, where I spent many hours during scanning. Their valuable expertise in scientific medical imaging helped me to learn how brain scanning is performed. I always looked forward to these sessions and appreciated the patience they all showed if any technical problems arose during scanning. You made this special part of my study really enjoyable and interesting.

The inclusion of patients with traumatic brain injury would not have been possible without the help of Dr Eirik Vikane, Department of Physical Medicine and Rehabilitation, Haukeland University Hospital, Bergen. Thank you for contributing your time and resources.

I would particularly like to thank the patients who took part in this study. They spent many hours a week playing the piano, in addition to the time spent during assessment before and after the intervention. The control groups who participated are also much appreciated. Thank you to you all! I enjoyed all the time I spent with you.

It is also important for me to thank some of the people who have inspired me along the way, both in music performance and in the field of neuro-musicology. First of all, I wish to mention Ingebrigt Bjelland who, as a lecturer in music at the University of Stavanger, was a positive mentor when I started my higher education in music. Thereafter, my supervisor during my master's degree in Music Psychology at the University of Sheffield, Dr Nicola Dibben, who introduced me to scholars who proved valuable to me in my further studies within music and neuroscience. I thank professor Lawrence Parsons of the University of Sheffield for taking time to discuss music and neuroplasticity and for giving me an opportunity to join his classes in psychology. Last, but not least, I wish to thank my GP, Dr Ivar Thomsen, for his highly positive attitude towards his TBI patient, I always felt welcome in your office during my recovering years. My thoughts also go to my friend, the late Bjørn Bjørnsen – his genuine interest in my research always inspired me in my work.

Finally, I wish to thank all my family who have supported me and contributed in different ways during these years. Thank you for always being there for me when I needed either a scientific discussion of my work, a cup of coffee and a talk, or technical support with my PC. My deepest thanks also go to my late parents who gave me and my sister Randi, a fundamentally musical upbringing which I have passed on to my children Kristin, Kjetil, Therese and Nina. Thank you for sharing my passion for music. In conclusion, a warm thank you to my dear husband Olav for supporting me in every way.

I dedicate this thesis to my father, Knud Dykesteen, who was my first mentor in playing the piano, but who sadly died at an early age. We shared the love of music.

LIST OF ABBREVIATIONS

BOLD	Blood oxygenation level dependent
CT	Computerized tomography
CVLT-II	California Verbal Learning Test II
CNS	Central nervous system
DAI	Diffuse axonal injury
DCM	Dynamic Causal Modelling
DTI	Diffuse Tensor Imaging
EF	Executive Functions
EPI	Echo-planar imaging
fMRI	Functional magnetic resonance imaging
GCS	Glasgow Coma Scale
HAD	Hospital Anxiety and Depression Scale
HISS	Head Injury Severity Scale
MMS	Mini Mental Status Test
MRI	magnetic resonance imaging
MT	Musical training
mTBI	mild traumatic brain injury
PCS	post-concussion syndrome
PEB	Parametric Empirical Bayes
PET	Positron emission tomography
PNS	Peripheral nervous system

RPQ	Rivermead Post Concussion Symptoms Questionnaire
RCT	Randomized Controlled Trial
Rs-fMRI	Resting-state fMRI
SMA	Supplementary motor area
spDCM	Spectral dynamic causal modeling

HYPOTHESIS

It is hypothesised that learning to play the piano as designed in the intervention protocol may stimulate the neural networks to re-route neural connections and link up inhibited neural circuits. The main objective of the designed music-supported intervention used in the study is to restore cognitive performance in patients with mild Traumatic Brain Injury.

LIST OF PUBLICATIONS

I.

'Effects of music production on cortical plasticity within cognitive rehabilitation of patients with mild traumatic brain injury'.

Vik, B.M.D., Skeie, G.O., Vikane, E., Specht, K. (2018. *Brain Injury, 32,2.*)

II.

'Neuroplastic Effects in Patients with Traumatic Brain Injury after Music-Supported Therapy'.

Vik, B.M.D., Skeie, G.O., Specht, K. (2019).

Frontiers in Human Neuroscience 13:177.

III.

'Music-based systematic treatment strategies for patients with executive dysfunctions following traumatic brain injury: Similarities and divergences in 7 case reports'.

Vik, B.D.M. (2019). *Music and Medicine. Volume 11. Number 3*

1. SUMMARY

The aim of this thesis was to explore the neuroplastic effects of playing the piano on patients with cognitive impairment following a mild traumatic brain injury (mTBI). It was hypothesised that playing the piano would stimulate neural networks to re-route neural connections and link up cortical circuits that had been functionally inhibited due to minor disruption of brain tissue. The objective of the intervention was to restore the patients' cognitive processing to pre-injury levels.

The study was designed as a pilot study with three experimental groups: (1) 7 patients with cognitive deficits following mTBI two years post-injury (Group 1), (2) 11 healthy subjects (Group 2), and (3) 12 further healthy subjects (Group 3). A between-group design and a longitudinal (pre-post-intervention) within-subject design were applied. Groups 1 and 2 were given eight weeks of piano training. A combination of cognitive and functional neuroimaging (task-based and resting-state fMRI) in addition to neuropsychological tests were performed pre- and post-intervention for all three groups.

The results concurrently demonstrated in two independent analyses and fMRI datasets that longitudinal changes in functional connectivity took place within the orbitofrontal cortex (OFC) in the mTBI patient group only (Group 1), showing increased connectivity between the OFC regions post-intervention. The OFC is involved in executive functions (EF), social cognition and emotional regulation.

This finding provides support for the contribution of the OFC as a key mechanism that potentially drives the cognitive benefit of piano training in TBI, and further suggests a network of other connected frontal regions that may be linked to this.

Results from fMRI and rs-fMRI fit well with the outcome of the neuropsychological test, the California Verbal Learning Test-II (CVLT II), which assesses attention, learning strategies, memorisation and retrieval of information. Post-intervention the patient group (Group 1) achieved the same scores in the neuropsychological tests (CVLT II) as

the healthy control groups pre-intervention, suggesting a normalisation of cognitive control.

Interviews were conducted pre- and post-intervention, with questions about present work situation, wellbeing and social interactions. The patients had either been on sick leave since their injury, or worked reduced working hours at the time of intervention. Post-intervention, six out of seven patients returned to work and worked as before the injury.

A follow-up study carried out one year after the intervention showed the same results as regards neuropsychological test results and functioning in work. Six out of seven patients reported a largely positive work experience and improved social interaction. It should be noted that one participant who reported a positive work situation still complained of problems with social functioning, as described in Paper III (see Table 2 in Paper III). Disturbances of social cognition may occur after a traumatic orbitofrontal brain injury despite relatively well-preserved neurocognitive abilities, as in this case (Cicerone & Tanenbaum, 1997).

This thesis is based on extensive research on music processing in the brain (Altenmüller, 2007; Altenmüller, Marco-Pallaares, & Schneider, 2009; Herholz & Zatorre, 2012; Jäncke, 2009; Jäncke, Shah, & Peters, 2000; Koelsch, 2013; Lehrer, 2011; Münte, Altenmüller, & Jäncke, 2002; Pantev, 2009; Parsons et al., 2005; Peretz, 2007; Peretz & Zatorre, 2003; Schlaug, 2009c; Schön, Anton, Roth, & Besson, 2002; Sloboda, 2005; Stewart & Walsh, 2001; Särkamö, Tervaniemi, & Huotilainen, 2013; M.H. Thaut & Hoemberg, 2016), neuroplasticity, and additional knowledge gained from a case study in which an mTBI patient, a pianist, with music alexia following mTBI, made a full recovery after playing the piano during the rehabilitation process (Vik, 2006).

Regular musical activity has been demonstrated to effectively change the structure, and may improve the functions, of many brain areas, making music a potential tool in neurologic rehabilitation (Altenmüller, 2016; Jäncke, 2009; Rojo et al., 2011; Schlaug, 2009c; Stewart et al., 2003). Musical performance is very likely the domain in which humans produce the most intricate, complex integration of expert perceptual, motor, cognitive, and emotive skills. Playing an instrument is a multimodal activity that engages auditory, motor and visual brain networks. Music performance includes components such as perception, sight-reading, motorsensory processes and attention (Parsons, Sergent, Hodges, & Fox, 2005).

The key findings of this study could suggest a causal relationship between musical training and a functional reorganisation of neural networks that promotes enhanced cognitive performance. These results might hold promise as regards adding a novel music-based intervention to the cognitive rehabilitation of mTBI patients.

In this thesis, I will present the reader with a definition of traumatic brain injury, knowledge about music perception and cognition, and about the effect of music processing on non-music-related cortical networks that may explain how the patient group achieved enhanced cognitive performance. Furthermore, I will discuss the results of the intervention and how musical training may induce cortical plasticity and generate new neural connections, and thereby offer the possibility of restoring cognitive function and social behaviour. I will discuss limitations of the study and, finally, discuss the relevance of these findings to a future music-intervention in the cognitive rehabilitation of patients with mTBI.

2. INTRODUCTION

Traumatic brain injury (TBI) is defined as damage to the brain as a result of external mechanical force (Heskestad, 2017). TBI has been recognised as a major public health problem worldwide (Hyder, Wunderlich, Pavanachandra, Gururaj, & O.C., 2007) and it represents a significant health problem in the general population. Major causes of TBI are traffic accidents, falls and assaults (Vikane, 2016). Military personnel and people in the sporting world, especially in American football, have contributed to increasing the number of cases of TBI in the USA (Hegde, 2014).

TBI can lead to impairment of sensory, motor, language and emotional processing, as well as cognitive functions such as attention, information processing and memory (Marshall, Bayley, McCullagh, & Berrigan, 2012). Disturbance of higher executive functioning due to acquired brain injury may also affect the ability to anticipate the effects of one's actions, to appreciate alternative perspectives, and to recognise other people's reactions to one's behaviour and modify one's actions accordingly (Cicerone & Tanenbaum, 1997).

The economic impact of mTBI injuries account for 44% of the annual cost of TBI in the United States (Balanger, Vanderploeg, Curtiss, & Warden, 2007). A study of hospital-treated TBI in Oslo, Norway, reported an incidence rate of 83 per 100,000 inhabitants (Andelic et al., 2008). Nine thousand TBI patients are hospitalised in Norway every year and as many as 86% of them were classified as mTBI (Andelic, Sigurdardottir, Brunborg, & Roe, 2008).

However, milder injuries may be underestimated. Studies which based their incidence rates on hospital-treated TBI revealed that fewer patients with mTBI attend emergency departments and that more patients are treated in outpatient settings (Bazarian et al., 2005; Carroll, Cassidy, Holm, Kraus, & Coronado, 2004), which means that the number of TBI patients diagnosed with mTBI might be higher.

Despite evolving research within this area, evidence is lacking for training-induced plasticity as a tool in the cognitive rehabilitation of patients with cognitive and emotional deficits following mTBI. These patients are a 'silent epidemic' group who may fall out of both work and social life (Heskestad, 2017).

Cognitive rehabilitation of patients with permanent brain damage has been shown to be difficult and with low outcomes (Skeie, 2017). Well-designed studies of the efficacy of interventions, in general, and of promoting return to work for patients with cognitive deficits after TBI, in particular, are still lacking (Gilbertson, 2005; Hegde, 2014; M.H. Thaut, 2010; Vikane, 2016).

Developing a well-designed rehabilitation treatment for this specific group of TBI patients is of interest to the patients, their family and society at large.

The present intervention is restricted to patients with mTBI. This category of TBI patients could apply their preserved cognitive capacity to reorganising their brain's neural networks and thereby rehabilitate their cognitive functions. The goal is to achieve normalisation of their lives.

2.1. *Definition of traumatic brain injury.*

According to the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health, TBI can be defined as 'an alternation in brain function, or other evidence of brain pathology, caused by an external force' (Salmi et al., 2014). Alteration of brain function was defined as the appearance of the following clinical signs: any period of decreased or lost consciousness, loss of memory immediately before or after the injury, neurological deficits such as weakness, loss of balance, sensory loss, change in visual, speech or language function or any change in mental state such as confusion, disorientation or slowed thinking (Salmi et al., 2014).

2.2. *Classification of traumatic brain injury*

TBI is traditionally classified from mild to moderate to severe (Teasdale & Jennett, 1974). The neurological injury severity scale most commonly used to assess the depth and duration of impaired consciousness and coma in adults is the Glasgow Coma Scale (GCS), which is a 15-point clinical scale ranging from 3–15. The scores are based on three different behavioural responses: eye, verbal and motor responses are measured. Each level of response is graded according to a defined scale. There are subscales for eye opening (1–4), verbal response (1–5) and best motor response (1–6) (van Velzen, van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009; Waljas et al., 2014).

Patients with a GCS score of 13–15 are classified as mild TBI, with a GSC score of 9–12 as moderate TBI, or a GCS score of 3–8 as severe TBI (Fourtasse et al., 2011).

The Head Injury Severity Scale (HISS) also classifies TBI based on the severity of the injury (Stein & Spettell, 1995). This divides head injuries into four severity categories: minimal, mild, moderate and severe. The HISS classification of TBI is based on the primary clinical examination and history taking, derived from the GCS scoring, the presence (and duration), or absence of loss of consciousness in the history, and the presence or absence of focal neurological deficits. (Heskestad, 2017).

2.3. *Definition of mild traumatic brain injury*

mTBI is defined as a GCS score from 13–15 at least 30 minutes after mTBI in an examination by a qualified health care provider (Lannsjo, Borg, Bjorklund, Geijerstam, & A., 2011). The neurological abnormalities can include seizures, intracranial lesions and neurological signs, such as weakness, loss of balance, sensory loss and changes in vision, speech or language (Lannsjo et al., 2011; Matuseviciene, Eriksson, & Nygen, 2015). The symptoms of mTBI must not be the result of alcohol or other substance use, other injuries, treatments or other problems such as psychological distress (Lannsjo et al., 2011). According to the International Collaboration on mTBI Prognosis, it is recommended to restrict the term mTBI to injuries caused by direct head trauma and exclude other aetiologies, such as blasts and whiplash, from the definition of mTBI (Saltychew, Eskola, Tenovuo, & Laimi, 2013). Others have defined slowed thinking in addition to confusion and disorientation as a sign of altered mental status (Matuseviciene et al., 2015).

Milder injuries to the head may cause microscopic damage to axons, dendrites or synapses that may be too small to be detected by neuroimaging techniques such as computerized tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scans (Balanger et al., 2007). Despite the recent emergence of MRI-based tools like Diffusion Tensor Imaging (DTI), which can reveal abnormalities in white matter fibres with increasing sensitivity, this imaging technique will not always reveal possible minor damage to a neural network. Diffuse axonal injury (DAI) is typical brain damage as result of TBI. DAI is widespread disruption of the brain tissue and affects interconnected processing in the brain (Levine et al., 2006). DAI lesions after mTBI have primarily been located in the white matter, areas of corpus callosum and the upper brainstem (Voller, Auff, Schnider, & Aichner, 2001).

2.4. *Music and the brain*

Research on music perception and cognition has increased significantly in recent decades. The combination of music neuroscience and medical and biological psychology has been a field of interest for researchers, especially since the development of neuro-imaging tools made it possible to investigate the brain’s neural networks in vivo.

Musical performance is a domain in which humans produce the most complex integration of perceptual, kinaesthetic, cognitive and emotive skills. Musical training has emerged as a useful framework for the investigation of training-related plasticity in the human brain (Altenmüller, 2016; Münte et al., 2002; Parsons et al., 2005; Peretz

& Zatorre, 2003; Rojo et al., 2011; Schlaug, 2009a, 2009c; Särkamö et al., 2014; Wan & Schlaug, 2010).

Playing an instrument produces highly complex stimuli for the brain and activates temporal, frontal, parietal, cerebellar and subcortical areas involved in auditory, cognitive, emotional and motor processing. Music activity simultaneously receives and transmits visual (music literacy), auditory (listening) and kinaesthetic (motor) information to a specialised brain network (M.H. Thaut, 2010).

These multimodal effects of music, together with music's ability to engage the emotion and the reward system in the brain, can facilitate and enhance therapeutic approaches aimed at achieving rehabilitation from neurological and psychiatric disorders (Altenmüller, 2016; Hegde, 2014; Jäncke, 2009; Schlaug, 2009c; Stewart & Walsh, 2001; Särkamö et al., 2013).

In the following, based on knowledge from music psychology (music perception and cognition) and cognitive neuroscience, I will outline some factors relating to how music production and neural processing may link up broken circuits in the brain. I suggest that, by stimulating neural networks while playing an instrument, it may be possible to re-route networks that have been inhibited due to the disruption of cortical circuits.

This assumption is supported by research on learning mechanisms in the brain. Moser et al. describe how an increase in dendritic spine density follows spatial learning, which suggests the formation of new synapses (Moser, Trommald, & Andersen, 1994). The repetition effect during the intervention period of eight weeks, in addition to the repetition effect within the musical structure, is supported by the Hebbian learning rules 'fire together, wire together' as regards how neural connections are strengthened by the repetition effect (Hebb, 1961).

I hypothesise that synaptic connections between areas activated during playing may stimulate neural networks by reconnecting cortical circuits. The analysis of the fMRI results revealed a patient-specific change in activation within the medial orbitofrontal cortex and improved cognitive and social performance. I will therefore start by describing the anatomy, functions and neural connections of the OFC in order to understand how music production can facilitate the reorganisation of neural networks and enhanced cognitive performance after brain damage. This will be followed by a discussion of what underlying neural circuits may be responsible for cognitive recovery in the patient group.

2.5. *Orbitofrontal cortex: anatomy, functions and neural connections.*

The OFC is defined as the cortex on the orbital surface of the frontal lobe. It is considered to be anatomically synonymous with the ventromedial prefrontal cortex (Phillips, MacPherson, & Della Bella, 2002). The OFC is distinguished from other parts of the cortex because it belongs to 'the old part of the brain', or allocortex, and has only five layers, in contrast to the neocortex, which has six layers (Willis & Haines, 2018).

The OFC has widely distributed, interconnected neural networks to almost all areas of the brain and a broad spectrum of functions (Rolls, 2004). The OFC networks regulate higher order cognitive processing, such as executive functions (EF) including attention, concentration, impulse control and social behaviour (Rolls, 2004). The neural structures of the OFC are defined as part of the paralimbic cortex, along with the cingulate cortex and paraolfactory region, which receives information from polysensory association areas via the dorsolateral temporal and limbic regions (Cicerone & Tanenbaum, 1997). This region also has extensive reciprocal connections with the anterior temporal, medial temporal and limbic regions (Cicerone & Tanenbaum, 1997).

The OFC stands out because of its distinct neural connections and the distinct functions it performs (Barbas, Ghashgahaei, & Rempel-Clower, 2002). It is defined as the part of the prefrontal cortex that receives projections from the magnocellular, medial nucleus of the mediodorsal thalamus, and is thought to represent emotion and reward in decision making (Rolls, 2004). This structure has also been associated with the default mode network (Hugdahl et al., 2015). In the present study, the latter notion is supported by the low to negative BOLD response during task performance in the controls (**see Fig. 3b in Paper I).** The patients demonstrated normalisation of the BOLD signal after training, from a strong deactivation before the training. Normalisation of this activation in the patients may indicate a better interplay with the systems of the executive system, or the so-called extrinsic mode network (Hugdahl et al., 2015) .

Nearly all detected brain areas that showed a recovery effect also received direct or indirect dopaminergic connections, such as the prefrontal cortex and the anterior insular cortex (Christopher et al., 2013). This may provide support for the assumption that actively playing a musical instrument could have a dopamine-releasing effect.

The OFC's connectivity to the association cortex is of special interest as this is one of the most important networks in terms of developing new pathways and emotional associations (Schlaug, 2009b). Research has shown that neural activity during music production promotes the association cortex by stimulating episodic and semantic memory networks (Chan, Ho, & Cheung, 1998) (Schlaug, 2009b).

2.6. *Music training, emotion and the learning mechanism*

The OFC plays an important role in stimulus-reinforcement association learning (Rolls, 2004, 2013; Rolls & Grabenhorst, 2008), which is evident in the learning mechanism. This learning mechanism is the ability to associate a sensory stimulus with a (positive) reinforcer. In this circumstance, auditory, visual, and motor areas are densely interconnected with other prefrontal cortical regions, reflecting the integration of executive motor control, which is evident in learning to play the piano. The OFC receives input from the temporal association cortex, amygdala and hypothalamus, making it the highest integration centre for emotional processing (Rudebeck, Mitz, Chacko, & Murray, 2013).

A positive experience of emotion enhances learning and facilitates improved learning and recall, as well as positive mood boost memory functions (Lehrer, 2011; M. H. Thaut et al., 2009). In a therapeutic setting, playing an instrument can thereby be a provider of positive emotions related to mastering a goal (Salamone & Correa, 2012).

Interestingly, the present task fMRI analysis revealed increased activation in the rostral anterior cingulate gyrus, which is called the emotional part of the anterior cingulate gyrus and is closely related to error monitoring. The learning process includes error monitoring as well as emotional responses related to both setting a goal and reaching a goal. These factors are evident throughout the present intervention (Salamone & Correa, 2012) and should support the methodology and my hypothesis that music production can facilitate neuroplasticity and have a positive cognitive rehabilitation effect.

Recent research has shown that music listening and production activates the reward circuitry cortical networks relating to emotional reward (Brodal, Osnes, & Specht, 2017), neural systems similar to those known to respond specifically to biologically relevant stimuli for food, sex and drugs. These systems are located in the brain areas for reward and motivation, which is part of the limbic system of the brain, located in the medial forebrain bundle (Blood & Zatorre, 2001). As mentioned, the OFC has connections to the limbic system. The activation of the limbic system is followed by a dopamine release, a neurotransmitter evident in the reward system (Brodal et al., 2017; Owessen-White et al., 2016). The increased activity in the bilateral OFC in the present study may be related to the increased scores for social interaction.

This raises the question of whether the role of dopamine released during music processing in the brain is a key explanatory factor for why the patient group showed increased cognitive performance post-intervention. The objective of the intervention was to learn to play the piano. The learning process in the intervention programme is goal-oriented, and mastering a goal is a provider of positive emotion (Salamone & Correa, 2012). The learning mechanism primarily consists of setting a goal, which is a provider of positive emotion (Salamone & Correa, 2012). According to Salamone et al., even when you set a goal, before starting on the task, you achieve a feeling of positive emotion, which is a dopamine-release factor (Salamone & Correa, 2012). The patients in the present study reported having a positive experience during both the learning process and the intervention in general. We can say that, in a therapeutic setting, playing an instrument may indeed be a provider of positive emotion related to mastering a goal (Salamone & Correa, 2012).

The joy of playing music per se can further be an important factor in the rehabilitation process. Together with the satisfaction of learning to play an instrument, a positive experience during the learning process may promote the release of dopamine (Brodal et al., 2017; Lehrer, 2011; Salamone & Correa, 2012), a neurotransmitter activating the brain's executive functions, such as attention, concentration, learning and memorisation (Salamone & Correa, 2012). As reported, the analysis of fMRI results of the patient group revealed increased activation in the OFC and normalisation of cognitive performance and social behaviour. The possible effect of dopamine will be discussed in more in detail in the next section.

2.7. *The role of dopamine*

As mentioned above, dopamine release during music training may have an effect on cognitive processes, resulting in enhanced cognitive performance and increased social behaviour. Playing the piano has a profound effect on the neural networks in engaging neural circuits evident in emotion and reward, which are important for stimulus-reinforcement learning, an essential factor in social interaction (Rolls, 2004). Playing an instrument is goal-oriented. And mastering a goal is a factor in the release of dopamine (Lehrer, 2011), a neurotransmitter evident in the reward system (Brodal et al., 2017). Dopamine plays a role in both the central nervous system (CNS) and peripheral nervous system (PNS). It is involved in feelings of pleasure, motivation, mental focus and energy, and activates neural structures in the brain's reward-signalling pathways, executive functions, sex drive, addiction, movement, setting a goal and mastering a goal (Salamone & Correa, 2012).

The enjoyment of playing the piano, as reported by the participants, may have a dopamine-releasing effect, thereby increasing the neurotransmitter effect between the neural networks affecting the OFC and executive functions, followed by the normalisation of emotional reactions that are fundamental to social interaction (Rolls, 2004). The participants reported enjoyment and motivation for playing both during lessons with the instructor and also when playing at home. It should be noted that home lessons were structured and came with accurate instructions to be followed, with a minimum of 15 minutes per day. This training programme was developed to avoid fatigue and dropping-out during the intervention.

Nearly all detected brain areas that revealed a recovery effect also received direct or indirect dopaminergic connections, such as the prefrontal cortex and the anterior insular cortex (Christopher et al., 2013). This provides support for the assumption that actively playing a musical instrument might have a dopamine-releasing effect.

2.8. *The neural basis of music perception and cognition*

Perceptual and cognitive aspects of listening to and playing music, with particular emphasis on underlying neuronal and neurocomputational representation and mechanisms, are a specific science within music psychology (Deutsch, 1982).

Research on the neural basis of music has revealed that different aspects of musical processing mobilise almost all regions of the neural networks (Chartrand, Peretz, & Belin, 2008; Koelsch & Siebel, 2005; Tramo, 2001; Zatorre, 2007). There is no single music centre in the brain (Altenmüller, 2007). Basic perceptual dimensions of hearing (pitch, timbre, consonance/roughness, loudness, auditory grouping), form salient qualities, contrasts, patterns and streams that are used in music to convey melody, harmony, rhythm and separate voices. Perceptual, cognitive, and neurophysiological aspects of the temporal dimension of music (rhythm, timing, duration, temporal expectation) are present during music processing.

Non-music neural networks are activated in both hemispheres during music production (M. H. Thaut et al., 2009; Tramo, 2001). There are shared and overlapping neural systems for music and language that may facilitate the re-routing of neural networks and an increase of synapses (Brown, Martinez, & Parsons, 2006; Koelsch & Siebel, 2005). Neural systems between musical cognition and parallel non-musical, cognitive functions may enable music to affect general non-musical functions, such as memory, attention and executive function (M.H. Thaut, 2010).

Playing an instrument activates both hemispheres since the different factors in musical structure are located in different parts of the brain. The following musical structures activate the right hemisphere: pitch, interval, melody (in terms of contour of pitch), timbre, rhythm (grouping of meter, foot-tapping), and tonal patterns. The left hemisphere is activated by rhythm processing (rhythmic pattern), chords (bilateral activity), words (in song), music lexica (single notes), and shared networks for music and speech (Münte et al., 2002; Tramo, 2001). The neural structures that are involved during playing are: the frontal cortex, hippocampus (association networks, episodic and semantic), limbic area (association, emotion, reward), amygdala (processing of memory and emotional responses), thalamus (involved in sensation-linking sensory and motor parameters), Broca's area (language pathways, overlapping music pathways), basal ganglia (involved in kinaesthetic movement during playing), occipital cortex (involved in reading music notation) (Tramo, 2001).

The intervention programme was designed to activate most neural networks. In other words, playing the piano should involve all the above-listed neural structures, and the curriculum consisted of well-known nursery rhymes in addition to familiar tunes.

There is evidence from the literature that music processing shares the brain's system with non-musical networks (M.H. Thaut, 2010). Links between music and cognitive functions have been the subject of a growing body of research that sheds lights on the links between music and a variety of cognitive functions, including temporal order learning (Hitch, Burgess, Towse, & Culpin, 1996), spatiotemporal reasoning (Sarnthein et al., 1997), attention (Drake, Jones, & Baruch, 2000) and auditory verbal memory (Chan et al., 1998; Deutsch, 1982; M.H. Thaut, 2005).

Several authors have shown that music practice activates neural pathways involved in language processing (Brown et al., 2006; Koelsch & Siebel, 2005). The OFC also receives input from the visual system. A number of studies suggest that a core distributed network of areas in the parietal, temporal, and occipital cortices supports sight-reading, together with activation in the frontal, subcortical, and cerebellar areas (Nakada, Fujii, Suzuki, & Kwee, 1998; Schön et al., 2002; Stewart et al., 2003).

The methodology in the piano-intervention programme included sight-reading notation, and it can be assumed that reading music notation activated and stimulated the OFC during performance. Sight-reading a score during music performance adds a major cognitive load (Parsons et al., 2005).

In other words, playing an instrument activates non-musical neural networks, which may facilitate dendritic sprouting that is fundamental to synaptic plasticity (Peretz, D, Lagrois, & Armony, 2015; M.H. Thaut, 2010).

The goal of the music lessons during the intervention was to engage the neural networks to the maximum, and to facilitate brain activation between the two hemispheres simultaneously.

The hypothesis for this thesis is that, during the repetitive actions involved in music performance, this activity facilitates the neural networks in re-routing neural connections that were inhibited due to disruption of axons following an injury.

2.9. *How do we know the neural structures of music?*

Different modules of music are processed, as described above, in different, but partly overlapping, neuronal networks in both hemispheres (Altenmüller, 2007; Koelsch et al., 2004; Parsons et al., 2005). Results from lesion studies and neuroimaging techniques have been widely presented in mapping different musical structures to the neural networks (Peretz & Zatorre, 2003). It is possible to lose one musical skill while keeping others intact (Cappelletti, Waley-Cohen, Butterworth, & Kopelman, 2000; Vik, 2006; Zatorre, 2007). It is especially lesion studies of musicians that have provided information about the neural processing of music (Hebert & Cuddy, 2006; Peretz & Zatorre, 2003).

One well-known example is the composer Maurice Ravel (1875-1937), who suffered from an illness in the cerebral cortex, more specifically the area for language. He lost the ability to write down notes for new compositions, and to sing or play new melodies he could hear in his 'inner ear'. Despite this partial deficit in his neural networks for language, on request, he could still write down, for example, an A or a C on the stave (Dietrichs & Gjerstad, 2007). Impairment of sight-reading is called music alexia, which is neurally and functionally distinguishable from reading words and numbers. Moreover, this musical reading disorder can be observed in relative isolation because playing, singing and musical memory can be well preserved, as described in the literature (Cappelletti et al., 2000; Hebert & Cuddy, 2006; Vik, 2006). The lesions responsible for music alexia are located in the left hemispheric structures (Parsons et al., 2005). Parsons and his colleagues conducted a study in which pianists were scanned using PET while they performed several conditions involving listening to scales, playing scales, sight-reading a score, and sight-reading a score while playing it. Analysis from the 'sight-reading of a score while playing' condition revealed activity in the left parietal cortex, and in the left occipitoparietal sulcus and bilateral superior parietal cortices.

Sixteen cases were investigated in a review of the literature on brain damage and music reading (Hebert & Cuddy, 2006). In most cases, the lesion site was located to the left posterior temporo-parietal lobe and the left parieto-occipital area of the brain. However, Cappelletti also reported a case of music alexia with lesion of both the left posterior temporal lobe and a small right occipito-temporal area (Cappelletti et al., 2000). In her paper, Vik describes how a professional pianist was injured in the left occipital lobe and lost the ability to read musical notation (Vik, 2006). In other words, brain damage might impair or spare connections in the neural networks. One of the most famous cases of selective disorder is probably that of Shebalin, a Russian composer who, following a vascular accident occurring in his left hemisphere, suffered an aphasic condition for the rest of his life. He nevertheless continued to compose. Shebalin displayed severe language deficits, yet retained his musical skills (Peretz, 2007). Peretz and Zatorre have contributed profoundly to the study of music and brain functions by exploring the neural substrates of musical activities using behavioural-lesion techniques as well as brain imaging methods (Peretz & Zatorre, 2003).

2.10. *Neuroplasticity*

The brain is a dynamically organised structure that changes and adapts in response to repeatedly performed actions or demands imposed by the environment. This process is called neuroplasticity and goes back to an old principle, originally discovered by the Canadian psychologist Donald Hebb in 1961. It has been shown that temporally coherent input to competitive neural networks changes the efficiency, density, and connectivity of synapses (Hebb, 1961). Multisensory integration during practice enhances training-related changes in sensory and association cortical areas during auditory cognition (Herholz, Coffey, Pantev, & Zatorre, 2015), and causes both structural changes in white matter and functional neuroplasticity, described as a change in the brain's interconnected processing (Schlaug, 2009c; Särkamö et al., 2014).

Playing an instrument is one example that provides such an enriched environment for the brain to promote dendritic sprouting, which is fundamental to synaptic plasticity (Goldberg, 2009). Because playing an instrument activates multisensory integration during practice (auditory cortex, visual cortex, motor cortex), this activity enhances training-related changes in sensory and association cortical areas during auditory cognition (Herholz et al., 2015; Herholz & Zatorre, 2012). It is widely documented that, over time, music making has been shown to effectively change the structure and enhance the function of many brain areas (Altenmüller et al., 2009; Jäncke, 2009; Rojo et al., 2011; Schiavio & Altenmüller, 2015; Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995; Sihvonen, Leo, Tervaniemi, Altenmüller, & Soinila, 2017; Särkamö et al., 2014). To quote G. Schlaug in summary of this section: 'Music may thus engage and link up brain centres that otherwise would not connect with each other' (Schlaug, 2009c) p.372.

However, the novelty of this thesis lies within the field of rehabilitation of cognitive deficits following mTBI.

2.11. *Music-based intervention.*

The definition of music-based intervention includes all experimental protocols that use music in various forms to study its therapeutic effects (Sihvonen et al. 2017).

There are several definitions of key terms that will be outlined in the following.

2.12 *Neurologic music therapy*

Neurologic music therapy (NMT) is a music-based intervention founded on principles from the neuroscience model of music perception and cognition, and the influence of music on changes in non-musical brain functions. It is founded on complex perception, cognition and motor control in re-training the brain (M.H. Thaut, 2010). NMT is a standardised music therapy comprising multiple techniques, implemented by a specialised music therapist.

The method stands in contrast to compensational therapy and is designed to stimulate the rewiring of broken neural networks that cause specific impairments in patients with disorders after brain damage (M.H. Thaut, 2010).

There is empirical evidence of the benefits of NMT in several areas. In a recent review of controlled studies of interventions in neurological rehabilitation, the main focus was on stroke rehabilitation, Parkinson's disease, dementia, multiple sclerosis and epilepsy (Sihvonen et al., 2017).

Music-based interventions have been shown to enhance verbal memory, focused attention and visual awareness in patients with stroke. The results have also demonstrated an improvement in mood and quality of life (Sihvonen et al. 2017). The therapeutic effects of music as a tool for improving 'well-being' and emotional factors in therapeutic settings are well known (M.H. Thaut, 2010).

2.13. *Music-supported training*

Music-Supported Training (MST) was developed for motor rehabilitation of stroke patients. In MST, gross and fine movements of the hemiparetic upper extremity are trained by playing musical instruments (e.g. drums, keyboard) (Sihvonen et al., 2017). A number of controlled studies of motor rehabilitation of the same category of patients provide clear experimental evidence of music-supported plasticity in cortical networks (Altenmüller et al., 2009; Hegde, 2014; Herholz & Zatorre, 2012; Jäncke, 2009; Pantev, 2009; Rojo et al., 2011; Särkamö et al., 2014).

Melodic intonation therapy is a singing-based intervention developed for the rehabilitation of stroke patients with aphasia. Inhibited language-related brain regions in the right prefrontal areas are reactivated after melodic intonation therapy (Schiavio & Altenmüller, 2015)..

Research on patients suffering from Parkinson’s disease has shown that entrainment with a rhythmically rich auditory feedback may alleviate Parkinsonian gait. There is evidence that patients are able to stabilise and synchronise their disturbed gait with the help of an external auditory rhythm, and that their motor coordination may be temporarily improved by familiar and stimulating music (Dalla Bella, Benoit, Farrugia, Schwartz, & Kotz, 2015; M.H. Thaut et al., 1996).

Cognitive benefits of music listening in early dementia have also been observed (Sihvonen et al., 2017).

2.14. *Music-based intervention in cognitive rehabilitation following mTBI*

The definition of NMT – ‘the therapeutic application of music to cognitive, sensory, and motor dysfunction due to neurologic disease of the human nervous system’ (M.H. Thaut, 2010) – has some components that are similar to those in the present study. The NMT method is based on neuroscience models of music perception and learning, and the influence of music on changes in non-music-related brain areas. However, the present study does not fit the standardised music therapy method, which comprises multiple techniques and is implemented by a specialised music therapist.

I would suggest that the intervention applied in the study fits the description of a music-based intervention that includes all experimental protocols that use music in various forms to study its therapeutic effect (Sihvonen et al., 2017).

Knowledge from music perception and cognition, neuromusicology and the results from evidence-based research on music and the brain supports the present approach to music-based intervention applied in the cognitive rehabilitation of patients with mTBI (Wan & Schlaug, 2010).

3. AIMS OF THE STUDY

The main aim of this thesis was to investigate the effects of musical training (MT) on the brain's neural networks with respect to reorganising neural circuits and thereby restoring cognitive functions in patients suffering from cognitive deficits after mTBI. To obtain this information, the author designed a music-based intervention programme consisting of a structured piano-tuition protocol lasting eight weeks. The question addressed was whether playing the piano would stimulate the neural networks to re-route neural connections and link up inhibited neural networks. The objective was to restore cognitive functions in the patients to what they were before their injury.

Paper I

The aim of Paper I was to evaluate the effects of playing the piano on cognitive performance and social behaviour in patients with cognitive deficits following mTBI.

Paper II

The aim of Paper II was to further investigate the results from the intervention, which revealed functional changes in the orbitofrontal cortex (OFC) in the patient group that were consistent with significant results from neuropsychological tests. Both task and resting-state fMRI provided evidence of a possible causal relationship between music intervention and functional reorganisation of neural networks in the OFC.

Paper III

The objective of Paper III, a case study of the seven participants in the patient group, was to identify clinical characteristics that could predict a positive or negative outcome of the intervention.

4. MATERIALS AND METHODS

4.1. *Study design*

In this study, I investigated the effects of an eight-week, intensive and structured piano-training intervention. I used a longitudinal design that enabled me to observe the causal influence of multisensory training on higher-order auditory cognition and possible functional and structural changes in the brain's neural networks. The intervention period and methodology were based on a case study in which a pianist with music alexia (deficit in reading musical notation following mTBI) used the present method and was restored to full functionality in reading musical notation, achieved improved concentration and memorisation, and returned to work (Vik, 2006).

A between-group design and a longitudinal within-subject design were used. All participants from the mTBI group and the first control group with music were examined pre- and post-intervention.

The second control group without music was also examined twice with an eight-week interval, but without any intervention.

An mTBI group with delayed or conventional/alternative training was considered as an additional patient group, but had to be omitted for technical reasons, due to a major scanner upgrade that terminated the study.

All participants were assessed using a neuropsychological test battery, functional and structural MRI scanning with two experimental fMRI paradigms and resting-state fMRI (Rs-fMRI).

Semi-structured interviews were administered pre- and post-intervention for the patient group only. Their purpose was to investigate health problems, work- and social-related conditions before and after training, and their subjective opinion of their cognitive performance pre- and post-intervention.

The pre-intervention questionnaire comprised three sections. The first section concerned the accident, hospitalisation and possible rehabilitation, the second part consisted of questions about present well-being and social status, including any problems with attention and cognition. The third and last part was related to their work situation pre- and post-accident up to the time of the intervention. The post-intervention questionnaire was designed differently, and the main questions concerned how the participant experienced the intervention, with individual follow-up questions concerning their different health issues pre-and post-intervention.

Both music groups filled in a daily log during the eight weeks of intervention. They reported daily practising time and any comments about the learning process. The patient group had an additional section for the purpose of reporting well-being from day to day.

4.2. *Participants*

Three groups of participants were recruited to the study: one group of 7 patients with mTBI learning to play the piano (please see 4.2.5. for details), one control group of 11 healthy participants learning to play the piano, and one control group of 11 healthy participants without piano tuition. All participants were non-musicians, and none had any formal music education or were amateur musicians.

Norway's school curriculum includes music lessons. The curriculum consists of learning notation up to a minimum of do-re-me (one scale) and playing a few songs on a recorder. Most of the music lessons consist of singing, folk dancing, learning music history, and listening to music. All participants were therefore novices in terms of learning to play an instrument, in this case the piano. It should be noted that in grade 9, students prepare and perform a musical. Participants in the musical, i.e. those playing instruments, consist of students who play instruments in one of the municipal music schools. In other words, the curriculum does not include any formal music tuition on instruments.

The participants were not screened for amusia, a severe form of musical impairment. Research provides evidence that the right temporal and frontal cortices are the core neural substrates for adequate perception and production of music (Teppo Särkamö et al., 2013).

I suggest that amusia would not have any relevance to the impact of the intervention on non-musical networks. The purpose of the intervention was to engage the brain in a multimodal activity, encouraging the brain to develop new pathways. The factors under assessment were based on training time, and not individual progressive advances made in playing the piano. Nevertheless, this factor is interesting and should be included in a future replication of the study.

Musicians were not included to avoid the possible confounding variable of neural brain differences in musicians and non-musicians (Stewart, 2008). Patients were recruited from Haukeland University Hospital, Norway, where they had been admitted at the time of accident. Control groups were recruited using posters at the University of Bergen, Norway. Participants in all groups varied between 18 and 65 years, the mean age was 36 years, and the gender distribution was equal between groups.

All participants in the music groups had access to a piano, except one. This participant was provided with a keyboard during the intervention period.

4.2.1. *Inclusion criteria – patients*

Patients aged 18–65 diagnosed with mTBI two years post-injury with cognitive and/or social deficits.

4.2.2. *Inclusion criteria – controls*

Participants in the control groups aged 18–65 were recruited, matching the patient group in terms of demographic, social and educational factors

4.2.3. *Exclusion criteria – all groups*

Participants with psychiatric disease, previous major head trauma or other diseases that would have an impact on cognitive performance and social behaviour, or diagnoses with substance abuse as stated in their medical records, were excluded.

Musicians were excluded to avoid the variable of possible differences in neural networks between musicians and non-musicians (Schlaug, 2009c; Stewart, 2008; Stewart & Walsh, 2001). The definition of musician is a person with more than four years of formal music education (Stewart, 2008). However, none of the participants included in the study had any formal music education, and none were amateur musicians.

4.2.4. *Ethics*

The Regional Ethics Committee of Western Norway (REK-Vest) approved the protocol. All participants were given information about the study, its aim and procedures, and were given an opportunity to withdraw from the study at any time. They signed a consent form before the start of the intervention.

4.2.5. *Patient group – clinical data*

The participants in the mTBI group were all out-patients recruited at least two years post-injury. The reason for the two-year time period post-injury was to avoid the possible confounding variable of self-recovery, which can take place during the two first years post-accident (Beaumont, 2008).

The patients were all admitted to hospital when injured and were diagnosed with mTBI in accordance with the WHO Task Force suggestion of a professional health care provider administering the GCS at the first meeting at least 30 minutes after injury (Lannsjo et al., 2011). The Glasgow Coma Scale (GCS) scores, ranging from 3 to 15, assess the level of consciousness based on eye, verbal and motor responses. Patients with a GCS score of 13–15 are classified as mild TBI, with a GCS score of 9–12 as moderate TBI, and with a GCS score of 3–8 as severe TBI (Heskestad, 2017). The patients were further assessed using the Rivermead Post Concussion Symptoms Questionnaire (RPQ) – a specific 16-item questionnaire that measures cognitive, emotional and physical symptoms (**see Table 1 in Paper I**). The patients' symptoms during the last 24 hours are compared to before the traumatic brain injury, and the response to each item is rated using a 5-point Likert scale as follows: 0 = not experienced at all; 1 = no more of a problem; 2 = a mild problem; 3 = a moderate problem; 4 = a severe problem. The Hospital Anxiety and Depression Scale (HAD) consists of 14 items detecting states of depression (7 items) and anxiety (7 items), rated on a 4-point scale from 0 to 3: 0 = no symptoms, and 3 = a severe symptom or symptoms most of the time.

Two years post-injury, all patients included in the study were still affected by specific individual cognitive deficits despite conventional rehabilitation provided by the Norwegian National Health Service at the time of injury. These deficits included problems with attention, working memory, memorisation, retrieval of memories, fatigue, sensitivity to sound and light, and social interaction. However, it should be emphasised that the deficits mentioned were individual for each participant in the mTBI group.

These data were obtained during semi-structured interviews when recruited for the study, within one month before the intervention start up (see 4.3.4 for details). They were all either on sick leave or worked part-time. None of the patients had been in work as before the accident.

The participants in the patient group received an invitation letter from Haukeland University Hospital, Bergen, Norway, to which they had been admitted after injury. Seven patients enrolled for the study.

4.2.6. *Control groups – healthy participants*

Eleven healthy participants in the first control group with music, and 12 healthy participants in the second control group were included in the study. All participants were given detailed information about the aim of the study, assessment using pre/post fMRI and neuropsychological tests. Participants in the first control group learned to play the piano. The second control group was a baseline group and did not receive any musical training.

4.3. *Procedures*

4.3.1. *Piano training protocol*

The author developed an eight-week piano tuition intervention programme, with structured 30-minute lessons consisting of both playing and music theory. Reading musical notation was part of the tuition. The piano protocol was based on a standardised curriculum with an applied tuition book for beginners (Agnestig, 1958). 39 progressive pieces were set as the curriculum. The participants were informed about the song material, which mainly consisted of well-known nursery rhymes. The repertoire was chosen based on knowledge of good tuition methodology. The very last piece, played using two hands, was a piece by Beethoven, *Ode to Joy*, a popular piece, that gave the participants a feeling of mastering the piano.

The focus was on repeating the learned material to facilitate neuroplasticity (Hebb, 1961). Every new lesson therefore always started by reinforcement of the previous lesson. (See the appendix to Paper 1 for the detailed intervention programme.)

The participants in both music groups received two lessons per week in the lab, with the author as instructor (the author has a BA in music teaching and a master's degree in music psychology), and each lesson lasted 30 minutes. They were scheduled two days apart with instructions to practice for a minimum of 15 minutes every day of the week.

The methodology was to use both hands simultaneously from the very first lesson, thereby developing equal motor movements in both hands to stimulate inter-hemispheric coordination of motor areas in the brain. Playing the piano demands kinaesthetic movement of both hands, which excludes the confounding variable of right/left-handed participants (Stewart, 2008).

The goal was to play pieces with both hands, the melody in the right hand and chords in the left. In general, playing an instrument activates the whole brain since musical elements such as pitch, rhythm, melodic contour and chords are processed in different parts of the brain. Reading and playing single notes with one hand, while at the same time reading and playing a chord with the other hand, will cause increased inter-hemispheric communication and coordination, since it is assumed that single notes are mainly processed in the left hemisphere, whereas chords are perceived as patterns and therefore predominantly activate the right hemisphere (Gordon, 1983).

Sight-reading a score during performance adds a considerable cognitive load. Parsons and colleagues found that reading a score activated the posterior occipital cortex. Other areas in the frontal, subcortical and cerebellar areas were also mobilised, depending on whether the score was merely read, read and imagined to be heard, or read while being performed (Parsons et al., 2005).

The protocol was structured to include all participants in a stepwise manner.

However, since music students vary in their ability to learn, the material was flexible as regards the number of pieces learned during the whole period (8 weeks). A few of the participants in both music groups finished the curriculum after four weeks and were given a few additional pieces, easily arranged classical pieces. The same participants wanted to extend their practising time. Approval was given for longer practising time than the set 15 minutes each day. Individual training time was controlled for in connection with personal reports. The question of training time versus cognitive enhancement is an interesting aspect.

It can be asked whether these factors would confound the final result. However, the focus was on the actual time spent on training and not on the ability to play the piano. Further, differences in training time could be a variable affecting the final result. This factor will be discussed in section 6.1.7.

Participants in both music groups were given instructions to keep a log of their actual training times.

4.3.2. *Instruction form – patient group*

Playing an instrument is a complex task for the brain and can result in headaches and fatigue during practising, in particular. The participants were instructed to stop practising if they experienced problems with vertigo, headaches, fatigue or other health issues while playing.

The same factors relating to feeling unwell during music lessons were listed in the information. The instructor kept a detailed log of every lesson for all participants during the intervention period, including all factors relating to actual playing time and health issues.

4.3.3. *Assessment of participants pre- and post-intervention*

Participants in all three groups were assessed before and after the intervention period using neuropsychological tests, fMRI and resting-state fMRI. Additional information was obtained from semi-structured interviews with the patient group only, and from logs kept by both music groups in addition to the log kept by the instructor.

4.3.4. *Semi-structured interviews*

The author developed and carried out semi-structured interviews pre- and post-intervention for the patient group only. The interviewer did not strictly follow a formalised list of questions. Semi-structured interviews allow for open-ended questions and responses from the participants, and can provide more in-depth information. The disadvantage of this method is that it can make it more difficult to analyse and compare answers from participants within the same group.

The pre-intervention questionnaire was divided into three sections. The first comprised questions about the actual accident, hospitalisation, and whether any rehabilitation had been provided. The second section concerned post-concussion symptoms, and the participant was asked to outline problems of an emotional, behavioural, cognitive and physical nature. The third section consisted of questions about the work situation. They were informed about the purpose of the different sections and were asked to freely describe their difficulties with reference to the section in question.

The post-intervention questionnaire was also divided into three sections. The first concerned how the participants would describe the intervention. This was an open-ended question and had follow-up questions concerning any positive or negative effects they experienced during the eight-week intervention period.

The second part contained questions about when during the intervention period they noticed any improvements in the problems they reported in the pre-intervention questionnaire.

The third section concerned their opinion of a possible return to working or studying as before the accident.

The patient group kept a log of every practice session, with the emphasis on issues related to well-being and fatigue, which is often a major factor following TBI.

The pre-intervention data are presented in Table 1 Paper II, which covers well-being and social behaviour, including the work situation pre- and post-intervention. However, it would be more appropriate to also present data from the post-intervention questionnaire and data obtained from logs during the intervention period. These data have been reported in a general way, since 6 out of 7 patients reported improved wellbeing and social interaction. (See Paper III for detailed qualitative data).

4.3.5. *Neuropsychological tests*

A test battery of three different neuropsychological tests was applied during the pre- and post-intervention examination of the participants. The test battery contained the Mini Mental Status Test (MMS) (Folstein, Folstein, & McHugh, 1975). This test measures cognitive impairment and is commonly used in clinical and research settings. It should be noted that the MMS test was withdrawn from the total assessment after testing before the intervention. Both the patient group and the control group with music displayed a ceiling effect.

4.3.5.1. *California Verbal Learning Test II*

The California Verbal Learning Test (CVL-II) (Delis & Ober, 2000) is a widely administered neuropsychological test, which, firstly, assesses verbal learning, but also learning strategies, memorisation and retrieval of information. The test is efficient in charting encoding, learning, working memory and long-term memory in a systematic manner. I administered the Norwegian version of the CVLT-II test. The test consists of several tasks, the starting point being five repetitions (trials) of a 16-word list that the participants repeat after each presentation. I concentrated on three measures targeting general memory impairment (the sum score of correct repetitions in trials 1–5), a composite score of memory and learning (the sum score of correct repetitions in trials (2-5) and, finally, the learning slope (of trials 1–5) for encoding abilities.

The 16-word list consisted of four categories, comprising words from four unrelated categories, but randomly listed in the trial. It was therefore a challenge for the participants to observe the four categories of words that would expose the learning slope. Learning strategies (i.e. semantic versus serial clustering) were therefore an important part of the test.

Group I demonstrated an increase in performance up to the level of Group 2 and Group 3 before the intervention, where the patient's end-point corresponds to the starting point of Group 2 and Group 3.

4.3.5.2. *The Stroop test*

The Stroop test (Golden & Freshwater, 1978) tests attention ability and ability to switch attention by measuring verbal processing and response inhibition. The test consists of three tasks: a word-reading task (a randomly ordered list of the words 'green', 'red' and 'blue'), a colour naming task, (a randomly ordered list of Xs with the same three colours), and, finally, a colour-word task, where participants have to name the colour and the colour of the ink in the same three written words, e.g. 'red' written in green ink.

The data collected from CVLT II and the Stroop test were analysed using a 3 (group) x 2 (repetition) repeated-measure ANOVA model, using SPSS 22 (www.ibm.com).

The results from the CVL II test demonstrated a significant effect on executive functions related to attention, learning strategies and retrieval of memories in Group I (the mTBI group). Group 2 (healthy participants with music) also achieved a significant effect of the intervention with music (see Fig.1. Paper I).

The results from the Stroop test produced a different picture. Only Group 2 and Group 3 demonstrated a repetition effect.

Interestingly, these results give reason to speculate on a specific cognitive target for the intervention, which will be outlined in the following discussion.

4.3.6. *fMRI scanning sessions*

fMRI scans were carried out pre- and post-intervention for all three groups. The fMRI examinations took place at the Department of Radiology, Haukeland University Hospital, using their 3T General-Electrics Signa MR system. Besides a high resolution, T1-weighted scan, two task-related fMRI sessions were included in the scanning protocol, where one task was a pitch discrimination task and the other one was a passive listening task. In addition, resting-state fMRI was performed to examine functional connectivity.

fMRI investigates neuronal activity by measuring changes in blood oxygenation over time, since oxygenated and deoxygenated haemoglobin have distinct magnetic properties that differentially affect tissue relaxation. The change in the magnetic properties of water molecules is detected using $T_{2.}$ Different molecules have different relaxation times in the longitudinal T_1 transverse T_2, T_2 plane, which can be exploited to investigate specific properties of the tissue in question. The relaxation causes signal emission, which is detected by a radiofrequency coil and is transformed into spatially informative MR images.

When conducting an fMRI study, it is important to keep in mind that the BOLD response is a metabolic correlate of neuronal activity, not an actual measure of the neuronal firing itself. The term 'activation' is therefore used to describe the BOLD response, while 'activity' refers to the actual neuronal response (Ogawa & Lee, 1990).

4.3.6.1. *Pitch discrimination task*

The pitch discrimination task was designed to measure group differences in reaction time pre- and post-intervention. This is considered to be a low-level cognitive task. It is adapted from Zatorre (Zatorre, 2007). The paradigm aims to measure low-level attention as well as, through the responses, response latency.

The task was administered as a block design, where the participants were instructed to judge whether the second of two tones was higher or lower in pitch than the first one. The participants listened through MR compatible headphones and were instructed to press a button in response.

This task was the first of the two to be set. The intention was to get all the participants to relax in the scanner with a low-level cognitive activity, before administering the second task, a high-level cognitive task aiming to activate most regions of the brain, including neuronal networks responsible for executive functions (Zatorre, 2007). Executive functions were of special interest because the patients' deficits were in higher-order executive functions, especially attention and concentration.

The fMRI data were acquired through an echo-planar imaging (EPI) sequence with the following parameter: TR 3s, TE 30ms, matrix size 128x128, 30 slices, voxel size 1.72 x 1.72, 4.4. The block design consisted of 5 blocks on and 5 blocks off, and each on-off block cycle lasted for 40 seconds. In total, 100 EPI volumes were acquired.

4.3.6.2. *Listening task – Tonika-Dominant-Tonika*

To investigate which neural networks had a possible change in activation before and after the intervention, I designed a passive listening task, containing extracts of a Western musical cadence pattern of Tonika-Dominant-Tonika (TDT) chords based on the first, fifth and first tones of the scale. The relationship between individual tones forms the basis for the most fundamental aspect of music processing and recognition of melodies (Zatorre, 2007). TDT is a melodic pattern in Western music that activates semantic and episodic networks that are important for long-term representation of familiar tunes. The paradigm was adapted from Zatorre (Zatorre, 2007). All participants in the study were familiar with Western music.

This paradigm was intended to act as a mnemonic device activating association cortices, in addition to activating higher cognitive functioning systems such as executive control, specifically attention and concentration.

It was presumed that this passive listening task would activate most regions of the brain to facilitate assessment of possible changes in the neural networks pre- and post-intervention. This assumption was based on knowledge of how music listening, and to well-known music in particular, activates the brain and the following neural networks: the frontal lobe, association cortices, and the mesolimbic system

According to the neural basis of music perception and cognition (see 2.8. for details), music listening activates non-musical networks in both hemispheres.
Stronger involvement of the prefrontal cortex and association cortices was predicted, which was also one of the results of the analysis of the fMRI results of the TDT task, but there was also a significant change in activation of the OFC in the patient group.

Music is a powerful stimulus for the human brain, engaging not just the auditory cortex but a vast bilateral cortical network of temporal, frontal, parietal, cerebellar and limbic brain areas that govern auditory perception, syntactic and semantic processing, attention and memory, emotion, mood control and motor skills.

All melodic perception involves the working memory mechanism (Zatorre, 2007). Neural structures involved in music perception and production go from the auditory cortex to the frontal cortex in interaction with working memory, association networks (semantic and episodic memory foundations in the hippocampus), limbic systems and the amygdala, which processes emotional reward and emotional responses, language pathways overlapping music pathways in the Broca's area, basal ganglia involved in motor movement and the occipital cortex, which is activated when reading musical notation.

The extracts were taken from classical and popular Western music. Twenty-eight extracts were presented in an event-related design, with varying delays between each stimulus. The total length of the paradigm was about 7:33 minutes, and the length of the single stimuli varied between 2 and 19 seconds, with a variable delay between stimuli that varied between 4 and 18 seconds. In total, 160 images were acquired with the same imaging parameter as described above.

4.4. *Analysis of functional neuroimaging scans – effects*

4.4.1. Pitch discrimination task

To explore the average effects of the pitch discrimination task, mean contrasts across repetitions have been specified for each group and then summarised as a conjunction analysis across groups. The result indicates a widespread, mostly bilateral network, comprising a supplementary motor area (SMA), anterior insular, cerebellum, thalamus, putamen, Heschl's gyrus/superior temporal gyrus, and supramarginal gyrus (**see Table 3a. Figure 2 in Paper I**).

The ANOVA results revealed neither significant main effects of group nor a significant interaction. The response data from this paradigm, which was a simple reaction time task, have also been analysed using a repeated-measure ANOVA. The results demonstrated a significant main effect of repetition and of a group repetition, but only a strong trend towards a main effect of group. These significant effects were mainly driven by improved performance in Group 2.

4.4.2. Listening task – TDT

The results of the TDT task revealed a significant group x repetition interaction in the medial orbitofrontal gyrus (see Figures 3a and 3b in Paper I). This effect was followed up by a 2 x 2 ANOVA between Group 1 and Group 2. This confirmed the previous results and was followed up with a t-test, which indicated that the activation in the medial orbitofrontal gyrus increased in Group 1, and slightly decreased in Group 2 (**see Figure 3 in Paper I**).

The conjunction across group averages mainly activated the left and right auditory cortex. The ANOVA results showed no main effect of group x repetition.

The increased activation of the medial orbitofrontal gyrus in the mTBI group strengthens the evidence that active training in music production influences neural activity and cognitive functioning in both patients and healthy controls.

4.4.3. Resting-state fMRI

Resting-state fMRI has its origins in Biswal (Biswal, Yetkin, & Haughton, 1995) who studied functional connectivity in the somatosensory networks of the resting human brain using fMRI. Resting-state data are BOLD signals acquired when participants are awake and not performing any specific motor or cognitive task (Azeez & Biswal, 2017). Resting-state networks consist of regions known to be involved in motor function, visual processing, executive functioning, auditory processing, memory, and what is known as the default-mode network (DMN) (Damoiseaux et al., 2006). Biswal's discovery has been widely replicated by several groups (Raichle, MacLeod., & Snyder, 2001; Sharaev, Zavyalova, Ushakov, Kartashoc, & Velichkovsky, 2016).

In 2001, Raichele and colleagues discovered the Default Mode Network (DMN) (Raichle et al., 2001). The DMN is an interconnected and anatomically defined brain system that is active when the brain is at rest and awake, in other words when the brain is not focusing on a particular task, but lets the 'mind wonder', and when retrieving memories. The brain is constantly active in resting state in contrast to when the brain is focusing on a particular task (Sharaev et al., 2016).

The use of rs-fMRI is now widespread. It is used to characterise differences in functional connectivity between subject groups (Friston et al., 2014). Resting-state functional connectivity can be used to detect brain plasticity (Guerra-Carillo, Mackey, & Bunge, 2014), which is the focus of this thesis.

Resting-state fMRI data in the present study were acquired both in the pre- and post-intervention sessions. Based on the results from the TDT task fMRI in which there were functional changes in the orbitofrontal cortex in the patient group only, the seven regions of interest for further analysis were based on the results from the non-parametric analysis of the pre- and post-intervention differences. The rs-fMRI examination lasted almost nine minutes, and the following parameters were used: 256 EPI images, TR 2s, TE 30ms, matrix size 64 x 64, 30 slices, voxel size 3.44 x 3.44 x 4.5 mm. Data were pre-processed with SPM. Prior to the analysis, the time series from the seven regions were corrected for some global signal fluctuations. The cleaned time series were analysed using spectral dynamic causal modelling (spDCM) for resting state (Friston et al., 2014; Kandilarova, Stayanov, & K., 2018; Razi, Kahan, Rees, & K.J., 2015). The spDCM model was a fully connected model where each node was connected to every other node.

4.4.4. Dynamic causal model analysis for resting-state fMRI

Importantly, the effects discovered within the OFC have been confirmed and replicated by the resting-state fMRI data, using dynamic causal modelling **(see Figure 2, Paper II**).

A Dynamic Causal Modeling analysis (DCM) (Friston, Kahan, Biswal, & A., 2014) of the underlying connectivity pattern revealed five connections where there was an interaction effect between the patient and control groups. All differential effects for the patient group were exclusively found for the OFC.

The patient group's significant change of activation within the medial orbitofrontal cortex (**see Fig.3 Paper II)** demonstrated normalisation of this activation and may indicate a better interplay with a network in the executive system, the extrinsic mode network (Hugdahl, Raichle, Mitra, & Specht, 2015). The changes in the OFC's connectivity, as discovered by the spDCM analysis (**see section 4.3.4.4 for definition)** indicate that the connectivity within this network mostly increased and that the discovered recovery process was indeed restricted to this area of the explored network (**see Figure 2, Paper II**).

To understand the increase in activation and thereby normalisation of the BOLD signals in the mTBI group post-intervention, I would suggest that this may indicate a better interplay with systems of the executive system, known as the extrinsic mode network (Hugdahl et al. 2015). Likewise, the strong deactivation before the training could indicate a deficit in the EF neural system.

The control group showed a decrease in activation post-intervention. One could speculate whether the decrease was the result of lower attention to the TDT task, a repetition effect within the healthy controls.

The dynamic causal model for analysing resting-state data was developed with the aim of facilitating group comparisons of effective connectivity (Friston et al., 2014). A spectral DCM analysis was carried out to detect any functional changes in the neural networks of interest, that is, the OFC network that showed functional plasticity from the results of the TDT task paradigm. In contrast to stochastic DCM on resting-state fMRI data, a spectral DCM estimates the effective connectivity from the cross spectra of the fluctuations in neuronal states instead of their time courses directly.

To examine the overall underlying connectivity pattern, only connections with a posterior probability of *P*p > 0.95 were explored.

fMRI data only revealed normalisation of the interplay between systems in the executive systems in the patient group. Furthermore, there were changes in the left-sided homologue, the right middle prefrontal cortex, right anterior insular cortex, left rostral anterior cingulate cortex, and the right supplementary motor area, (**see Figure 1, Paper II).** Moreover, the changes in the OFC's connectivity, as discovered by the spDCM analysis, indicate that the connectivity within this network mostly increased and that the recovery process discovered was indeed restricted to this area of the explored network (**see Figure 2, Paper II**).

Interestingly, nearly all detected brain areas that showed a recovery effect receive direct or indirect dopaminergic connections, such as the prefrontal cortex and the anterior insular cortex (Leigh, Marras, & S., 2013).

The patient group's significant change in activation within the medial orbitofrontal cortex (**see Fig.3 Paper 2)** demonstrated normalisation of this activation and may indicate a better interplay with systems in the executive system, known as the extrinsic mode network (Hugdahl et al., 2015).

The patients' increased scores for social interaction post-intervention correlate with increased activation in the neural areas called the emotional part of the anterior cingulate gyrus, and the rostral anterior cingulate gyrus as evidenced by results from the task-fMRI. This is closely related to error monitoring (Bush, Luu, & Posner, 2000). Other areas from the task fMRI analysis showed that increased activation was mostly related to different attentional systems, with the anterior insula as the central area for the saliency network (Menon & Uddin, 2010), and the middle frontal gyrus as part of the central executive network (Hugdahl et al., 2015).

The repeated-measures ANOVA of the connection strength revealed five connections where there was an interaction effect between the patient and control groups. The non-parametric Wilcoxon rank sum test showed that the patient group primarily demonstrated a dominating change in functional connectivity **(see Fig.2 in Paper II)**.

Without any restrictions on the analysis, all differential effects for the patient group were exclusively found for the OFC, while all other examined connections remained unchanged, irrespective of group, repetition, or perceived training.

Although the explored sample is rather small, this study concurrently demonstrated in two independent analyses and fMRI datasets that a recovery process took place within the OFC. It is important to underline that both analyses were not restricted to the OFC and that both results emerged in two unrestricted analyses.

5. SUMMARY OF RESULTS I–III.

The main finding of this thesis suggests that a structured music intervention as presented in Paper I (Vik, Skeie, Vikane, & Specht, 2018) and Paper II (Vik, Skeie, & Specht, 2019) led to enhanced cognitive performance and improved social interaction in patients with cognitive deficits following mTBI. Two independent analyses and fMRI datasets documented that a recovery process took place within the OFC in the patient group.

In Paper II (Vik et al., 2019), the aim was to extend the findings of the first study and further investigate factors associated with piano training that could be responsible for enhanced social interaction in mTBI patients. The increased activity in the bilateral OFC in the study could be seen in light of the increased scores for social interaction.

The result from the analysis of the combined task-based and resting-state fMRI data provides support for the contribution of the OFC as a key mechanism that potentially drives the cognitive benefit of piano training in TBI.

In Paper III (Vik, 2019), using a case study methodology, I investigated in greater depth which possible clinical factors could predict patients' potential positive or negative outcome of the intervention. In order to develop an evidence-based systematic treatment strategy, this study was concerned with examining and analysing the factors that might have an impact on the intervention outcome. The results revealed that pre-injury depression could be a risk factor for a positive outcome of the intervention. Multiple head-injuries could also be a factor in a negative outcome, depending on the injury's severity. These two factors replicate well-known variables in predicting a positive rehabilitation outcome for patients following mTBI.

Unfortunately, there is an error in the reported test scores relating to the bar graph for each participant. The bar graphs represent correct values, but the scores for each bar graph are incorrect.

The correct scores are reported in Paper I, Table 2, Paper II, Table 1, and Paper III, Table 3.

5.1. Paper I

'Effects of Music Production on Cortical Plasticity within Cognitive Rehabilitation of Patients with Mild Traumatic Brain Injury'.

In Paper I (Vik et al., 2018), there is evidence of a possible causal relationship between musical training and the reorganisation of neural networks promoting enhanced cognitive performance. Neuropsychological tests showed a significant enhancement of cognitive performance in both music groups and correlated with results from fMRI in which there was functional plasticity in the OFC. The results from the CVLT II in the patient group demonstrated an increase in performance up to the level of the healthy control groups, where the patients' end-point corresponds to the starting point of Group 2 and Group 3 before the intervention.

Hence, the performance in the patient group improved up to the normal level. Qualitative data from semi-structured questionnaires support these results. According to an analysis of fMRI, TDT-task, the patient group demonstrated a significant change in activation within the medial orbitofrontal cortex. The OFC network regulates higher-order cognitive processing, such as executive functions, including attention, decision-making, impulse control and social behaviour.

5.2. Paper II

'Neuroplastic Effects in Patients with Traumatic Brain Injury after Music-Supported Therapy'.

In the second paper (Vik et al., 2019), we focused on cognitive systems relating to deficits in social interaction among patients following mTBI.

The main result showed increased connectivity between OFC regions in the patients after the intervention. This finding provides support for the contribution of the OFC as a key mechanism that potentially drives the cognitive benefit of piano training in TBI, and further suggests a network of other connected frontal regions that may be linked to this.

5.3. Paper III

'*Music-supported Systematic Treatment Strategy for Patients with Executive Dysfunction Following Traumatic Brain Injury: Similarities and Divergences in 7 Case Reports*'.

In the third paper (Vik, 2019), I explored which clinical factors can predict a positive or negative outcome in terms of cognitive enhancement and improved social behaviour after a music-supported intervention for patients following mTBI.

This was a cohort study and based on clinical data, observational data from during the intervention, information from logs kept by the patients during the intervention, and data from semi-structured interviews pre- and post-intervention. I used a multiple case-study methodology that allows in-depth analysis of each participant's data. The aim of this study was to develop a systematic treatment strategy using music training to improve cognitive and behavioural domains of functioning in patients with cognitive deficits following mTBI. The qualitative results indicate that patients with a clinical record of depression could achieve an improvement in their cognitive performance post-intervention, but not necessarily improve their social interaction. Furthermore, patients with a previous TBI injury were at risk of a negative outcome of the intervention. These results replicated well-known risk factors for a positive rehabilitation process (Vikane et al., 2014).

6. DISCUSSION

The aim of this thesis was to investigate the effects of musical training (MT) on the brain's neural networks with respect to reorganising neural circuits and thereby restoring cognitive functions in patients suffering from cognitive deficits following mTBI.

The results demonstrated that longitudinal changes in functional connectivity took place within the OFC, which was a key mechanism that potentially drove the cognitive benefit of piano training in relation to TBI. As outlined in 2.5., the OFC has a widely distributed interconnected neural network to almost all areas of the brain and it regulates higher-order cognitive processing, such as executive functions (EF), including attention, concentration, impulse control and social behaviour. It could therefore be speculated that the increased activity in the OFC was responsible for the promising result in the patient group, and for six of seven patients returning to work post-intervention.

Enhanced cognitive performance in the mTBI group and subjective reports of well-being and increased social interaction during the intervention have been reported in subjective reports and also in logs kept by the patient group.

I would suggest that the participants were encouraged by improved cognitive ability, attention and memorisation during the intervention, and that these improvements activated networks in the OFC that are responsible for well-being and social behaviour. The ensuing increased well-being and social interaction could then encourage the participants to return to work.

However, there may be other potential reasons for returning to work, e.g. potential bias, concurrent changes in life situation etc., which were not specifically controlled for. These factors should be controlled for in future studies, as this is an important part of analysing TBI patients potentially returning to work.

With reference to the hypothesis, I suggest that the recovery process in the patient group may be a result of the music training. However, the question is how music training can enhance cognitive cognition and social interaction in mTBI patients.

Extensive research on music perception and cognition supports the present hypothesis of functional neuroplasticity in the brain following music training, and the possibility of reconnecting broken networks leading to neurocognitive recovery (Altenmüller, 2007, 2016; Altenmüller et al., 2009; Amengual et al., 2013; Brown et al., 2006; Chan et al., 1998; Herholz et al., 2015; Herholz & Zatorre, 2012; Jäncke, 2009; Schiavio & Altenmüller, 2015; Särkamö et al., 2014; M.H. Thaut, 2010).

The rehabilitation process triggered by the intervention may reflect the fact that active music training goes beyond simple training of new skills, and also involves several brain areas and networks that have to interact.

Interestingly, the task-fMRI results showed normalisation of activation within the medial orbitofrontal cortex, which may indicate a better interplay with systems in the executive system. The healthy controls showed a decrease in activation post-intervention. It can be speculated whether the reduction in activation in the control groups can be explained by lower attention being given to the fMRI listening task the second time it was presented.

There may be several variables that could have an impact on the final result. Variables such as the learning mechanism and possible dopamine effect, instructor/participant bias during the music intervention in relation to administering and reporting neuropsychological test results and semi-structured interviews, the effect of increased cognitive performance (attention and memorisation) on improved well-being and social interaction, will be discussed in the following.

My main hypothesis is that cognitive enhancement within the patient group may be a result of the music training, and I will start by outlining and discussing possible reasons for how the reorganising of neural circuits and recovery of cognitive functions can be responsible for the clinical group's improved cognitive functioning.

6.1. *How can musical training generate new neural connections?*

I would argue that it is not just one factor that is responsible for functional neuroplasticity during music training, but that several brain areas and networks have to interact. A powerful firing of neurons takes place in the whole brain during playing (Schlaug, 2009c), which facilitates overlapping of several neural networks and could thereby be one possible explanation for the reorganisation of neural networks.

I suggest that there are four different sources of neural activity during piano playing that may generate new neural connections and link up broken circuits.

These four factors, outlined in the following, are densely interconnected during piano playing and may facilitate the sprouting of new synapses and thereby re-connect broken circuits in the brain (Schlaug, 2009c).

6.1.1. *Association/priming/mnemonic neural activity*

Association cortices are activated during playing (Chan et al., 1998; Schlaug, 2009a). This process may help the neural networks to promote new neural connections. As we saw in section 2.5. (Anatomy, functions and neural connections of the orbitofrontal cortex), the OFC's connectivity to the association cortex is of special interest since it is one of the most important networks in developing new pathways and emotional associations (Schlaug, 2009b). Research has shown that neural activity during music production promotes the association cortex by stimulating episodic and semantic memory networks (Chan et al., 1998) (Schlaug, 2009b).

When playing an instrument, there are two different sources of associating, priming or mnemonic neural activity that stimulate episodic and semantic memory networks (Meyer, 1956; Schlaug, 2009a; Vik, 2009). This is outlined in the following and may play a role in how the brain develops new neural connections.

6.1.1.1. *Intrinsic – linked to semantic memory*

In 1956, the music theorist Leonard B Meyer introduced a theory based on *intrinsic* emotional responses to music, schematic expectancies linked to musical structure (Meyer, 1956; Sloboda, 2005). His theoretical approach was based on the psychological insight that emotions in general are normally experienced due to a violation of expectancy of some kind. Schematic expectancies are built up through the pattern of melodic, rhythmic, harmonic and other structural elements, and are linked to semantic memory (Sloboda, 2005). In other words, the intrinsic semantic memory network is activated in relation to emotional responses, which, in turn, is a part of the OFC's networks (Schlaug, 2009c).

6.1.1.2. *Extrinsic – linked to episodic memory*

In the present study, the listening task TDT was intended to act as a mnemonic device. The extracts included familiar tunes, both from classical works and popular music. The purpose was to activate association cortices, in addition to higher cognitive functioning systems such as executive control.

There are two kinds of extrinsic sources and they are linked to veridical expectations.

Episodic memory forms the basis for veridical expectations in music, and listening to familiar music will thereby elicit neural networks linked to episodic memory (Vik, 2009). Iconic sources arise through resemblance between a musical structure and some event or 'agent' that has an emotional tone (Juslin & J.A., 2001). For example, the music may remind the listener of some features in nature: the shape of a mountain, birds flying in time with the music, such as seagulls in a summer breeze, or birdsong, to name just a few. It is the listener's own correlation with their experience that is at the core of this emotional effect, thereby acting as a *mnemonic* neural activity.

The second kind of extrinsic sources are *associative.* They are premised on arbitrary relationships between the music being experienced and a range of non-musical factors, such as *autobiographical memories* stored in *episodic memory.* However, there is an interplay between *intrinsic* and *extrinsic* episodic memory. These networks have neural connections to the OFC, as described in section 2.7.

6.1.2. *Shared neural networks language/music*

I suggest that shared neural networks may facilitate the re-activation of inhibited neural connections. Several studies have found evidence of overlapping neural networks between music and language (Brown et al., 2006; Koelsch, 2013; Koelsch & Siebel, 2005; Parsons et al., 2005; Patel, Peretz, Tramo, & Labreque, 1998). Brown and colleagues examined the neurological structural similarities between music and language and found that both linguistic and melodic phrases (songs without words) triggered activation in almost identical functional brain areas, including the primary motor cortex, Broca's area, anterior insula, primary and secondary auditory cortices, temporal pole, basal ganglia, ventral thalamus, and posterior cerebellum (Brown et al., 2006). I would argue that, during piano playing, shared neural networks between language and music facilitate a functional reorganisation of neural networks because synapses that are active in both music and language processing could share new pathways within the OFC's network.

6.1.3. *Chunking principles in memory – hierarchical formation*

Analyses of perceptual patterns in music show that music stimulates perception and cognition by activating non-musical neural networks in the frontal area of the brain, which is activated during executive functions, such as attention, information processing, planning, making decisions, memory and social interaction (Deutsch, 1982). The neural networks for higher cognitive processing, the OFC, are precisely where the analysis revealed functional neuroplastic changes pre- and post-intervention in the patient group. Phrasing and grouping patterns in music are parallels to what are known as chunking principles in non-musical memory patterns in the episodic and semantic memory. In other words, neural mechanisms that drive cognitive processes in music have shared attention and memory systems with equivalent processes in non-musical cognition (M.H. Thaut, 2010), This may facilitate activation of executive neural networks in the OFC. Areas from the task fMRI analysis revealed that increased activation was mostly related to different attentional systems, with the anterior insula being the central area for the saliency network (Menon & Uddin, 2010), and the middle frontal gyrus being part of the central executive network (Hugdahl et al., 2015). In other words, music training activates non-musical attentional networks, which is one source among these four factors and a possible reason for neural plasticity.

6.1.4. *Repetition as a tool in neuroplasticity*

An important way of sustaining newly fired new neural connections during an activity is to strengthen the neurons through repetition of the same activity (Hebb, 1961). Research has found evidence that permanent neuroplasticity will take place after approximately 8–10 weeks (Porter, 2019). This is due to the repetition effect during the neural process of synaptic plasticity (Porter, 2019). The brain is dynamic and it changes and adapts in response to repeatedly performed actions, or as the psychologist Donald Hebb put it, 'fire together, wire together' (Hebb, 1961). The repetition factor is evident in musical structure, and music can thereby be an effective tool for strengthening new neural connections (Goldberg, 2009; Koelsch et al., 2004; Münte et al., 2002; Ockelford, 1999). Based on this knowledge, to facilitate the neural networks and make permanent new neural connections, I designed the intervention for an eight-week period.

The music-supported intervention contains all the factors described above that may be responsible for neuroplastic changes in the brain. I would argue that all the variables mentioned above work together to produce the final outcome, cognitive and social enhancement. However, there are additional factors to consider during the intervention that may have an effect on the final outcome. They are discussed in the following.

6.1.5. *The impact of emotional responses to music on the brain's neural networks*

The answer to question of why the participants in the patient group reported increased well-being and social interaction may be an element that activates the reward system.

Activation of neural networks in association cortices and the limbic system was one of the factors in my hypothesis on the process of how music production can facilitate neuroplasticity. As reported in 2.7, the OFC receives information from polysensory association areas via the dorsolateral frontal lobe, and it also has extensive reciprocal connections with the anterior temporal, medial temporal and limbic regions that are evident in the learning process.

I would like to quote the pianist Stephen Kovacevich who describes many elements of musical structure that may have the power to produce emotional responses in the listener (Kovacevich, 2008) and thereby activate neural networks between the OFC and association cortices, including the limbic system:

> *The 'Diabelli' was the piece that made me love Beethoven, through the marvellous Serkin recording of the Fifties, and since then it is the third period of Beethoven that has been the music I most needed to play and listen to. It has all the wild, tender, brusque, and introspective qualities of late Beethoven and then of course parody and comic energy too. It also seems to me that as much Variations he was often unconsciously writing Etudes. Some of them are quite specific: trills, quick chords, broken octaves, leaps.*

In addition to these intra-musical relations, the pianist also implicitly indicates that this piece has a special emotional effect in one way or another, that is: 'the music I most *need* to play'. In other words, Kovacevich points to elements of significance to understanding the music's effect on our emotional state. Emotional responses to music may be one of several factors during music production that activate the limbic system and trigger dopamine release (Sloboda, 2005; Tramo, 2001).

Music listening and production activates the reward circuitry cortical networks relating to emotional reward, followed by a dopamine release, a neurotransmitter evident in the reward system (Brodal et al., 2017; Owessen-White et al., 2016).

The enjoyment of playing the piano reported by the participants may have a dopamine-releasing effect and thereby increase this neurotransmitter effect between neural networks affecting the OFC and executive functions, followed by normalisation of emotional reactions that are fundamental to social interaction. However, the learning mechanism itself may be a core factor in increased neuroplasticity, as described and discussed in the following.

6.1.6. *Learning mechanism and dopamine effect*

As mentioned, dopamine may be a core factor in relation to increased neuroplasticity during musical training. It can be speculated whether the learning mechanism per se causes additional stimulation of the limbic system, followed by dopamine release (Brodal et al., 2017; Owessen-White et al., 2016). The learning process may activate the limbic system and lead to it producing dopamine, as in the process of setting a goal and mastering a goal (Salamone & Correa, 2012). I would emphasise that, in the present study, all participants in the music groups reported that playing the piano and mastering the curriculum were a positive experience.

I would suggest that, by producing dopamine, the emotional part of the present intervention that is due to the learning mechanism has an important impact on the final positive result in the patient group.

We can ask whether dopamine might also be released as a result of another task than music training. To rule out this possible variable, I would therefore suggest that future studies should investigate this factor using a patient control group who are given another goal-oriented task.

6.1.7. *Training time*

Training time could be a variable affecting the final result of cognitive performance as measured by the neuropsychological test results. According to the logs kept by both music groups, there were substantial differences in training times. This evaluation of training times will be restricted to the patient group, since it was only this group that showed functional changes in the OFC.

There were no consistency between the amount of training time and the total score in the CVLT test, **(see Table 3 in Paper III**). The mean training time was 24 hours during the intervention period of 8 weeks, i.e. three hours per week. As we can see from the overview of individual CVLT results and total training time, participant P1, who had less training time than the rest of the group, achieved the highest increase in test scores post-intervention.

It is interesting to register that the minimum total training time of 15 hours indicates a norm for improved cognitive performance, as in P7. However, it is an open question whether prolonged training time would have had an improved cognitive effect on some of the patients who did not achieve maximum scores post-intervention. There were differences in total scores in the CVLT test **(see Table 3, Paper III)** between the participants in the patient group. Future studies should replicate the training protocol with respect to training time to ensure a controlled methodology.

6.1.8. *Possible bias of social interaction between instructor and participant*

Because piano tuition is an activity involving substantial interaction between the instructor and the participant, it is natural to ask whether this interaction can promote increased social behaviour. The impact of a positive experience during tuition may promote activation of the mesolimbic system and thereby promote dopamine release in the participant. I therefore suggest that further studies be carried out on larger samples, and with a patient control group to determine which effects are due to the music intervention and which effects might be the result of increased social interaction during and because of the training. Another issue is that the study should be blinded to avoid any possible bias in assessing the results of neuropsychological tests and in the reporting from semi-structured interviews and logs.

6.1.9. *Pre-accident clinical factors a confounding variable*

There are important clinical factors to consider that may predict a positive or negative outcome of the intervention. Clinical issues that have been registered before the accident may have an impact on the final outcome. In the case report study, Paper III, we have seen that a depression diagnosis registered before the injury may predict a negative outcome, as well as multiple head injuries. These two factors are a replication of previously reported variables, however (Finch, Copley, Cornwell, & Kelly, 2016). It should be noted that both these two conditions were listed in the exclusion criteria, but were unknown at the time of the study.

7. SUMMARY OF DISCUSSION

The outcome of the study demonstrated that longitudinal changes in functional connectivity took place in the patient group's OFC, and I suggest that this may be a result of the music training and propose a causal relationship between pianoplaying and reorganisation of the neural networks.

Literature reviews support cognitive rehabilitation programmes and interventions with multi-task exercises that are congruent with the music training in the present study. Solbakk et al. found an increased effect on neurocognitive functioning after training in complex tasks demanding high attentional control, compared to aspects of training involving continuous attentional tasks, and training of reaction times (Solbakk, Schanke, & Krogstad, 2008).

However, there are several variables that could have an impact on the clinical group's improved cognitive and social functioning that has been described and discussed in the foregoing sections.

In this summary, I would like to list the factors that may have an impact on the final result in order to make some suggestions for future replications of the study.

Firstly, I would argue that playing an instrument is the key factor in stimulating broken neural connections to regenerate lost connections and rewire the neural networks. The **neural substrates** activated by music training are interconnected and stimulate networks that have connections to the whole brain. Due to music's ability to engage and stimulate neural circuits that overlap with non-musical networks, music has the power to reorganise neural networks and reconnect broken circuits. In the foregoing, I have listed the following factors that may be important for neural activity promoting new neural connections:

Association/priming/mnemonic neural activity

Shared neural networks language/music

Chunking principles in memory – hierarchical formation

Repetition as a tool in neuroplasticity

However, there may be other factors to consider that may be responsible for the final result, the **emotional impact** on the neural networks of learning mechanisms and **dopamine release** (Salamone & Correa, 2012). Mastering piano playing may produce a positive emotion, which is a dopamine release factor (Brodal et al., 2017; Salamone & Correa, 2012). An interesting aspect for future research would be to investigate the level of dopamine release during piano playing and to explore the impact of dopamine on social behavioural changes and changes in OFC neural networks. Another aspect of dopamine release is that there may be other goal-oriented tasks that could be performed that could produce the same results as in the study. This should be considered in future studies.

Training time could be a variable. When evaluating the impact of neuropsychological test-results, there was no consistency between the amount of training time and the total score for the CVLT test. It would be interesting, however, to replicate the training protocol with respect to training time to ensure a controlled methodology. However, research has found evidence that, as regards neuroplastic changes, interventions should last for at least eight weeks (Porter, 2019). I found that the minimum training time during the period of eight weeks was 24 hours, or three hours per week. All patients achieved significantly increased scores, but there were individual differences within the group (**see Table 3 in Paper III**).

It can be speculated whether longer training time would also have a positive cognitive effect on patients who had a lower total score for the CLVT test.

Limitations apply, however, as regards drawing conclusions about the impact of training time on neuropsychological tests scores because of the small sample size.

The fact that there were only significant changes in the CVLT test results, and no signs of an effect on the Stroop test results, leads us to speculate that a specific cognitive target should be set for the intervention on executive systems, such as attention and memorisation. Future studies should therefore include a broader spectrum of neuropsychological tests to evaluate the different categories of cognitive performance.

Future studies should apply a blinded methodology to avoid any potential bias.

The social interaction between instructor and participant may be a variable of interest. This factor could be eliminated by having a patient control group who perform another task-based intervention to determine which effects are due to the music intervention and which effects might be the result of increased social interaction during and because of the training.

With respect to the repertoire, I would like to make following comments. The protocol included 39 pieces for beginners since the participants were non-musicians. The repertoire of nursery rhymes may be less interesting for adult participants. However, one of the reasons for choosing them was that these pieces had a good progressive learning methodology, which gave the participants a feeling of mastering playing the piano. I informed both the music groups about the idea behind the chosen repertoire, and they looked forward to learning and being able to play and choose their own pieces after the intervention.

I find it important to point out that the intervention will suit any participant regardless of musical level. As explained in the foregoing, the key element in the intervention is to activate the brain's neural circuit. The protocol could then be adjusted to each participant's playing ability, and to give each participant an individual, progressive learning programme lasting eight weeks.

With reference to the literature on music training's strong activation of neural networks (Altenmüller, 2016; Herholz & Zatorre, 2012; Jäncke, 2009; Schlaug, 2009c), the case of the pianist who achieved enhanced cognitive performance after playing piano during the rehabilitation period (Vik, 2006), and the results of the study, I suggest that playing piano may stimulate the neural networks in re-routing neural connections and link up inhibited neural circuits.

8. LIMITATIONS

This study has a number of limitations. Firstly, the sample size is small. The reason for this is twofold. In the recruitment process, few patients with TBI enrolled. The intervention period started with only seven participants in the patient group. During the scanning period, I was not able to recruit more patients due to an upgrade of the scanner. The scanning pre- and post-intervention had already been done for this group when the scanner was removed and a new scanner was to be installed. It was therefore not possible to continue the process of sampling data. However, it should be taken into account that these patients were all in a stable phase of chronic PCS following TBI two years post-injury, and that a self-recovery process would therefore not be a confounding variable. I therefore recruited two control groups of healthy participants, one with a music intervention and one as a baseline group to investigate cognitive performance pre- and post-intervention over a period of eight weeks. As reported, only the music groups achieved enhanced cognitive performance as measured by the CVL-II test. The baseline control group's scores increased by 10%, which is the normal average learning effect of the test.

Another limitation is due to the lack of a patient control group without music. I would suggest that future studies should use a clinical group who perform another goal-oriented task as mentioned above. This clinical control group could act as a waiting list group who would receive the same music training intervention after the study had concluded. The reason for this is the ethical aspect of giving all patients who are recruited to the study the same opportunity to improve their cognitive performance and social interaction. This methodology would strengthen the present results of enhanced cognitive performance and positive behavioural performance.

The aspect of dopamine as a key factor should also be investigated in a replication of the study. The learning mechanism is a factor that may produce the same result with an alternative learning task as regards dopamine release (Salamone & Correa, 2012).

Future studies should therefore use a control group with a goal-oriented learning task to investigate the role of learning versus playing an instrument.

Due to the interesting divergences in the test results for the CVLT test and Stroop test, replications of the intervention programme should use a broader spectrum of neuropsychological tests to refine the target of the intervention in relation to cognitive performance.

As mentioned above, there are methodological limitations to the study. There is only one patient group, which limits the opportunity to draw any conclusions about the intervention. The neuropsychological tests were limited, and we had to withdraw the MMS test from the study because of the ceiling effect. I assume that the high scores from all participants were due to the patients being an mTBI group recruited two years post-injury. Interestingly, they all suffered from PCS with selective deficits in both attention, memorisation and social interaction. With respect to attention and memorisation, the participants who reported pre-intervention having problems with cognitive-related issues, showed enhanced cognitive performance post-intervention, both in the CVL II test results and in subjective reports. Table 2 in Paper III shows PCS in the seven participants in the patient group. These data were obtained from semi-structured interviews and logs kept both by the participant during the intervention period and the instructor.

Semi-structured interviews do not strictly follow a formalised list of questions. It is possible to ask follow-up questions, and open-ended questions may be difficult to analyse in a structured way within a group (for the structure of the semi-structured questionnaire, see 4.3.4). I therefore suggest using a standard questionnaire for all group participants in future replications of the intervention. This would avoid confusing reports as in Paper III, where, on pages 169–171, only three of seven patients report a specific enhancement of cognition (e.g. attention, concentration), whereas, in Table 2, none of the patients report problems with concentration or memorisation at the post-intervention stage. It should be noted that Table 2 reports the correct answers.

Finally, a future study and replication of the intervention should use a Randomized Controlled Trial (RCT) to reduce bias when testing the effectiveness of the intervention.

9. CONCLUSION AND FUTURE DIRECTIONS

The key findings of this study suggest that there may be a causal relationship between musical training and reorganisation of neural networks that promote enhanced cognitive performance in patients following mTBI. This view finds support in the promising result of the study. The task –fMRI results showed normalisation of activation within the medial orbitofrontal cortex, which may indicate a better interplay with systems in the executive system. These results correlates with a normalisation of cognitive control in the CVLT test. As described, the OFC networks regulates higher order cognitive processing, such as executive functions (EF). Attention and concentration were the patient group's main problems following TBI.

These findings provides important and valuable support for the contribution of the OFC as a key mechanism potentially driving the cognitive benefit of piano training in TBI and further suggest a network of other connected frontal regions that may be linked to this.

However, there are some limitations to this study that should be considered in future studies to develop the method and optimize its clinical application.

Firstly, larger samples are required with a patient control group with another task, a patient control group to determine which effects are due to the music intervention, and which effects could be the result of other potential bias. The patient control group should be given a goal-oriented task to investigate learning effect and the role of dopamine during the learning process.

Further, future studies should use an RCT study design to avoid possible bias when testing the effectiveness of the intervention

To ensure a more robust study, a standardised measure in reference to obtain self-reported deficits pre-injury and, pre-post intervention should be implemented.

The study applied a semi-structured questionnaire measuring subjective pre- and post-intervention functioning and quality of life, social issues and work situation. The disadvantages of this method is that it can make it more difficult to analyse and compare answers from participants within the same group.

I would like to make some remarks about the piano protocol for future application of the method. The protocol consisted of pieces for beginners because the recruited participants were all non-musicians. This was a pilot study, and I wanted to eliminate any possible confounding variable, as mentioned, there are differences in neural cortical networks between musicians and non-musicians. However, as the main purpose of the intervention is to activate the brain during piano playing, any repertoire suitable for the patient could be applied. In other words, the methodology of piano playing for a period of eight weeks described in the protocol can also be used for musicians. The repertoire will have to be adapted to the participants' piano-playing level. The key element of the intervention is to engage the brain's neural networks through playing the piano.

Finally, I would argue that a multidisciplinary outpatient programme should be added to future interventions in order to capture patients who would otherwise drop out or influence those prone to negative outcomes, as seen in the examples in Paper III.

I would like to mention the enthusiasm and good spirit of the participants during the eight-week intervention period. The tuition took place on premises belonging to the University Hospital in Bergen, Norway, in a quiet room with a piano provided for the intervention period. I think this practical part of the arrangement gave the participants a confidential atmosphere.

These results might hold promise for alleviating cognitive dysfunction in mTBI patients and thereby offer a novel music-based intervention in cognitive rehabilitation of patients with mTBI.

It is my hope that the knowledge gained from this study can be replicated and refined in future studies, as this pilot study may be the first step to an optimized methodology applied in music-based interventions for patients with TBI.

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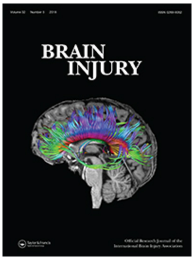

Brain Injury

ISSN: 0269-9052 (Print) 1362-301X (Online) Journal homepage: https://www.tandfonline.com/loi/ibij20

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BRAIN INJURY
2018, VOL. 32, NO. 5, 634–643
https://doi.org/10.1080/02699052.2018.1431842

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Effects of music production on cortical plasticity within cognitive rehabilitation of patients with mild traumatic brain injury

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ABSTRACT

Objective: We explored the effects of playing the piano on patients with cognitive impairment after mild traumatic brain injury (mTBI) and, addressed the question if this approach would stimulate neural networks in re-routing neural connections and link up cortical circuits that had been functional inhibited due to disruption of brain tissue. Functional neuroimaging scans (fMRI) and neuropsychological tests were performed pre–post intervention. *Method*: Three groups participated, one mTBI group (n = 7), two groups of healthy participants, one with music training (n = 11), one baseline group without music (n = 12). The music groups participated in 8 weeks music-supported intervention. *Results*: The patient group revealed training-related neuroplasticity in the orbitofrontal cortex. fMRI results fit well with outcome from neuropsychological tests with significant enhancement of cognitive performance in the music groups. Ninety per cent of mTBI group returned to work post intervention. *Conclusion*: Here, for the first time, we demonstrated behavioural improvements and functional brain changes after 8 weeks of playing piano on patients with mTBI having attention, memory and social interaction problems. We present evidence for a causal relationship between musical training and reorganisation of neural networks promoting enhanced cognitive performance. These results add a novel music-supported intervention within rehabilitation of patients with cognitive deficits following mTBI.

ARTICLE HISTORY
Received 11 January 2017
Revised 18 October 2017
Accepted 20 January 2018
Published online 1 January 2018

KEYWORDS
Mild traumatic brain injury (mTBI); neuroplasticity; cognitive rehabilitation; fMRI; music-supported intervention

Introduction

Musical training has emerged as a useful framework for the investigation of training-related plasticity in the human brain (1). Playing an instrument simultaneously receives and transmits visual, auditory, and kinaesthetic information to a specialised brain network (2), engages emotion and reward systems in the brain, which may facilitate and enhance therapeutic approaches aimed towards rehabilitation from neurological and psychiatric disorder (3–8).

The brain is a dynamically organised structure that changes and adapts as response to repeatedly performed actions and has shown that temporally coherent inputs in competitive neural networks change the efficiency, density, and connectivity of synapses (9). Music-making provides an enriched environment for the brain in promoting dendritic sprouting that is fundamental for synaptic plasticity (10). Multisensory integration during practise enhances training-related changes in sensory and association cortical areas during auditory cognition (1), and causes both structural changes in white matter and functional neuroplasticity, described as a change in the brain's interconnected processing. Music may engage and link up brain areas that otherwise would not connect with each other (10). There is increasing evidence that music making could be a possible tool in neurologic rehabilitation (1,11,12).

Traumatic brain injury (TBI) has been recognised as a major public health problem worldwide and can lead to neurological, physiological, cognitive, psychological and social dysfunction (13). TBI is traditionally classified from mild to moderate to severe (14). A study of hospital-treated TBI in Oslo, Norway, reported 9000 TBI patients hospitalised every year. A total of 79–90% of all treated brain injuries are mild (13,14). Milder injuries may however be underestimated. In studies that based their incidence rates on hospital-treated TBI, revealed that fewer patients with mild TBI attend emergency departments and more patients are treated in outpatient settings (15,16). This means that the number of TBI patients diagnosed with mild TBI might be higher. Milder injuries to the head may cause microscopic damage to axons, dendrites and synapses. Diffuse axonal injury (DAI) is a typical brain damage as result of TBI. DAI is a widespread disruption of brain tissue and affects interconnected processing in the brain (17). This category of patients with TBI are often inhibited from normal functioning and may benefit from music-supported cognitive rehabilitation as they can employ their rest capacity in playing an instrument in facilitating neurorehabilitation.

There is little knowledge about the potential neuroplastic changes induced by musical training in cognitive rehabilitation of patients with TBI. The scientific evidence for effectiveness of music to improve cognition (18) is weak and

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there are no studies examining the improved functions over time (3). In contrast, there is extensive research confirming the benefits of music-supported therapy in other areas of neurologic music therapy. In patients with non-fluent aphasia after left frontal lobe damage there is reactivation of inhibited language-related brain regions in right prefrontal areas after intense melodic intonation therapy (19). Results from motor-rehabilitation in stroke patients give evidence for music-supported plasticity in cortical networks (3,4,12,20). Patients with Parkinson's Disease have stabilised and synchronised their disturbed gait with the help of external auditory rhythm (21).

The aim of the present study is to investigate the effects of musical training on the brain's neural networks in respect of reorganising neural circuits and thereby restore cognitive functions in patients suffering from cognitive deficits after mild TBI. We address the question if learning to play an instrument may stimulate the neural networks in re-routing neural connections and link up inhibited neural networks. More specifically, we examined whether this intervention reconnects areas that were disconnected or inhibited through minor damage to axons, dendrites or synapses. We developed a longitudinal design that enabled us to observe the causal influence of multisensory training on higher-order auditory cognition and possible functional and structural changes in the brain's neural networks.

Methods

Participants

Three groups of participants were recruited for the study:

Group 1: 7 patients with mTBI receiving piano tuition; Group 2: control group of 11 healthy participants with music; Group 3: control group of 12 healthy participants without music. Musicians were excluded in avoiding the possible confounding variable regarding neural brain differences in musicians and non-musicians (23). Participant's gender and age distribution: Group 1: 4 male (*m*) and 3 female (*f*), mean age (*m.a.*) 38 years; Group 2: $m = 5$ and $f = 6$, *m.a.* 33 years; Group 3: $m = 4$ and $f = 7$, *m.a.* 33 years. Patients with a medical history of psychological problems were excluded. The patients were recruited by invitation, and seven patients enrolled. Participants in the two control groups were recruited by posters located at University of Bergen and at Haukeland University Hospital Bergen. Participants received detailed information about the aim of the study, assessment with pre–post fMRI and neuropsychological tests and signed a written consent with information that they can withdraw from the study at any time.

Patients – clinical data

All patients were diagnosed mild traumatic injury (mTBI), as indicated by the Rivermead Post Concussion Symptoms Questionnaire (RPQ) (Table 1). Inclusion criteria was 2 years post injury to omit self-recovery in the acute phase.

Procedures

Study design

We designed a between-group as well as a longitudinal within-subject design. Group 1 and Group 2 were examined pre–post intervention and, Group 3 was examined twice without any intervention in between. Assessment consisted of a neuropsychological test battery and neuroimaging. Semi-structured interviews pre-post were conducted in Group 1 to investigate their subjective opinion of cognitive performance and social interaction pre–post intervention.

Piano training protocol

Eight-weeks piano-tuition programme was developed and carried out by BV (22) based on knowledge from a case study in which a patient with music alexia (memory loss of reading musical notation) following mTBI recovered after some month of regular piano playing. The patient, a pianist, lost the ability to read musical notation following mTBI. Two years after the accident, still unable to read music and with persistent cognitive impairment she started to denote a score (a written piece of music), by playing what she knew from memory and at the same time look at the score. During this process, she re-learned the notes and improved her cognitive performance in general. The methodology has been modified to fit the present intervention in reference to repertoire, intervention length and structured practise instructions. The curriculum focused on reinforcement of learned material as repetition is one of the factors for possible generating of new neural connections in the brain. Repertoire consisted of small tutorial pieces with progression as described in the appendix. The methodology was to apply both hands simultaneously from the start developing equal motor-movements of both hands to stimulate inter-hemispheric coordination of motor areas. Playing the piano activates the whole brain as musical elements as pitch, rhythm, melody are processed in different parts of the brain. Further, reading and playing single notes with one hand while at the same time read and play a chord with the other hand, will cause increased inter-hemispheric communication and coordination, as single notes are mainly processed in the left hemisphere, whereas chords are perceived as patterns and therefore predominantly activates the right hemisphere (23). Sight-reading a score during performance adds a considerable cognitive load (24). The participants received two lessons a 30 minutes per week with instructor scheduled two days apart with instructions to practise a minimum of 15 minutes each day of the week. Participants in both music groups filled in a form of daily practising time. Group 1 was instructed to report any problems in reference to physical symptoms, such as fatigue, headache, dizziness, blurred vision during practising.

Neuropsychological tests

A test battery of three different neuropsychological tests was applied during the pre–post examinations of the participants containing: Mini Mental Status Test (MMS), California Verbal Learning Test (CVLT 2), which assesses learning strategies, memorisation and retrieval of information, and Stroop Word/

Table 1. Scores obtained in the rivermead post-concussion symptoms questionnaire (RPQ): a specific 16-item questionnaire that measures cognitive, emotional and physical symptoms. The patients symptoms during the last 24 hours are compared to before the traumatic brain injury, rating the responses of each item using a 5-point Likert scale as follows: 0 = not experienced at all; 1 = no more of a problem; 2 = a mild problem; 3 = a moderate problem; and 4 = a severe problem. Hospital anxiety (*a*) and depression scale (*d)* (had) consists of 14 items detecting states of depression (7 items) and anxiety (7 items, rated on a 4-point scale from 0 to 3:00 no symptoms, and 3 = a severe symptom or symptoms most of the time. The Glasgow Coma Scale (GCS) scores, ranging from 3 to 15, assess the level of consciousness based on eye, verbal and motor responses. Patients with a GCS score of 13–15 are classified as mild TBI, GCS score of 9–12 as moderate TBI or GCS score of 3–8 as severe TBI.

Patient	Injury date and date of examination	MRI/CT scan	Prior treatment	Intracranial injury on CT	RPQ (064)	HAD (0–42)	GCS (3–15)
42M	Commotio. 12.01.11. Examination date 10.03.11	Orbit and nose fracture	Outpatient rehab.	No	48	25 *A15 D10*	15
41F	Commotio. 02.12.11 Examination date 05.03.13	N	Outpatient rehab.	No	18	6 *A4 D2*	15
31M	Contusions. 05.06.11 Examination date 22.08.11	Small epidural haematom and contusion bleeds frontal lobe right side and both temporal lobes	1 month in TBI Unit	Yes	6	6 *A5 D1*	14
52F	Commotio. 11.03.12 Examination date 30.03.12	Normal (Acach.cyst)	Outpatient TBI Rehab. 4 weeks	No	21	8 *A4 D4*	14
55F	Subdural haematoma (concervative management). 09.07.09. Examination date 07.09.09	Orbit fracture and nose fracture	Outpatient TBI Unit	Yes	10	1 *A0 D1*	14
30M	1991 and 2012. 08.07.91. Examination date 01.10.12 Contusions Frontal and temporal lobes, subdural haemotoma evacuated	MR and CT micro bleeds contusions in frontal and temporal lobes bilat.	TBI unit 1 month	Yes	28	18 *A9D9*	Missing Probably Severe TBI. Intubated For approx.. 1 week. PTA 10 days
19M	Epidural haematoma evacuated. 09.12.11 Examination date 08.01.12	Diffuse axonal injury; Epidural haematoma contusions	TBI unit	Yes	7	16 *A8 D8*	15

Colour Test for assessing reading speed and attention and ability to switch attention. Data were analysed with a 3 (group) × 2 (repetition) repeated-measure ANOVA model, using SPSS 22 (www.ibm.com).

fMRI scanning session

Functional and structural MRI scans were collected pre-post intervention for all groups. The fMRI investigation took place at the radiological department, Haukeland University Hospital, using their 3T General-Electrics Signa MR system. Besides a high-resolution T1-weighted scan, two task related fMRI sessions were included in the scanning protocol, where one task was a pitch-discrimination task and the other one was a passive listening task to Tonika-Dominant-Tonika chords, as will be explained further down.

Pitch discrimination task

The pitch discrimination was administered as block design where participants got the task to judge whether the second of two tones is higher or lower in pitch than the first one. If the

Table 2. Patient group: Scores pre-post intervention neuropsychological tests including training-time during 8 weeks intervention.

Patient	MMS Pre-interv.	MMS Post-interv.	Stroop Pre-interv.	Stroop Post-interv.	CVLT 2 Pre-interv.	CVLT2 Post-interv.	Training- time. Total 8 weeks. Hours plus minutes
42M	28	28	25	33	17	60	7 h 45 min.
41F	30	30	65	59	58	65	36 h 45min
31M	28	30	42	45	60	60	8h
52F	30	30	57	60	54	70	28 h 35 min.
55F	22	30	44	25	32	48	23 h 55 min.
30M	30	30	30	27	62	74	21 h 20 min.
19M	30	30	55	69	60	75	15 h 20 min.

tone was higher in pitch they should press their right hand button, if the pitch was lower in pitch they should press their left hand button. The paradigm was controlled by E-Prime 2.0 Professional (https://pstnet.com) that was programmed to present the stimuli and to collect the participants' responses. During each of the five stimulation blocks 10 trials of tone-pairs were presented. Each trial started with a reference tone (440 Hz, duration 500 ms), followed by 500 ms silence, before the second tone was presented which was either higher (520 Hz, duration 500 ms) or lower (360 Hz, duration 500 ms) in pitch. The next trial started after addition 2500 ms of silence. In total, each block lasted 40 seconds. The order of the stimuli was randomised within each block. To guarantee correct timing of the stimulus presentation, the start of each block of trials was triggered by the MR-machine, using a sync-box. For technical reasons, the responses from in total 10 participants (3 controls with music, 6 controls without music, 1 patient) are not complete with missing data either from the pre- or post-session, but never from both sessions. This was caused by an undiscovered temporary malfunction of the response device. The participants listened through MR compatible headphones and were instructed to press a button as response. This is considered a low level cognitive task adapted from Zatorre (25) and aims to measure low-level attention as well as, response latency. The fMRI data were acquired with an echo-planar imaging (EPI) sequence with the following parameter: TR 3s, TE 30ms, matrix size 128 × 128, 30 slices, voxel size 1.72 × 1.72 × 4.4 mm^3. The block design consisted of five blocks with stimulation and five blocks of rest. Each On–Off block cycle lasted 80 seconds. In total, 140 EPI volumes were acquired.

Tonika-dominant-tonika task

A passive listening task was designed, containing extracts of classical and popular Western musical cadence pattern of Tonika-Dominant-Tonika (TDT) chords based on the first, the fifth, and the first tone of the scale. The relationships between individual tones form the basis for a fundamental aspect of musical processing and recognition of melody and there is a melodic pattern in Western music activating semantic networks that are important for long-term representation of familiar tunes (25). Twenty-eight extracts were presented in an event-related design with varying delays between each stimulus. The total length of the paradigm was 08:00 minutes, and stimulus presentation was controlled by E-Prime, as described above. The length of the single stimuli varied between 2 and 19 seconds, with a variable delay between stimuli that varied between 4 and 18 seconds. In total, 160 images were acquired with the same imaging parameter as described earlier.

fMRI data analysis

Image processing and statistical analyses were performed using Statistical Parametrical Mapping (SPM12; Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB (Mathworks, Inc. Natick, MA, USA). The preprocessing of the fMRI data contained first a correction of head movements and movement related distortions (realigned and unwarp). This process was followed by transforming each individual brain into a standard space, defined by a template defined by the Montreal Neurological Institute (MNI). This was achieved by warping the mean image, created in the first step, into to the standard space and applying this transformation to all other images. Finally, the data were smoothed with a Gaussian filter of 8mm FWHM (full-width at half maximum). First-level statistical analyses of the two task-related paradigms were performed by defining a general-linear model (GLM) for each individual participant and for the two tasks separately. The GLM model comprised the onsets and duration of the stimulations, as well as the realignment parameters. Contrasts were defined that tested the difference between stimulation and the rest condition.

Group statistics were performed by using the resulting contrast images from the first-level analysis. For the two paradigms separately, a 3 (group) × 2 (repetition) repeated-measure ANOVA model was defined within the GLM framework to test for averaged effects across groups and repetitions, main effect of group, main effect of repetition, and for any interactions. All results were initially explored at a family-wise error (FWE) corrected threshold of p (FWE) < 0.05. In case of significant effects, follow-up tests were performed between Group 1 and Group 2 as 2 (group) × 2 (repetition) repeated-measure ANOVAs, followed by t-tests.

Ethics

The Regional Ethics Committee of Norway (REK-Vest) approved the protocol.

Results

Semi-structured interviews – patient group

Patients were interviewed pre-post intervention to receive subjective information of the individual's status regarding cognitive performance and social functioning. The pre-intervention questionnaire was divided into three sections. The first was questions about the actual accident, hospitalisation, and if any rehabilitation had been carried out. All patients had received rehabilitation programme within the national health service. The second section was in reference to post-concussion symptoms in which they were asked to outline problems of emotional, behavioural, cognitive and physical signs. Common problems were fatigue, blurred vision, light sensitive, dizziness, vertigo, headache, sensitive to sound. Some reported problems in finding words. The third section was questions about their present work situation. They were either sick-listed or had part time jobs with adjusted work. Post-intervention questionnaire were also divided into three sections. Firstly, how they would describe the intervention. All patients found the intervention pleasant. However, one patient did not participate in all lessons because his priorities were other activities or he forgot to meet up. This was an open question and had follow up questions about the eventually positive and negative effect they experienced during the 8 weeks intervention period. There were no report on negative issues, on the contrary, all patients had a positive experience of the intervention. Secondly, there were questions about when they noticed any improvements of the problems reported in the pre-intervention questionnaire. The average time for improved ability to concentrate and less fatigue was after four weeks of training. These answers correlated with the individual training logs where the participants were instructed to write notes of any changes in cognitive ability and social functionality. A total of 90% of the participants reported progressive improvement of both cognitive and social functioning during the remaining four weeks of intervention period. Six out of seven patients reported improved mental capacity after the intervention and better function of social interaction. The third section was about their opinion of a possible return to work or studies as before the accident. Six participants (90%) were able to return to their previous employment as before accident or studies post intervention.

Neuropsychological tests

CVLT 2 test demonstrated a highly significant effect of musical training on executive functions related to attention, learning strategies and retrieval of memories in Group 1 and Group 2. A 3 (group) × 2 (repetition) repeated-measure ANOVA was performed for the three groups on CVLT and Stroop Word/Colour test. MMS test has been excluded from the study because of a ceiling effect of all participants.

The CVLT test revealed no significant but strong trend of a main effect of group ($F\ (2,26) = 3.15$, $p = 0.059$), but a significant main effect of repetition ($F(2,26) = 35.66$, $p < 0.001$), and a significant group by repetition interaction ($F\ (1,26) = 4.067$, $p = 0.029$). Group 1 demonstrated an increase in performance up to the level of Group 2 and Group 3, where the patient's end-point corresponds to the starting point of Group 2 and Group 3 before the intervention Figure 1a. Both groups receiving music intervention, Group 1 and Group 2 demonstrated a significant effect of musical training on performance, as indicated by a post hoc Fisher's LSD-test (Group 1: $p < 0.001$, Group 2, $p < 0.001$). Group 3 has only the expected 10% increase of learning effect for pre–post testing, but the differences did not reach significance (Fisher's LSD-test $p = 0.155$). There was no correlation across Group 1 and Group 2 between the improvement and the total number of hours, spent for the training ($r = -0.436$, $p = 0.104$).

For the Stroop test, we found a slightly different picture. There was no significant main effect of groups ($F\ (2,26) = 0.855$, $p = 0.437$) and no group × repetition interaction ($F(2,26) = 1.038$, $p = 0.368$). However, there was a significant repetition effect ($F(1,26) = 4.640$, $p = 0.041$). Only Group 2 and Group 3 demonstrated a repetition effect, hence there was no significant effect of training Figure 1b. Accordingly, there were no correlations between the changes of the test scores and the total number of hours, spent for the training ($r = -0.302$, $p = 0.273$).

It should be noted that there are only 11 participants in Group 3 performing neuropsychological tests post-intervention. There was one person in this group unable to attend post testing.

Functional neuroimaging scans

Pitch discrimination task

To explore the averaged effects of the pitch discrimination task, mean contrasts across repetitions have been specified for each group and then summarised as conjunction analysis across groups. The result indicated a widespread, mostly bilateral network, comprising supplementary motor area (SMA), anterior insular, cerebellum, thalamus, putamen, Heschl's gyrus/superior temporal gyrus, supramarginal gyrus (Table 3a. Figure 2). The ANOVA results revealed neither significant main effects of group or repetition nor a significant interaction. The response data from this paradigm, which was a simple reaction time task, have also been analysed with a repeated-measure ANOVA. The result demonstrated a significant main effect of repetition ($F(1,16) = 5.626$ $p = 0.031$) and

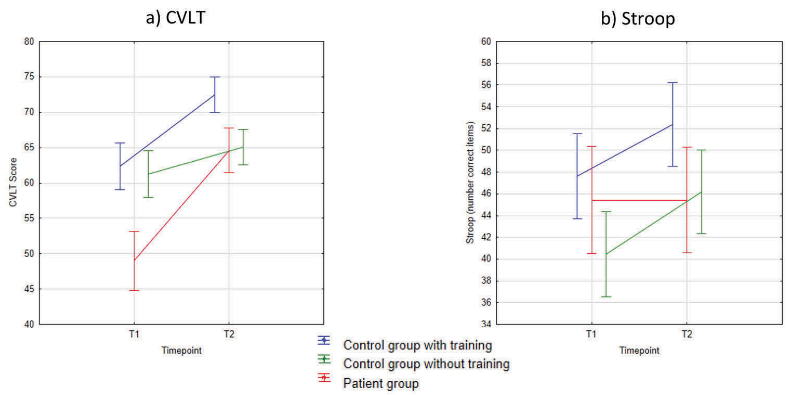

Figure 1. Neuropsychological tests.
Figure displays the results from (a) CVLT and (b) Stroop tests. Error bars denote standard errors. Note that there is a highly significant improvement in the two training groups for the CVLT test (a), while the Stroop test (b) showed a significant improvement only for control groups, irrespective of training.

Table 3. fMRI results for the two conditions as conjunction across group means. Table describes areas of activation in terms of anatomical localisation, MNI coordinates, as well as *t*-statistics and cluster size with related FWE corrected *p*-values.

Localisation		MNI coordinates			Peak		Cluster	
Structure	Side	*x*	*y*	*z*	*T*-value	*p*(FWE)	Size(# voxel)	*p*(FWE)
(a) Pitch discrimination task								
Supplementary Motor Area	Bilateral	−4	2	56	9.32	<0.001	663	<0.001
Operculum, Anterior Insula	Left	−48	−2	2	7.31	<0.001	138	<0.001
Cerebellum	Left	−22	−54	−28	7.05	<0.001	339	<0.001
Cerebellum	Right	24	−56	−28	6.50	0.001	59	0.001
Thalamus	Right	12	−12	0	6.47	0.001	127	<0.001
Heschl's Gyrus, Superior Temporal Gyrus	Left	−58	−30	8	6.44	0.001	149	<0.001
Operculum, Anterior Insula	Right	50	0	0	6.31	0.001	35	0.004
Heschl's Gyrus, Superior Temporal Gyrus	Right	60	−26	2	6.27	0.001	151	<0.001
Thalamus	Left	−10	−18	0	5.89	0.004	72	0.001
Supramarginal gyrus	Left	−46	−40	46	5.67	0.008	45	0.002
Anterior Insula	Left	−34	12	2	5.63	0.009	23	0.007
Precentral Gyrus	Right	52	2	44	5.42	0.018	9	0.017
Superior Temporal Sulcus	Right	48	−22	−10	5.39	0.020	9	0.017
Putamen	Right	24	12	0	5.29	0.026	11	0.015
(b) Tonika-Dominant-Tonika Task								
Heschl's Gyrus, Superior Temporal Gyrus	Right	58	−22	2	7.90	<0.001	591	<0.001
Heschl's Gyrus, Superior Temporal Gyrus	Left	−44	−28	8	7.74	<0.001	434	<0.001

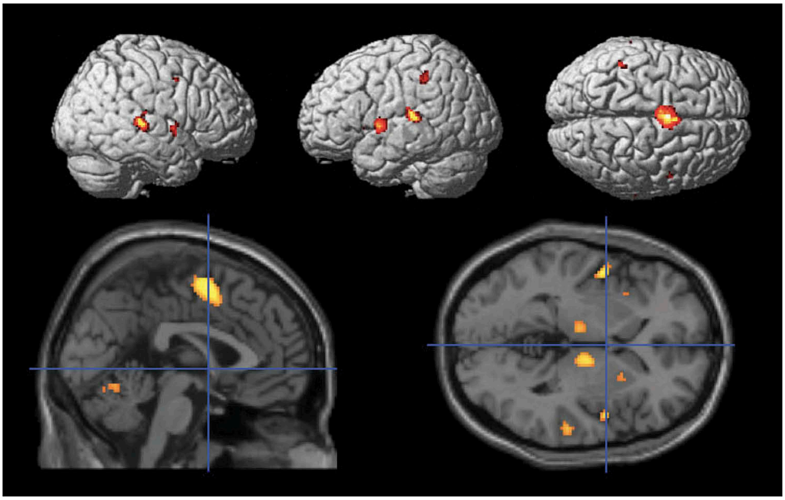

Figure 2. Pitch discrimination task.
Figure displays the results from a conjunction across group means, with a threshold of FWE-corrected threshold of *p*(FWE) <0.05.

a group by repetition effect ($F(2,16) = 4.247$, $p = 0.033$), but only a strong trend towards a main effect of group ($F(2,16) = 3.409$, $p = 0.058$). These significant effects were mainly driven by an improved performance of Group 2 (Fisher's LSD $p < 0.001$).

Tonika-dominant-tonika task

The conjunction across group averages revealed for the Tonika-Dominant-Tonika task that this task activated mainly the left and right auditory cortex (Table 3b, Figure 3). Further, the ANOVA results revealed no main effect of group or repetition, but, more importantly, a significant group × repetition interaction in the medial orbitofrontal gyrus [MNIxyz: 10, 24, −20], peak-level: $F(2,51) = 19.82$, $p(FWE) = 0.016$, cluster-level: 2 voxel, $p(FWE) = 0.028$. This effect was followed up by a 2 × 2 ANOVA between Group 1 and Group 2. This analysis confirmed the previous results with the following statistical values: [MNIxyz: 10, 24, −22], peak-level: $F(1,30) = 40.36$, $p(FWE) = 0.020$, cluster-level: 7 voxel, $p(FWE) = 0.014$. A follow-up, directed *t*-test indicated that the activation in the medial orbitofrontal gyrus increased in Group 1, against a slight decrease in Group 2. It should be noted that there were 12 participants in Group 3 (Figure 3).

Discussion

The results strength the evidence that active training of music production influence neural activity and cognitive functioning in both patients but also healthy controls. We found distinct changes in cognitive performance but also focal changes in brain activation. Some of these effects appeared only in Group

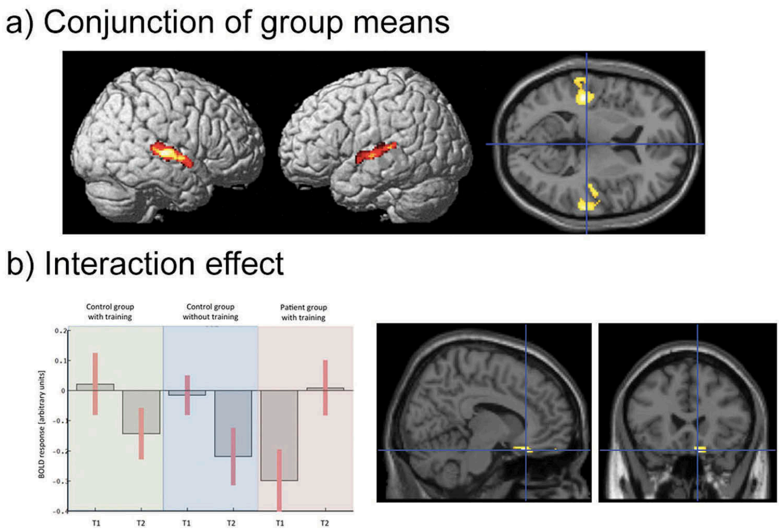

Figure 3. Tonika-dominant-tonika task.
(a) Figure displays the results from a conjunction across group means, with a threshold of FWE-corrected threshold of p(FWE) <0.05.
(b) Figure displays BOLD response and localisation of significant the group × repetition interaction effect (p(FWE) <0.05). For display purpose, the threshold is set to $p < 0.001$

1 and Group 2, others only in Group 2 and Group 3, and some only in Group 1. The data from neuropsychological tests pre–post music intervention demonstrated significant enhancement of cognitive performance in both Group 1 and Group 2. The results of the CVLT clearly indicated an effect of musical training on cognitive performance in Group 1 and Group 2, which was absent in Group 3 (Figure 1a). It is also important to note that Group 1 had a post-intervention score that was at a comparable level as the baseline of Group 2 and Group 3. Hence, the performance improved up to the normal level. Qualitative data from interviews pre–post in Group 1 supports these results.

The Stroop word/colour test result were a contradiction to the CVLT result. In the Stroop word/colour test, the Group 1 did not have any increase in score post-intervention and only Group 2 and Group 3 showed a repetition effect (Figure 1b). However, one has to bear in mind that these two tests measure different cognitive abilities. CVLT is sensitive in measuring functions as perception, memorisation and retrieval of information, as well as learning strategies. This test fits well with the aim of the study to enhance cognitive performance of patients with memory deficits. By contrast, the Stroop word/colour test measures tempo as reading speed, switch of attention, and inhibition, specific cognitive abilities other than those for the CVLT. Accordingly, the patient's post-intervention score were highly significant on the CVLT but not on the Stroop word/colour test. This indicates that the intervention method promoted a specific effect on the neural networks in reference to attention, learning strategies and retrieval of information. Nevertheless, the patient group's outcome of the Stroop test was lower than expected. Future studies should investigate the absence of a transfer effect, to disentangle the different mechanisms that cause specific changes in some cognitive functions, while performance in another cognitive function remains.

For the fMRI data, we do not find any differences in activation for the pitch discrimination task. However, we do find a significant improvement of reaction time in Group 2, reflecting a possible transfer effect of the training that may also appear in Group 1 if the training would be continued.

More importantly, we found a patient specific change in the Tonika-Dominant-Tonika task. Group 1 demonstrated a significant change of activation within the medial orbitofrontal cortex (OFC) (Figure 3), which is part of the pre-frontal cortex. The OFC network regulates higher order cognitive processing, such as executive functions, including attention, decision-making, impulse control and social behaviour (26). This structure has also been associated with the default mode network (27). The latter notion is supported by the low to negative BOLD response under task performance in the controls. Moreover, Group 1 demonstrated a normalisation of the BOLD signal after training, from a strong deactivation before the training. A normalisation of this activation may indicate a better interplay with systems of the executive system, or the so-called extrinsic mode network (27). OFC, in general, has a widely distributed interconnected neural network to almost all areas of the brain and has a wide spectrum of functions. For instance, OFC plays an important role in stimulus-reinforcement associations learning (26,28,29), which is the ability to associate a sensory stimulus with a (positive) reinforcer. In this circumstance, auditory, visual, and motor areas are densely interconnected with other prefrontal cortical regions, reflecting integration for executive motor control, which is evident in learning to play the piano. OFC's connectivity to association cortex is of special interest as this is one of the most important networks in developing new pathways and emotional associations (10). Neural activity during music production promotes neural cross activity between music and non-music brain areas and activates association cortex by stimulating episodic and semantic memory networks (10,33).

Although speculative, a possible explanation for the reorganisation of neural networks during musical training may be the factor of shared neural networks for language/music (30–33). Association is a key word in explaining how new neural pathways may be facilitated by interaction of neural networks between musical cognition and non-musical cognitive functions as brain areas serving cognition and emotion are overlapping and interconnected. Additional information from the literature within cognitive rehabilitation provides evidence that music stimulates cognition and perception in activating neural networks engaged in attention by analysing perceptual patterns in music. Fundamental organisational processes for memory formation in music have their parallels in temporal chunking principles in non-musical memory processes (semantic and episodic memory) (34). Together with Hebbian learning rules, whereby synapses are driven to change by coherent inputs in a competitive neural network (9), these four interconnected factors may be the major basic elements in how music supported interventions may reorganise a broken brain system.

Conclusion

The key findings of this study are the clear evidence of a causal relationship between musical training and cognitive improvement, as well as reorganisation of neural networks. The results demonstrated significant training-related effects and enhanced cognitive performance in both music groups. These findings support the aim of the study to restore cognitive function in patients with brain injury and add a novel music-supported intervention within rehabilitation of patients with cognitive deficits following mTBI. Limitation to the study is the small number of participants in the patient group. Future research may consider the variable of intervention length and practising time, together with increased number of participants to establish an intervention adapted to future cognitive rehabilitation programmes for patients with mTBI.

Acknowledgements

The authors thank all the participants who took time to participate in the study and the staff of the radiological department of the Haukeland University Hospital (Bergen, Norway) for their help during data acquisition. The study was supported by a grant to KS from the Research Council of Norway (217932: It’s time for some music).

Declaration of interest

The authors report no declarations of interest.

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Appendix

Piano training protocol – 8 weeks.
OBJECTIVES TEACHING MATERIAL: Tuition book: Agnestig,C.B. AB Carl Gehrmans Musikforlag, Stockholm, Sweden.

Week 1	Listen to Twinkle, twinkle little star.
1.1 «Sound before symbol» Listen to melody played by instructor. Introduce middle C. Kinaesthetic (motor) movement with both hands with both hands on middle C.Introduce fingering system. Introduce treble clef and bass clef.	Play without any score on middle C with both hands alternatively. Write middle C and clefs in work book.
1.2 Repetition of previous session. Including listening to the melody (Twinkle, twinkle little star). New: Learn to play with second finger (index). Right hand and left hand.Learn the new notenames: d in treble clef and b in bass clef.	Play without score first, and then play from the book. There are 6 different pieces applying these first 3 notes. Write new learned notes in the work book
Week 2	
2.1 Repetition of previous session. Reinforcement of 3 notes c-d-b. New: Introduce note values: Quarter notes, half notes. Singing,clapping/tapping. New notes: Treble clef e.	Write notes in different constellations and play. Write new note in work book.
2.2 Repetition of previous session. New: Bass clef note a.	Write new note in work book. Play pieces with new notes.From no 8 to 14. Repeat pieces 1–7.
Week 3	Practise notewriting in work book.
3.1 Reinforcement of notation and motor skill. Varying hand movements in playing the notes in different orders. New: Barlines and time signature. 2 beats in a bar.	
3.2 Play all pieces from 1–14. New: Introduce 3 beats in a bar. Treble clef: f. Motor skill exercises. Introduce whole note and rests.	Write new note in work book. Play new pieces with new note f in treble clef. No 15–17
Week 4	Write new note in work book. Play new pieces with new note g in bass clef. No 18–21. Practise new note value together with quarter note, half note and whole note.
4.1 Repetition and reinforcement. New: Bass clef g Finger-exersises of both hands playing simultaneously from middle C to treble g and bass f. New: Note value 3 beats.	
4.2 New:repetition sign. New note: Bass clef f. Sight read small pieces composed by the instructor in order to reinforce the notes. Individual exercises according to individual problems with sight reading	Individual work book exercises. New pieces 22–23.
Week 5	New pieces: 24 and 25.
5.1 Repetition and reinforcement of previous learned material New: Applying both hands simultaneously with chords in left hand and melody in right hand.	
5.2 New: Dynamics; play piano = soft, play forte = loud.	New pieces: 26–29.

(*Continued*)

(Continued).

Week 6	New pieces: 30–34
6.1	Work book: writing new notes.
Repetition of previous material. New note: Bass clef e, d,c	
Practise chords in different patterns. New:eight-notes.	
6.2	
Reinforcement of pieces from no.24–34.	
Week 7	New piece: 35 and 38
7.1 Playing with all notes from bass c up to treble g. New note in treble clef: a. New handposition.	Finger-exercises in right hand. New handposition including treble a.
7.2	Introduce new piece for next week. Twinkle,twinkle little star.
Playing pieces no: 33–34-35 and 38	This piece is a challenge with new handposition.
Week 8	
8.1	
Practise new piece: Twinkle, twinkle little star.	
8.2	39 easy progressive pieces from beginner's tutor book is the curriculum.
Revision of pieces no 33.34,35. Play new piece Twinkle,twinkle little star.	

frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 25 June 2019
doi: 10.3389/fnhum.2019.00177

Neuroplastic Effects in Patients With Traumatic Brain Injury After Music-Supported Therapy

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Damage to the orbitofrontal cortex (OFC) often occurs following a traumatic brain injury (TBI) and can lead to complex behavioral changes, including difficulty with attention and concentration. We investigated the effects of musical training on patients with behavioral and cognitive deficits following a mild traumatic brain injury (mTBI) and found significant functional neuro-plastic changes in the OFC's networks. The results from neuropsychological tests revealed an improved cognitive performance. Moreover, six out of seven participants in this group returned to work post intervention and reported improved well-being and social behavior. In this study, we explore the functional changes in OFC following music-supported intervention in reference to connecting networks that may be responsible for enhanced social interaction. Furthermore, we discuss the factor of dopamine release during playing as an element providing a possible impact on the results. The intervention consisted of playing piano, two sessions per week in 8 weeks, 30 min each time, with an instructor. Additional playing was required with a minimum of 15 min per day at home. Mean time playing piano in reference to participant's report was 3 h per week during the intervention period. Three groups participated, one mTBI group (n = 7), two control groups consisting of healthy participants, one with music training (n = 11), and one baseline group without music training (n = 12). Participants in the clinical group had received standardized cognitive rehabilitation treatment during hospitalization without recovering from their impairments. The intervention took place 2 years post injury. All participants were assessed with neuropsychological tests and with both task and resting-state functional magnetic resonance imaging (fMRI) pre-post intervention. The results demonstrated a significant improvement of neuropsychological tests in the clinical group, consistent with fMRI results in which there were functional changes in the orbitofrontal networks (OFC). These changes were concordantly seen both in a simple task fMRI but also in resting-state fMRI, which was analyzed with dynamic causal modeling (DCM). We hypothesized that playing piano, as designed in the training protocol, may provide a positive increase in both well-being and social interaction. We suggest that the novelty of the intervention may have clinical relevance for patients with behavioral problems following a TBI.

Keywords: social interaction, emotional control, neuroplasticity, mTBI, orbitofrontal cortex, music-supported therapy, dynamic causal modeling

OPEN ACCESS

Edited by:
Mikhail Lebedev, Duke University, United States

Reviewed by:
Karli K. Watson, University of Colorado Boulder, Unites States
Zhen Yuan, University of Macau, China
Michael J. Silverman, University of Minnesota Twin Cities, United States
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Received: *08 March 2018*
Accepted: *16 May 2019*
Published: *25 June 2019*

Citation:
Vik BMD, Skeie GO and Specht K (2019) Neuroplastic Effects in Patients With Traumatic Brain Injury After Music-Supported Therapy. Front. Hum. Neurosci. 13:177. doi: 10.3389/fnhum.2019.00177

INTRODUCTION

Traumatic brain injury (TBI) can be devastating and cause changes in a human's life. Optimal treatment and rehabilitation of patients with head injuries can mean the difference between disability or normal functioning. Despite the potential high relevance for the practice and management of mild traumatic brain injury (mTBI), few controlled studies have been carried out on the impact of long-term post-traumatic interventions (Heskestad, 2017). Well-designed studies of the outcome and efficacy of interventions in general, and in promoting patients with mTBI to return to work, is still lacking (Nygren-de Boussard et al., 2014). Vikane (2016) concluded in a longitudinal study of patients with mTBI, that multidisciplinary outpatient clinical treatment did not have a positive effect on whether the patient return to work (RTW) or stay on sick-leave. These results indicated that subsequent intervention studies should consider a different approach to promote RTW (Vikane, 2016).

Injury to the orbitofrontal cortex (OFC) alone, or combined with temporal pole damage, can result in complex behavioral changes (Mah et al., 2005). The orbitofrontal networks are in close proximity to bony protrusions and are vulnerable to trauma-induced rotational acceleration of the brain (Clark et al., 2018). Disturbances of higher cognition and social behavior have long been recognized as a common sequelae of lesions of the prefrontal cortex (Mah et al., 2005). Emotional recognition is important in social interactions, helping individuals to understand intentions and thereby guide behavior (Drapeau et al., 2017). The OFC receives input from the temporal association cortex, amygdala, and hypothalamus, making it the highest integration center for emotional processing. It also receives inputs from the visual system, taste, and somatosensory regions (Rudebeck et al., 2013). Behavioral changes have been linked with damage specifically involving OFC (Mah et al., 2005). Milder injuries to the head may cause microscopic damage to axons and thereby affect interconnected processing in the brain (Sigurdardottir, 2010). The injury may include white matter damage from a diffuse axonal injury (DAI), which can remain undetectable on structural neuroimaging (Balanger et al., 2007; Clark et al., 2018). A common impairment after mTBI is post-concussion syndrome. These often exist as a combination of symptoms and are categorized within three groups: cognitive problems (concentration and memorization); somatic symptoms (headache, vertigo, balance-problems, nausea, fatigue, sleep disorders and double vision problems) and behavioral problems such as an irritability, depression and anxiety, as well as response inhibition. These factors may have a negative impact on the individual's social outcome (Heskestad, 2017).

The intervention method presented may be categorized within Neurologic Music Therapy (NMT), defined as "the therapeutic application of music to cognitive, sensory, and motor dysfunction due to neurologic disease of the human nervous system" (Thaut, 2010). The NMT method is based on neuroscience models of music perception and the influence of music on changes in non-music related brain areas. However, the present study does not strictly follow one of the cognitive techniques outlined in NMT. The intervention program is structured with a standardized curriculum.

Why Is Music so Special and How Does Making Music Achieve Its Rehabilitation Effects?

A musical performance is a demanding task for the brain, involving the interaction of several modalities recruiting almost all regions of the brain (Koelsch and Siebel, 2005; Parsons et al., 2005; Zatorre, 2007; Jäncke, 2009). Learning to play an instrument requires complex multimodal skills involving simultaneous perception of several sensory modalities: auditory, visual, and somatosensory as well as those of the motor system (Pantev, 2009). Music-making provides an enriched environment for the brain by promoting dendritic sprouting that is fundamental for synaptic plasticity (Goldberg, 2009). Increasing evidence suggests that music making could be used as a possible tool in neurologic rehabilitation (Jäncke, 2009; Särkamö et al., 2014; Herholz et al., 2016). The psychological effects and neurobiological mechanisms underlying the effects of music interventions are likely to share common neural systems for reward, arousal, affect regulation, learning, and activity-driven plasticity (Sihvonen et al., 2017).

What May be the Underlying Cognitive Processes Leading to Functional Neuroplasticity in OFC When Playing the Piano?

There is no specific music center in the brain. Different factors of music such as pitch, tempo, melody and dynamics are perceived in different neural networks (Parsons et al., 2005). Playing an instrument promotes an interaction between the two hemispheres and may strengthen the connections between neural networks (Schlaug, 2009b).

Based on knowledge from music psychology, music perception and cognition, as well as the effects of music production on changes in neural networks, we designed a music supported intervention to explore the behavioral and neuronal changes in patients with cognitive deficits following a mTBI (Vik et al., 2018). In this study, we were particularly interested in examining whether and how the intervention affects social interaction and behavior with a focus on the OFC as an area involved in social cognition but also most often damaged in TBI patients.

The previous report in Vik et al. (2018) demonstrated an interaction effect within OFC, where patients showed a specific increase of activity, compared to healthy controls. The present report explores this effect even further by examining explicitly which areas showed an increase in the patient, compared to both control groups. There is little knowledge about the potential neuroplastic changes induced by musical training within the emotional control and social enhancement of mTBI patients. According to a literature review by Hegde (2014), there are no studies that examine the improved functions over time. We may, therefore, suggest that this study fills a gap in the existing literature. We provide knowledge of how and why music-supported interventions for patients with deficits in social behavior may experience a positive enhancement of social interactions and thereby live a better life. The aim of the present study is to investigate factors during piano training that may be responsible for enhanced social interaction in patients with social deficits, following mTBI. We predict that piano training may enhance emotional control, thereby improving social behavior.

MATERIALS AND METHODS

Participants

For this study, seven volunteers (three females) with cognitive deficits following mTBI were recruited with the help of the Department of Physical Medicine and Rehabilitation, Haukeland University Hospital, Bergen, Norway. Two control groups of healthy participants were recruited through posters at The University of Bergen and Haukeland University Hospital Bergen, Norway; one with music intervention (n_{K1} = 11), and one baseline group without music (n_{K2} = 12). All participants were aged between 18 and 60 years with a mean age of 38 years and a group matched for gender, age and education level. Inclusion criteria were 2 years post injury to avoid spontaneous recovery processes during the intervention period. Participants had received rehabilitation treatment prior to the intervention without any improvement of their deficits and had persistent problems with attention, concentration, memorization, fatigue, and social behavior, and were either on sick-leave, or working part time with adjusted work; see **Table 1** for the clinical data of the patient group. We did not include a control clinical group. The reason for this was that these patients had received cognitive training and had participated in rehabilitation programs during hospitalization without any progress. We found that since the time post-injury was at least 2 years, we could avoid the confounding variable of spontaneous recovery, which takes place within the first month or year post injury. A longitudinal study of patients following mTBI supports this view. The authors concluded that for the group of patients with persistent symptoms at 2 months post-mTBI, this result represented a negative predictor for RTW (Vikane, 2016). Excluding parameters in all three groups were psychological problems before the accident. Musicians were excluded because of possible differences in brain structure between musicians and non-musicians (Stewart, 2008). Classification of musicians was that only persons with no formal training of music were accepted. All participants signed a consent form. The protocol was approved by Regional Ethical Committee (REK-Vest), Norway.

Study Design

We designed a between-group and a longitudinal within-subject design. All groups were examined pre-post intervention. Participants in the baseline group were examined without intervention in between. We applied neuropsychological tests as described in the following; neuroimaging, semi-structured interviews in the patient group only, self-report, training log and neuroimaging for all groups.

Piano Training Protocol

The music groups received two 30 min, one on one piano-lessons per week, for 8 weeks. They were instructed to practice at home for a minimum of 15 min a day. The tuition repertoire consisted of 28 pieces for beginners; see Vik et al. (2018) for a detailed tuition program. The curriculum consisted of learning to play melodies, first with each hand separately, then after learning to play two octaves, playing with both hands simultaneously. The curriculum can be found in the Norwegian piano-tuition book for beginners in which the first 28 pieces served as the curriculum (Agnestig, 1958). Reading musical notation, theory and playing scales were included in the curriculum. Additional pieces were provided if the participant had reached the 28 pieces before the end of the 8 weeks of training. We did not evaluate the level of performance, because the main focus was on actual training time. An important aspect of the lesson was a repetition of previous lesson's objectives to facilitate neuroplasticity as described in the "Introduction" section. We, therefore, performed a log of the participant's attendance. The instructor of the intervention, was an experienced piano teacher with a Masters in Piano Pedagogy and in Music Psychology, with over 25 years of teaching experience. The piano-training took place at Haukeland University Hospital, Bergen, Norway.

Participants in both music groups kept a log of their actual training-time. The clinical group was instructed to report possible headache, vertigo or other somatic issues while playing the piano. Training-time could be an important variable in analyzing the results in reference to possible functional and structural changes in the brain's neural networks, between the music groups and within the clinical group.

Assessment Pre-post

Semi-structured Interviews

Semi-structured interviews were conducted pre-post intervention in the patient group. A summary of the answers can be found in **Table 1**. Of special interest was their subjective opinion of well-being, social interaction and cognitive performance pre-post intervention.

Neuropsychological Tests

A test-battery of three different neuropsychological tests was applied: Mini Mental Status Test (MMS), California Verbal Learning Test (CVLT 2), Stroop Word/Color test. Data were analyzed with a 3 (group) × 2 (repetition) repeated-measure analysis of variance (ANOVA), using SPSS 22[1].

Functional and Structural MRI

Functional and structural magnetic resonance imaging (MRI) scans were collected-pre-post for all groups; for detailed information see Vik et al. (2018). In short, participants were examined on a 3T GE Signa MR scanner. They performed a passive listening task in which they listened to extracts of classical and popular Western musical cadence pattern of Tonika-Dominant-Tonika (TDT) chords, based on the first, the fifth, and the first tone of the scale. The relationship between individual

[1] www.ibm.com

TABLE 1 | Data of the clinical group.

Time to first examination after injury	Gender, Age	MRI/CT scan	Prior Intervention <2 years post injury	CVLT scores pre-post intervent.	Social behavior pre interv. and wellbeing	Work situation pre intervention	Work situation post intervention
Examination date: 2 months after concussion	P1, M42	Orbit and nose fracture	Outpatient Rehab.	17–60	Depressed. Isolated.	Sick leave 100%.	100% sick leave. Psychological problems
Examination date: 3 months after concussion	P2, F41	N	Outpatient rehab.	58–65	Depressed. Fatigue, isolated.	Sick leave 50%. Change of work adjusted to PTA.	Return to previous work 100%.
Examination date: 2 1/2 month after contusions	P3, M31	Small epidural hematoma and contusion bleeds frontal lobe right side and both temporal lobes	1 month in TBI unit	60–60	Sleep-disorders, fatigue.	Adjusted work following PTA	Return to previous work 100%.
Examination date: 20 days after concussion	P4, F52	Normal (Acach.cyst)	Outpatient TBI unit Rehab. 4 weeks	54–70	Avoiding gatherings, fatigue.	Adjusted work following PTA	Return to previous work 100%.
Examination date: 2 months after subdural hematoma (conservative management)	P5, F55	Orbit fracture and nose fracture	Outpatient TBI unit	32–48	Fatigue	Adjusted work following PTA	Return to work 100%.
First incidence 21 years prior to second incidence. Second incidence: Hospitalized. Examination date: 14 years after 2nd incident.	P6, M30	MR and CT micro bleeds contusions in frontal and temporal lobes bilateral 1st incidence. 2nd examination: MR.Post-traumatic changes in frontal- and temporal lobes.	TBI unit 1 month	62–74	Isolation after 1st incident. Difficult in decoding people's faces and intensions. No changes post-intervention	Sick-leave 100%	Change of work. 100% work.
Examination date: 1 month after evacuated epidural hematoma	P7, M19	Diffuse axonal injury, Epidural hematoma contusions	TBI unit	60–70	Pre-:fatigue. Post-interv. Improved social interaction	Difficulties in following school-work due to fatigue.	100% back to school. Started study university.

Clinical data was obtained from patient's medical records, neuropsychological test results from a California Verbal Learning Test (CVLT) test and, social behavior and wellbeing prior to intervention was obtained from semi-structured interviews. Data on the work situation prior and post-intervention was also obtained from semi-structured interviews. All patients have been diagnosed with mild traumatic brain injury (mTBI) according to scores obtained in the Rivermead post-concussion symptoms questionnaire and The Glasgow Coma Scale. Scores are not included in this figure.

tones forms the basis for the most fundamental aspect of musical processing and recognition of melodies (Zatorre, 2007). TDT is a melodic pattern in Western music activating semantic networks that are important for long-term representations of familiar tunes (Zatorre, 2007). This paradigm was selected because all participants were Norwegian, and Western music has a familiar structure that will activate association cortices. A key factor in the listening task is to activate most parts of the brain. As all melodic perception involves a working memory mechanism, a stronger involvement of the prefrontal cortex and other association cortices was predicted. The paradigm was adapted from Zatorre (2007) and is defined as a high cognitive task.

In total, 28 extracts from melodies were presented with varying delays between each stimulus as an event-related design. In total, 160 echo-planar imaging (EPI) images were acquired with the following parameters: repetition time (TR) 3 s; echo time (TE) 30 ms; matrix size 128 $\times$ 128; 30 slices; voxel size 1.72 $\times$ 1.72 $\times$ 4.4 mm. Data were analyzed using SPM12, and data processing included realignment, unwarping, normalization to the MNI reference space and smoothing (8 mm).

As described earlier, the initial 3 (groups) $\times$ 2 (repetitions) repeated-measure ANOVA, revealed a significant (FWE-corrected) group $\times$ repetition interaction for details (see Vik et al., 2018), showing an increased activity in OFC in patients, but not in the controls. In the present report, we aimed at exploring this effect even further by re-analyzing the data. A non-parametric approach was selected since the patient group was too small for ordinary linear statistics. Using the SnPM13 toolbox (Nichols and Holmes, 2001; Winkler et al., 2014), the two control groups were pooled and treated as one control group and compared to the patient group. This increases the specificity of those effects that occurred in the patient group only. A variance smoothing of 8 mm was applied and 5,000 permutations were estimated. The SnPM analysis was performed as a two-sample test with the pre-post difference images as an input, with the hypothesis that both groups are equal. The results were explored with a nonparametric p-value of $p < 0.001$ and only clusters with at least 10 voxels were considered. The pre-post difference images were estimated manually within SPM, using the ImCalc function. These data were also analyzed in conjunction with performance on cognitive tasks and are published separately (Vik et al., 2018). This analysis served as a precursor for the following dynamic causal modeling (DCM) analysis of the resting-state functional magnetic resonance imaging (rs-fMRI) data. Therefore, and since the sample size in this study is low (seven patients with mTBI and complete dataset), we selected an explorative analysis with a liberal statistical threshold for the fMRI results (10 voxels). This resulted in seven areas of interest, which were then entered into the rs-fMRI analysis.

Resting-State fMRI

Resting-state fMRI data were also acquired both in the pre- and post-session. The rs-fMRI examination lasted almost 9 min, and the following parameters were used: 256 EPI images; TR 2 s; TE 30 ms; matrix size 64 $\times$ 64; 30 slices; voxel size 3.44 $\times$ 3.44 $\times$ 4.5 mm. Data were pre-processed in the same way as described above. Prior to the analysis, the time series from the seven areas of interest were corrected for some global signal fluctuations. Therefore, fluctuations co-occurring in white matter and the ventricles were regressed out. The cleaned time series' were analyzed with spectral dynamic causal modeling (spDCM) for resting state, with the seven areas of interest (Friston et al., 2014; Razi et al., 2015; Kandilarova et al., 2018). The spDCM model is a fully connected model, where each node is connected to each other node.

In contrast to a stochastic DCM on resting-state fMRI data, a spectral DCM estimates effective connectivity from the cross spectra of the fluctuations in neuronal states instead of from their time courses directly. Further, the individual spDCM models were not separately but jointly estimated, using the Parametric Empirical Bayes (PEB) framework, implemented in SPM12.2. This was followed by Bayesian model reduction to restrict the number of parameters and a second level PEB analysis, where different design-matrixes were tested against each other, and the model with the highest Bayesian model evidence was analyzed further. The different designs parameterized that there were no-effects, a pre-post effect (independent of groups), a pre-post effect only for training (for patients and the control group with training), general differences between the patient and control groups (across pre-post measurements), or group-specific effects. The overall network connectivity of the winning model was explored across groups and repetitions in terms of posterior probabilities (Pp > 0.95) of the estimated parameter. For the analysis of interaction effects, the estimated parameter (A-matrix) were extracted from the individual spDCM models and further analyzed, using repeated-measure ANOVAs. Due to the small number of patients, the resulting interaction effects were further investigated with non-parametric Wilcoxon rank sum tests. To keep the number of performed test low, only group differences in pre-post changes in connectivity were analyzed.

RESULTS

Emotional and Social Interaction—Semi-structured Interviews—Group 1 (Patient Group)

Data from semi-structured interviews demonstrate a qualitative increase in social interaction and well-being post-intervention (see **Table 1**). Common problems before intervention were fatigue, blurred vision, light sensitivity, dizziness, vertigo, headache and sensitivity to sound. Increased irritability, mood changes and withdrawal from social gatherings were also reported. This subjective information corresponds with the patient's medical records from hospitalization. Post-intervention there were no reports of negative issues in reference to the intervention. On the contrary, all patients had a positive intervention experience. The answers corresponded with the individual training logs in which the participants were instructed to write notes of any changes in cognitive ability and social functionality during the intervention. Six out of seven of the participants reported progressive improvement of cognitive performance during the remaining 4 weeks of intervention and improved mental capacity after 8 weeks. However, two of seven patients did not improve their social behavior as reported in **Table 1**, P1 had developed post-traumatic depression and felt isolated, and P6 reported difficulties in emotional recognition in social settings, followed by poor social activity and a feeling of isolation, despite a positive work-situation post intervention.

Training Time vs. Neuropsychological Test Results—Clinical Group

Training time may be a variable of interest. The question is if there was a relationship between training time, scores on the CVLT test and the final outcome. As we found functional changes in the OFC's neural networks only in the clinical group, we have limited these analyses to this particular group. In **Table 2** we can see there is no consistency between scores in CVLT, amount of training time and outcome in reference to RTW, **Table 1**. There were extensive individual differences of training time within this group. Mean training time was 3 h per week. P7, **Table 2**, played the minimum time per week for 8 weeks, namely 15 h and 20 min. This participant was present at all lessons and reported to follow the scheduled 15 min home-playing. He had a significant increase in CVLT scores and returned to his studies post-intervention, which he had not been able to attend after injury.

P1 and P3 had a total training time below the set minimum time which was estimated as 15 h 30 min, for 8 weeks. P1's total training time was 7 h 45 min which indicates no training at home between lessons with the instructor. P1 was present at all lessons except one. He self-reported to have developed a post-depression condition. He achieved a significant increase of scores in the CVL test post intervention. P3 did not provide any explanation for not following the intervention program strictly. This participant did not have any increase in scores from the CVL test.

Neuropsychological Tests

As reported earlier, the CVLT test demonstrated a significant effect of musical training on executive functions related to attention, learning strategies, and retrieval of memories in the patient group and the healthy control group with music intervention. More precisely, in the post-intervention examination, the patient group demonstrated an increase in performance up to the level of the pre-intervention level of both control groups (for statistical details see Vik et al., 2018).

TABLE 2 | Clinical group data.

Patient	CVLT 2 Pre-interv	CVLT2 Post-interv	Total training-time
P 1 42 M	17	60	7 h 45 min
P 2 41 F	58	65	36 h 45 min
P 3 31 M	60	60	8 h
P 4 52 F	54	70	28 h 35 min
P 5 55 F	32	48	23 h 55 min
P 6 30 M	62	74	21 h 20 min
P 7 19 M	60	75	15 h 20 min

Total training time and test-results from neuropsychological test CVLT pre- and post-intervention.

However, the Stroop test did not show any group-specific effects, but a main effect of repetition (for statistical details see Vik et al., 2018). The MMS test was excluded from this study because of a ceiling effect of all patients.

fMRI-Tonika-Dominant-Tonika Task

The nonparametric SnPM analysis was examined with a nonparametric p-value of $p < 0.001$ and only clusters with at least 10 voxels were considered. This revealed seven areas that showed an increase in the patient group only. These were the right medial orbitofrontal gyrus, middle frontal gyrus (MFG), anterior insular cortex, two distinct clusters within the left medial orbitofrontal gyrus (hereafter called left anterior OFC and left posterior OFC), the supplementary motor area (SMA), and the rostral anterior cingulate cortex (ACC). There were no areas showing a decrease in patients/increase in controls (**Table 3**, **Figure 1**).

rs-fMRI—Dynamic Causal Modeling

The model with the highest Bayesian model evidence (relative log-evidence of BF = 11) was the one that parameterized a general group difference between the patients and control groups. To examine the overall underlying connectivity pattern, only connections with a posterior probability of $Pp > 0.95$ were explored, as estimated by PEB, implemented in SPM12.2. This overall connectivity pattern of the investigated network is displayed with shaded colors in **Figure 2**. The repeated-measures ANOVA on the connection strength, revealed five connections where there was an interaction effect between the patient and control groups. The non-parametric Wilcoxon rank sum test revealed that the patient group primarily demonstrated a dominating change in functional connectivity. Compared to the control group that received the same training, patients showed reduced functional connectivity from the right OFC to the left posterior OFC and increased functional connectivity from the left posterior to the left anterior OFC (bold colored, continuous lines in **Figure 2**) after the intervention. When compared to the control group without training, the same increased functional connectivity between the two left-sided OFC nodes was found again, as well as an increased functional connectivity from left posterior to the right OFC, an increased self-inhibition of the left anterior OFC (i.e., less activity), and a reduced self-inhibition of the left posterior OFC (i.e., higher activity; broken lines in **Figure 2**). When comparing the two control groups, only an increased self-inhibition of the left anterior OFC and increased connectivity between the anterior insula and ACC was discovered for the control group with training (not displayed in **Figure 2**). Interestingly, without any restrictions of the analysis, all differential effects for the patient group were exclusively found for the OFC, while all other examined connections remained unchanged, independent of group, repetition, or perceived training.

DISCUSSION

The present results document functional changes in several dimensions. The qualitative outcome from semi-structured

TABLE 3 | Table reports results from the nonparametric functional magnetic resonance imaging (fMRI) analysis with anatomical description, MNI coordinates, statistical values, and cluster size (number of voxels, voxel size 2 × 2 × 2 mm).

Area	Side	Co-ordinates	Pseudo T	*p* (non-para)	Cluster size
Medial orbitofrontal gyrus	R	10, 22, −20	4.88	0.0002	92
Middle frontal gyrus	R	28, 46, 24	3.96	0.0004	44
Anterior insular cortex	R	42, 12, −2	3.85	0.0004	52
Medial orbitofrontal gyrus (anterior)	L	−12, 26, −22	3.73	0.0002	25
Medial orbitofrontal gyrus (posterior)	L	−16, 16, −16	3.39	0.0004	25
Supplementary motor area	R	14, 8, 58,	3.24	0.0006	21
Rostral anterior cingulate cortex	L	−12, 38, 0	2.90	0.0002	14

The results were explored at a nonparametric p threshold of p < 0.001 and only clusters with at least 10 voxels per cluster were considered.

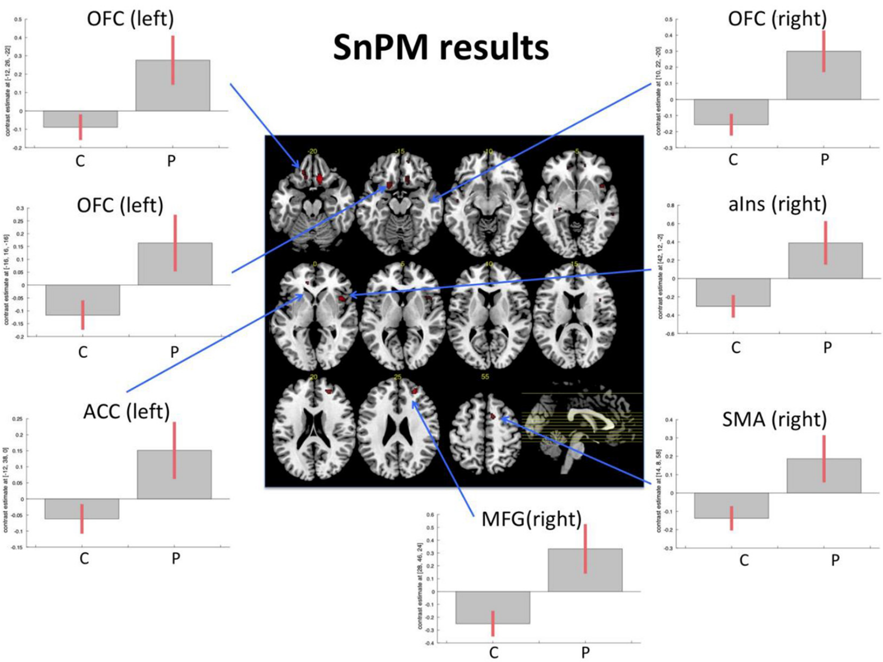

FIGURE 1 | Functional magnetic resonance imaging (fMRI) task. Figure displays the results from the non-parametric analysis on the pre-post differences. The results highlighted areas where patients (P) demonstrated an increase of activity from pre- to post-examination, while control subjects (C; irrespective of music intervention) did not show an increase or even a slight decrease. The results are explored with a non-parametric *p*-value of $p < 0.001$. Bar plots show contrast estimates (with 90% confidence interval). OFC, orbitofrontal cortex; MFG, middle frontal gyrus; aIns, anterior insula; ACC, anterior cingulate cortex; SMA, supplementary motor area.

interviews in which six out of seven participants in the clinical group reported improved well-being and social interaction together with a normal work-situation, supports the view of increased social behavior after music intervention. This was accompanied with functional neuroplasticity predominantly in the orbito- and prefrontal cortex following music-supported intervention in the patient group, as concordantly seen in both task and resting-state fMRI. There may be several possible reasons regarding the clinical group's improved social functioning, further discussed below.

The fact that playing a musical instrument is a complex activity for the brain and activates almost all region of the brain (Zatorre, 2007), may be an essential key factor in the enhancement of cognitive functions and thereby the improvement of well-being and social interaction. Evidence-based research on how music activates the brain supports this view. Schlaug (2009b) documented that the corpus callosum, the fiber-bundle between the two hemispheres, was larger in musicians than in non-musicians, demonstrating that musical training relies on inter-hemispheric brain networks.

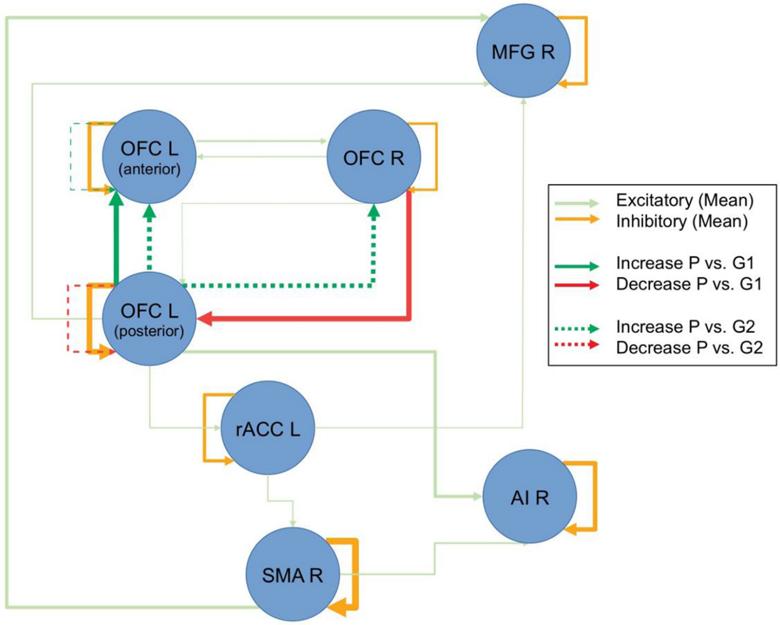

FIGURE 2 | Resting-state dynamic causal modeling (DCM) analysis. Figure displays the overall connectivity of the discovered network in the shaded colors, independent of groups and repetitions. The line thickness for the shaded lines is an indicator of the averaged estimated parameter. Pre-post group differences are displayed in strong colors. Connections, where there was a difference between the patients (P) and the control group with intervention (G1) are displayed with continuous lines, and comparisons to the control group without intervention (G2) are displayed with broken lines. Line thickness inversely scales with the *p*-values (Note: line thicknesses of the lines in shaded and strong colors are not related and should only illustrate the relative strength of the respective effects).

Training time could be a variable. However, as seen in **Table 2**, there is no causal relationship between the amount of training time and the scores from CVLT. As reported earlier, P1 and P3 had a total training time below the set minimum time, which was estimated at 15 h 30 min over 8 weeks. P1's total training time was 7 h 45 min which indicates no training at home between lessons with the instructor, as he was present at all lessons except for one. It is an open question why there is a gap between CVL test scores and an improvement of social interaction. One could speculate if attending lessons would enhance attention, concentration and memory function, but not have an impact on neuroplasticity in OFC and thereby enhanced social behavior. P3 differed from P1. P3 was not present more than every other lesson, however, he practiced at home and achieved 8 h of total practicing time according to a self-report. His scores on the CVL test did not differ from pre-post intervention. This could perhaps be interpreted as an importance of regular attendance during 8 weeks of intervention. Limitations to draw any conclusion of the impact of training time vs. neuropsychological tests scores are linked to the low participant numbers of the sample size.

It is interesting to register that the minimum training time of a total 15 h over 8 weeks indicates a norm for improved cognitive performance and social behavior. Future studies should replicate the training protocol of training time to establish a controlled method.

How May Piano-Playing Improve Cognitive Functioning?

There are specific interconnected cognitive processes which may lead to functional neuroplasticity in OFC and behavioral changes during playing the piano. A number of studies have evidenced that there are shared neural networks between language and music (Patel et al., 1998; Koelsch and Siebel, 2005; Parsons et al., 2005; Brown et al., 2006). Music activity also activates areas involved in episodic and semantic memory networks (Chan et al., 1998; Schlaug, 2009a), and stimulates and strengthens perception and cognition by activating neural networks that are involved in analyzing perceptual patterns in music (Deutsch, 1982). Finally, repetition, evident in musical structures, may contribute to strengthening new neural connections through neuroplastic changes—a core mechanism of learning (Hebb, 1961; Ockelford, 1999; Münthe et al., 2002; Goldberg, 2009).

There are other aspects to consider in reference to neural activity during music production in reference to what may influence well-being and an enhanced social life. An intriguing question is if dopamine release during active and successful playing of a musical instrument could be responsible for the improvement of cognitive performance. This activity is goal oriented and mastering of a goal is a dopamine release factor (Lehrer, 2011). Music listening and production activate the reward circuitry cortical networks in reference to emotional reward, followed by a dopamine release—a neurotransmitter evident in the reward system (Owessen-White et al., 2016; Brodal et al., 2017). Dopamine may be a core factor for increased neuroplasticity during musical training. When playing an instrument, like a piano, there are certain factors working together in concert to achieve dopamine release: motivation to reach a goal and the satisfaction of mastering a goal. One could speculate that positive emotional responses to music cause an additional stimulation of the limbic system, followed by a dopamine release. The amygdala and association cortices may also be activated when processing those emotional responses (Tramo, 2001).

Last, but not least, the enjoyment of playing the piano, as reported by the participants, may have a possible dopamine-releasing effect, thereby increasing the neurotransmitter-effect between the neural networks affecting OFC and executive functions, followed by the normalization of emotional reactions that are fundamental in social interactions. Playing the piano has a profound effect on the neural networks in engaging neural circuits evident in emotion and reward, which is important for stimulus-reinforcement learning, an essential factor in social interaction (Rolls, 2014).

Further evidence comes from the two present fMRI analyses. When explicitly exploring the recovery in patients, the results demonstrated that besides the earlier reported functional change in the right OFC (see Vik et al., 2018) changes in the left-sided homolog, the right middle prefrontal cortex, right anterior insular cortex, left rostral ACC, and the right SMA (see **Figure 1**) also occurred. Importantly, the discovered effects within OFC have been confirmed and replicated by the resting-state fMRI data, using DCM (see **Figure 2**). The three explored areas of the left and right OFC mostly showed increased connectivity and increased activity, which corresponds to the findings from the task-related fMRI. The areas that showed signs of recovery are all areas related to attention and cognitive control, but also to social cognition (Zald and Raucht, 2010; Clark et al., 2018) Interestingly, nearly all detected brain areas that showed a recovery effect also received direct or indirect dopaminergic connections, like the prefrontal cortex and the anterior insular cortex (Christopher et al., 2013). This might provide further support to the earlier proposed assumption that actively playing a musical instrument might have a dopamine-releasing effect. More importantly, the changes in OFC connectivity, as discovered by the spDCM analysis, indicates that the connectivity within this network mostly increased and that the discovered recovery process was indeed restricted to this area of the explored network. Although the explored sample is rather small, this study concurrently demonstrated in two independent analyses and fMRI datasets, that a recovery process took place within the OFC. It is important to emphasize that both analyses were not restricted to the OFC and that both results emerged out of two unrestricted analyses. Future studies, however, have to replicate this finding with a larger sample of patients, before final conclusions can be drawn.

Finally, the increased activity of the bilateral OFC could be seen in light of the increased scores in social interaction. Interestingly, this present task fMRI analysis also revealed increased activation in the rostral anterior cingulate gyrus, which is also called the emotional part of the anterior cingulate gyrus and is closely related to error monitoring (Bush et al., 2000). Furthermore, the other areas from the task fMRI analysis that showed increased activations are mostly related to different attentional systems, with the anterior insula as the central area for the saliency network (Menon and Uddin, 2010), and the MFG as part of the central executive network (Corbetta et al., 2008; Hugdahl et al., 2015). The involvement of these areas in the rehabilitation processes, triggered by the intervention, may reflect that active music training goes beyond the simple training of new skills, but involves several brain areas and networks that have to interact, in addition to the fact that piano training is an activity with substantial social interaction. Although this was a mostly explorative analysis, we should mention that virtually all areas showed an increase of the levels of activations from pre- to post-intervention measurement in patients, while the control subjects showed almost no changes or a slight decrease (see **Figure 1**). However, given the size of the sample, this description remains of a more qualitative nature, and further studies with larger samples, with a control patient group to rule out which effects are dedicated to the music intervention and which effects might result from increased social interaction during and because of the training, are required.

CONCLUSION

We have demonstrated that playing the piano may induce neuroplasticity and thereby enhance social interaction and well-being in patients with cognitive deficits following mTBI. The results from both task and resting-state fMRI revealed significant evidence for a causal relationship between music intervention and functional reorganization of neural networks in the OFC. The fact that six out of seven patients with chronic mTBI returned to work post-intervention is a promising outcome of this intervention. We suggest that neural activation during 8 weeks of intense and structured music intervention, promoted social interaction and enhanced cognitive performance in the clinical group, a view supported by the literature of neuroplastic changes in the brain during music-training. However, an interesting aspect of future research is to investigate the level of dopamine released during playing the piano in exploring the impact of dopamine on social behavioral, in reference to changes in OFC neural networks. A central limitation to the study is the low number of participants. Another limitation is the lack of a patient control group. Although the participants within the patient group had already received rehabilitation within the health system and were in a chronic phase of post-concussion syndrome, a control patient group would add more significance to the final results. Future studies should, therefore, include a patient control group. In conclusion, we propose that the novelty of this intervention may have clinical relevance for patients with problems in social interaction, following mTBI.

ETHICS STATEMENT

The protocol was approved by Regional Ethical Committee (REK-Vest), Norway.

AUTHOR CONTRIBUTIONS

BV: doctoral thesis. GS: medical records. KS: MATlab fMRI.

FUNDING

The study was supported by a grant to KS from the Research Council of Norway (217932: It's time for some music).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CG declared a shared affiliation, though no other collaboration, with the authors to the handling Editor.

Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, Trond, Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
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1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
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	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
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	Fylkesnes, Marte Knag	Frykt, forhandlinger og deltakelse. Ungdommer og foreldre med etnisk minoritetsbakgrunn i møte med den norske barnevernstjenesten.
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Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230862810 (print)
9788230845806 (PDF)