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The Effect of Music on Stress Parameters in Acute Stroke

Master's Degree Program in Human Neuroscience
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Master's thesis

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Abstract

Treatment success and patient recovery are influenced by the physical and psychological stress responses the patient experiences after a sudden stroke event. Research shows that elevated stress levels after stroke are associated with worse recovery and even death. The present block randomized, controlled study (N=16+16) investigates the effect of music intervention on mental, cognitive, and cardiovascular levels of stress in acute stroke patients. Patients of the music group listened to self-selected music intensely during the third post-stroke day. The control group received standard care. Music group showed a significant increase in positive moods, decrease in symptoms of mental distress, and improved cognitive performance compared to controls, as observed immediately after the intervention and even at six-month follow-up. No significant differences were detected in cardiovascular stress between the two groups. These findings are consistent with previous studies confirming beneficial effects of music in neurological patients and are the first to show stress-relieving potency of music in acute stroke. The present study supports the idea of implementing music listening in routine clinical treatment and acute care of stroke.

Key words: acute stroke; stress; music intervention; mood; cognition; cardiovascular stress.

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1. Introduction

1.1 Background

A stroke, also known as a cerebrovascular accident (CVA), refers to neurologic symptoms and signs that occur when blood flow to the brain is interrupted (Nestler et al., 2002). It is the second commonest cause of mortality worldwide with 5.5 million deaths in 2016 (World Stroke Organisation, 2016). According to the World Stroke Organisation, there are above 13.7 million new stroke victims globally each year (World Stroke Organisation, 2016).
Acute treatment of stroke consists of gathering data on the patient's condition, restoring vascularisation, and limiting the extent of further neuronal injury. This includes neurologic assessments and laboratory tests, brain scans and administration of tissue plasminogen activator (tPA) injection. The patient is then transferred to a stroke unit where they are closely monitored. Stroke has a strong impact on an individual's quality of life. Survivors of stroke are typically left with long-term disabilities, cognitive and emotional deficits (Neidert et al., 2011). Consequently, long-term rehabilitation procedures are required which result in growing public financial burden (Villa et al., 2018). A 2019 systematic review on the economic burden of stroke, reveals that in the European Union the annual costs for stroke treatment and post-stroke care are estimated to be around 27 billion euros. In 2008, stroke medical treatments cost $65.6 billion in the United States (Rajsic et al., 2019). According to The American Heart and Stroke Associations, these numbers are predicted to increase to $184.1 billion by 2030 (Rajsic et al., 2019). These findings illustrate the economic burden of stroke and indicate that there is an obvious need for advancement in cost-effective treatment methods enhancing the effectiveness of rehabilitation.

Stroke can be classified as ischemic or haemorrhagic. Ischemic strokes account for 88% of all strokes and are caused by either an embolism or a thrombosis resulting in decreased blood flow (Nestler et al., 2002). The remaining 12%, are caused by rupture of blood vessel which leads to a haemorrhage into the brain tissue or, in the case of ruptured aneurysm, into the subarachnoid space (Nestler et al., 2002). The term "acute stroke" refers to the days up to two weeks following the CVA. Although this project focuses on acute ischemic stroke only, to fully appreciate the concept of stroke and distinguish the mechanisms of the two types from one another, it is necessary to discuss both.

1.2 Haemorrhagic stroke

Haemorrhagic stroke results from cerebral bleeding that interferes with healthy brain functioning. It is further categorised based on the location of the haemorrhage. An intracranial haemorrhage (ICH) occurs due to the rupture of a blood vessel within the brain and has a 40% risk of death. Risk factors to this specific type of haemorrhage include hypertension, advanced age, heavy alcohol consumption or use of drugs affecting the coagulation system. Symptoms depend on the anatomic location of the haemorrhage. Bleeding at a hemispheric level may cause sudden hemiparesis or speech disturbances. Symptoms caused by bleeding in the brainstem include paralysis, dizziness, and visual disturbances. In addition, non-localizing symptoms, such as nausea, headache or loss of consciousness may occur upon large-volume haemorrhages. Subarachnoid haemorrhage (SAH) is caused by a ruptured aneurysm or rarely by an accident, and it leads to bleeding into the subarachnoid space: the gap between the arachnoid meningeal layer and the pia mater. The space is normally filled with cerebrospinal fluid (CSF), a colourless fluid that provides protection, nourishment and waste removal for the brain. When blood enters the space, it mixes with CSF and increases the pressure around the brain. Sudden intense headache, weakness and loss of consciousness are typical symptoms.

Although magnetic resonance imaging (MRI) is sometimes used for diagnosis, computerized tomography (CT) scan is more sensitive. Treatment depends on the type of haemorrhage and the extent of damage. Use of medication or surgery are typical procedures in treatment. Common long-term deficits are motor, sensory, or cognitive difficulties and fatigue.

1.3 Ischemic stroke

Quantitative estimates of the neuronal loss in acute ischemic stroke indicate that a typical stroke patient loses about 1.9 million neurons each minute when stroke is untreated (Saver, 2005). Ischemic strokes cause tissue damage and death on areas of the brain depending on the site of the blood flow blockage. Figure 1 below illustrates infarcts in different locations shown by CT and MRI.

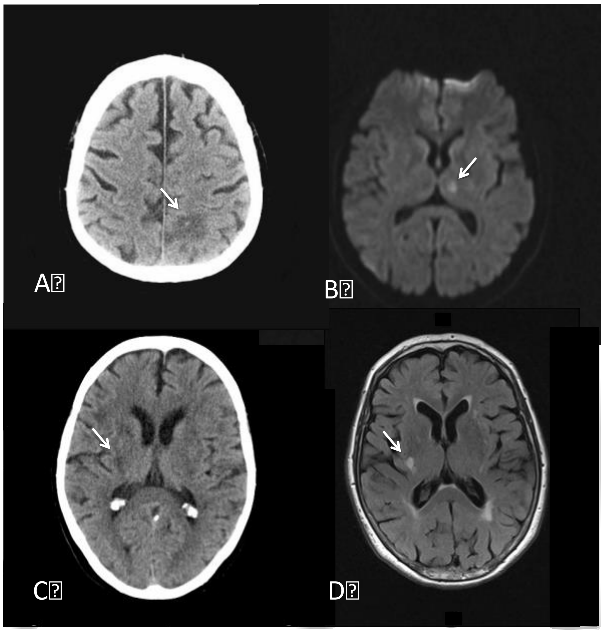


Figure 1. Acute ischemic stroke (arrows) shown by computerized tomography imaging (CT) (A, C) and MRI (B, D). Medium-sized infarct in the left posterior parietal cortex (A), small left thalamic infarct (B). Small right striatal infarct of the same patient imaged by CT (C) and MRI (D). Note that images are viewed by clinical convention (patient lying in horizontal resting position and viewed from caudal direction, i.e., left side in the image represents the right side of the brain.)

Thrombosis. The lumen of an artery may narrow due to cholesterol plaque formation. Plaque changes the inner surface of blood vessels in a way that platelets begin to stick to it and accumulate. A thrombus (blood clot) may form around atherosclerotic plaque inside the lumen which causes the blood vessels to further narrow and thus block the arterial blood flow. Thrombosis can affect both large and small arteries in the brain. Plaque and clots can also detach from the thrombotic vessel into the bloodstream and cause a blockage somewhere downstream. This is the thromboembolic mechanism. The symptoms depend largely on the affected arteries (large or small) and the affected brain area. The most common symptoms include sensory-motor hemiparesis, sometimes accompanied by sudden headache, dizziness, loss of control or body sensation, visual and speech disturbances. Symptoms appear suddenly and can gradually worsen over hours or days. Interestingly, some people may experience sudden, stroke-like symptoms only for a short period time after which the symptoms completely disappear. This is known as a transient ischemic attack (TIA), which typically lasts between a few minutes to an hour and leaves no permanent neurological deficits.

Embolism. Another common cause for an ischemic stroke is embolism. An embolism occurs when an unattached piece of material, particle or debris, travels in the bloodstream and causes a sudden blockage in a blood vessel. The embolic source originates either outside the brain somewhere in the body, usually in the heart or in the aorta and other large arteries, or in an atherosclerotic intracranial artery. Extracerebral sources of embolus result in pure embolic stroke. Main risk factors are disturbances in blood flow and atrial fibrillation. Others are heart failure and large vessel stenosis. The symptoms are similar to those in thrombotic stroke. Therefore, the symptoms do not allow to determine whether the stroke is thrombotic or embolic.

Diagnosis and treatment of ischemic stroke. CT scans and MRI are generally utilised for diagnosis. Additional tests are applied to the patients to determine whether the stroke is thrombotic or embolic. These include blood tests, electrocardiogram, chest X-ray, Doppler ultrasound of the carotid arteries and echocardiogram. If the patient arrives in the hospital within 4.5 h from symptom onset, ischemic stroke can be treated with a clot-busting drug, such a tissue plasminogen activator (t-PA). After being delivered into a vein, the medicine dissolves clots and restores blood flow. Another effective alternative is the use of a special device to perform mechanical thrombectomy, i.e., removal of the blood clot through a catheter. If the brain's blood supply is restored fast, the patient may recover even completely. However, when treatment is delayed, the stroke patient may not survive, or may recover with a disability. After a stroke, the patient is hospitalised and monitored closely in specialised stroke unit to observe whether symptoms worsen, or complications occur.

2. Stroke-related Stress

Stress is commonly understood as a mental or emotional state of tension and strain caused by sudden changes or demanding external events and circumstances. Stroke-related stress can manifest in different forms and multiple levels: at cellular, cognitive, cardiovascular and endocrinological levels, or finally at individual and societal level. These stress reactions are biological mechanisms that protect and allow the body to adapt to new circumstances. This study investigates a wide range of stress parameters related to ischemic stroke and illustrates the relationship between stroke patients stress and recovery.

2.1 Stress at cellular level

The penumbra is defined as hypoperfused tissue surrounding the ischemic core in which blood flow is too low to maintain electric activity but sufficient to preserve ion channels (Ramos-Cabrer et al., 2011). This area is subject to numerous toxic and delirious metabolic processes including excitotoxicity and inflammation. This may result in the expansion of the ischemic core and lower clinical outcome or in recovery of normal function – depending on the success of the treatment procedures (Ramos-Cabrer et al., 2011).

Necrosis. Often considered as the end-result of cellular stress, necrosis is a form of cell death that occurs in the central nervous system as a response to some type of environmental stressor, such as ischemia (Nestler et al., 2001). Necrosis is found at the heart of the ischemic tissue. Cellular stress activates a number of intracellular pathways that are designed to limit the internal damage, activate repair mechanisms, shut down non-essential cellular mechanisms and save the cell (Nestler et al., 2001). However, following a significant neuronal injury, demand of energy is too high and stress response pathways become saturated. This results in a loss of membrane integrity and permanent damage of the cell (Nestler et al., 2001).

Excitotoxicity. When neurons are deprived of oxygen, they fail to maintain their resting membrane potential and thus lose their capability to fire action potentials. The firing neuron releases excitatory neurotransmitters such as glutamate, which in return depolarises the target neurons synaptically connected to it (Nestler et al., 2001). This may create a toxic cycle of neuronal activation called excitotoxicity, whereby excessive stimulation by glutamate causes neural damage as a result of failure of glutamate transporters (Nestler et al., 2001). These transporters are expressed both in glial cells and neurons and they remove glutamate from the synaptic cleft (Nestler et al., 2001). However, the process is adenosine triphosphate (ATP)-dependent and since ATP resources and oxygen supply are limited following a stroke, the neurons undergo energy depletion and die.

Failure of ion pumps. The sodium-potassium-ATPase, also known as $Na+$ (sodium) -$K+$ (potassium) -ATPase, is a protein pump found in the cell membrane of neurons. It is responsible for the maintenance of the membrane potential and it functions at the cost of ATP. Following

ATP depletion, Na+-K+- ATPase activity is lost, and neurons tend to depolarise rapidly (Nestler et al., 2001). This strongly impacts another protein pump, the Na+ - calcium (Ca^{2+}) exchangers, as its activity is dependent on the transmembrane Na+ gradient. When the Na+ gradient declines, the activity of the exchangers diminishes respectively. In return, the ionic equilibrium is disrupted, and the neuron fails to maintain its membrane potential (Nestler et al., 2001).

Increase in intracellular calcium levels. An important feature of necrosis is the leakage of cytoplasmic and organelle contents (Jayaraj et al., 2019). Such leakage may cause inflammatory processes as they can be toxic to neighbouring cells (Nestler et al., 2001). For instance, cytoplasmic leaking increases calcium influx. Although Ca^{2+} is necessary for several cellular functions, excessive Ca^{2+} influx is toxic (Nestler et al., 2001). Ca^{2+} levels are maintained by a variety of mechanisms including ATP-dependent Ca^{2+} pumps and Na+ - Ca^{2+} exchangers. However, these mechanisms are compromised in ischemia. As mentioned, Na+ - Ca^{2+} exchangers require ATP as well. As the Na+ gradient disappears, the process of calcium flux may reverse, and the system instead pumps Ca^{2+} into the cell. Furthermore, the excessive depolarisation of cells and the firing of excitatory neurotransmitters may cause Ca^{2+} channels to open, and further pump Ca^{2+} into the cell through *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) glutamate receptors (Nestler et al., 2001). This results in excitotoxicity and Ca^{2+} overload and consequently causes cellular damage (Nestler et al., 2001).

Formation of free radicals. Free radicals are unstable yet highly reactive molecules with an unpaired electron on their outer orbital (Nestler et al., 2001). Their formation is associated with excitotoxicity (Nestler et al., 2001). Free radicals damage cells by peroxidising membrane fatty acids through series of steps (Nestler et al., 2001). This degradation alters membrane integrity and fluidity (Nestler et al., 2001).

Acidosis. Intracellular acidosis is a key component of ischemic cell damage (Fan et al., 2014). Ischemia provokes an increase in CO2 tension and enhances anaerobic glycolysis, which leads to lactic acid accumulation (Nestler et al., 2001). The combination of these events causes acidosis, due to drastic decrease in tissue pH values around the ischemic region. These circumstances impact cellular functions in several ways, for instance Na+ -

Ca^{2+} exchangers inhibition, free radical formation, and inhibition of neurotransmitter reuptake (Nestler et al., 2001), all of which contribute to neuronal damage.

2.2 Stress at systemic level: Endocrine responses

Cerebral ischemia initiates several physiological changes observed at stroke onset and continuing for the first weeks after acute stroke. Endocrine changes of the hypothalamic-pituitary-adrenal (HPA) axis are one of the first measurable changes (Neidert et al. 2011).

Cortisol. A classical endocrine stress response is the activation of the HPA-axis, stimulated by a stressor. Following acute ischemia, cortisol is secreted in increased amounts by the adrenal cortex as a response to an increase in adrenocorticotropic hormone (ACTH) secretion from the pituitary gland (Murros et al., 1993). Other examples of stress events in which serum cortisol values have been found to increase include cerebral injuries, severe illness, surgical procedures and mental stress (Gaillard & AI-Damluji, 1987). A dysregulated or stimulated HPA-axis fails to suppress cortisol secretion (Neidert et al., 2011) which results in excessive levels of circulating cortisol. Elevated cortisol levels have been associated with severity, poor outcome, and increased mortality in acute stroke (Murros et al., 1993; Christensen et al., 2004; Barugh et al., 2014).

β-Endorphins. β-Endorphins are opioid neuropeptides and peptide hormones that are produced in neurons within the central and peripheral nervous system. β-endorphins are primarily used by the body to reduce stress and maintain homeostasis. In acute stroke β-endorphin levels are significantly higher than in those recorded in healthy subjects (Franceschini et al., 1994).

Inflammation: IL-6 and CRP. Inflammatory changes such as the elevation of serum interleukin-6 (IL-6) and C-reactive protein (CRP) are visible in acute stroke. IL-6 is a cytokine that regulates inflammatory responses and is an essential inflammatory mediator associated with chronic stress (Hedley et al., 2008). A significant increase in IL-6 levels have been reported in stroke patients shortly after an ischaemic event (Hedley et al., 2008). CRP levels increase in the blood in conditions causing inflammation somewhere in the body. High levels of CRP have also been associated with poor outcome of stroke, as they reflect either an inflammatory reaction or tissue damage (Hedley et al., 2008).

Oxytocin. Oxytocin (OT) is a peptide hormone and neuropeptide, well known for its role in human parturition and lactation (Quirin et al., 2011). It seems to exert several additional functions, such as relaxation effects, anti-stress responsiveness and anti-anxiety effects (Heinrichs et al., 2003; Ring et al., 2006). Experimental stroke studies suggest that OT treatment results in diminished infarct size (Karelina et al., 2011). In addition, some evidence suggests that OT is related to lower cardiovascular and sympathetic reactivity to stress (Grewen & Light, 2011). OT has been shown to have anti-stress and antidepressant actions in humans (Matsushita et al., 2019) and may thus have a role in stroke-related mental stress.

Blood glucose. Hyperglycemia is characterized by blood glucose levels >6.0 mmol/l and it occurs in two thirds of ischemic stroke patients in acute stroke (Lindsberg & Roine, 2003). Experimental evidence suggests a potential association between hyperglycemia and poor functional outcome.

Although causes of acute hyperglycemia vary, the majority of patients are believed to experience stress-related hyperglycemia (Lindsberg & Roine, 2003). Such response is mediated by the releases of cortisol and norepinephrine and can further injure the ischemic brain. Hyperglycemia contributes to neuronal injury especially in the area of ischemic penumbra (Anderson et al., 1999; Lindsberg & Roine, 2003). By osmotic mechanism, hyperglycemia subjects the stroke patient to increased intracranial pressure and thus slows cerebral circulation.

2.3 Stress at cardiovascular level

Autonomic dysfunction is a common complication in acute ischemic stroke. The body's cardiac manifestations to autonomic dysfunction in acute ischemic stroke are associated with worse functional recovery and increased mortality (De Raedt, De Vos & De Keyser, 2015).

Cardiac dysfunction. Different forms of cardiac complications occur in approximately 20% of patients with ischemic stroke within the first days following the event (Sheitz et al., 2018). Particularly for patients in advanced age, acute ischemia is a major risk factor for not only stroke, but also for cardiac injury. Studies have reported that acute ischemic stroke often involves reduced heart rate variability (HRV) and reduced baroreflex sensitivity (BRS) (De Raedt et al., 2015). 25-39% acute ischemic stroke patients are estimated to develop cardiac arrythmias even without pre-existing cardiac disease (De Raedt et al., 2015). These arrythmias typically involve atrial fibrillation, premature ventricular contractions and ventricular arrythmias. However, most of them are transient and disappear within days following stroke onset (De Raedt et al., 2015).

Moreover, blood pressure-related complications are another form of cardiac dysfunction that occur as a co´nsequence of stroke. Variations in blood pressure occur naturally during day and night-time: in healthy individuals, blood pressure decreases by 10-20% at night due to reduced sympathetic activity (De Raedt et al., 2015). Approximately 80% of patients experience arterial hypertension during acute stroke (De Raedt et al., 2015). However, acute stroke patients often exhibit abnormal dipping patterns, sometimes known as "reverse dipping". In this phenomenon, patients exhibit a reduced blood pressure at daytime and an increase blood pressure at night-time (De Raedt et al., 2015). A few underlying mechanisms such as increased sympathetic tone and norepinephrine levels have been suggested (De Raedt et al., 2015). The role of research in stroke induced cardiac variations is central as these variations often contribute to further damage. For instance, changes in blood pressure variability during early ischemic stroke may influence brain perfusion and contribute to infarct growth and oedema formation (De Raedt et al., 2015).

In their article, Scheitz et al. (2018) describe the cardiovascular complications in acute ischemic stroke as a "stroke-heart syndrome". The term was established by the authors in attempt to summarise and illustrate the numerous stroke-associated cardiac alterations that take place shortly after an ischemic attack.

2.4 Stress at individual level: Post-stroke depression

As a result of excessive stress, some patients develop pathological responses such as psychological distress and psychiatric disorders (Ferro et al., 2016). Post-stroke depression (PSD) is the most frequent psychiatric problem of stroke patients and involves a complex combination of numerous ischemia-induced neurobiological dysfunctions (Villa et al., 2018). Common mental disturbances include mood and anxiety disorders, post-traumatic stress disorder and even personality changes. Patients may also experience anhedonia, a condition in which the individual develops a diminished interest or pleasure in activities that they used to enjoy (APA, 2013). Other clinical features include loss of energy and appetite, insomnia, changes in concentration and psychomotor retardation (Ferro et al., 2016).

Generally, treatment of severe depression includes psychotherapy, medication and sometimes neurostimulation (Harmandayan et al., 2012). Although psychotherapy is known to be an effective method in treating depression, no existing evidence suggests a significant preventive effect on stroke-associated depression. Furthermore, availability of psychotherapy with short notice for acute stroke patients is usually not an option. Therefore, pharmacotherapy is the main treatment method for depressive disorders attributed to acute stroke. While post-stroke depressive disorders are highly prevalent, they remain underdiagnosed and undertreated (Hermann et al., 2011).

SSRI-antidepressants and neuroplasticity. Neuroplasticity is the brain's ability to structurally change and adapt by forming new connections or eliminating old ones (Kraus et al., 2017). Serotonin (5-HT) is an important neurotransmitter that is involved in a wide variety of brain function, including neuromodulation. Animal studies have demonstrated that the neuroplastic functions exerted by serotonin are central in shaping serotonergic neural networks during development and maintaining them throughout adulthood (Kraus et al., 2017). Dysfunctions in serotonergic system and neuroplasticity are also known to contribute to major depression (Kraus et al., 2017). Selective-serotonin reuptake inhibitors (SSRIs) are a class of anti-depressant medication. They are commonly the first line medication in the treatment of post-stroke depression (Zhou et al., 2020).

Interestingly, research on animals and human subjects have demonstrated that elevated extracellular 5-HT levels after SSRIs treatment resulted in short-term and long-term neuronal plasticity (Kraus et al., 2017). Moreover, SSRIs as well as other types of antidepressants are known to affect glutamatergic system by influencing NMDA receptors which may increase synaptic plasticity (Sanacora et al., 2008). Studies have repeatedly shown that patients with major depression demonstrate reductions in grey matter volumes (Kraus et al., 2017). Interestingly, Arnone et al. (2013) found an increase in grey matter in the hippocampus and other limbic areas in depressed patients, after an 8-week SSRIs treatment. These results suggest that SSRIs, in addition to being related to clinical treatment of depression, may trigger neuroplasticity, and related to clinical treatment of depression. However, SSRIs also have numerous adverse effects. More importantly, SSRIs and other antidepressants are associated with an increased risk of haemorrhagic stroke and myocardial infarction, especially among elderly population (Taylor-Rowan et al., 2019). Therefore, alternative treatment methods should be considered in the management of post-stroke depression.

Oxytocin – potential usefulness in treatment of post-stroke depression. Oxytocin (OT) is synthesised predominantly in the paraventricular and supraoptic nuclei of the thalamus and plays a major role in social contact and behaviour (Karelina et al., 2011). In addition, OT has been found to have several neuroprotective effects and anti-inflammatory properties. The study by Windle et al. (1997) is among the early ones to demonstrate that OT reduced anxiety-like behaviour. Research has since consistently shown evidence of OT counteracting stress-induced activity of the autonomous nervous system (Light et al., 2000) and inhibition of cortisol secretion Quirin et al., 2011). Evidence for beneficial effect of OT in experimental stroke has been published (Karelina et al., 2011). No studies on OT in human stroke have been published yet. In an interesting double study, Quirin et al. (2011) randomly assigned male students with either high or low emotional regulation abilities (ERA) to receive either OT intranasally or placebo. Cortisol levels were then measured before and after a social stress. Their results indicate that individuals with impaired ERA showed reduced cortisol response to stress after oxytocin but increased cortisol after placebo application. These findings suggested that OT reduces cortisol responses to stress (Quirin et al., 2011). Moreover, Karelina et al. (2011) examined the effects of pharmacological manipulation of OT in mediating the influences of social interaction on stroke outcome using mice. Mice were treated with exogenous OT or OT receptor antagonist beginning one week prior to induction of experimental stroke. Their results are also consistent with previous findings on OT and provide evidence of OT mediating the neuroprotective effect of social interaction on stroke outcome.

2.5 Stress at societal level

Stroke often causes a sudden and significant decrease in everyday task performance ability. In such situation, patients typically rely on their families and close ones. Research shows that the stress of becoming dependent on others, is a major source of health concern. The psychosocial aspect of stroke such as social isolation contribute to stroke pathophysiology (Lowry & Jin, 2020). Research shows that social isolation is associated with increased infarction volume, a higher risk of developing post-stroke depression, greater long-term disability, and worse functional recovery (Lowry & Jin, 2020). Weerd et al. (2011) investigated the stroke patient's wellbeing one year post stroke in comparison to average population of the same age. Their results indicate that stroke patients showed significantly higher rates of depression and anxiety disorders. This finding correlates with lower quality of life and greater burden for the caregivers. Attention has been given to stroke patients' caregivers and their mental health. Numerous studies found that caregivers of stroke patients suffer show stress of mental distress (Byun et al., 2019). Stroke increases the risk of being isolated from society and their usual surrounding. Due to limited healthcare and financial resources, the increase in stroke cases due to the aging of population, is the core source of societal stress. Cost-effective, safe, and easily implementable methods to enhance conventional stroke treatment and rehabilitation are in increasing demand in the health care systems.

3. Music

3.1 Brain Networks in Music processing

Music is a common and powerful auditory stimulation tool for the human brain. Music listening activates numerous networks that are associated with brain areas in frontal, temporal, parietal, and occipital lobes (Sutoo & Akiyama, 2004; Peretz & Zatorre, 2005). These networks and associated brain areas are illustrated in Figure 2 below.

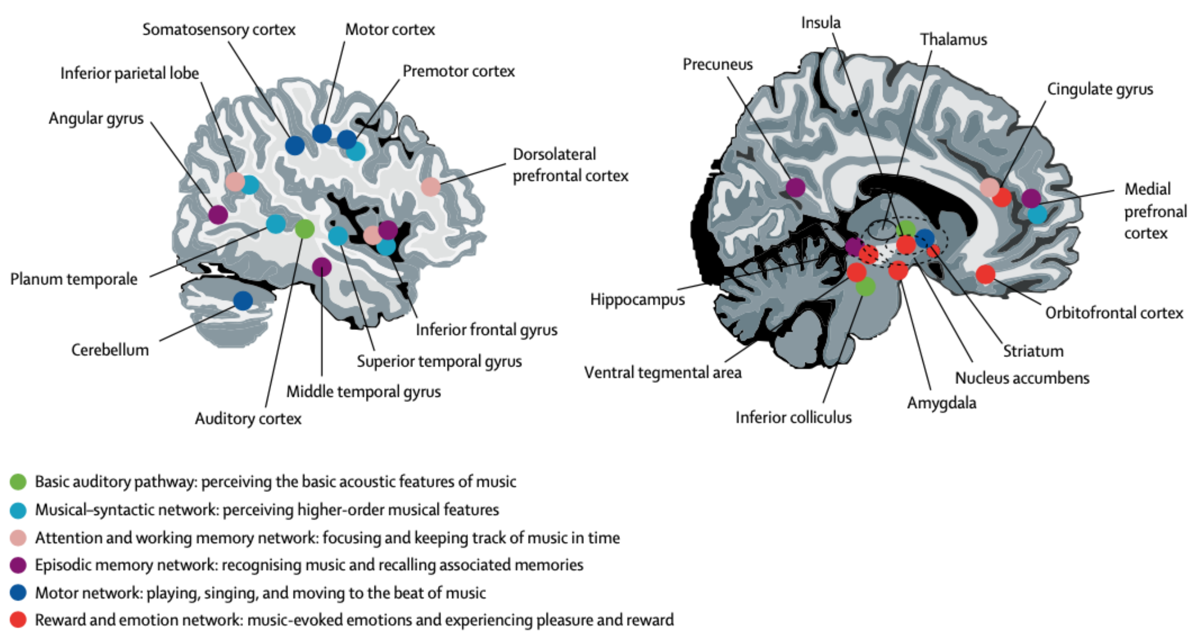


Figure 2. Key brain areas associated with music processing. Images taken with permission from article: Sihvonen et al. (2017).

Auditory pathway and Music-syntactic Network. Initially, information on basic features of music, such as pitch, intensity, and temporal variation, enters from the inner ear to the brain stem and thalamus, eventually projecting to the auditory cortex (Skoe & Kraus, 2010). After this initial stage, the brain begins to analyse higher-order music features such as harmony and melody (Särkämö, 2018). These features include spectral and temporal fluctuation patterns within the sound stream and are analysed in a system known as the musical-syntactic network

(Särkämö, 2018). This network comprises the inferior and medial prefrontal areas, premotor area, anterior/posterior superior temporal areas and inferior parietal areas (Alluri et al., 2012).

Attention. Focusing on and keeping track of music causes several cognitive processes to activate. For instance, activation of the inferior and dorsolateral prefrontal cortex, cingulate cortex and inferior parietal cortices are involved in the attention maintenance and working memory systems (Schulze et al., 2011).

Memory. Episodic memory systems are engaged when the music is familiar (Voss et al., 2017). Familiar music is associated with episodes of personal experiences that involve contextual information such as events, sights, sounds and locations (Voss et al., 2017) and thus, this process involves the hippocampus (Voss et al., 2017). Musical cues often trigger autobiographical memories that consist of memories of one's personal life experiences (Ford et al. 2011). Such memories are processed in regions of parietal and frontal lobes (Ford, Addis & Giovanella, 2011).

Motor pathways. Rhythm and beat are processed by the brain's motor and premotor cortices, as well as prefrontal, striatal, and cerebellar regions (Bengtsson et al., 2009). Research has shown that sensory prediction and motor preparation share similar mechanisms as both involve states of prediction (Engel et al., 2001). Interestingly, rhythm perception is shown to share the same areas as motor preparation. This suggests that rhythm perception alone may activate prediction mechanisms associated with motor preparation behaviours (Bengtsson et al. 2009).

Limbic and dopaminergic system. Music causes stimulation of the limbic and dopaminergic areas that contribute to the emotional impact of music and complements memory systems. Hearing pleasant music projects to certain areas of the limbic system such as the amygdala and the medial orbitofrontal cortex that function in response to emotional stimuli (LeDoux, 2000). These areas work as an interconnected network with other cortical and subcortical regions including ventral tegmental area (VTA), ventral striatum, insula, nucleus accumbens, cingulate cortex, hippocampus, hypothalamus anterior cingulate cortex and ventral medial prefrontal cortex (Koelsch et al., 2006). VTA secretes dopamine and projects to the amygdala, hippocampus, anterior cingulate and prefrontal cortex (Ashby et al., 1999). Together, these regions form the reward system and regulate arousal, emotion, reward, motivation, memory, and executive functions (Ashby et al., 1999).

High levels of OT receptors have been identified in olfactory bulb, amygdala, hippocampus, parahippocampal gyrus, regions in the temporal lobe, anterior cingulate cortex, hypothalamus, preoptic area, and certain brainstem nuclei (Quintana et al., 2019). These regions overlap with the limbic and dopaminergic system (see section above). Research has shown that intranasal oxytocin administration alters neural activity in structures of limbic areas such as amygdala, hippocampus, olfactory bulb, and prefrontal areas (Wang et al., 2017; Kumar et al., 2020; Wu et al., 2020).

In summary, music listening involves auditory pathways for perception of basic acoustic features and musical-syntactic network for higher-order musical features. Music activates attention and working memory networks as well as episodic and autobiographical memory networks. Motor networks are involved in rhythm and beat perception of music. Finally, music-evoked dopaminergic and limbic pathways activate and control experiences of pleasure and reward. Altogether, research on music processing demonstrates that music activates numerous networks that involve all four lobes. This indicates a wide-spread bilateral activation.

3.2 Music in Neurological Recovery

The brain's functional recovery relies upon the spared neurons' ability to compensate for lost functions by forming new synapses and networks and remodeling the damaged and lost ones (Cramer, 2008) As discussed, music induces a bilateral widespread activation of the brain which leads to an increased blood flow (Peretz & Zatorre, 2005). An increased blood flow and neuronal activity in return enhances synapse formation and thus improves neuronal connectivity. Additionally, an extensive body of literature suggests that engagement in musical activities promotes neural plasticity and induces grey and white mater changes (Wan et al., 2010). Research shows that music has impressive benefits in a range of major neurological conditions, such as stroke, dementia, and Parkinson's disease, and evidently at least some refreshing effects also in multiple sclerosis and epilepsy (Sihvonen et al., 2017). In stroke, music-induced improvements are mostly visible in cognitive and emotional deficits, motor symptoms and aphasia (Sihvonen et al., 2017). A study by Leo et al. (2020) suggests that vocal music has positive effects on stroke and post-stroke aphasia, especially in verbal learning, long-term cognitive and emotional recovery. This study shows that engagement in musical activities induces neural plasticity and enhances early language recovery in stroke-induced aphasia. In addition, music was beneficial for cognitive and emotional recovery of stroke. The rehabilitative effects of music are visible at both structural and functional levels.

As discussed previously, music increases dopamine levels through the reward system. Sutoo & Akiyama (2004) investigated the topic further by examining the mechanisms by which music modifies the brain. Their results indicate that music increases Ca^{2+}/calmodulin-dependent dopamine synthesis in the brain which in return, reduces blood pressure. This finding is relevant in neurological conditions that involve dopamine dysfunction. In the case of stroke, this finding is important for cognitive, emotional and motor dysfunction. Furthermore, Okada et al., (2009) found that music therapy reduces the secretion of certain catecholamines and cytokines in elderly patients with cerebrovascular disease and dementia. These studies and numerous others compile evidence to conclude that music has numerous physiological and cognitive benefits, in both healthy and pathological conditions.

3.3 Stress and Music

Research shows that music induces psychological, emotional, neurological, and cardiovascular changes. Music can reduce stress by modulating emotional and arousal responses. For a long time, it has been known that music has relaxing effects on psychological stress levels. Khalfa et al. (2003) compared the effects of relaxing music and silence on students' psychological stress recovery. They measured salivary cortisol levels during a social stress test and found that cortisol levels had decreased significantly in the music condition. This suggests that music-based interventions and engagement in music activities induces measurable stress changes in hormonal stress responses.

Numerous studies have concluded that music to reduces stress by detecting music-induced OT changes. OT level is associated with strong emotional valence and therefore induces activity in the limbic system (Harvey, 2020). A study investigating the effects of music on responses of anxiety in patients receiving mechanical ventilation, shows that a single session of music listening as short as 30min, reduces physiological symptoms of stress and increases comfortable resting behaviour (Lee et al., 2005). Moreover, Yuhi et al. (2017) reported evidence of increased salivary OT levels in maltreated children who followed a group drumming session. Similar results were reported by Grape et al. (2003) who found an increase in OT levels among adults after group singing lessons. One may argue that the OT levels may have increased partly due to the psychosocial experience that involved group activity.

However, a sensory study suggests that listening to slow relaxing music was associated with increased salivary OT levels and lower heart rate, while fast music had no impact on OT but only reduced cortisol levels (Ooishi et al., 2017). These findings indicate that music increases OT-plasma concentrations, which are associated with positive mood and increased wellbeing.

Music seems to have therapeutic effects on cardiovascular stress parameters as well. A study by Bernadi et al. (2006) shows that music listening can reduce stress manifesting in cardiovascular and respiratory activity. They measured cardiovascular and respiratory variables during a music listening task, to assess induced changes and to evaluate its clinical use in stress modulation. Their results show that even a short exposure to music can have measurable effects at cardiovascular and respiratory levels. They further argue that music may be used for relaxation purposes when selection is done appropriately.

Furthermore, Leardi et al. (2007) investigated music-induced changes in plasma cortisol level changes in patients during day surgery. Results show that cortisol levels had decreased among the patients who had listened to their self-selected music compared to controls. Their results support the idea of implementing music therapy into patient care for day surgery. Similar results were found in a study investigating music therapy as a clinical intervention and its effects on mood states in neurological patients (Magee & Davidson, 2002). The results show a significant positive difference in anxiety, sense of energy, and agreeableness between pre- and post- intervention. Moreover, Siedliecki et al. (2006) tested the effects of music interventions on empowerment, chronic pain, depression, and disability. They found that the patients in the music group felt more empowered and less pain, depression, and presented less disability signs than the controls. These results suggest that music can be used to decrease pain, depression, and disability.

These studies show that music reduces mental, emotional, and physiological stress symptoms in many contexts. In addition, engaging in musical activities either alone or in group seems to increase emotional wellbeing. Thus, these findings have clinical implications.

4. Aims

While a large amount of research has reported on the effects of music in healthy condition and pathological contexts, the existing research has largely focused on symptom alleviation, such as recovery from motor (Scholz et al., 2016), cognitive and emotional deficits (Särkämö et al., 2008) or aphasia (Magee et al., 2017). Although the favourable effects of music are evident, there is very little research, if any, examining the effects of music on stroke-related stress. The aim of this thesis is to investigate music induced changes on stress in acute ischemic stroke. As discussed, stress is a broad concept that can be measured at different levels. Thus, the first objective of this study, is to present a comprehensive review of published literature considering stress from neurobiological, psychological, and clinical point of view. The second objective is to examine the efficacy of a short music intervention in a patient cohort and controlled setting at the acute phase of stroke. Finally, the third aim is to evaluate potential clinical implications in adding music into routine acute stroke care.

Research Questions. Since symptoms of mental distress and biological mechanisms of stress are interrelated, the main questions this project aims to answer are (1) Does music alleviate symptoms of mental distress in acute stroke? (2) What is the impact of music intervention on cognition? (3) Does listening to music result in short-term cardiovascular changes? (4) What potential role might acute music intervention have in relieving the mental burden during the recovery process of stroke?

Hypotheses. Based on the existing literature, we hypothesise that, (1) A music intervention at the acute phase of stroke will reduce symptoms of psychological stress and increase mental wellbeing, (2) The implementation of a music intervention in acute stroke will improve cognitive recovery of stroke, (3) Due to the numerous physical and psychological benefits music will reduce cardiovascular stress in acute stroke.

5. Methods

5.1 Participants

For this study, 32 ischemic stroke patients from the TYKS T-Hospital (Turku, Finland) were recruited within 24h from stroke onset. Eligible participants were randomly assigned into a music group (N=16) and a control group (N=16). Recruitment was based on written consent. The data was collected between October 2017 and June 2019. The study conforms with the Finnish legislation and Helsinki Declaration concerning medical research and it was approved by the Ethical Committee of Southwest Finland Hospital District.

5.2 Study protocol

Music Group:

- The 3-day intervention was started within 24h from stroke onset as soon as the patient´s condition allowed him/her to participate.
- Blood samples were taken 3 times a day on days 1-3.
- Stress, mental alertness, and mental state were estimated three times a day on days 1-3. The tests on stress and cognition are described in detail below.
- The neurological status was taken daily, including the stroke severity scale (NIHSS).
- Day 2: The patients listened to music they had selected from the music library as much as possible, a minimum of 3 hours under instruction by a music therapist.
- Day 3, a short cognitive test was taken.
- Basic clinical data (stroke type and severity, demographic details) as well as general notes on the patient's state and given treatment were collected.
- The tests were conducted on patients again 6 months after stroke.

Control Group followed the same protocol, except that they did not listen to music on day 2.

5.3 Music

Music therapists gathered up a music library on a laptop, which included the most common and appreciated songs representing a variety of music genres. These songs were classified into their genres and organised into song lists. The patients of the music group chose their favourite music genre and listened to the music via MP3-players. The number listening hours was documented.

5.4 Stress indicators

Visual Analogue Mood Scale (VAMS). Mood is strongly influenced by emotions and influences cognitive processes and actions following thoughts. Numerous mood assessment scales exist, but speech difficulties and impaired communication skills especially due to neurological conditions can be problematic. This issue can be solved with visual scales in which the patient self-estimates his/her mood using a visual graphic rating scale. The Visual Analogue Mood Scales (VAMS) was developed by Stern et al. (1977) for the purpose of mood assessment in neurological conditions, such as stroke and aphasia (Athanasou, 2019). The assessment contains eight internal mood states: fear, confusion, sadness, anger, energy, exhaustion (being tired), happiness and tenseness. Each mood is estimated on a 100mm line, one end representing neutral state and the other end representing maximal intensity of the mood in question. The patients were requested to indicate internal experience of their mood by making a mark along the length of the line. Figure 3 below provides an illustration example of the VAMS. Simultaneously, a nurse completed the scale as well, based on objective impression of the patient's state. VAMS is a validated and reliable instrument with low intra-individual variation (Athanasou, 2019). Therefore, it was used as a screening instrument in this study to track mood changes over time.

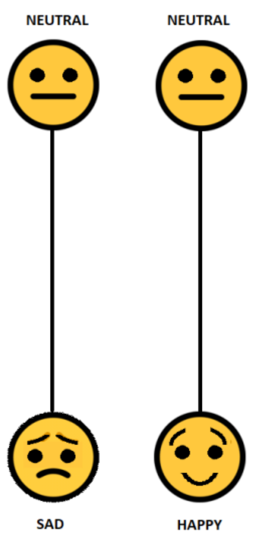


Figure 3. An example of the VAMS. This figure illustrates mood states sadness and happiness.

Depression, Anxiety, Stress Scale (DASS-21). The DASS-21 was used in this study to identify symptoms of depression, anxiety, and stress over time. The twenty-one-item self-report questionnaire measures psychological distress (Gloster et al., 2008) and shows good psychometric properties for this assessment: good internal consistency, good discriminative validity, and excellent convergent validity (Gloster et al., 2008).

Montreal Cognitive Assessment (MoCa). MoCa is a neuropsychological screening assessment that was developed to measure mild cognitive impairment (MCI). MCI is common following a stroke, and so it was used in this study to detect changes in cognitive performance over the follow-up time of 6 months. Research suggests that MoCa is a highly sensitive and specific tool (Nortunen et al., 2018). The psychometric properties of the Finnish version of the MoCa have been validated (Nortunen et al., 2018).

Cardiovascular stress indicators. Cardiovascular parameters taken for routine clinical purposes were analysed in this study. Scheitz et al. (2018) brought up the concept of heart-stroke syndrome to describe the cardiac complications in acute ischemic stroke. The cardiovascular parameters used in this study were changes in systolic and diastolic blood pressure, pulse rate, and electrocardiography changes (extrasystole, atrial fibrillation, elevated ST-segment, T-inversion, prominence of U-wave).

Indicators of stroke severity. Type of stroke-related deficit (side of hemiparesis, presence of aphasia, level of cognition at admission), stroke severity scale (NIHSS) and estimate of infarction volume in CT/MRI images were recorded.

Other clinical parameters. These included blood glucose level, leukocyte count, C-reactive protein level, thorax X-ray. Prior diagnosis of diabetes or hypertension was documented.

5.5 Statistical Analyses

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) software and Microsoft Excel. Results from demographic patient data assumably conforming to normal distribution were analysed using averages, standard deviations (SD) and t-tests to compare group differences. Data based on classification were analysed using chi-squared test. Psychological stress variables (VAMS, DASS-21 and MoCa) as well as cardiovascular variables were transferred and first analysed on Excel. Scores were first averaged and compared between groups (controls vs music group) using the two-tailed *t-test* or paired t-test.

In some cases, Wilcoxon rank sum or Wilcoxon signed rank test were used as nonparametric tests.

6. Results

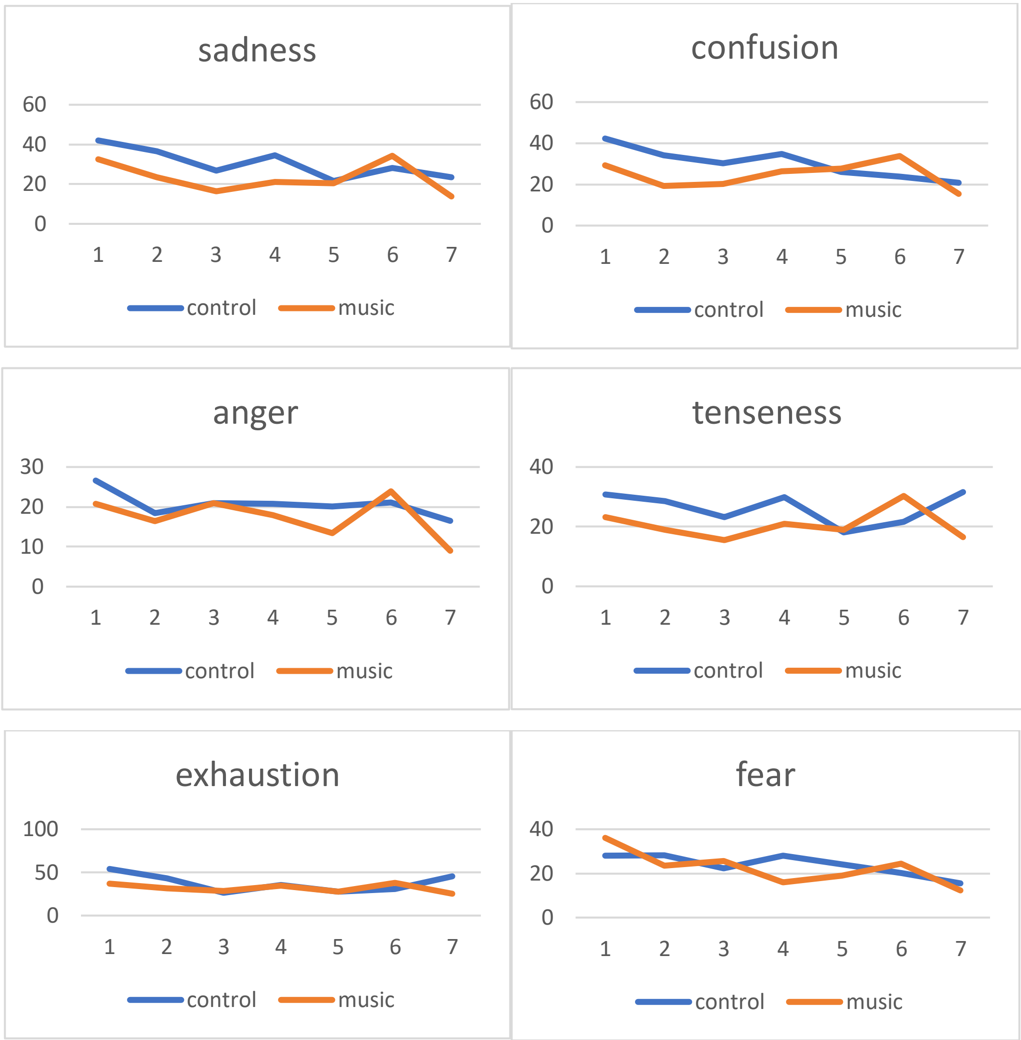
6.1 Demographic and clinical baseline data

The demographic and clinical characteristics (Table 1) of the patients shows that the music and control groups differed in terms of gender, with a female predominance in the control group (62.5%) and male predominance in the music group (81.25%) ($p < 0.05$). This is a random difference and should not have any influence and conclusions on the results of this study. Otherwise, the groups did not differ on any other level.

	Control group (n=16) Mean	Music group (n=16) Mean	p-value
Age (years)	74,1 (6.5)	72,2 (7.3)	0.240
Gender (male/female)	F=10 / M= 6	F=3 / M=13	**p<0.05**
Length of education (years)	11.3 (3.1)	10.7 (3.5)	p=0.659
Musical activities score	2.93 (0.70)	3.38 (1.00)	$\chi 2$= 0.233
Time from stroke onset to intervention	>24h	>24h	n.s.
Laterality of hemiparesis (left/right)	8 = right / 7 = left	9 = right / 3 = left	0.247
Lesion visible on day 0	10	8	0.476
Lesion invisible on day 0	6	8	0.476
Lesion size (max area mmxmm)	277 (435)	98 (124)	0.277
NIHSS at recruitment	2,6 (2)	3,7 (4)	0.410
Consciousness (GCS score)	14.6 (1.3)	14.9 (0.25)	2.270
Aphasia (yes/no)	2	2	n.s.
Cognition	19,4 (3.8)	22,9 (3.6)	0.080
Other cognitive deficits	3	2	0.626
Hypertension diagnosed	8	8	n.s.
Diabetes diagnosed	3	4	0.426
Pneumonia diagnosed	0	0	n.s.
CRP	4,2 (3.9)	6,4 (10.4)	0.490
Blood Glucose	6,63 (0.9)	6,68 (1.8)	0.930

Table 1. Demographic and clinical baseline characteristic of patients

6.2 Results 1: Visual Analogue Mood Scale (VAMS) - Negative Moods from day 1 – 6 months



Visual Analogue Mood Scale (VAMS) – Positive Moods from day 1 – 6 months

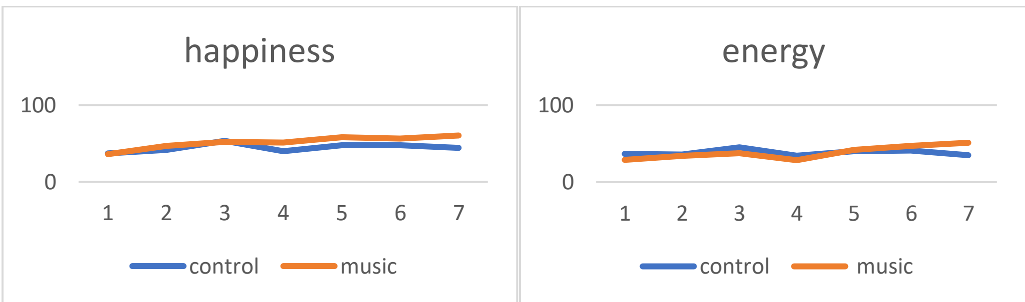


Figure 1. The graphs above represent the average scores of the VAMS at all timepoints of this experiment. 1= day 1 morning, 2= day 1 daytime, 3= day 1 evening, 4= day 2 morning, 5= day

2 daytime, 6= day 2 evening, 7= 6 months later. These graphs illustrate the direction of the mood changes. Group differences at all timepoints are not significant.

Paired comparison Day 1 Morning – Day 2 Daytime		
	Control	**Music**
Negative feelings ↓	**<0.01**	**0.016**
Positive feelings ↑	0.25	**0.04**
Paired comparison Day 1 Morning – Day 2 Evening		
	Control	**Music**
Negative feelings ↓	**<0.01**	0.1
Positive feelings ↑	0.23	**0.04**
Paired comparison Day 1 morning - 6 months		
	Control	**Music**
Negative feelings ↓	**<0.01**	**0.011**
Positive feelings ↑	0.3	**0.031**

Table 2. Comparison of pooled negative and pooled positive VAMS results in control and music groups over time. The arrows indicate increase/decrease in the parameter. The figures are p-values obtained by two-tailed t-test. Significant results are marked in bold.

We pooled the values of VAMS moods into positive and negative mood categories and analysed the changes over time in both groups. The trend of these changes over time is visible in the above graphs illustrating the average change in negative moods. From these graphs, it is visible that the negative moods tend to diminish over time. Comparison of pooled material revealed significant decrease in negative moods in both groups at two different time points: from day 1 morning-day 2 daytime (control: $p<0.01$, music: $p<0.05$), from day 1 morning - 6 months post-stroke (control: $p<0.01$, music: $p= 0.01$). However, table 2 shows significant increases in positive moods at all timepoints only in the music group: day 1 morning - day 2 daytime ($p<0.05$), day 1 morning – day 2 evening ($p<0.05$), and day 1 morning – 6 months ($p<0.05$). The direction of these changes can be visualised in the VAMS graphs of positive moods above. Overall, these results show a significant decrease in negative moods from day 1 of the protocol and 6 months later in both groups, but a significant increase in positive moods in the music group only.

Positive Moods	Control	Music
Energy	0.74	0.6
Happiness	0.26	**p<0.05**

Table 3. Day 1 Morning vs Day 2 Daytime. VAMS scores for positive mood were pooled for all timepoints from day 1 morning until day 2 daytime. A paired analysis was conducted to statistically analyse the changes over time. The numbers indicate the p-value for group difference.

Positive Moods	Control	Music
Energy	0.71	0.37
Happiness	0.12	**p<0.05**

Table 4. Day 1 Morning vs Day 2 Daytime/Evening. Data collection and denotation as in Table 3. The same method of analysis was used for the statistical analysis of changes from day 1 morning until day 2 evening.

Positive moods were pooled and analysed separately over time in a paired comparison to detect which positive mood(s) was/were significantly higher. Tables 3 and 4 indicate that "happiness" was the mood that had increased significantly over time in the music group. Such results were not found in the control group.

6.3 Results 2: Depression, Anxiety, Stress Scale (DASS-21)

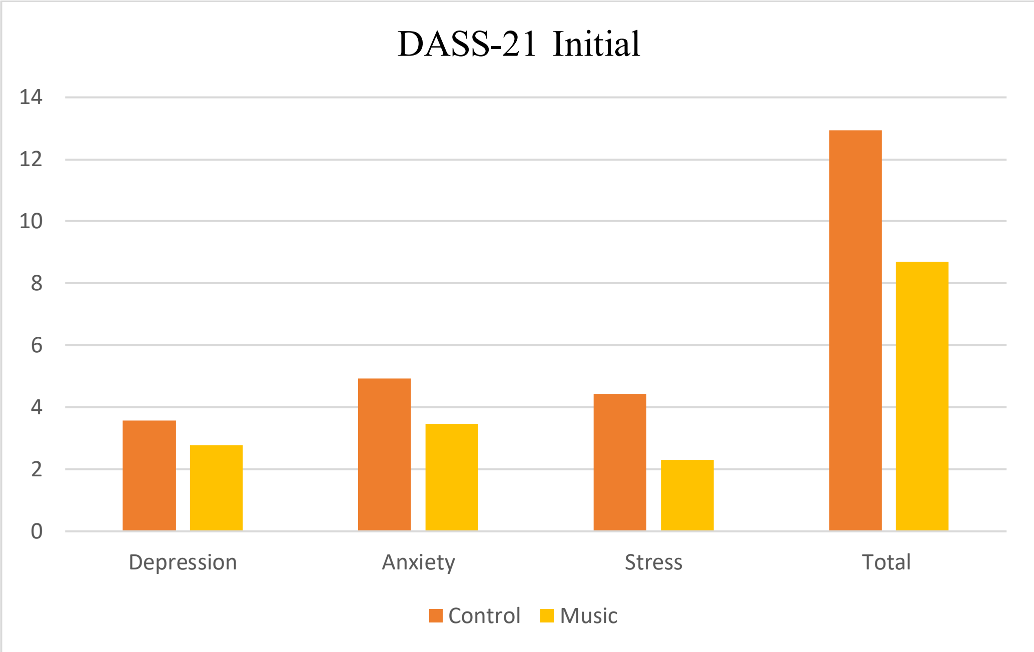


Figure 2. Average DASS-21 scores for states of depression, anxiety, stress, and overall assessment scores for music and control groups at the initial stage of the experiment.

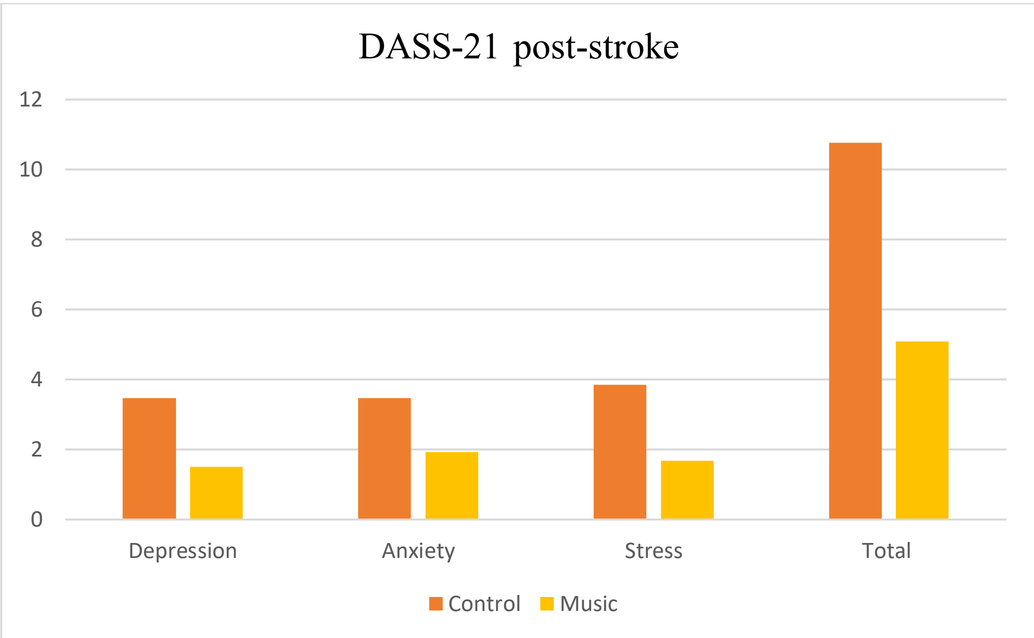


Figure 3. Average DASS-21 scores for states of depression, anxiety, stress, and overall assessment scores for music and control groups 6 months post-stroke.

	Control	**Music**
Changes in depression	n.s.	**p= 0.05**
Changes in anxiety	n.s.	**p<0.05**
Changes in stress	n.s.	n.s.
Total changes	n.s.	**p<0.05**

Table 5. Changes in DASS-21 scores over time (start of the experiment – 6 months after).

Figures 2 and 3 illustrate the average values of the components of DASS-21 self-report questionnaires from the beginning of this experiment and 6 post-stroke. The trend of music group experiencing less stress is obvious, though the significance of the differences in group averages did not reach the level of $p<0,05$. Further statistical analysis was conducted to examine change in depression, anxiety, and stress in both groups over time. The results are indicated in table 5. Wilcoxon-Rank-Sum test revealed significant decrease in depression the music group ($SD= 16.1$, $p= 0.05$) but not in the control group. Similar results were found for state of anxiety ($SD= 14.7$, $p<0.05$), as well as in the analysis total changes in depression, anxiety, and stress assessment scores ($SD= 19$, $p<0.05$). No significant changes were found in the control group.

6.4 Results 3: Montreal Cognitive Assessment (MoCa)

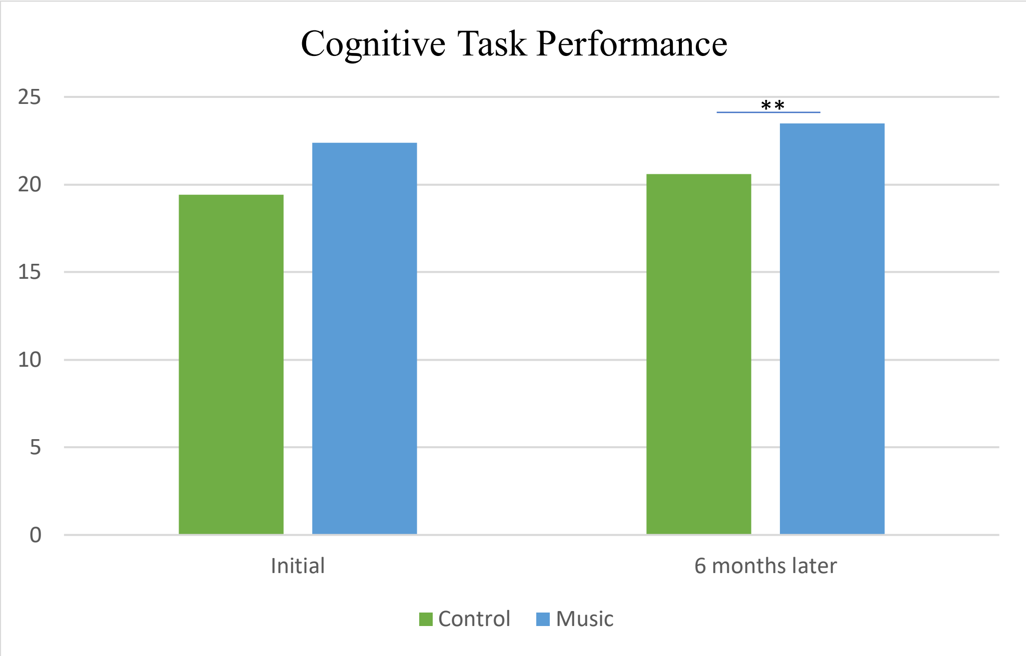


Figure 4. Illustration of average MoCa scores on day 1 of the experiment and 6 months later. Green bars represent the initial scores, while the blue bars represent the score 6 months after.

Statistical analysis was conducted to investigate differences in cognitive performance in the initial stage of the experiment and again 6 months after. A Wilcoxon rank-sum test revealed no significant difference between control and music group at initial stage. However, a significant difference was found in cognitive performance 6 months later (SD= 3.8, $p<0.05$). The music group scored slightly but significantly higher than the control group in cognitive performance. While it is obvious from Figure 4, that the music group scored higher than controls on the MoCa already at the start of the experiment, this difference was not significant. Cognitive performance had improved in both groups 6 months post-stroke.

6.5 Results 4: Cardiovascular measures

	Average RR Day 1	Average RR Day 2	p-value
Controls	154.1/73.4	151.2/77	n.s
Music	152/80	147/75	n.s

Table 6. Average blood pressure (RR) in day 1 and day 2 and p values.

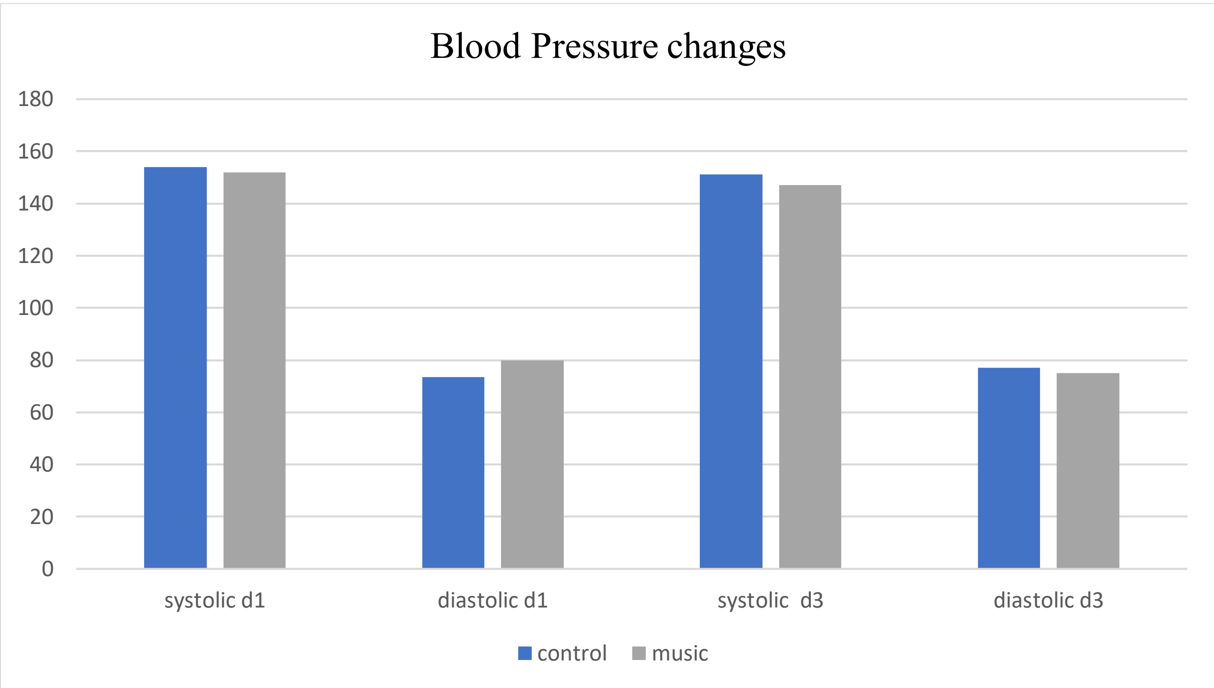


Figure 5. Average systolic and diastolic blood pressures in day 1 and day 3.

Statistical analyses were conducted cardiovascular parameters. No significant differences were found in blood pressure between groups or over time.

7. Discussion

This study presents a review on stroke-related stress extending the concept from the level of single neurons (cellular level) to brain (organ level), and further to endocrine and cardiovascular regulation (biological system level), to the emotional and cognitive processes (psychological level), to stroke patient´s interaction with others (social level) and finally to the health-economic burden of stroke (societal level). In its experimental part, this study investigated the effect of a short music intervention during acute stroke on different levels of stress. The purpose was to examine the immediate and long-term effects of music on different stress factors. Finally, this study aims to apprehend the conditions for effective music implementation in acute stroke care. The results of this study are consistent with past published research on the beneficial effect of music on stress parameters in other clinical conditions. As a novel observation, this study was able to demonstrate short and long-term benefits of music in the context of mood and cognition after acute stroke.

7.1 Mood and Mental Stress

We hypothesised that the music intervention will reduce symptoms of psychological stress and increase mental wellbeing in acute stroke patients. There was an overall significant decrease in negative moods (fear, anger, sadness, tenseness, tiredness, confusion) over time in both groups (from the beginning of the protocol vs six months later).

Lack of difference between the groups may be explained by frequent attention received by both groups, probably relieving negative moods, particularly fear and confusion (see Figure 1).

Interestingly, there was a significant increase in positive moods, happiness specifically, only in the music group, suggesting that music has a specific stress-reducing effect. In support of this conclusion, the assessment of stress-related mental health revealed a statistically significant decrease in depression, anxiety, and the overall stress assessment exclusively in the music group. The improvement in mood is illustrated by reduced symptoms of mental distress and further emphasized by the significant difference in reports of happiness in the music group supporting the idea that music reduces symptoms of psychological stress and increases mental wellbeing. The effects of music intervention observed both in mood states (VAMS) and in psychological distress (DASS-21) were still present 6 months after the stroke, which suggests that even a short music intervention can induce long-term benefits. These findings are consistent with the first hypothesis of this study and with the past research (Särkämö et al., 2008).

7.2 Cognition

Based on the existing literature, it was hypothesised that implementation of a music intervention in acute stroke will improve cognitive recovery of stroke. Initially, control and music groups did not differ in terms of cognitive performance. However, a slight but significant difference in cognitive performance in favour of the music group was indeed found 6 months post-stroke. These results indicate that the music intervention had a positive effect on cognitive functioning in acute stroke.

Research shows that music can enhance cognitive recovery especially in the domains of verbal memory, attention, and language (Leo, 2020; Särkämö et al., 2008). Särkämö et al. (2008) also found that music listening decreases experiences of negative mood (anxiety and confusion). They further argued that music-induced cognitive recovery may be mainly mediated by the increase in positive mood. This reasoning follows the arousal-and-mood-hypothesis by Thompson et al. (2001) which argues that music does not directly act on cognitive functioning, instead the influence is mediated through emotional reactions instead. Although our results are consistent with music-induced benefits on cognition, it is highly unlikely that a short music-intervention such as the one used in this study, would have had that strong of an impact on cognition by itself. In the study by Särkämö et al. (2008), the patients received a daily 2-month post-stroke music-intervention, which resulted in a significant improvement in cognition. In the present study, the intervention lasted just one day. Thus, a more realistic explanation is that a boost in psychological wellbeing plays a key role explaining the present results. Moreover, as demonstrated in the Introduction (3. Music Processing), music activates numerous brain networks, particularly the emotion and reward networks. These networks involve limbic and dopaminergic areas that contribute to regulation of emotional response, motivation, arousal as well as executive functions. In addition, the network complements memory systems which further triggers emotion. The emotion and reward networks are stimulated by positive external stimuli. In this study, the music group patients chose and listened to their own favourite music genre, which may well be a plausible explanation behind the improvement in cognitive performance. Thus, these results support the arousal-and-mood-hypothesis.

7.3 Cardiovascular Stress Parameters

Music is closely associated with modulation of emotion and stress reduction in healthy individuals (see Koelsch, 2018). Past studies have also focused on the physiological effects of music which are closely linked to emotions and arousal (Bernadi et al., 2006; Siedliecki et al., 2006). They show that music listening reduces biological stress indicators and even enhances the recovery of cardiovascular and respiratory functions (Bernadi et al., 2006). For this reason, it was hypothesised that music would reduce cardiovascular stress in acute stroke. In contrast to the expectation, this study showed no significant differences in cardiovascular stress measures between the groups. Mean systolic and diastolic blood pressure readings over the protocol did not vary significantly nor were there any group differences, not even in the most acute phase. A plausible explanation is simply the assumption that the participants were most likely under proper medication for treatment of hypertension. It is common for patients to experience elevated blood pressure even without constant hypertension in acute stroke, and part of the acute treatment is to control blood pressure for optimal level. Past studies on physiological effects of music have involved healthy participants or chronic, rather than acute phase neurological patients. Therefore, no contradiction of our results and past research exists. Nevertheless, the present results do not realize the third hypothesis of this study.

7.4 Clinical implications

It was significant and unexpected to find the positive effects of music still present and visible 6 months post-stroke, considering the short duration of the music intervention. It may be, that patients in the music group were inspired by the theme of this study and carried on listening to music more that they normally would after they completed the 3-day protocol. If this is true, it emphasizes cost-effectiveness of a short intervention. At any rate, a short intervention like this is easily implemented in clinical routine. Although a music therapist supervised the music group, routine implementation does not require special professional input, since instruction and support may well be provided by a nurse staff and, after short instruction, even by the patient´s close ones.

Although numerous studies have investigated the topic of music-induced benefits, to our knowledge, this is the first study to investigate the effect of music on specific and multiple mental stress parameters in acute stroke. As discussed in the introduction, costs for acute stroke care and post-stroke treatment are high and they are predicted to increase in the upcoming years (Rajsic et al., 2019). Chronic stress is a factor that contributes to long-term difficulties at many levels including rehabilitation failure and post-stroke depression and even mortality (Murros et al., 1993; Christensen et al., 2004; Hedley et al., 2008; Ferro et al., 2016; Lowry & Jin, 2020). There is a clear need for cost-effective treatment methods that reduce post-stroke stress at different levels.

7.5 Strengths and Limitations

This study includes a comprehensive literature review that considers multiple levels of stress, their consequences, and the role of music in neurological recovery. In addition to the thorough description of stroke, the Introduction points out current issues such as the impact of stroke-related costs on the economy. The present study is an intervention study that explores novel cost-effective intervention methods which are currently highly needed. The topic is therefore relevant, and the findings are significant. To our knowledge, this is the first study to investigate the efficacy of a short music-intervention on different levels of stress in the acute phase of a stroke and 6 months post-stroke. This design allowed the detection of short-term and long-term benefits of music on mental, cognitive, and cardiovascular stress parameters.

However, some limitations must be taken into consideration. This study contained a relatively small sample size (16 participants per group). Since these participants were acute care patients, a few patients had to interrupt the experiment for clinical or other compelling reasons, such as early discharge from hospital. The clinical condition of some patients deteriorated to the extent that they were unable to continue the experiment. Dropouts weaken the statistical power, and this may have hidden some effects of the intervention. Another limitation was that the researchers had no control over the amount of music exposure of the control group.

7.6 Future research

Future research should conduct a similar study with a larger number of participants, whilst considering the limitations of this study. In order to address more accurately specific music-induced effects, implementing a third group that would use a different form of auditory stimulation, such as listening to audiobooks, would be worthwhile.

8. Conclusion

Implementing music-based interventions in the acute phase of a stroke has significant short-term and long-term benefits on different parameters of psychological stress. Music listening in acute stroke improves positive moods, reduces symptoms of psychological distress, and induces cognitive benefits. The findings of this study support the idea of implementing music intervention in acute stroke treatment protocol.

9. References

Alluri, V., Toiviainen, P., Jääskeläinen, I. P., Glerean, E., Sams, M., & Brattico, E. (2012). Large-scale brain networks emerge from dynamic processing of musical timbre, key and rhythm. Neuroimage, 59, 3677–3689.

Almeida, O. P. et al. (2010) B-vitamins reduce the long-term risk of depression after stroke: the VITATOPS-DEP trial. *Ann. Neurol.* 68, 503–510.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Association, 2013).

Anderson, R. E., Tan, W. K., Martin, H. S., & Meyer, F. B. (1999). Effects of glucose and PaO2 modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. *Stroke*, *30*(1), 160–170.

Arnone, D., McKie, S., Elliott, R. *et al.* State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry* 18, 1265–1272 (2013). https://doi.org/10.1038/mp.2012.150

Ashby, F.G., Isen, A.M. & Turken, A.U. (1999) A neuropsychological theory of positive affect and its influence on cognition. *Psychol Rev*; 106, 529–50.

Athanasou, J. (2019). The background, psychometric qualities, and clinical application of the visual analog mood scales: A review and evaluation.

Ayerbe, L., Ayis, S., Crichton, S. L., Rudd, A. G. & Wolfe, C. D. (2014) Explanatory factors for the increased mortality of stroke patients with depression. *Neurology* 83, 2007–2012.

Bengtsson, S. L., Ulleen, F., Ehrsson, H. H., Hashimoto, T., Kito, T., Naito, E., Sadato, N. (2009). Listening to rhythms activates motor and premotor cortices. Cortex, 45, 62–71.

Bernardi, L., Porta, C., & Sleight, P. (2006). Cardiovascular, cerebrovascular, and respiratory changes induced by different types of music in musicians and non-musicians: the importance of silence. *Heart (British Cardiac Society)*, *92*(4), 445–452.

Burford, N. G., Webster, N. A., & Cruz-Topete, D. (2017). Hypothalamic-pituitary-adrenal axis modulation of glucocorticoids in the cardiovascular system. *International journal of molecular sciences*, *18*(10), 2150.

Christensen, H., Boysen, G., Johannesen, H.H. (2003) Serum-cortisol reflects severity and mortality in acute stroke. *Journal of the Neurological Sciences*, 217, 175-180.

Constantinescu, V., Matei, D., Cuciureanu, D., Corciova, C., Ignat, B., & Popescu, C. D. (2016). Cortical modulation of cardiac autonomic activity in ischemic stroke patients. *Acta Neurologica Belgica*, *116*(4), 473-480.

Cramer S. C. (2008). Repairing the human brain after stroke. II. Restorative therapies. *Annals of neurology*, *63*(5), 549–560.

Den Hertog, H. M., van Rossum, J. A., van der Worp, H. B., van Gemert, H. M., de Jonge, R., Koudstaal, P. J., Dippel, D. W., & PAIS investigators (2009) C-reactive protein in the very early phase of acute ischemic stroke: association with poor outcome and death. *Journal of neurology*, *256*(12), 2003–2008.

Emsley, H. C., Smith, C. J., Tyrrell, P. J., & Hopkins, S. J. (2008). Inflammation in acute ischemic stroke and its relevance to stroke critical care. *Neurocritical care*, *9*(1), 125-138.

Fan, Y. Y et al. (2014) A novel neuroprotective strategy for ischemic stroke: transient mild acidosis treatment by CO2 inhalation at reperfusion. *Journal of cerebral blood flow and metabolism, 34*(2), 275–283.

Ferro, J.M., Caeiro, L., & Figueira, M.L. (2016) Neuropsychiatric sequelae of stroke. *Nature Reviews Neurology*, 12, 269-280.

Ford, J. H., Addis, D. R., & Giovanello, K. S. (2011) Differential neural activity during search of specific and general autobiographical memories elicited by musical cues. *Neuropsychologia*, *49* (9), 2514–2526.

Franceschini, R., Gandolfo, C., Cataldi, A., Del Sette, M., Cianciosi, P., Finocchio, C., Rolandi, E. & Barreca, T (1994) Twenty-four-hour beta-endorphin secretory pattern in stroke patients. *Stroke*, 25(11), 2142-2145.

Gertz, K., Kronenberg, G., Kälin, R. E., Baldinger, T., Werner, C., Balkaya, M., Eom, G. D., Hellmann-Regen, J., Kröber, J., Miller, K. R., Lindauer, U., Laufs, U., Dirnagl, U., Heppner, F. L., & Endres, M. (2012). Essential role of interleukin-6 in post-stroke angiogenesis. *Brain*, *135*(Pt 6), 1964–1980.

Gloster, A. T., Rhoades, H. M., Novy, D., Klotsche, J., Senior, A., Kunik, M., ... & Stanley, M. A. (2008). Psychometric properties of the Depression Anxiety and Stress Scale-21 in older primary care patients. *Journal of affective disorders*, *110*(3), 248-259.

Grape, C., Sandgren, M., Hansson, L. O., Ericson, M., & Theorell, T. (2003) Does singing promote well-being? An empirical study of professional and amateur singers during a singing lesson. *Integr. Phys. Behav. Sci.* 38, 65–74.

Grewen, K.M. & Light, K.C. (2011) Plasma oxytocin is related to lower cardiovascular and sympathetic reactivity to stress. Biol Psychol. 87(3): 340–349.

Harmandayan, M., Romanowicz, M. & Sola, C. (2012) Successful use of ECT in post-stroke depression. *Gen. Hosp. Psychiatry* 34, 102–102.

Harvey, A.R. (2020) Links Between the Neurobiology of Oxytocin and Human Musicality. *Front. Hum. Neurosci.*, 14, 350.

Herrmann, N. *et al.* (2011) Detection and treatment of post stroke depression: results from the registry of the Canadian stroke network. *Int. J. Geriatr. Psychiatry* 26, 1195–1200.

Jayaraj, R.L., Azimullah, S., Beiram, R. et al (2019) Neuroinflammation: friend and foe for ischemic stroke. *J Neuroinflammation* 16, 142.

Karelina, K., Stuller, K.A., Jarrett, B., Zhang, N., Wells, J., Norman, G.J. &DeVries, A.C. (2011) Oxytocin mediates social neuroprotection after cerebral ischemia. *Stroke* 42(12): 3606–361.

Khalfa S, Dalla Bella S, Roy M, Peretz I, Blondin JP. Effects of relaxing music on salivary cortisol level after psychological stress. Ann NY Acad Sci 2003; 999: 374–6.

Koelsch, S. (2018). Investigating the neural encoding of emotion with music. *Neuron*, *98*(6), 1075-1079.

Koelsch S. (2014) Brain correlates of music-evoked emotions. *Nat Rev Neurosci*; 15: 170–80.

Koelsch, S., Fritz T.V., Cramon, D.Y., Muller, K. & Friederici, A.D. (2006) Investigating emotion with music: An fMRI study. *Hum Brain Mapp*, 27, 239–250.

Kraus, C., Castrén, E., Kasper, S., & Lanzenberger, R. (2017). Serotonin and neuroplasticity–links between molecular, functional, and structural pathophysiology in depression. *Neuroscience & Biobehavioral Reviews*, *77*, 317-326.

Kumar, J., Iwabuchi, S. J., Völlm, B. A., and Palaniyappan, L. (2020). Oxytocin modulates the effective connectivity between the precuneus and the dorsolateral prefrontal cortex. *Eur. Arch. Psychiatry Clin. Neurosci.* 270, 567–576

Kutlubaev, M. A. & Hackett, M. L. (2014) Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. *Int. J. Stroke,* 9, 1026–1036.

Lee, O. K. A., Chung, Y. F. L., Chan, M. F., & Chan, W. M. (2005). Music and its effect on the physiological responses and anxiety levels of patients receiving mechanical ventilation: a pilot study. *Journal of clinical nursing*, *14*(5), 609-620.

Leo, V. (2020) Effects of vocal music on verbal learning and long-term recovery after stroke. University of Helsinki, Helsinki, Finland.

Lindsberg, P. J., & Roine, R. O. (2004). Hyperglycemia in acute stroke. *Stroke*, *35*(2), 363–364.

Magee WL, Davidson JW. The effect of music therapy on mood states in neurological patients: a pilot study. J Music Ther 2002; 39: 20–9.

Magee, W.L., Clark, I., Tamplin, J., Bradt, J. (2017) Music interventions for acquired brain injury. *Cochrane Database Syst Rev*, 1, CD006787.

Matsushita, H., Latt, H.M., Koga, Y., Nishiki T. & Matsui, H. (2019) Oxytocin and Stress: Neural Mechanisms, Stress-Related Disorders, and Therapeutic Approaches. *Neuroscience*, 417, 1-10.

Murphy T.H. & Corbett D. (2009) Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci*; 10**:** 861–72.

Murros, K., Fogelhom, R., Kettunen, S., Vuorela, A.L. (1992) Serum cortisol and outcome of ischemic brain infarction. *Journal of the Neurological Sciences*, 116, 12-17.

Nestler, E. J., Hyman, S. E., & Malenka, R. C. (2001). *Molecular neuropharmacology: A foundation for clinical neuroscience*. New York: McGraw-Hill, Medical Pub. Div.

Nortunen, T., Puustinen, J., Luostarinen, L., Huhtala, H., & Hänninen, T. (2018). Validation of the finnish version of the montreal cognitive assessment test. *Acta Neuropsychologica*, *16*(4), 353-60.

Ooishi, Y., Mukai, H., Watanabe, K., Kawato, S., and Kashino, M. (2017). Increase in salivary oxytocin and decrease in salivary cortisol after listening to relaxing slow-tempo and exciting fast-tempo music. *PLoS One* 12:e0189075.

Okada K., Kurita A., Takase B., et al. (2009) Effects of music therapy on autonomic nervous system activity, incidence of heart failure events, and plasma cytokine and catecholamine levels in elderly patients with cerebrovascular disease and dementia. *Int Heart J*; 50**:** 95–110.

Peretz, I. & Zatorre, R.J. (2005) Brain organization for music processing. *Annu Rev Psychol*, 56, 89–114.

Quintana, D. S., Rokicki, J., van der Meer, D., Alnæs, D., Kaufmann, T., Córdova- Palomera, A., et al. (2019). Oxytocin pathway gene networks in the human brain. *Nat. Commun.* 10:668.

Quirin, M., Kuhl, J. & D¨using, R. (2011) Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities. *Psychoneuroendocrinology,* 36, 898-904.

Rajsic, S., Gothe, H., Borba, H.H. *et al.* Economic burden of stroke: a systematic review on post-stroke care. *Eur J Health Econ* **20,** 107–134 (2019).

Ramos-Cabrer, P., Campos, F., Sobrino, T., Castillo, J. (2011) Targeting the Ischemic Penumbra, *Stroke*, 42, S7-11.

Ring, R.H., Malberg, J.E., Potestio, L., Ping, J., Boikess, S., Luo, B., Schechter, L.E., Rizzo, S., Rahman, Z. & Rosenzweig-Lipson, S. (2006) Anxiolytic-like activity of oxytocin in male mice: behavioral and autonomic evidence, therapeutic implications. *Psychopharmacology*, 185(2): 218-225.

Sanacora, G., Zarate, C., Krystal, J. *et al.* Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 7, 426–437 (2008).

Saver, J.L. (2006) Time Is Brain – Quantified. *Stroke,* 37(1), 263-266.

Scheitz, J. F., Nolte, C. H., Doehner, W., Hachinski, V., & Endres, M. (2018). Stroke-heart syndrome: clinical presentation and underlying mechanisms. *The Lancet. Neurology*, *17*(12), 1109–1120.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW (1996) Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci*, 93, 3908–3913.

Scholz, D.S., Rohde, S., Nikmaram, N., et al. (2016) Sonification of arm movements in stroke rehabilitation—a novel approach in neurologic music therapy. *Front Neurol*, 7, 106.

Siedliecki, S. L., & Good, M. (2006). Effect of music on power, pain, depression, and disability. *Journal of advanced nursing*, *54*(5), 553–562.

Sihvonen, A., Särkämö, T., Leo, V., Tervaniemi, M., Altenmuller, E. & Soinila, S. (2017) Music-based interventions in neurological rehabilitation, *The Lancet Neurology*, 1-13.

Soros P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. *Lancet Neurol* 2012; **11:** 179–88.

Skoe, E., & Kraus, N. (2010). Auditory brain stem response to complex sounds: A tutorial. Ear and Hearing, 31, 302–324.

Sutoo, D. & Akiyama, K. (2004) Music improves dopaminergic neurotransmission: demonstration based on the effect of music on blood pressure regulation. *Brain Res*, 1016, 255–62.

Särkämö, T. (2018) Music for the ageing brain: Cognitive, emotional, social, and neural benefits of musical leisure activities in stroke and dementia. *Dementia*, 17(6), 670–685.

Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., Autti, T., Silvennoinen, H. M., Erkkilä, J., Laine, M., Peretz, I., & Hietanen, M. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain: a journal of neurology*, *131*, 866–876.

Taylor-Rowan, M., Momoh, O., Ayerbe, L., Evans, J. J., Stott, D. J., & Quinn, T. J. (2019). Prevalence of pre-stroke depression and its association with post-stroke depression: a systematic review and meta-analysis. *Psychological medicine*, *49*(4), 685-696.

Voss, J. L., Bridge, D. J., Cohen, N. J., & Walker, J. A. (2017) A Closer Look at the Hippocampus and Memory. *Trends in Cognitive Sciences*, *21*(8), 577-588.

Wan CY, Schlaug G. Music making as a tool for promoting brain plasticity across the life span. *Neuroscientist* 2010; 16: 566–77.

Wang, D., Yan, X., Li, M., and Ma, Y. (2017). Neural substrates underlying the effects of oxytocin: a quantitative meta-analysis of pharmaco-imaging studies. *Soc. Cogn. Affect. Neurosci.* 12, 1565–1573.

Weber, H., Hühns, S., Lüthen, F., & Jonas, L. (2009) Calpain-mediated breakdown of cytoskeletal proteins contribute to cholecystokinin-induced damage of rat pancreatic acini, *International journal of experimental pathology*, *90*(4), 387–399.

World Stroke Organisation (2016) Global Stroke Fact Sheet. Retrieved from: https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf

Wu, H., Feng, C., Lu, X., Liu, X., and Liu, Q. (2020). Oxytocin effects on the resting- state mentalizing brain network. *Brain Imaging Behav.* doi: 10.1007/s11682- 019-00205-5

Yuhi, T., Kyuta, H., Mori, H. A., Murakami, C., Furuhara, K., Okuno, M., et al. (2017). Salivary oxytocin concentration changes during a group drumming intervention for maltreated school children. *Brain Sci.* 7: E152. doi: 10.3390/brainsci7110152

Zatorre R.J., Chen J.L., Penhune V.B. (2007) When the brain plays music: auditory-motor interactions in music perception and production. *Nat Rev Neurosci, 8, 547-558.*