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Structural grey matter changes induced by sound environment after stroke: a voxel-based morphometry study

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ABSTRACT OF THE
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Music is a universal yet subjectively perceived form of art, which can be used as a therapeutic means in the treatment of various psychological disorders and medical conditions. While actively participating in making music is found to be beneficial, also passive music listening can decrease depressed and confused mood and improve cognitive outcome after stroke.

In this thesis, the subjects were 51 stroke patients randomly assigned to a music group, an audio book group, or a control group. During the recovery, the music and the audio book group listened daily to self-selected music or audio books, while the control group received no listening material. Magnetic resonance (MR) images within two weeks of stroke onset and six months later were analysed using voxel-based morphometry (VBM) to detect regions with decreased and increased grey matter volumes in each group.

The results show that compared to the audio book group and the control group, the music group experienced more recovery-related changes in grey matter volume in the insula, in the precentral gyrus, and in the inferior frontal gyrus in the right hemisphere when studying the subjects with right hemisphere damage (RHD).

In addition, the music group experienced relatively more grey matter increase in the frontal and limbic areas than the audio book group or the control group. All the three groups underwent grey matter decrease in the frontal lobes, but the music group differed from the two other groups by showing no decrease at all in the right hemisphere. Furthermore, grey matter volumes in frontal areas correlated with neuropsychological test scores measuring cognitive outcome as well as with mood scores.

This study provides evidence that listening to music can shape the brain and promote neural plasticity in certain brain regions and encourages the use of music listening in stroke rehabilitation. Future research would be important to investigate the effects of music on the brain in more detail.

Keywords: stroke, music therapy, VBM, insula, frontal areas, limbic areas

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Musiikki on universaali, joskin subjektiivisesti hahmotettava taidemuoto, jota voidaan käyttää terapeuttisesti psykiatristen ja somaattisten sairauksien hoidossa. Aktiivinen musiikin harjoittaminen on todettu toimivaksi terapiamenetelmäksi, mutta viime aikoina on myös raportoitu passiivisen musiikin kuuntelun vähentävän masentuneisuutta ja hämmentyneisyyttä aivohalvauksen jälkeen.

Tässä diplomityössä koehenkilöinä oli 51 aivohalvauspotilasta, jotka jaettiin satunnaisesti musiikki-, äänikirja- ja kontrolliryhmiin. Toipumisensa aikana musiikki- ja äänikirjaryhmät kuuntelivat päivittäin itse valitsemaansa musiikkia tai äänikirjoja. Analyysissä käytettiin akuuttivaiheessa ja kuusi kuukautta myöhemmin otettuja magneettikuvia, joista etsittiin vokselipohjaista morfometriaa (VBM) käyttäen alueita, joilla harmaan aineen määrä oli muuttunut seurannan aikana.

Tulokset osoittavat, että verrattuna äänikirja- ja kontrolliryhmiin, musiikkiryhmällä harmaa aine lisääntyi enemmän tai väheni vähemmän oikeassa insulassa, presentraalipoimussa sekä alemmassa frontaalipoimussa koehenkilöillä, joilla oli leesio oikeassa aivopuoliskossa.

Lisäksi havaittiin harmaan aineen lisääntyvän frontaalisilla ja limbisillä aivoalueilla suhteellisesti enemmän musiikkiryhmällä kuin muilla ryhmillä. Harmaa aine väheni frontaalialueilla kaikilla kolmella ryhmällä, mutta musiikkiryhmällä harmaa aine ei vähentynyt ollenkaan oikeassa aivopuoliskossa toisin kuin äänikirja- ja kontrolliryhmillä. Harmaan aineen määrän frontaalisilla alueilla havaittiin myös korreloivan kognitiivista paranemista mittaavien neuropsykologisten testien sekä mielialamittarien kanssa.

Tämä tutkimus tarjoaa näyttöä siitä, että musiikin kuunteleminen voi muokata aivoja ja edistää neuraalista plastisiteettia tietyillä aivoalueilla, ja siten kannustaa kuuntelemaan musiikkia aivohalvauksen jälkeen. Musiikin vaikutusten yksityiskohtaisempi tutkimus on tärkeää myös jatkossa.

Avainsanat: aivohalvaus, musiikkiterapia, VBM, insula, frontaalialueet, limbiset alueet

Preface

Writing this thesis has been a single most stressing, laborious, and time-consuming assignment I have encountered during my studies, which undoubtedly is quite common. Still, as the process evolved, it proved also to be a fascinating and most interesting task with both ups and downs. Therefore, I am truly grateful to docent Minna Huotilainen for hiring me to Cognitive Brain Research Unit as a summer worker and to head of the Brain and Music Team, Professor Mari Tervaniemi for offering me the opportunity to work on such an interesting topic.

My special thanks go to my instructor, Teppo Särkämö, Ph.D., whose insightful comments were absolutely priceless and who always had the time to read drafts and discuss problems emerged during the early stages of the project. The rest of the CBRU staff did its part to make me feel welcome at work. Thanks also to Kaupo Viitanen, whose help with SPM8 was truly important. In addition, I would like to thank Docent Taina Autti for radiological consultation and Eero Salli, D.Sc. (Tech.), for technical support.

Last but not least, I want to express my appreciation for my family, who encouraged me to study mathematics and physics and waited patiently for this thesis to finally, after so many years of academic freedom, be completed. Thanks also to my friends who were the best people to spend time with whenever this thesis did not require my full attention. Last, but not least, thanks to Klave for grammar help, proof-reading, and mental support.

Siltavuorenpenger, 12.5.2011

Henna Vepsäläinen

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Symbols and abbreviations

Abbreviations

BA	Brodmann area
CSF	Cerebro-spinal fluid
CT	Computed tomography
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GM	Grey matter
LHD	Left hemisphere damage
M1	Primary motor cortex
MIT	Melodic intonation therapy
MEG	Magnetoencephalography
MMNm	Magnetic mismatch negativity
MRI	Magnetic resonance imaging
PMV	Ventral premotor cortex
RAS	Rhytmic auditory stimulation
RHD	Right hemisphere damage
SPM	Statistical parametric map / mapping
TIA	Transient ischaemic attack
TMS	Transcranial magnetic stimulation
VBM	Voxel-based morphometry
WM	White matter

1 Introduction

William Shakespeare, a famous English poet and playwright, is said to have believed that music is the food of love. Indeed, in many cultures, music has been part of man's everyday life since prehistoric eras. Music has the ability to evoke emotions in a way most art forms are not capable of. Although not all people can be described as musical, most people are able to perceive and enjoy music.

There is no ultimate definition for music: you can say that a rock concert or an orchestral piece is definitely music, and, on the contrary, the sound of an aeroplane flying in the sky or the background noise in a clothes shop is not music. To sum up, music is sound, or patterns of sound, but not all sounds are musical. Some patterns of sound are generally interpreted as music in different cultures, but we also learn to decode certain sounds that in some other cultures might sound like nothing but noise, as music. One could define music as an artistic, aesthetic, and most importantly, subjective experience consisting of organized sounds.

Although the musical cultures of the world are diverse, it seems that music is in our nature. Recently researchers have began to view music as a biological function rather than a cultural invention [1]. Music is an ancient capacity and appears to transcend time, place, and culture. Regardless of one's social status and educational background, almost everyone is able to enjoy and produce music. Music appears to be as natural a form of expression as language.

1.1 Good vibrations

As mentioned before, music is patterns of sound, whereas sound can be explained as being vibrations of material, usually air. These vibrations can be interpreted as music because of our auditory system, which consists of the external ear, the middle ear, the inner ear, the auditory nerve, and the auditory areas of the brain. The sound is received and intensified by the external ear, then transmitted into the inner ear by the middle ear, and finally transduced into neural impulses in the inner ear. These electrical signals are then transmitted to various parts of the brain, which we shall discuss in the next subsection.

The actual organ of hearing, the organ of Corti, is located in the cochlea in the inner ear. The organ of Corti transduces the mechanical vibrations into electrical signals. The cochlea is a spiralled, snail-like arrangement of three parallel tubes filled with fluid: the vestibular, median, and tympanic canals [2]. The median canal is separated from the tympanic canal by the basilar membrane, on top of which lie two rows of hair cells constituting the organ of Corti [2]. Figure 1 shows the Organ of Corti and the hair cells. Mechanical energy delivered by the fluid makes the hair cells bend, and an action potential is created in them. The action potential is sent further to the first neuron of the auditory nerve and finally to the brain.

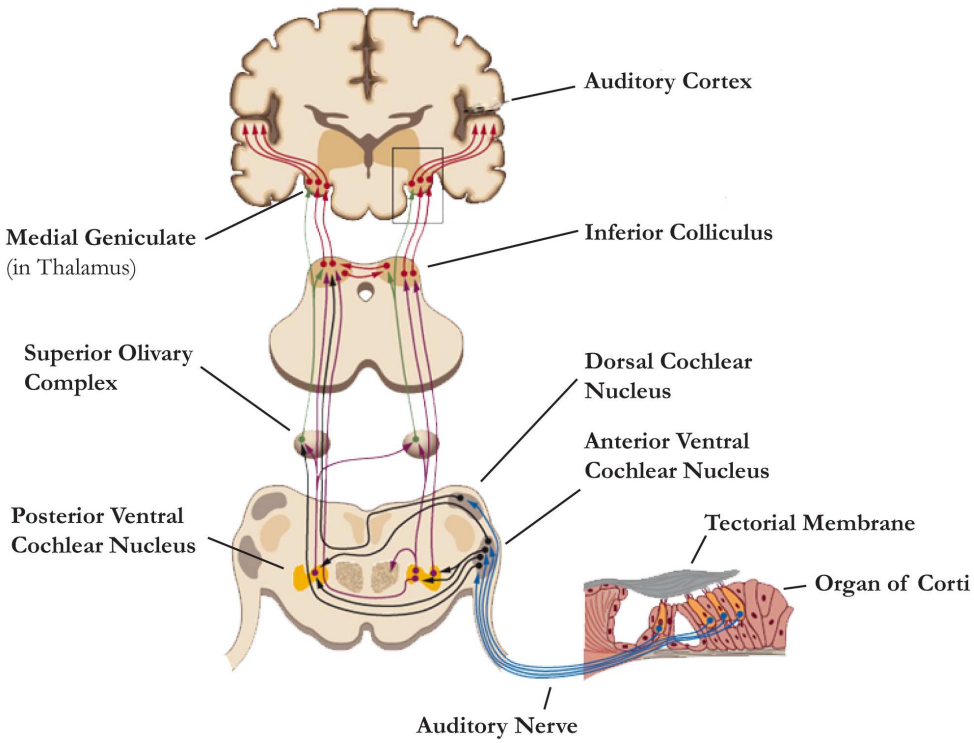

Figure 1: Auditory information travels from the cochlea to the auditory cortex via cochlear nucleus, superior olivary complex, inferior colliculus, and medial geniculate body. Frequency and temporal information are analysed in different locations. Figure adapted from [3].

1.2 Music to my brain

The sound information travels down the auditory nerve to reach the ipsilateral cochlear nucleus. The dorsal region of the cochlear nucleus is specialised in analysing the frequency components of the sound, while the ventral region is more focused on the temporal analysis of the sound. From the dorsal cochlear nucleus the information proceeds to the inferior colliculus and further to the medial geniculate body and finally to the auditory cortex [4]. Respectively, the information from the ventral cochlear nucleus proceeds to the contralateral superior olivary complex and further to the inferior colliculus and finally via the medial geniculate body to the auditory cortex [4].

The inferior colliculus is located in the midbrain and it processes information from both ears in the same regions. The thalamus uses also visual and tactile information in analysing the information making it easier to tell from which direction the sound is coming [4]. The auditory pathway is shown in Figure 1.

The auditory cortices are located on the temporal lobes in the Sylvian Fissure. The primary auditory cortices are tonotopically organized, which means that neurons reacting to adjacent frequencies are located next to each other. The primary auditory cortices connect to the secondary auditory cortices surrounding them. These

secondary regions get information from other senses and connect auditory cortices to other regions in the temporal, parietal, frontal, and occipital lobes [4].

When it comes to music, it is not just the auditory cortices that are activated. Music processing is distributed throughout the brain: the auditory, visual, motor, sensory, and prefrontal cortices are involved, as well as the cerebellum, the corpus callosum, the hippocampus, the nucleus accumbens, and the amygdala [5, 6]. All these parts of the brain are in charge of different tasks related to music, and are visualized in Figure 2.

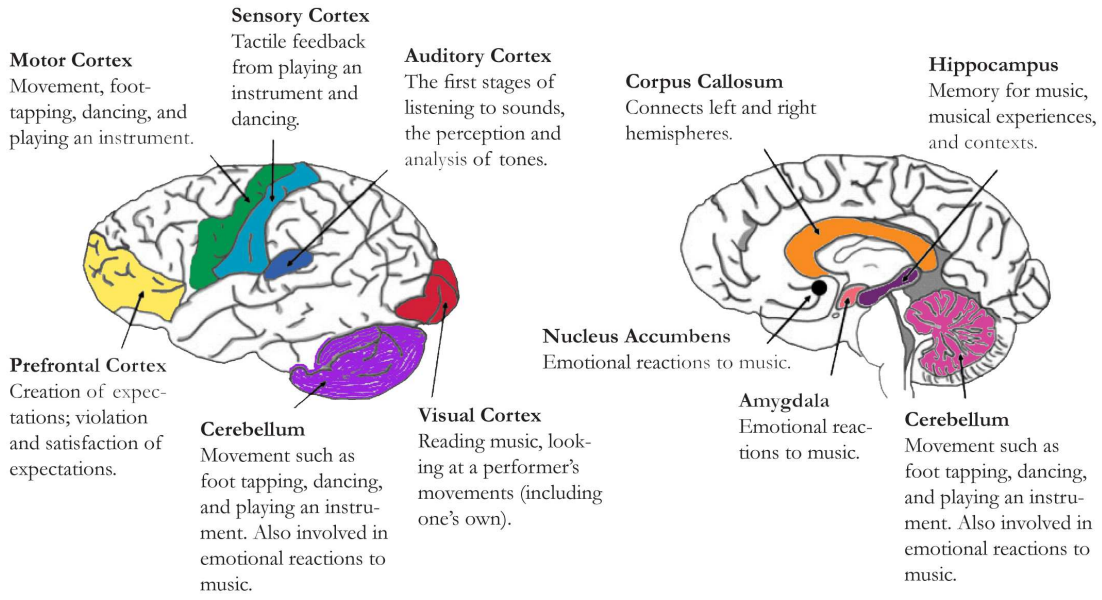

Figure 2: A view of the brain from the side (left) and the inside of the brain (right) showing the brain's major computational centers for music. Figure adapted from [5].

Previously, it was thought that music is predominantly a right-hemisphere activity. However, when the distributed nature of specialized processing mechanisms acting on the individual musical attributes became evident, the right-hemisphere dominance was interpreted as an oversimplification [6]. Still, some laterality effects do exist: for example, in a magnetoelectrographic (MEG) study [7], an infrequent chord change elicited a stronger response compared to the response elicited by a phoneme change in the right hemisphere, whereas in the left hemisphere the responses did not significantly differ.

1.3 Music cures

Because of its ability to evoke emotions, experiences, and memories, music can be used as a therapeutic means in the treatment of many different psychological and medical conditions. In Finland, music therapy has been used for over 50 years in the clinical field with mentally disabled and psychiatric patients [8]. Music therapy has no universally applicable definition, but the American Music Therapy Association

defines it as use of music interventions to attain individual goals within a therapeutic relationship [9].

Participating in music is a chance to express and control distressing feelings. When verbal communication cannot be used, music can open a channel of communication and prevent the patient from isolating from the environment. Music can be seen as an alternative for speech: for instance, mothers frequently use many musical elements, such as pitch, prosody, and rhythm, in their speech when they communicate with their children [10]. The physical and emotional effects of music are undeniable, but currently we do not yet fully understand how these effects are generated. Modern neurological techniques allow us to investigate the impact of music on the brain.

Although there is evidence showing the effectiveness of music therapy for treating certain diseases, the question still remains: what is it in music therapy that works? There are at least five factors contributing to the effects of music therapy: 1) music automatically captures attention thus distracting attention from negative experiences such as pain or anxiety; 2) music can modulate activity in brain structures involved in the initiation, maintenance, and termination of emotions; 3) music can interact with memory processes such as interpretation and storing of musical information, as well as with processes related to the analysis of musical syntax and meaning; 4) music can evoke and condition behaviour, such as movement patterns; and 5) music can be used to train skills of non-verbal communication [11].

1.4 Old dogs, new tricks

Despite the old proverb, it is perfectly possible for old dogs to learn new tricks. This also is the case with the brain: reorganization of brain tissue during life can lead to changes in personality, acquisition of new skills, or relearning of disrupted functions, for example. On the other hand, it can be suggested that for example acquisition of new skills, such as riding a bicycle, shapes one's brain structure. To modify its structural and functional organization, the brain requires environmental input, such as auditory, visual, motor, or sensory stimuli. Thus, owing to its diverse nature, music is an ideal stimulus for stimulating almost all of the brain.

Plastic, structural changes in the brain can be investigated by using voxel-based morphometry (VBM), a technique used to identify regional differences in relative total amount or density of grey matter between two or more groups. For example, using VBM, it has been shown that compared to control subjects London taxi drivers had significantly larger posterior hippocampi, which are thought to store spatial representations of the environment [12]. In addition, hippocampal volume was also found to correlate with the amount of experience in being a taxi driver [12]. Thus, it seems possible that environmental demands can lead to local plastic changes in the healthy adult brain [12].

Later, VBM studies related to the effects of music on the brain have been conducted. For example, Sluming et al. [13] showed that professional musicians had significantly increased regions of grey matter in Broca's area, a major neuroanatomical substrate for spoken language and various musically relevant abilities. Gaser

and Schlaug [14], for one, found that compared to amateur musicians and non-musicians, professional musicians had grey matter volume changes in motor, auditory, and visuo-spatial brain regions, and they also suggested that these differences might represent structural adaptations in response to long-term skill acquisition and repetitive rehearsal.

In this thesis, magnetic resonance images of 51 stroke patients were studied using VBM. Results are presented as statistical parametric maps, which can tell us if the total amount of grey matter has changed more in patients who actively listened to music while recovering from stroke compared to patients who were not encouraged in musical activities. Originally, the data consisted of 60 subjects recruited into the study already during 2004–2006, but because of missing MR images, only 51 subjects were included in this study.

In the beginning, some background concerning stroke, its symptoms, standard treatment, and pathobiology, as well as the theoretical subtext of VBM are presented. The subjects and the interventions are also described in more detail in section 3. Finally, we will discuss and sum up the findings and suggest some future development in relation to musical therapy and VBM.

2 Stroke

As all cells and tissues use oxygen and glucose, neurons too need these substances to produce energy and make transmitters for neural communication. Four primary arteries are in charge of distributing oxygen and glucose to the brain: the two internal carotid arteries and the two vertebral arteries. The internal carotid arteries supply blood to the front three-fifths of cerebrum, whereas the vertebral arteries join to form a single basilar artery at the base of the skull and supply blood to the posterior two-fifths of the cerebrum, part of the cerebellum, and the brain stem [15].

The internal carotid and vertebral arteries connect through the Circle of Willis, and from this circle arise the anterior cerebral artery (ACA), the middle cerebral artery (MCA), and the posterior cerebral artery (PCA), which proceed to all parts of the brain [15]. In this thesis, we were interested in the occlusions occuring in the MCA, which together with the ACA and smaller arteries supply parts of the cortex with blood. In particular, the middle cerebral artery is responsible for the circulation of cortical regions essential for processing of music and language. Figure 3 shows the Circle of Willis and the vascular territories in the brain.

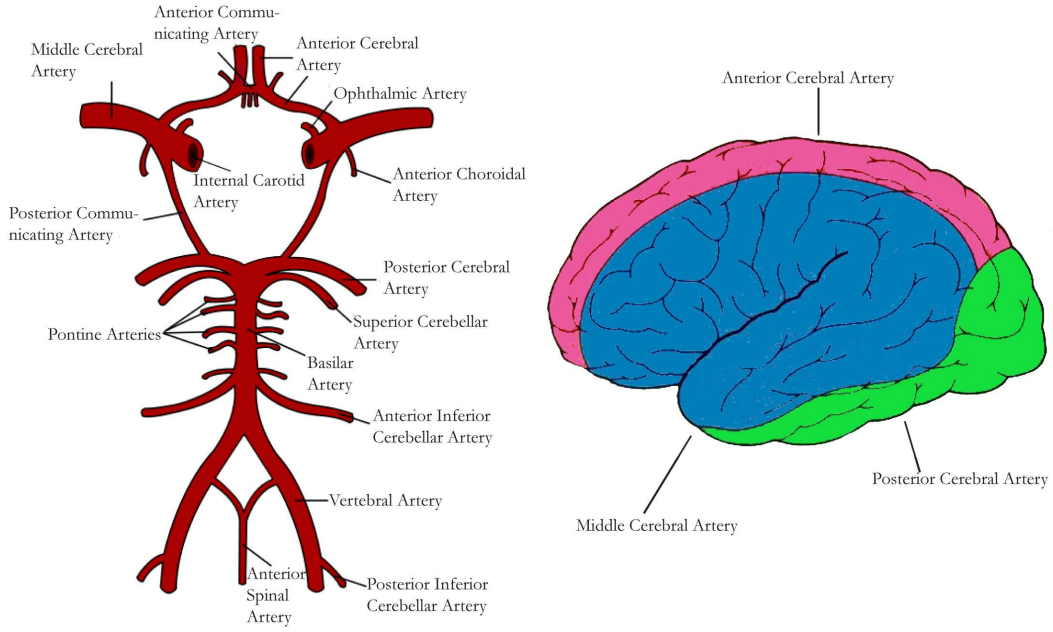

Figure 3: The Circle of Willis and the arteries supplying the brain with blood (left) and the vascular territories supplied by anterior cerebral artery (red), middle cerebral artery (blue), and posterior cerebral artery (green) (right).

Stroke, or cerebral vascular accident, occurs when the blood flow to the brain is suddenly disrupted, usually due to a blood clot occluding the normal passage of blood. Eventually, this blockage prevents the tissue from getting oxygen and glucose and it becomes dysfunctional. The resulting area of tissue death due to a local lack of ogygen is called an infarction. In the following subsections, we will discuss the signs, symptoms, and causes of stroke; physiology and diagnosis of stroke; as well

as standard and modern therapeutical interventions of stroke in more detail.

In industrialised countries, such as Finland, stroke is the third most common cause of death after heart disease and cancer, and in people over 60 years, it is also the most important cause of disability [16]. Since half of the stroke survivors suffer from permanent disability and need either institutionalization or domestic help, the expenses of stroke are vast. It has been estimated that altogether lifelong costs of stroke amount to around 60 000 Euros per patient [17]. To bring down the expenses caused by stroke, research concerning novel therapeutic treatments and interventions is of great importance.

2.1 Symptoms and diagnosis

The word "stroke" is used to describe two different conditions: either ischaemic stroke caused by locally occuring disruption of blood flow in the brain or haemorrhagic stroke caused by haemorrhage in an artery in the brain. Ischaemic strokes can further be divided into ischaemic events lasting 24 hours or less (transient ischaemic attack, TIA) and cerebral infarctions. In Finland, about 80% of all strokes are infarctions [18].

Patients with stroke usually have various neurological impairments, such as aphasia, hemiparesis, or sensory loss. If the infarction occurs in the left hemisphere, motor and sensory impairments can be seen in the right side of the body and vice versa. Patients can also suffer from headaches, nausea, and vomiting, and the symptoms can gradually worsen or wax and wane [19]. Major hemispheric infarctions, basilar artery occlusion, or cerebellar strokes with oedema can decrease the level of consciousness, but most patients remain alert during the stroke incident [19].

Although most physicians can diagnose stroke on the basis of the patient's clinical condition, computed tomography (CT) or magnetic resonance imaging (MRI) are widely used. While CT is an advanced version of the conventional x-ray study, the MRI exploits the magnetic properties of organic tissue: protons in hydrogen atoms are constantly spinning about their principal axis creating a tiny magnetic field. When a powerful magnetic field is applied to tissue containing protons, they become oriented in the direction parallel to the magnetic force. Finally, radio waves (RF pulse) are used to change the orientation of the protons, and when the radio waves are turned off, the protons rebound toward the orientation of the magnetic field producing signals that can be measured by detectors around the head [20]. Thus, the MRI system can construct the actual image reflecting the distribution of the protons and other magnetic agents in the tissue [20]. The behaviour of the protons in magnetic field is illustrated in Figure 4.

The protons in the tissue return to their normal state in two phases: the transverse component in relaxation time *T2* and the longitudinal component in relaxation time *T1*. The contrast differences between separate tissues are due to relaxation times and proton densities which are tissue-specific and can be altered because of pathologies. Using different imaging parameters (echo time (T_{E}), repetition time (T_{R}), and features of the RF pulse etc.) distinct information and contrasts are obtained. Usually, short echo and repetition times are employed to get a *T1* weighted

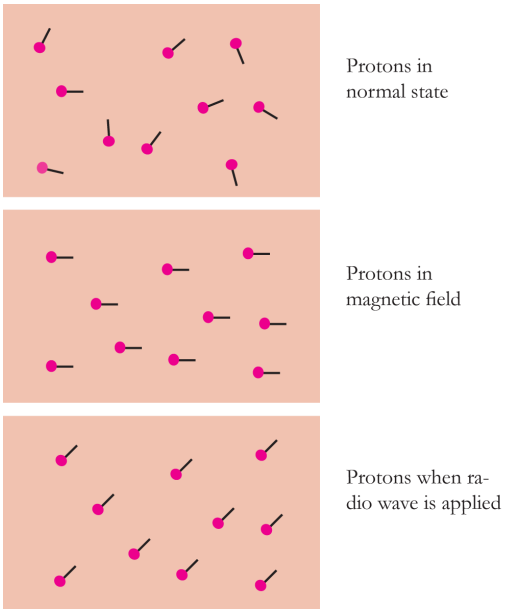

Figure 4: Protons in their normal state orienting randomly in different directions (top), in an external magnetic field (middle), and perturbed by radio waves (down).

MR image using spin echo sequence, in which an extra RF pulse is applied after the actual RF pulse to eliminate unhomogeneities arising from environment [21].

T1 weighted images are anatomically accurate, whereas in *T2* weighted images, pathological changes can be seen more easily. However, when examining a stroke patient, other imaging sequencies, such as diffusion imaging or fluid-attenuated inversion recovery (FLAIR) images are often used. Diffusion weighted imaging (DWI) produces diffusion maps reflecting the rate of water diffusion in the brain and is more sensitive to early changes after stroke than the more traditional *T1* and *T2* weighted images [18]. In the resulting diffusion map, regions of active diffusion, such as infarcted brain tissue, produce a weak signal, whereas a strong signal is acquired from regions of slow diffusion [18].

In the evaluation of stroke, the fluid-attenuated inversion recovery (FLAIR) sequence offers increased sensitivity when compared to the more conventional *T1* and *T2* images [22]. FLAIR imaging produces heavily *T2* weighted images with cerebro-spinal fluid (CSF) suppression. Stroke displays increased signal intensity on *T2* weighted images, which can be seen in Figure 5, where an infarct in the right temporal lobe is shown.

2.2 Pathophysiology of ischaemic stroke

Normally, the blood flow in the brain is on average 55 ml/100 g/min, but thanks to its physiological compensation mechanisms, even a 50% reduction in the blood flow can be tolerated by the brain [18]. Once the occlusion in an artery has occured and the blood flow is remarkedly reduced, an infarction takes place: due to lack of ogygen, brain tissue will gradually die. The ischaemic core is surrounded by a

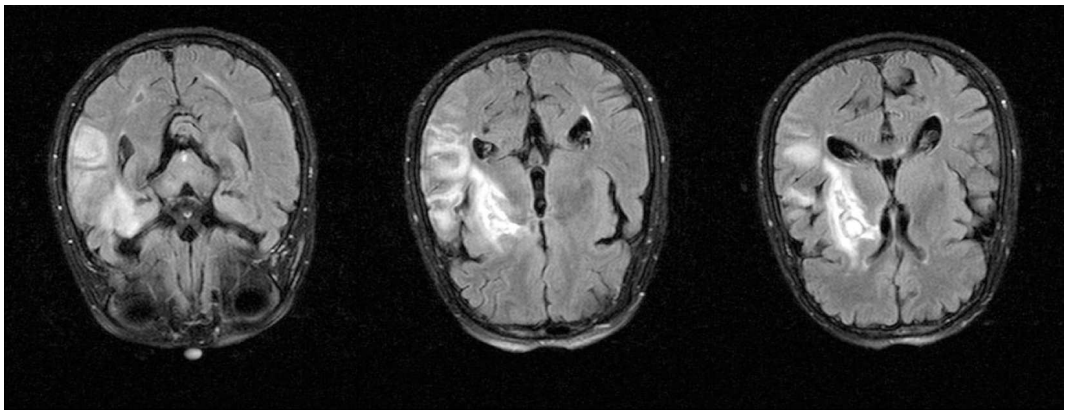

Figure 5: A fluid attenuated inversion recovery (FLAIR) MR image showing infarcted tissue medially in the right temporal lobe and extending to the cortex.

volume of functionally impaired but structurally intact tissue, which is known as the ischaemic penumbra [23].

Ischaemic brain injury results from complex pathophysiological events evolving over time. The major pathogenic mechanisms causing brain injury include excitotoxicity, peri-infarct depolarizations, inflammation, and programmed cell death (apoptosis) [24]. In Figure 6, a rough sketch of these pathophysiological events is shown.

In the cellular level, several acute processes take place. Lack of energy leads to depolarization of the neurons and activation of specific glutamate receptors increases intracellular Na^+, Ca^{2+}, and Cl^- levels [24]. Consequently, K^+ and glutamate diffuse in the extracellular space arousing a series of spreading waves of depolarization [24]. Due to the osmotic gradient, water diffuses into the cells making them swell. Numerous enzyme systems are overactivated, free radicals are generated, and inflammatory mediators are formatted [24].

In the ischaemic core, energy failure and ionic disruption are severe, and cells are quickly exposed to programmed cell death, apoptosis, leading to permanently damaged tissue. However, in the ischaemic penumbra, where some perfusion might remain, the cells die more slowly. Hence, the ischaemic penumbra is a promising area for therapeutic interventions, whereas within the core territory, salvage of rapidly dying brain cells might not be feasible without early perfusion [25].

2.3 Treatment and rehabilitation

As stated before, in the ischaemic penumbra, the damage developes quite slowly. In the ischaemic penumbra, neurons can survive quite a long time and neurological deficits can progress as time goes by. Still, it is common that the symptoms begin to improve during the first week after the insult. As time goes by, the structural lesion becomes stable and a part of the ischaemic penumbra can be recruited into infarction, which can lead to the regression of symptoms while the lesion actually expands [24]. After a couple of weeks, the neurological deficits reflect the size and

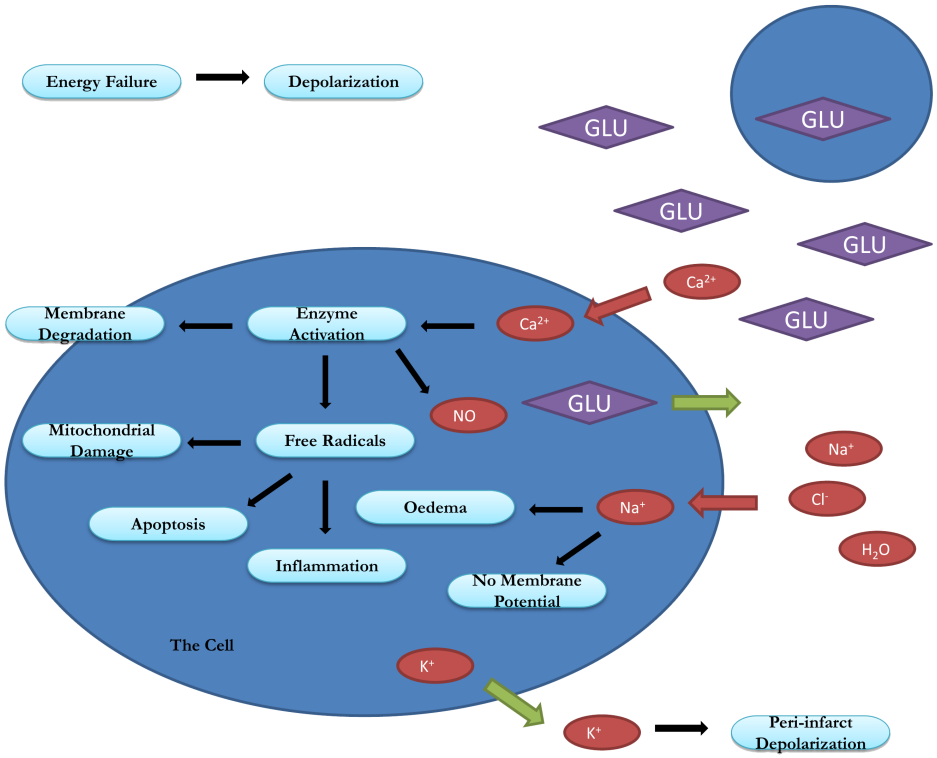

Figure 6: A diagram of the pathophysiological events in the infarcted region. Due to the energy failure, ionic gradients can not be maintained and neurons and glia depolarize. Ca^{2+} channels activate and excitatory amino acids (glutamate) are released into the extracellular space. Na^{+} and Cl^{-} enter the neurons followed passively by water which makes the cells swell causing oedema. The increase in intracellular Ca^{2+} activates enzymes which in turn induce inflammation, apoptosis, and mitochondrial damage by releasing free radicals.

location of the structural lesion quite closely [24]. From this point on, recovery of function is best explained by plasticity and tissue reorganization. Figure 7 shows how the structural lesion typically grows in a couple of weeks time.

In the treatment of stroke, the first hours are crucial because there still might be a chance to restore perfusion and thus save the brain tissue in the area of the ischaemic penumbra. Thrombolysis with intravenous rt-PA (recombinant tissue Plasminogen Activator) is effective for strokes due to acute ischaemia when introduced within three hours of symptom onset [26]. After thrombolysis, the patients are usually taken care of in a specialized stroke care unit, which is stated to be of importance for the recovery [23].

In the post-acute phase, about 40% of the stroke patients need long-lasting rehabilitation. Many of them recover well, but there is a large amount of patients who suffer from permanent ill effects (see for example [17]) reflecting muscle- and sensory functions as well as higher brain functions. Although it is often suggested that the neurons are not capable of regenerating, still, there is evidence that the adult

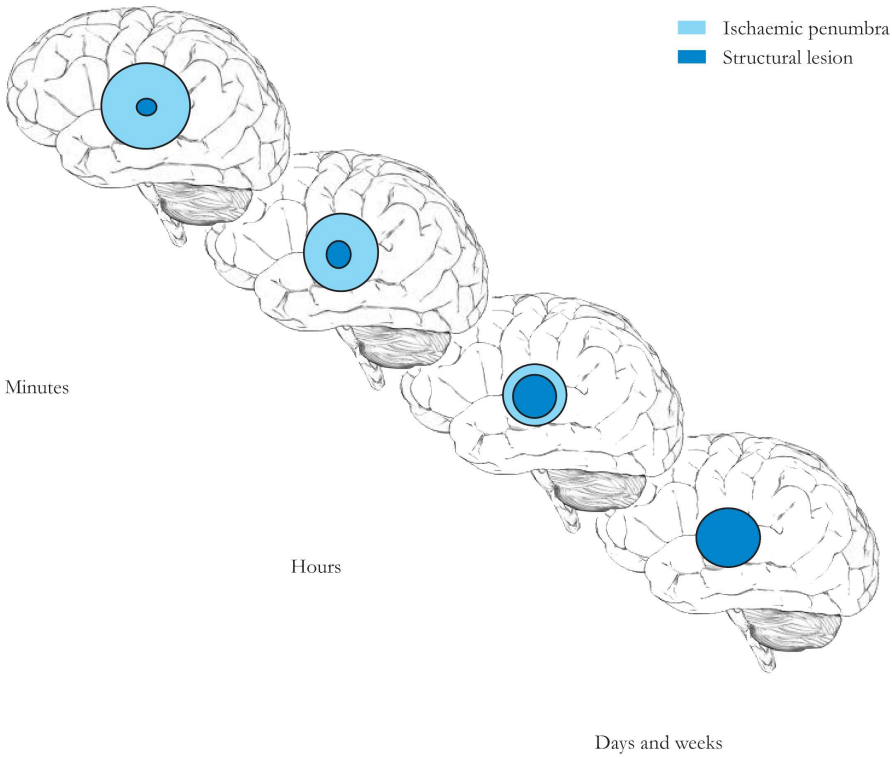

Figure 7: Growing of the structural lesion during first weeks after stroke. In the final phase, the neurological deficits reflect the size and location of the structural lesion.

human brain can undergo plastic changes and reorganization of neurons. Moreover, this plasticity can even be encouraged by repeated rehabilitative exercises [27].

After stroke, brain plasticity, which is a process associated with learning by adding or removing connections between neurons, can help the patients to relearn the disrupted functions. Experiments conducted with adult squirrel monkeys over 20 years ago showed that rehabilitative training after an ischaemic infarct is beneficial and can induce plastic changes in the brain: monkeys receiving training experienced a 14.9% increase of the digits' and a 58.5% increase of the wrist-forarm's representations in the representation area of the hand compared to spontaneously recovered monkeys [28]. This was assumed to be the result of reorganized neurons, but still the question remained: were the axons physically growing or did the existing synapses modulate somehow?

To date, several animal studies concerning stroke recovery have now been conducted. When studying spontaneous recovery from stroke, Frost et al. [29], for example, found that squirrel monkeys with an ischaemic infarction in the primary motor cortex (M1) had increased hand representation areas in the ventral premotor cortex (PMV) 12 weeks after the stroke. In the same time, the hand representation areas in the primary motor cortex had decreased [29]. This result might imply that the recovery of motor functions after stroke might be related to the reorganization of the secondary motor areas [29].

Also studies concentrating on the recovery environment instead of rehabilitative training have been carried out. Passineau et al. [30] studied rats with severe parasagittal fluid percussion injury and found that environmental enrichment has significant effects on the recovery. For example, rats recovering in cages containing a variety of toys, a running wheel, hammock, tunnels, and other motor, tactile, and olfactory stimuli, showed significantly smaller lesion sizes compared to rats housed in standard plastic cages [30]. This result suggests that environmental enrichment is beneficial in attenuating cognitive deficits.

The effects of multimodal stimuli and enriched environment together have been studied with rats suffering from lateral fluid percussion brain injury. After the brain injury, one-third of the animals were placed under conditions of standard housing, one-third were kept in an enriched environment (horizontal and inclining platforms and various toys), and one-third received an enriched environment, which included also multimodal early onset stimulation (exposure to a variety of visual, auditory, olfactory, and motor stimuli). The researchers found that the enriched environment and the enriched environment combined with the multimodal early onset stimulation significantly reduced the lesion volume [31].

When it comes to human stroke patients, there is also evidence of reorganization of neurons in the brain. Liepert et al. [32] used focal transcranial magnetic stimulation (TMS) to map the cortical motor output area of a hand muscle on both sides in stroke patients in the chronic stage before and after a 12-day constraint-induced movement therapy. They found that after the treatment, the cortical representation area of the affected hand muscle was significantly enlarged corresponding to a greatly improved motor performance of the paretic limb [32].

It has also been suggested that plastic changes contributing to the recovery of motor functions take place in the ipsilateral, non-infarcted hemisphere, but not all studies have confirmed these changes. In a functional magnetic resonance (fMRI) study, increased activation in the unaffected hemisphere of stroke patients was detected during ipsilateral hand finger-tapping compared to that of control subjects [33].

2.3.1 Music in the treatment of stroke

Since neural plasticity is a known fact and the stroke patients usually need therapeutic interventions to restore their independence by relearning everyday skills, it is of importance to develop therapeutic means capable of promoting plasticity. Hence, music therapy appears to be a promising field worthy of deeper examination.

It has been shown that engaging in musical activities not only shapes the organization of the developing brain but also produces long-lasting changes even after brain maturation is complete. Owing to the diverse nature of music, it is a suitable medium for rehabilitation treatments aimed at inducing plastic changes in brain [34]. Music is usually experienced as a pleasurable activity, which increases motivation to engage in music therapy.

Music can be used in the treatment of stroke patients both actively (the patient plays, sings, or otherwise contributes to the music) and passively (the patient listens

to music). Although music therapy with set goals and a trained therapist can be used, simply listening to music can be profitable after stroke. With stroke patients, rhytmic auditory stimulation (RAS, auditory rhythm used as a timekeeper) has been found to significantly improve walking velocity and stride length and to reduce the electromyogram (EMG) amplitude variability of the gastrocnemius muscle [35].

A considerable number of stroke survivors suffer from aphasia, a language disorder constricting the ability to communicate verbally. Usually aphasic stroke patients have problems with speaking, reading, writing, naming objects, or understanding speech, and the infarction is typically located in left frontal lobe in the so called Broca's area. Although many of the patients benefit from ordinary speech therapy, a more efficient treatment has been introduced quite recently: Schlaug et al. [36] found that melodic intonation therapy (MIT), which transposes spoken phrases into melodic intonation patterns, was superior to standard treatment with no melodic extent.

In previous studies, listening to self-selected music has also been found to positively affect cognitive recovery and mood after stroke [37]. In this particular study, patients were assigned to a music group, an audio book group, or a control group and the subjects in the music and audio book groups listened to self-selected music or audio books during the following two months. The results showed that recovery in the domains of verbal memory and focused attention improved significantly more in the music group than in the audio book and control groups [37]. In addition, the music group also experienced less depressed and confused mood than the control group [37]. Still, the neural mechanisms underlying these effects are not yet clear.

Subjectively, the patients felt that listening to music helped them to calm down, relax, and sleep better [38]. Music also increased the patients' motor activity and invoked memories and reflective thoughts about the future [38]. In addition, the nurses considered music to be beneficial to recovery: they perceived less depression, better mood, and facilitated communication as well as more human patient-nurse relationship [38].

It was also found that the amplitude of the frequency magnetic mismatch negativity (MMNm) increased significantly more in both music and audio book groups than in the control group during the 6-month follow-up [39]. In addition, changes in the frequency MMNm amplitude correlated significantly with the behavioural improvement of verbal memory and focused attention induced by music listening [39]. In this thesis, cognitivie recovery, mood, and MMNm amplitudes are being compared to local grey matter volumes to investigate the changes induced by sound environment after stroke.

As already mentioned before, music has extensive effects on brain. It has been shown that music activates structures used to modulate emotions: the amygdala, the hippocampus, the parahippocampal gyrus, and the temporal pole are involved in the emotional processing of music [40]. Emotional processes, for one's part, have effects on the vegetative nervous system and hormonal system which, in turn, modulate the activity of the immune system [41].

Since music can modulate the activity of such central structures of the limbic system as the hippocampus and the amygdala, it has been suggested that music

therapy could be helpful to patients with depression or pathologic anxiety, because these disorders are partly related to dysfunction of the amygdala [41]. Since 17–64% of stroke survivors suffer from post-stroke depression [42] associated with poor functional recovery of patients. Music as a pleasurable and easily available amusement could help depressed stroke patients. In addition, early diagnosis and treatment of depression might help patients to recover more completely and thus save healthcare resources by shortening the time of institutional care or reducing the need for home care [43].

3 Methods

3.1 Subjects

Subjects were 60 stroke patients recruited from the Department of Neurology of the Helsinki University Central Hospital (HUCH) between March 2004 and May 2006. All subjects had been admitted to the hospital for treatment of acute stroke in the left or right temporal, frontal, parietal, or subcortical brain regions. The following additional inclusion criteria were also used: no prior neurological or psychiatric disease, no drug or alcohol abuse, no hearing deficit, right-handed, $\leqslant$ 75 years old, Finnish speaking, and able to co-operate.

As soon as possible after hospitalization, the patients were randomly assigned to one of three groups ($n = 20$ in each): a music group, an audio book group, or a control group. Randomization was performed with a random number generator by a researcher not involved in the patient enrollment. All patients signed an informed consent, and the study was approved by the HUCH Ethics Committee. All patients received standard treatment for stroke in terms of medical care and rehabilitation.

All patients underwent a clinical neuropsychological assessment and a magnetoencephalographic (MEG) measurement one week (baseline), three months and six months post-stroke, and magnetic resonance imaging (MRI) within two weeks of the stroke and six months post-stroke. Stroke diagnosis as well as the location and size of the lesion were evaluated from MR images.

Of the 60 subjects originally recruited into the study, 55 completed the study up to the 3-month follow-up (music group $n = 19$, audio book group $n = 19$, and control group $n = 17$). Of the five drop-outs, one was due to false diagnosis (transient ischaemic attack), one due to a new stroke, one due to dementia, and two due to refusal. One further subject died from myocardial infarction before the 6-month follow-up (music group $n = 18$, audio book group $n = 19$, and control group $n = 17$). Later, three more subjects were excluded from the analysis because their MR images were not available. The data included in VBM analysis consisted of 51 subjects (music group = 16, audio group = 19, and control group = 16). The baseline demographic and clinical characteristics of the three subject groups can be seen in [37]. There were no statistically significant differences between the groups in the baseline demographic or clinical variables [37].

3.2 Interventions

After agreeing to participate in the study, all patients were contacted by a music therapist who interviewed them about their pre-stroke leisure activities and hobbies, such as music listening and reading, and informed them about the group allocation. The patients in the music group were provided with portable CD players and CDs of their own favorite music in any musical genre. Similarly, the therapist provided the audio book group with portable cassette players and narrated audio books on cassette selected by the patients from a collection of the Finnish Celia library for the visually impaired. The control group was not given any listening material.

The music and audio book groups were trained in using the players and instructed to listen to the material by themselves at least one hour per day for the following two months while still in the hospital or at home. During these two months, the music therapist kept close weekly contact with the patients to encourage listening and to provide more material and practical aid in using the equipment, if needed. After that, the patients could continue listening to the material on their own.

The music and audio book groups kept listening diaries during the intervention, and also questonnaires on leisure activities, which all patients filled after the intervention period and at the 6-month follow-up, were used to verify participation. In addition, the three groups received similar amounts of rehabilitation (physical therapy, occupational therapy, speech therapy, and neuropsychological rehabilitation) in public health care during the 6-month follow-up period.

3.3 Structural brain imaging

MRI was performed within two weeks of stroke onset and six months post-stroke using the 1.5 T Siemens Vision scanner of the HUCH Department of Radiology. The first MRI was used to verify the stroke diagnosis and the second to evaluate the size and location of the lesion without the interfering effect of the acute stage oedema. In VBM analysis, 3D *T1* images from acute and six months post-stroke stage were used. The imaging sequence used was inversion recovery with following values: T_{E} = 3.68 ms, T_{R} = 1900 ms, T_{I} = 1100 ms, and flip angle = 15°. Slice thickness was 1 mm.

3.4 Voxel-based morphometry

Voxel-based morphometry was used to analyse grey matter volumes from MR images. As already mentioned before, it is a technique used to study local composition of brain tissue while discounting large-scale differences in gross anatomy and position. The basic idea is to identify a particular tissue type, in this case grey matter, in the scan of each subject and warp these grey matter maps to a common anatomical space [44]. These deformed tissue maps are then spatially blurred, and finally, a statistical analysis of the data is performed [44].

VBM consists of several stages: pre-processing of the data, normalizing, segmenting, modulating, and smoothing of the data, and finally statistically analysing the data voxel-by-voxel. Figure 8 describes the VBM process used in this study. Previously, VBM has been used to indentify structural abnormalities among unhealthy subjects (see for example [45, 46]) and to study the impact of learning and practice on brain structure among healthy subjects (see for example [47]). In this thesis, we will try to find out if listening to music can influence the structure of the brain in stroke patients and specifically, the total amount of grey matter by using VBM. SPM8 package in MATLAB was used in analysis.

Before the actual pre-processing, all the MR images were checked to be of good quality. Then they were manually realigned using the SPM8 display option so that the anterior commissure was close to coordinate (0,0,0) and the orientation

within a few degrees of the tissue probability map data. After realigning the images, they were pre-processed with cost function masks covering the infarcted area. The procedure is described in more detail in the next subsection.

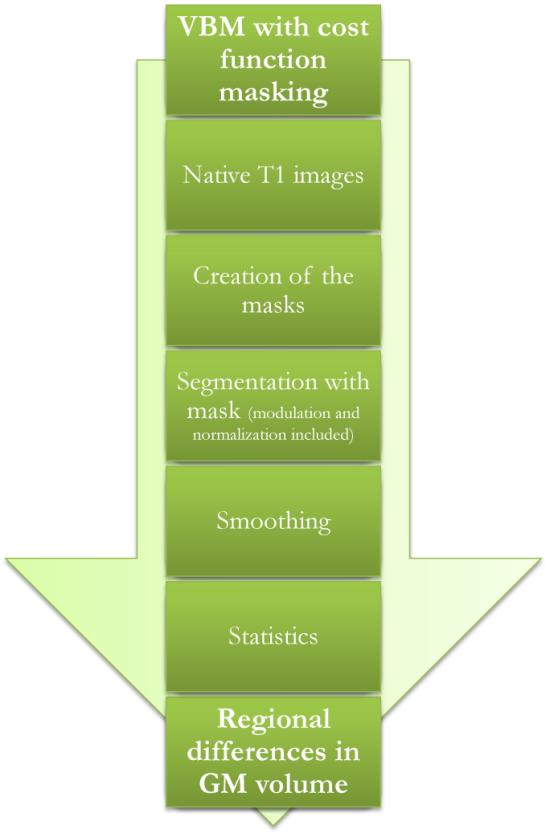

Figure 8: A flow diagram showing the different steps of VBM.

3.4.1 Pre-processing

When normalizing images with focal lesions, such as infarctions, automated normalization algorithms attempt to reduce image mismatch between template and image at the site of the lesion, which can lead to significant inappropriate image distortion [48]. A lesion or artefact in the image is usually of very different intensity from the equivalent area in the template causing the cost function (the differences in intensity values of the source image and the template used to derive mathematical measure of mismatch between the images, in SPM the sum of the squared differences) to be high in the area of the lesion [48]. Thus, even when the rest of the brain is well matched, the normalization might suffer from the lesion.

There are two standard options for pre-processing of images with focal lesions: one solution is to use only linear (affine) transformations in normalization, that is, translations, rotations, zooms, and shears, and not to implement non-linear functions, such as discrete cosine transforms [48]. The other solution is to restrict the cost function to areas of brain outside the abnormality, in other words, masking the

lesion so that the calculated transforms are no longer biased by the effect of the lesion. In 2001, Brett et al. [48] suggested that cost function masking is superior to the standard approach when normalizing brains with focal lesions.

Later, Andersen et al. [49] examined the effects of cost function masking in normalization using unified segmentation model in SPM5 with actual, chronic, focal lesions resulting from stroke. They found that masking had a significant effect on the accuracy of normalization even when unified segmentation was used: non-masked lesions resulted in enlarged lateral ventricles and reclassifying of the damaged area as ventricle thus decreasing the total lesion volume [49]. In addition, they suggested that there is no significant difference between cost function masking performed with masks that precisely follow the lesion boundaries and those that only roughly track the borders [49].

Following these principles, cost function masks for each subject were created by roughly drawing the lesion outline on each slice using MRIcron software. The damaged region was fully obscured but no attention was paid to fine, local details of the lesions. The time required to construct rough lesion masks was on average slightly more than 17 minutes per brain, which is notably less than the time required to produce precise masks reported by Andersen et al. [49] (from 1 to 8 hours per brain). Only one mask per subject was created using the 6-month MR images because all of the lesions were not clearly visible in the acute phase images. Figure 9 shows how the lesion masks were drawn.

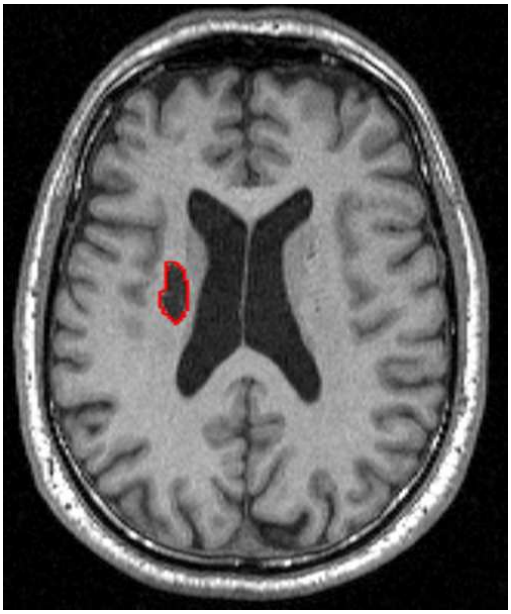

Figure 9: The drawing of a lesion mask: first, a red circle was drawn around the lesion. Then the area inside the red circle was filled with red, and these steps were performed in each slice showing the lesion. A 3D lesion mask was finally created.

When the creation of the masks was completed, each brain image was segmented in SPM8 using the module "segment". Segmentation means dividing the voxels on each image into grey matter (GM), white matter (WM), cerebrospinal fluid (CSF),

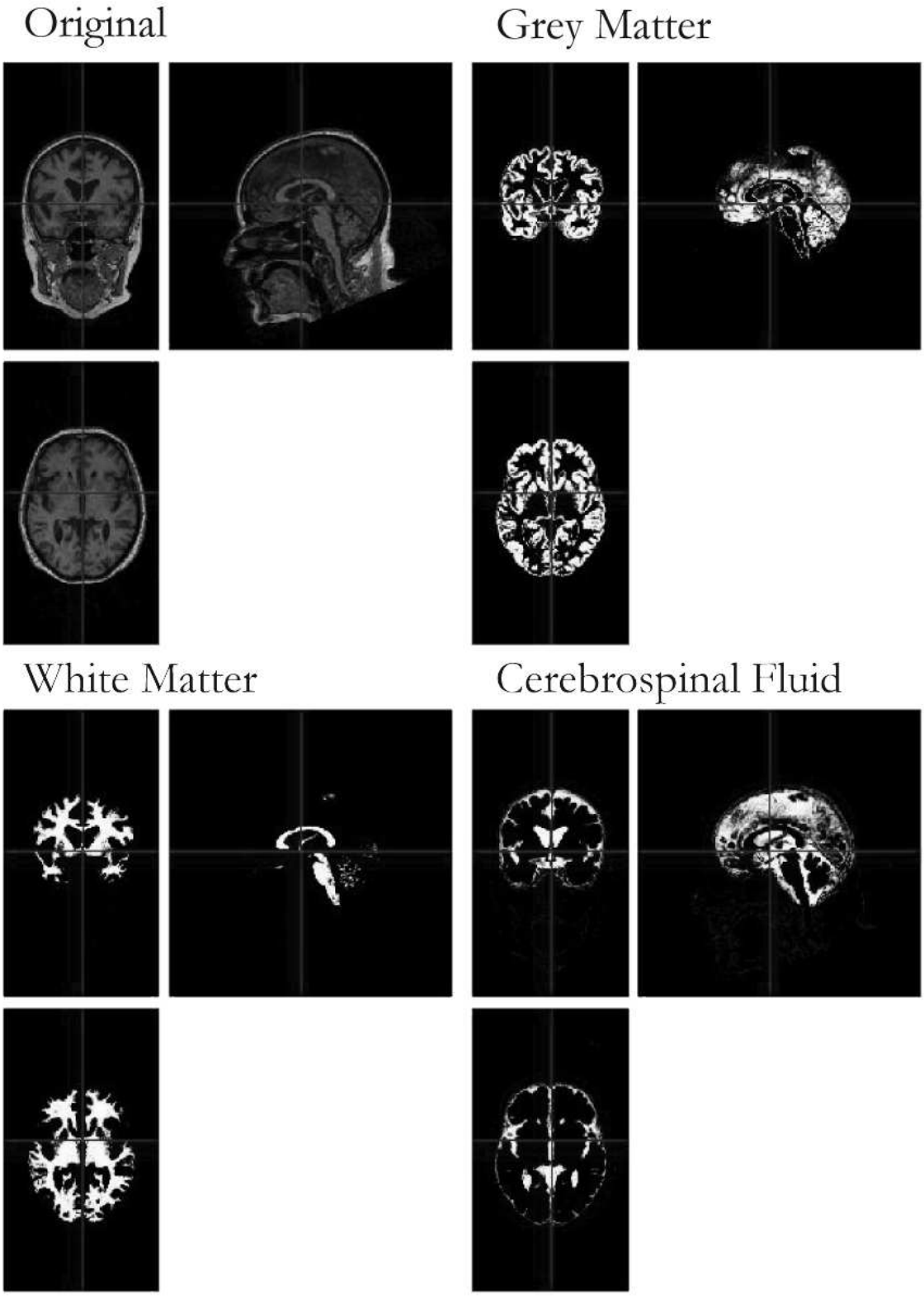

Figure 10: The original image, segmented grey matter, segmented white matter, and segmented cerebrospinal fluid.

and other tissue classes based on voxel intensities and a priori probability maps representing the spatial distribution of different tissues in normal subjects [50]. The same masks were used in the segmentation of both the acute and the 6-month MR images. The segmentation module combines both registration with tissue probability maps and tissue classification, thus providing better results than simple serial applications of each component (normalization and segmentation), which formerly was routine procedure [51]. Spatially normalized images with modulation were finally produced. Figure 10 shows the segmentation results.

Modulation was used to compensate for the effect of spatial normalization. It involves multiplying the spatially normalized grey matter (or other tissue type) by its relative volume before and after spatial normalization resulting in the same total amount of grey matter before and after spatial normalization [50, 51]. For instance, if the normalization will double the volume of the temporal lobe, the correction halves the signal intensity keeping the total amount of grey matter in the temporal lobe the same [50].

After segmentation, the images were smoothed using a 10 mm smoothing kernel. In the smoothed images, each voxel contains the average concentration of grey matter from around the voxel, and the resulting image is said to quantify the grey matter concentration. As a result, we now had spatially normalized, modulated, and smoothed grey matter images, which could be used in statistics. Figure 11 shows the final stage before statistical analysis.

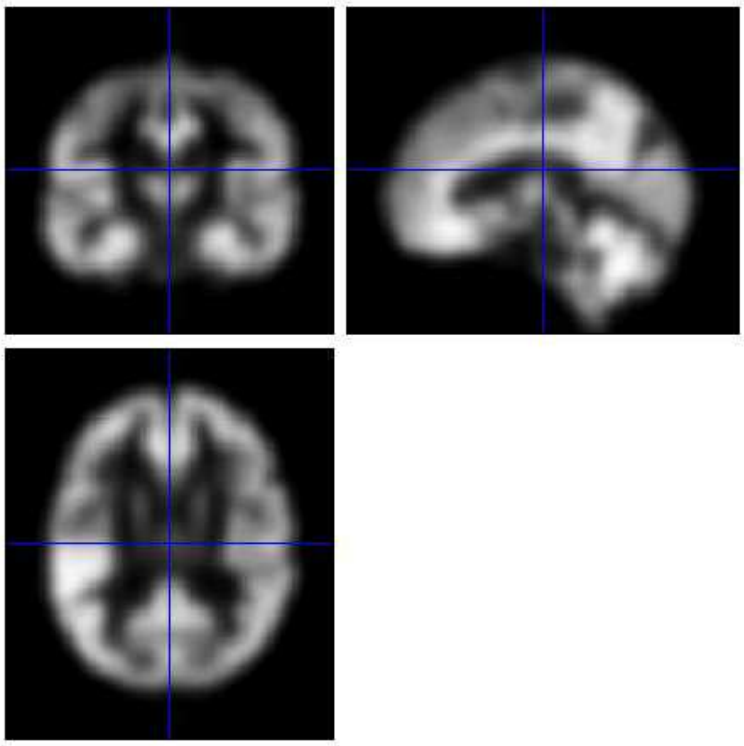

Figure 11: Spatially normalized, modulated, and smoothed grey matter image ready for statistical analysis.

3.4.2 Statistical analysis

After segmentation, statistical analysis was performed to identify regions of grey matter volume significantly relating to the particular effects under study. In statistical analysis, general linear model (GLM), which is a flexible framework allowing several different tests to be applied, was used. GLM can be used in group comparisons and detecting regions of grey matter concentration or volume that are related to specified covariates such as age or test scores [50, 52]. The results are presented in a voxel-wise statistical parametric map (SPM).

In this study, two different statistical designs were created: a full factorial model comprising of six different groups (acute and 6-month MR images of the three groups) and lesion laterality as a covariate as well as a multiple regression model to study correlation between grey matter volumes and neuropsychological test scores.

The full factorial model can be used to test for all main effects and interactions in one-way, two-way, or three-way ANOVAs, and in this particular case, a two-factor design was created. The first factor was named Repetition and was comprised of two levels (acute and 6-month stage). This factor was set to allow for dependencies because it was presumable that the two measurements of the same subjects were correlated. The second factor consisting of three levels (music, audio book, and control groups) was named Group. These measurements were assumed to be independent between levels. As mentioned before, lesion laterality was included in the model by indicating left with 0 and right with 1. The total volume of grey matter was used as global normalization to deal with brains of different sizes. The design of the full factorial model can be seen in Figure 12.

A multiple regression model was designed to study correlation between grey matter volume and neuropsychological test scores obtained previously. In this design, lesion laterality and the total volume of the grey matter were also used to compensate for the effects arising from different brain anatomies.

Several tests were performed to study different effects. First, a t-contrast measuring the changes occuring during the 6-month follow-up in all of the subjects was implemented. After that, the changes occuring during the follow-up in the music group were compared to that of the audio book group and the control group. Similar pairwise comparisons were made between the audio book group and the control group too.

Next, the data were divided into two subgroups: subjects with left hemisphere damage (LHD) and subjects with right hemisphere damage (RHD). For these LHD and RHD subgroups, the same pairwise comparisons between the three groups were performed to detect differences in the structural changes occuring during the follow-up. After these comparisons, the three study groups were examined without the LHD-RHD subdivision to identify regions with decreased and increased grey matter volumes separately for each group.

Finally, the 6-month stage MR images were compared to different neuropsychological test scores obtained six months after the stroke in the multiple regression model. The test scores used were focused attention, verbal memory, depression and confusion, which were found to be related to music listening after stroke [37], as

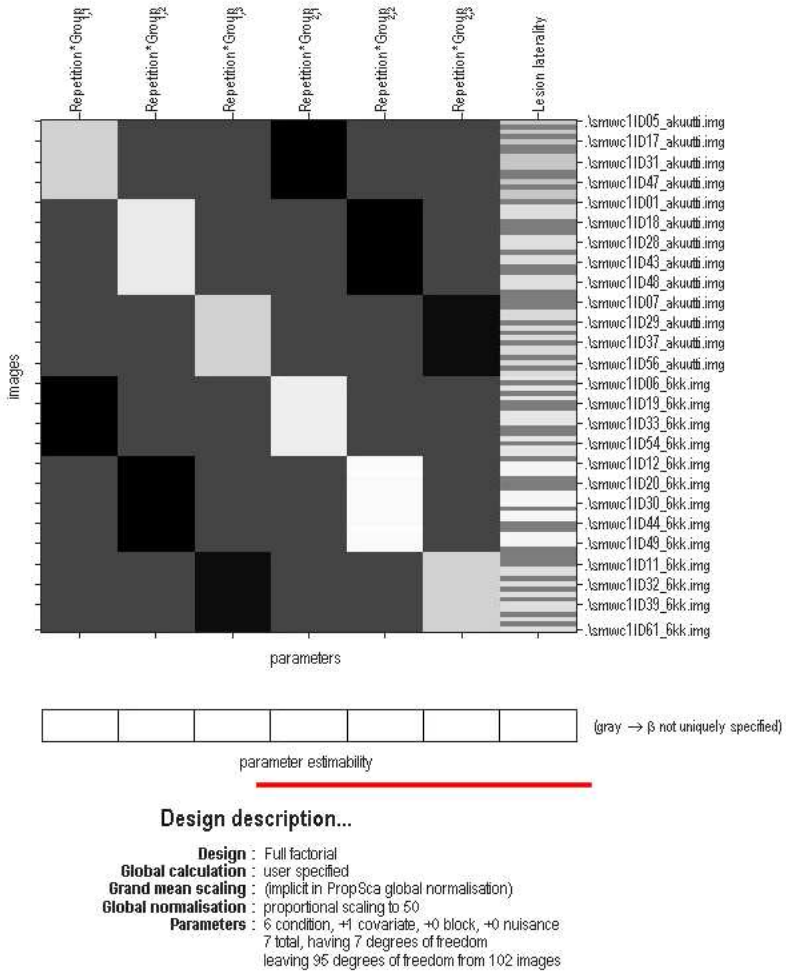

Figure 12: The design of the full factorial model. The first row represents the acute MR images of the music group allowing dependencies with the 6-months MR images of the music group. The second row represents the acute MR images of the audio book group, respectively, allowing dependencies with the corresponding 6-months images and so on. The seventh column shows the lesion laterality.

already mentioned before. In addition, the amplitude of magnetic mismatch negativity (MMNm) responses at six months, which also have been found to be influenced by music listening after stroke ([39]), were compared to the MR images.

After creating the statistical designs, they were estimated by fitting the data at each voxel to some linear combination of the columns of the design matrix generating a series of "beta" images and an "ResMS" image which provides the necessary standard deviations for computing the t statistics [53]. After finishing the fitting, SPM computes residual images, from which the smoothness of the data is computed [53].

The actual results of the statistical tests can be presented by specifying contrast vectors which indicate the linear combination of "beta" images to test. Different contrast vectors were used to identify where any regions significantly differ from

zero. No regions of interest were used in this stage, because the idea was to detect differences in the whole brain and no previous information about specific brain regions showing differences was available. In statistics, the p value was set to $<$ 0.001 (uncorrected). In addition, a brain mask offered by SPM8 was used to exclude voxels outside the brain, and an extent threshold of 100 voxels was applied to avoid clusters with very low statistical significance.

To interpret the results, MNI coordinates given by SPM8 were transformed to Talairach coordinates using GingerALE software, and Talairach coordinates were then entered into Talairach Client software to identify the nearest grey matter.

4 Results

In this section, the results of the VBM analysis are presented. In brief, differences in the changes occuring during the follow-up between the three groups were detected as well as different regions with decreased and increased grey matter volumes within the three groups.

First of all, grey matter changes (regions with decreased and increased grey matter volumes) were examined across the whole subject sample ($n = 51$). After that, the changes between the two measurements were studied and the music ($n = 16$), audio book ($n = 19$), and control groups ($n = 16$) were compared to each other. Thereafter, the sample was divided into left (LHD) and right hemisphere-damaged (RHD) subgroups and the same group comparisons were performed. Finally, regions with decreased and increased grey matter volumes were identified separately for the music, audio book, and control groups, and the grey matter volumes were correlated with neuropsychological test scores, mood scale scores, and MMNm responses.

4.1 Changes during the follow-up

The regions with significantly decreased and increased grey matter volumes were studied by comparing the acute stage images with the 6-month stage images across the whole subject sample. The results are presented in Table 1, and Figure 13 illustrates these regions.

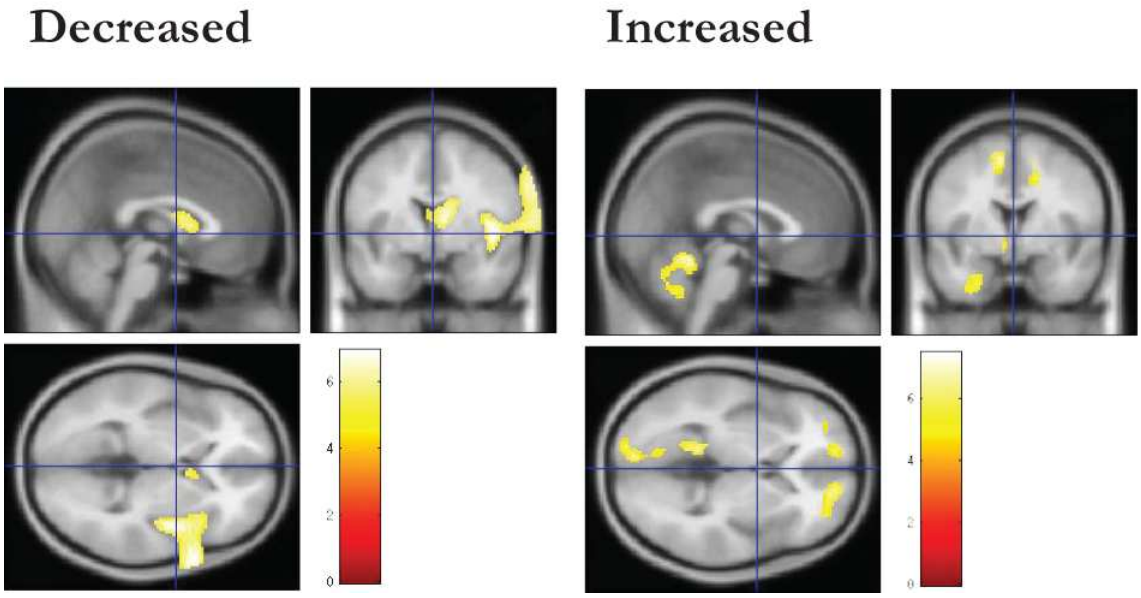

Figure 13: The regions with decreased and increased grey matter volumes. The colored bar describes the T values.

From Table 1 and Figure 13 we can see that the grey matter volumes decreased mostly in the right sub-lobar and frontal areas, such as the claustrum, the precentral gyrus, the caudate, and the thalamus. Increase in grey matter volume occured, in

Table 1: Regions with decreased and increased grey matter volumes. Clusters bigger than 100 voxels were accepted.

Regions with decreased grey matter volume	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, Claustrum	44, -4 4	6070	< 0.0001	< 0.0001	6.95
R, PrCG (BA 44)	70, 12, 0			< 0.0001	6.81
R, PrCG (BA 6)	68, 8, 42			< 0.0001	6.77
R, Caudate (Body)	8, 4, 10	1132	< 0.0001	< 0.0001	6.58
R, Thalamus	10, -18, 18			< 0.0001	5.47

Regions with increased grey matter volume	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, MFG (BA 10)	-32, 46, -10	2722	< 0.0001	< 0.0001	7.51
L, MeFG (BA 8)	-10, 36, 40			< 0.0001	7.17
L, IFG (BA 47)	-20, 24, -20			< 0.0001	7.09
R, CT	40, -60, -46	5699	< 0.0001	< 0.0001	7.20
R, ISLL	24, -74, -46			< 0.0001	6.87
R, Culmen	14, -48, -20			< 0.0001	6.81
L, PHG (BA 19)	-18, -46, -4	1269	< 0.0001	< 0.0001	6.96
L, PHG	-12, -42, 2			< 0.0001	6.43
L, PHG (Hippocampus)	-30, -20, -22			< 0.0001	5.89
L, MeFG (BA 6)	-10, 2, 56	421	0.0019	< 0.0001	6.74
L, MeFG (BA 6)	-10, -8, 54			< 0.0001	6.52
L, CG (BA 24)	-16, -12, 46			< 0.0001	5.46
R, Precuneus (BA 31)	12, -46, 42	328	0.0047	< 0.0001	6.73
R, Precuneus (BA 31)	14, -56, 34			< 0.0001	5.28
L, FG (BA 19)	-34, -88, -10	1028	< 0.0001	< 0.0001	6.51
L, LG (BA 17)	-10, -92, 2			< 0.0001	6.41
L, Cuneus (BA 17)	-6, -84, 18			< 0.0001	6.12
R, MeFG (BA 10)	16, 56, 2	853	< 0.0001	< 0.0001	6.49
R, SFG (BA 6)	14, 28, 48			< 0.0001	5.83
R, MeFG (BA 10)	18, 56, -14			< 0.0001	5.81
R, MeFG (BA 11)	10, 26, -20	388	0.0025	< 0.0001	6.42
R, AC (BA 24)	8, 40, -10			< 0.0001	5.14
L, Precuneus (BA 7)	-14, -48, 48	127	0.0772	< 0.0001	6.32
R, CG (BA 24)	16, 6, 44	178	0.0360	< 0.0001	6.30
R, MeFG (BA 6)	14, -8, 54			< 0.0001	5.46

L = left, R = right, AC = Anterior Cingulate, CG = Cingulate Gyrus, CT = Cerebellar Tonsil, FG = Fusiform Gyrus, IFG = Inferior Frontal Gyrus, ISLL = Inferior Semi-Lunar Lobule, LG = Lingual Gyrus, MeFG = Medial Frontal Gyrus, MFG = Middle Frontal Gyrus, PHG = Parahippocampal Gyrus, PrCG = Precentral Gyrus, SFG = Superior Frontal Gyrus

contrast, bilaterally in the frontal, limbic, parietal, and occipital areas, which are presented in more detail in Table 1. Table 2 shows the relative changes in different brain regions.

Table 2: Regions with decreased and increased grey matter volumes in subjects recovering from stroke.

Brain Region	**Decrease**	**Increase**
Cerebellum	0 (0%)	5699 (44%)
Frontal Lobe	4047 (44%)	4139 (32%)
Limbic Lobe	0 (0%)	1692 (13%)
Occipital Lobe	0 (0%)	1192 (9%)
Parietal Lobe	0 (0%)	291 (2%)
Sub-lobar	3155 (56%)	0 (0%)
Total	7202 (100%)	13013 (100%)

The regions with increased grey matter volumes were located all over the brain. Most of them took place in the cerebellum, in the frontal lobes, and in the limbic lobe. More specific analyses concerning grey matter changes in the three groups are presented later.

Next, the three groups in the acute stage were compared to each other to eliminate the differences already existing at baseline. The music group did not show increased grey matter volumes compared to the audio book group or the control group. The audio book group, in contrast, had one voxel cluster (256 voxels) indicating larger grey matter volume compared to the control group in the right anterior cingulate (Brodmann area 32).

After comparing the three groups in the acute stage to each other, the changes occuring during the follow-up in the groups were compared. Unfortunately, no voxel clusters bigger than 100 voxels were detected.

4.2 Changes in the LHD and RHD subjects

Since there is a degree of lateralization in the brain in processing speech and music [54], potential group differences were also studied separately within the LHD and RHD groups. The LHD subjects did not show any differences bigger than 100 voxels in the changes occuring during the follow-up.

The RHD subjects, in contrast, showed some significant differences: when comparing the change during the follow-up in the music group to the change occuring in the audio book group, a cluster of 123 voxels was found in the right insula (BA 13).

Respectively, when comparing the changes occuring during the follow-up in the music group to the change occuring in the control group, a statistically significant cluster of 486 voxels was found in the right hemisphere extending from the precentral

gyrus (BA 6) to the right insula (BA 13) and right inferior frontal gyrus (BA 44). The results are presented in more detail in Table 3. In addition, these results are illustrated in Figure 14.

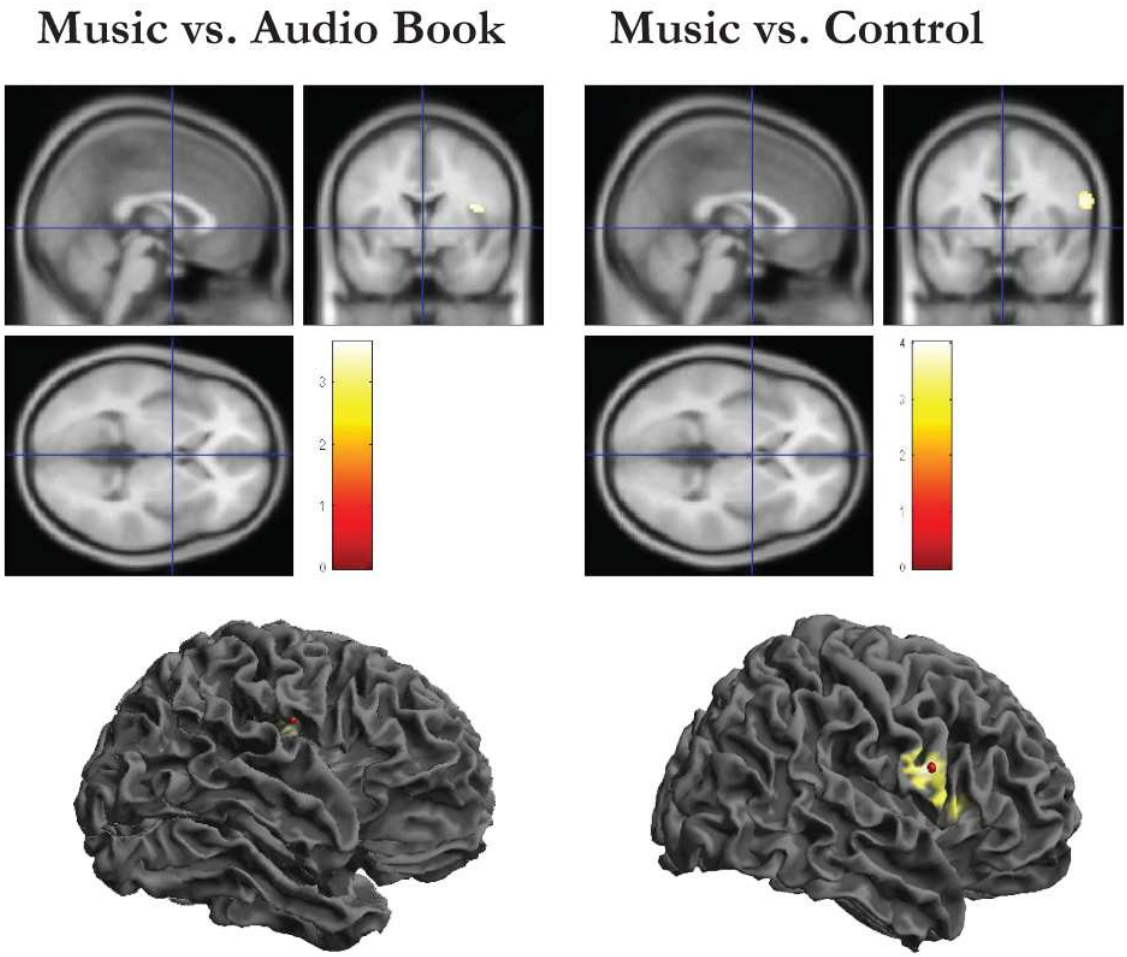

Figure 14: The regions differing significantly during the follow-up in the music group compared to the audio book group and in the music group compared to the control group within the RHD subjects. The coloured bar indicates the T values.

Although there were no statistically significant differences occuring in the whole sample, when comparing the music group and the audio book group, a cluster consisting of 28 voxels was found in the right insula (BA 13) indicating that the music group had either more increased or less decreased grey matter volume in that particular area. Although the extent threshold of 100 voxels was not exceeded, this result might be of importance because the same area was detected when studying the RHD subjects.

Table 3: Regions showing more increased or less decreased grey matter volumes during the follow-up in the music group compared to the audio book group and the control group.

Change in the music group vs. change in the audio book group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, Insula (BA 13)	38, -10, 20	123	0.4299	0.0003	3.66

Change in the music group vs. change in the control group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, PrCG (BA 6)	60, 2, 22	486	0.0214	0.0001	4.03
R, Insula (BA 13)	42, 20, 6			0.0002	3.81
R, IFG (BA 44)	56, 8, 8			0.0003	3.67

R = right, IFG = Inferior Frontal Gyrus, PrCG = Precentral Gyrus

4.3 Changes in the three groups

The three groups were also investigated separately without the LHD-RHD subdivision to compare the changes occuring during the follow-up in each group to the changes found in the whole data set (presented in the subsection 4.1). Regions with decreased and increased grey matter volumes were identified using appropriate contrast vectors, and the results are presented in Tables 4 and 6. Figure 15 illustrates these regions.

All the three groups had decreased grey matter volumes in the frontal areas, but in the music group the frontal areas made up only 7% of the total decrease, whereas in the audio book group and in the control group the proportions were 36% and 100%, respectively. The music group and the audio book group had also decreased grey matter volumes in the sub-lobar areas: the music group bilaterally in the caudate, and the audio book group in the right insula and in the right caudate. Table 5 summarizes the relative decreases in the three groups.

From Table 5 we can see that the music group had decreased grey matter volumes also in the right temporal area. Minor decreases were detected in the left frontal lobe, in the right cerebellum, and in the hypothalamus. The audio book group, in contrast, showed decreases bilaterally in the frontal lobes and in the right sub-lobar areas, such as the insula and the caudate. Minor decreases could be seen in the parietal and temporal lobes.

Both the music and the audio book group showed major decreases in the sub-lobar areas. The music group had a voxel cluster constituting 67% of the total decrease in the caudate body in the middle of the brain, and, respectively, the audio book group had a large voxel cluster extending from the right insula to the caudate body and the precentral gyrus constituting 55% of the total decrease.

The music group had decreased grey matter volume in the left middle frontal gyrus (BA 6), whereas the audio book group showed decreased grey matter volumes

Table 4: The regions with decreased grey matter volumes in the music group, in the audio book group, and in the control group.

Decreased Grey Matter The Music Group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak** T
L, Caudate (Body)	-2, 10, 8	1081	0.0467	< 0.0001	4.50
R, Caudate (Body)	8, 2, 12			< 0.0001	4.31
L, MFG (BA 6)	-40, 18, 68	109	0.7394	0.0001	3.88
Hypothalamus	6, 2, -22	127	0.7394	0.0002	3.75
R, CT	62, -50, -48	119	0.7394	0.0002	3.73
R, MTG (BA 21)	80, -42, -6	186	0.7394	0.0002	3.73

Decreased Grey Matter The Audio Book Group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, Insula (BA 13)	36, -10, 16	17725	0.0049	< 0.0001	6.15
R, PrCG (BA 44)	68, 12, 0			< 0.0001	5.46
R, Caudate (Body)	6, 2, 10			< 0.0001	5.13
R, PCG (BA 3)	22, -24, 78	1540	0.0049	< 0.0001	5.18
R, PCG (BA 5)	34, -38, 72			< 0.0001	4.11
L, MeFG (BA 6)	2, -6, 72			0.0001	3.91
L, SFG (BA 6)	-2, 36, 68	822	0.1812	0.0001	4.03
R, MFG (BA 10)	34, 72, -2	219	0.3473	< 0.0001	4.11
R, SFG (BA 6)	20, 18, 74	163	0.3473	0.0001	3.92
L, PCG (BA 1)	-68, -20, 44	358	0.3473	0.0001	3.90
L, STG (BA 39)	-64, -66, 36	370	0.3473	0.0002	3.75
L, IPL (BA 40)	-50, -64, 78			0.0003	3.60
L, PCG (BA 5)	-20, -34, 78	174	0.3473	0.0002	3.62
L, PCG (BA 5)	-40, -36, 72			0.0009	3.21

Decreased Grey Matter The Control Group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, PrCG (BA 6)	68, -2, 28	6156	0.3050	< 0.0001	4.74
R, PrCG (BA 6)	64, 8, 44			< 0.0001	4.50
R, PrCG (BA 6)	72, 2, 16			< 0.0001	4.48
L, IFG (BA 9)	-68, 14, 18	229	0.6014	0.0002	3.73
R, IFG (BA 46)	56, 42, 2	101	0.6014	0.0006	3.36

L = left, R = right, CT = Cerebellar Tonsil, IFG = Inferior Frontal Gyrus, IPL = Inferior Parietal Lobule, MeFG = Medial Frontal Gyrus, MFG = Middle Frontal Gyrus, MTG = Middle Temporal Gyrus, PCG = Postcentral Gyrus, PrCG = Precentral Gyrus, SFG = Superior Frontal Gyrus, STG = Superior Temporal Gyrus

Table 5: Regions with decreased grey matter volumes in the three groups.

Brain Region	**Music Group**	**Audio Book Group**	**Control Group**
Cerebellum	119 (7%)	0 (0%)	0 (0%)
Frontal Lobe	109 (7%)	7626 (36%)	6486 (100%)
left	109 (100%)	1335 (18%)	229 (4%)
right	0 (0%)	6290 (82%)	6257 (96%)
Parietal Lobe	0 (0%)	1744 (8%)	0 (0%)
Sub-lobar	1081 (67%)	11817 (55%)	0 (0%)
Temporal Lobe	186 (11%)	185 (1%)	0 (0%)
Hypothalamus	127 (8%)	0 (0%)	0 (0%)
Total	1622 (100%)	12371 (100%)	6486 (100%)

both in the left (18%) and in the right hemisphere (82%): in the left medial frontal gyrus (BA 6), in the left and right superior frontal gyruses (BA 6), and in the right middle frontal gyrus (BA 10). The control group, in contrast, showed the same effect than the audio book group, only the respective percentages were 4% in the left and 96% in the right hemisphere the exact locations being the left and right inferior frontal gyruses (BAs 9 and 46) and the right precentral gyrus (BA 6).

In addition, the music group showed decrease in the right middle temporal gyrus (BA 21), whereas there was a decrease in the left superior temporal gyrus (BA 39) of the audio book group. These two groups showed also minor decreases in the cerebellum (the music group), in the parietal lobe (the audio book group), and in the hypothalamus (the music group).

From Table 6 we can see that the music group had major increases bilaterally in the frontal areas as well as in the left limbic and sub-lobar areas, whereas the audio book group showed increase bilaterally in the cerebellum and in the frontal areas. The control group, in contrast, had increased grey matter volumes bilaterally in the parietal areas and in the cerebellum as well as in the frontal areas. Table 7 shows the relative proportions of the different brain regions making up the total increase in the three groups.

All the three groups showed increased grey matter volumes during the follow-up in the frontal lobes. Still, it is noteworthy, that where in the music group the increase in the frontal areas made up 58% of the total increase, in the audio book group the proportion was only 25% and in the control group 18%.

In the music group, the increases in the frontal area were located mostly in the left inferior, middle, and medial frontal gyruses (BAs 11, 10, and 6), but also in the right medial frontal gyrus as well as in the right superior frontal gyrus (BAs 8, 6, 9, and 10). There was also increasing in the grey matter volume in the limbic lobe: mainly in the left parahippocampal gyrus (BAs 30 and 27) and in the left cingulate gyrus (BA 32) constituting altogether 18% of the total increase.

The audio book group had the most remarkable increase in grey matter volume

Table 6: The regions with increased grey matter volumes in the music group, in the audio book group, and in the control group.

Increased Grey Matter The Music Group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, IFG (BA 11)	-22, 24, -18	826	0.0533	< 0.0001	5.23
L, MFG (BA 10)	-28, 50, -12			< 0.0001	4.30
L, MeFG (BA 10)	-10, 40, -16			0.0004	3.47
L, PHG (BA 30)	-20, -40, -4	1024	0.0335	< 0.0001	5.11
L, PHG (BA 27)	-26, -32, -6			< 0.0001	4.66
L, Thalamus	-14, -30, -2			0.0001	3.98
L, MeFG (BA 6)	-10, 2, 58	2109	0.0031	< 0.0001	4.98
L, CG (BA 32)	-10, 32, 42			< 0.0001	4.98
L, MeFG (BA 6)	-10, -8, 54			< 0.0001	4.72
R, ISLL	26, -70, -42	400	0.2376	< 0.0001	4.73
R, MeFG (BA 8)	12, 32, 46	1686	0.0055	< 0.0001	4.56
R, MeFG (BA 6)	14, 36, 34			< 0.0001	4.45
R, MeFG (BA 9)	12, 48, 28			< 0.0001	4.31
R, FG (BA 37)	36, -42, -16	151	0.5819	< 0.0001	4.25
R, FG (BA 37)	32, -54, -10			0.0004	3.47
R, MeFG (BA 11)	8, 26, -20	255	0.3352	0.0001	4.04
R, SG	36, 50, -8	275	0.3352	0.0001	4.04
R, SFG (BA 10)	26, 56, -8			0.0003	3.60
R, Uvula	10, -74, -32	113	0.6519	0.0001	4.01
R, Precuneus (BA 31)	14, -56, 36	277	0.3352	0.0001	3.99
R, Precuneus (BA 7)	12, -52, 44			0.0001	3.99
L, ISLL	-22, -70, -44	394	0.2376	0.0001	3.98
L, CT	-22, -52, -52			0.0005	3.42
L, Declive	-16, -72, -8	106	0.6519	0.0004	3.50
L, LG (BA 18)	-16, -80, -4			0.0004	3.46

Increased Grey Matter The Audio Book Group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, CT	40, -60, -44	19555	< 0.0001	< 0.0001	6.89
R, ISLL	20, -74, -50			< 0.0001	6.75
L, Declive	-32, -90, -12			< 0.0001	6.68
L, MFG (BA 47)	-34, 44, -12	6441	< 0.0001	< 0.0001	6.48
R, MeFG (BA 25)	16, 24, -22			< 0.0001	5.63
L, MeFG (BA 10)	-10, 40, -22			< 0.0001	5.50
R, LG (BA 17)	12, -88, 4	555	0.0948	< 0.0001	4.51
R, Cuneus (BA 18)	8, -78, 24			< 0.0001	4.31
R, Precuneus (BA 31)	10, -60, 28	239	0.2841	< 0.0001	4.25
R, MeFG (BA 8)	14, 36, 36	353	0.1885	< 0.0001	4.13
R, MeFG (BA 8)	14, 28, 46			0.0001	4.02
R, MeFG (BA 9)	10, 52, 28			0.0004	3.50
R, Precuneus (BA 31)	12, -44, 42	157	0.3418	< 0.0001	4.11
R, Precuneus (BA 7)	12, -52, 50			0.0001	3.93
R, Precuneus (BA 7)	18, -58, 48			0.0003	3.59
R, Red Nucleus	4, -18, -18	169	0.3418	0.0001	4.02

Increased Grey Matter The Control Group	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, Precuneus (BA 7)	-16, -44, 44	311	0.5846	< 0.0001	4.37
R, Culmen	14, -50, -20	2580	0.0008	< 0.0001	4.34
R, CT	16, -56, -50			< 0.0001	4.14
R, Culmen	26, -54, -24			< 0.0001	4.06
R, Precuneus (BA 7)	14, -50, 50	1036	0.0464	< 0.0001	4.28
R, PCL (BA 5)	18, -28, 52			< 0.0001	4.14
L, AC (BA 32)	-14, 48, -12	188	0.5846	< 0.0001	4.09
L, IOG (BA 17)	-16, -98, -6	206	0.5846	< 0.0001	4.09
L, IOG (BA 17)	-10, -94, -2			0.0001	3.97
L, LG (BA 17)	-12, -92, 10			0.0004	3.49
L, Declive	-24, -76, -10	283	0.5846	0.0001	3.94
L, FG (BA 19)	-30, -82, -10			0.0001	3.87
L, MeFG (BA 10)	-14, 58, 4	145	0.6501	0.0001	3.81
L, MeFG (BA 10)	-10, 62, -6			0.0006	3.33
L, MeFG (BA 9)	-12, 52, 22			0.0007	3.27
L, SCG (BA 47)	-16, 20, -18	201	0.5846	0.0001	3.79
R, MeFG (BA 10)	14, 60, 0	178	0.5846	0.0001	3.77
R, MeFG (BA 10)	14, 54, -14			0.0004	3.44

L = left, R = right, AC = Anterior Cingulate, CG = Cingulate Gyrus, CT = Cerebellar Tonsil, FG = Fusiform Gyrus, IFG = Inferior Frontal Gyrus, IOG = Inferior Occipital Gyrus, ISLL = Inferior Semi-Lunar Lobule, LG = Lingual Gyrus, MeFG = Medial Frontal Gyrus, MFG = Middle Frontal Gyrus, PHG = Parahippocampal Gyrus, PCL = Paracentral Lobule, SCG = Subcallosal Gyrus, SFG = Superior Frontal Gyrus, SG = Sub-Gyral

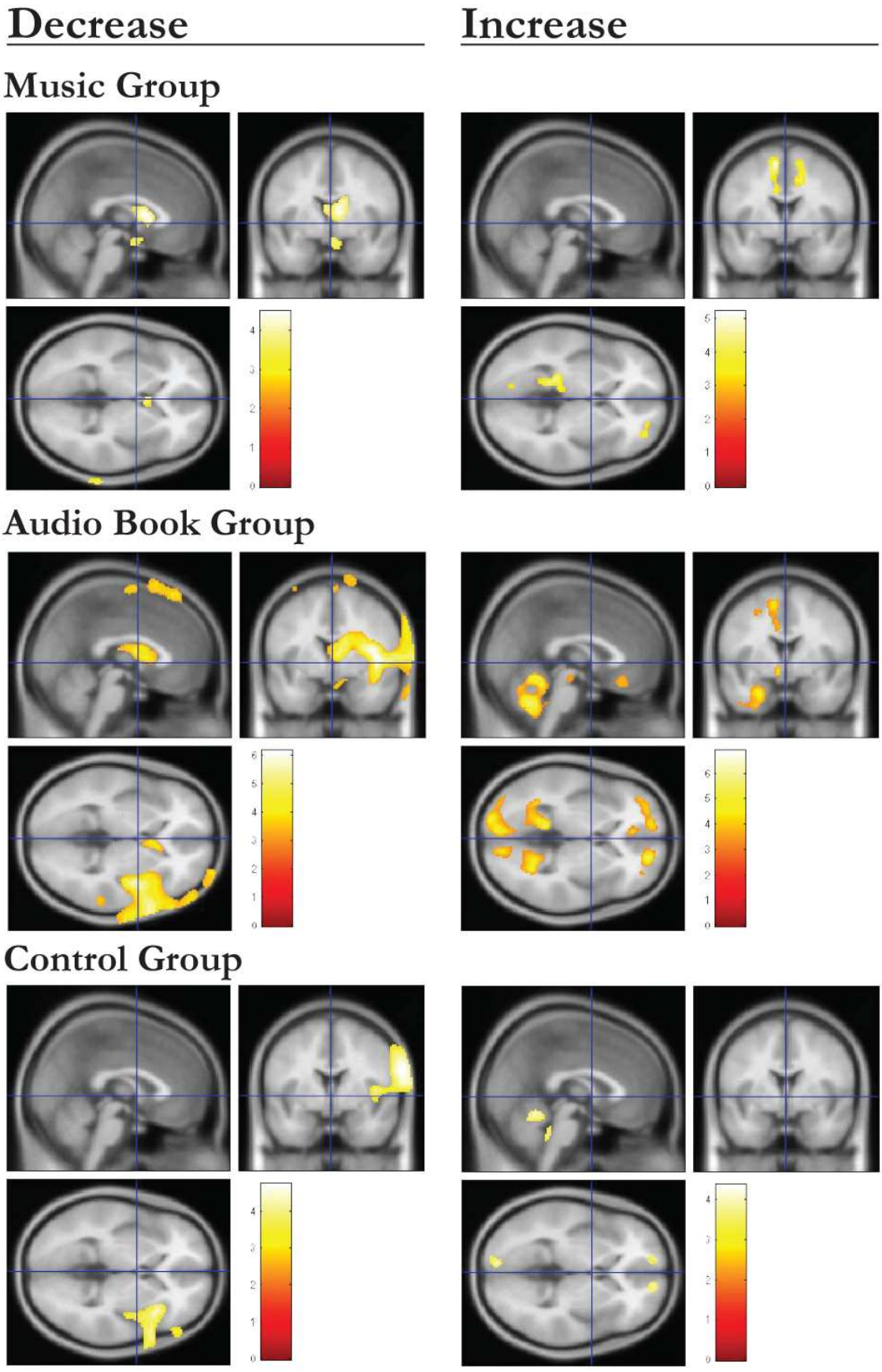

Figure 15: Regions with decreased and increased grey matter volumes in the music group, in the audio book group, and in the control group. The coloured bar indicates the T values.

Table 7: Regions with increased grey matter volumes in the three groups.

Brain Region	**Music Group**	**Audio Book Group**	**Control Group**
Cerebellum	960 (13%)	19555 (71%)	2722 (53%)
Frontal Lobe	4448 (58%)	6794 (25%)	942 (18%)
left	2232 (50%)	4294 (63%)	246 (26%)
right	2216 (50%)	2500 (37%)	696 (74%)
Limbic Lobe	1386 (18%)	0 (0%)	188 (4%)
Occipital Lobe	267 (4%)	555 (2%)	348 (7%)
Parietal Lobe	139 (2%)	396 (1%)	829 (16%)
Sub-lobar	341 (4%)	0 (0%)	101 (2%)
Temporal Lobe	76 (1%)	0 (0%)	0 (0%)
Midbrain	0 (0%)	169 (1%)	0 (0%)
Total	7616 (100%)	27469 (100%)	5128 (100%)

in the cerebellum (right cerebellar tonsil and inferior semi-lunar lobule as well as left declive) constituting as much as 71% of the total increase. Significant increases were also detected in the left and right middle and medial frontal gyruses (BAs 47, 25, and 10) as well as in the right medial frontal gyrus (BAs 8 and 9).

The control group showed major increases in the cerebellum (right culmen and cerebellar tonsil as well as left declive) and in the frontal lobe, to be exact, in the left and right medial frontal gyruses (BAs 10 and 9) and in the left subcallosal gyrus (BA 47), constituting 53% and 18% of the total increase, respectively.

All the three groups showed increase both in the left and right frontal lobes, but in the music group, the increase was evenly distributed through the two hemispheres. In contast, the audio book group showed more increase in the left than in the right hemisphere, and the control group had most of its frontal increase in the right hemisphere.

In summary, the three groups experienced different changes in the total amount of grey matter. The music group did not have decreased grey matter volumes in the right hemisphere at all, whereas both the audio book group and the control group showed decreased grey matter volumes mainly in the right hemisphere. In addition, the music group had regions with increased grey matter volumes in the limbic lobe unlike the two other groups. Furthermore, compared to the audio book and control groups, the music group had relatively more increase in the frontal lobes.

4.4 Correlation with test scores

Multiple regression model was used to see if there was any correlation between grey matter volume and neuropsychological test scores, which were obtained six months after the stroke. Test scores measuring verbal memory, focused attention, depression, and confusion were compared to the grey matter volumes to find out the possible

neural mechanisms promoting the recovery in the music group. In addition, MMNm responses measured six months after the stroke were correlated with the MR images. Table 8 shows the results of the multiple regressions.

Table 8: The regions correlating with neuropsychological test scores.

Verbal Memory (pos. correlation) **Brain Region**	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, IFG (BA 45)	-50, 22, 12	122	0.9128	< 0.0001	4.82

Focused Attention (pos. correlation) **Brain Region**	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, IFG (BA 47)	-46, 14, -14	711	0.1588	0.0001	4.07
L, Insula (BA 13)	-38, 16, 4			0.0001	3.92
L, Insula (BA 13)	-44, 4, -6			0.0002	3.91

MMNm Duration, right (pos. correlation) **Brain Region**	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, PCG (BA 40)	76, -16, 12	120	0.9129	0.0001	4.23

MMNm Frequency, right (neg. correlation) **Brain Region**	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, PHG (BA 36)	-34, -34, -18	294	0.2344	< 0.0001	4.39
L, Hippocampus	-30, -32, -8			0.0001	4.07

L = left, R = right, IFG = Inferior Frontal Gyrus, PHG = Parahippocampal Gyrus, PCG = Postcentral Gyrus

Positive correlation was found between the grey matter volume in the left inferior frontal gyrus (BA 45) and the verbal memory test scores. The same brain region extending from the left inferior frontal gyrus (BA 47) to the left insula (BA 13) was even more clearly positively correlated with focused attention test scores, as can be seen in Table 8. In both cases, no negative correlation was found. Experienced depression and confusion correlated with the grey matter volumes neither positively nor negatively. Figure 16 shows the brain regions correlating with verbal memory and focused attention.

As MMNm responses were previously found to increase significantly more in both the music and the audio book groups than in the control group during the follow-up [39], they were also correlated with the MR images. As can be seen in the Table 8, the amplitude of the right duration MMNm correlated positively with the grey matter volume in the right postcentral gyrus (BA 40). No negative correlation was found. The amplitude of the right frequency MMNm correlated, in contrast, negatively with the grey matter volume in the left parahippocampal gyrus (BA 36) and in the left hippocampus. No positive correlation was found. These correlations can be seen in Figure 17.

When comparing the changes in the test scores during the follow-up (six months minus one week), some correlations were again found. These correlations are presented in Table 9.

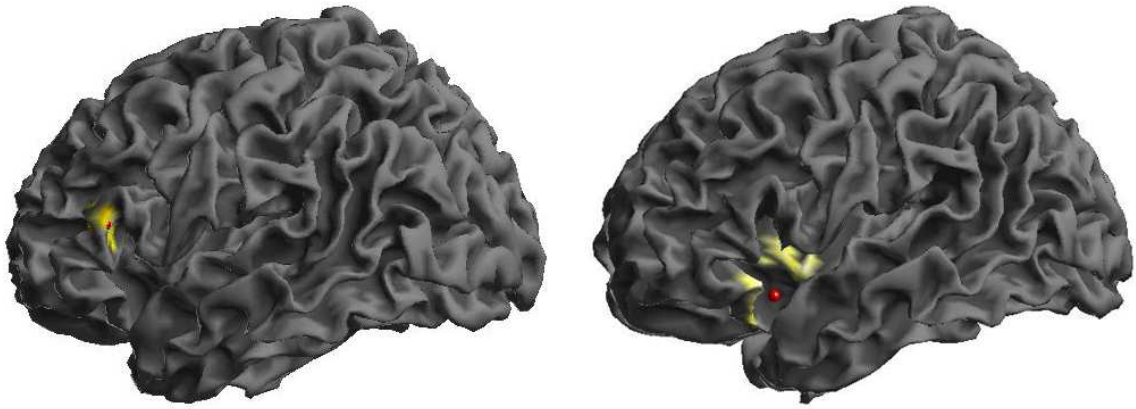

Figure 16: Brain regions showing positive correlation between verbal memory (left) and focused attention (right) scores and grey matter volume six months after stroke.

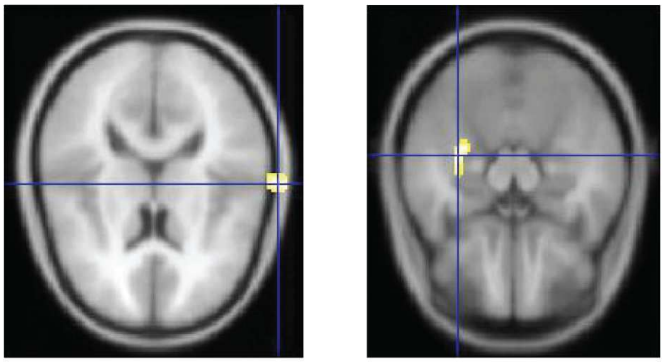

Figure 17: Grey matter volume correlates positively with the duration MMNm in the right postcentral gyrus (left) and negatively with the frequency MMNm in the left parahippocampal gyrus and in the left hippocampus (right).

From Table 9, a few clear results can be seen. First of all, the increase in the verbal memory test scores correlated positively with grey matter volume in the left caudate tail and in the left insula (BA 13). No negative correlation was found. Change in the focused attention scores, in contrast, had both positive and negative correlation with grey matter volume. Subjects with increased focused attention test scores had more grey matter in the right medial frontal gyrus (BA 32), in the left superior temporal gyrus (BA 39), in the left caudate tail, and in the left anterior cingulate (BA 32), whereas subjects with decreased focused attention test scores had more grey matter in the left middle frontal gyrus (BA 47). Figure 18 shows the regions where grey matter volumes correlated with improved verbal memory and focused attention test scores.

The change in the depression scores correlated negatively with the grey matter volumes in the left inferior frontal gyrus and in the left middle frontal gyrus (BA 10), in the right inferior frontal gyrus (BAs 10 and 47), and in the left cerebellar tonsil. This means that these regions correlated with reduced depression. No posi-

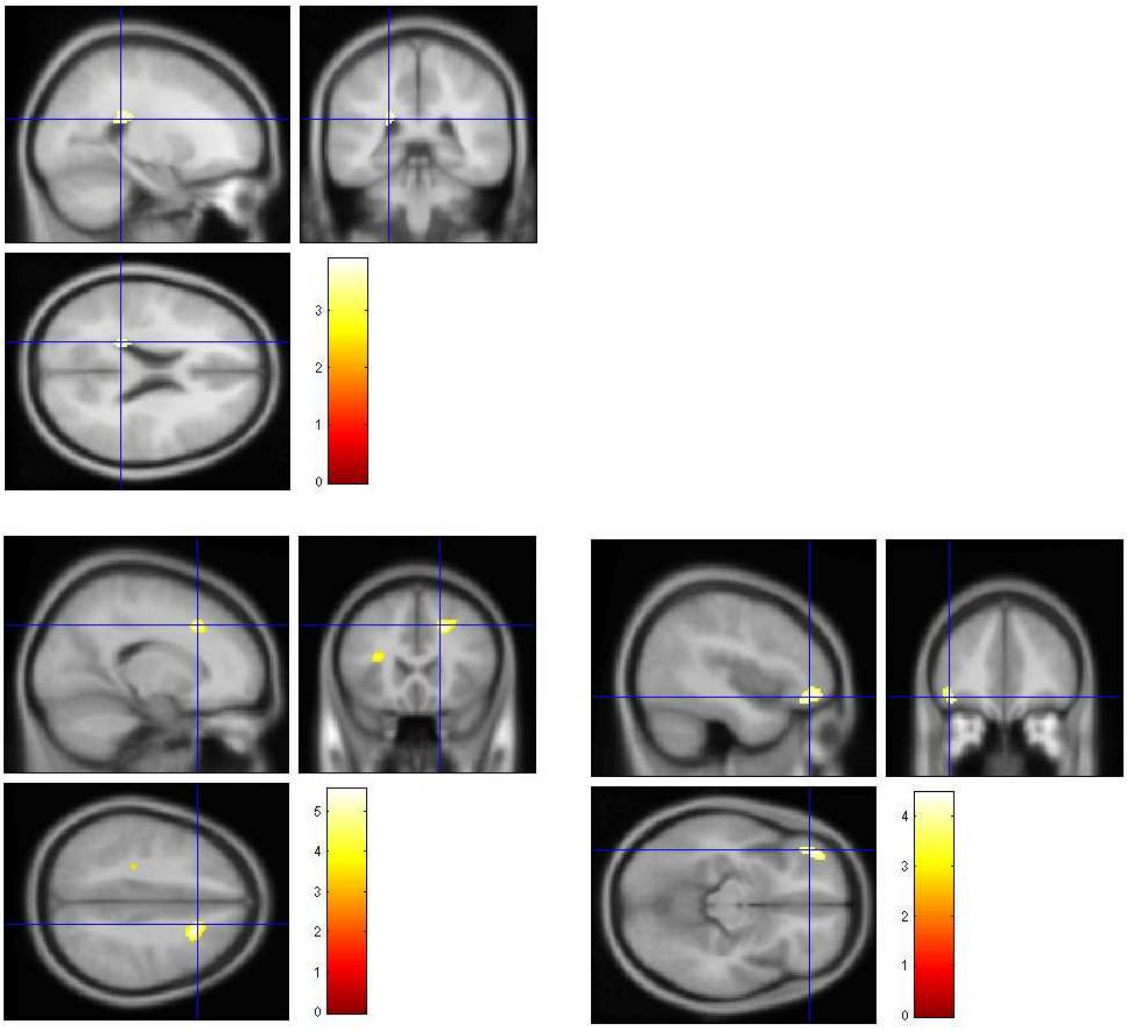

Figure 18: Grey matter correlating positively with the change in verbal memory test scores (top) and grey matter correlating positively (down, left) and negatively (down, right) with the change in focused attention test scores.

tive correlation was found. The change in confusion scores, in contrast, correlated positively with the grey matter volumes in the right nodule (in the cerebellum) and negatively in the left superior and inferior parietal lobules (BAs 7 and 40), in the left postcentral gyrus (BA 7), in the left inferior and middle frontal gyruses (BAs 10, 11, and 46), in the left superior occipital gyrus (BA 19), in the left precuneus (BA 39), in the left thalamus, in in the left cerebellar tonsil, and in the left cuneus (BA 18). Figure 19 illustrates the regions correlating with the change in the mood scores.

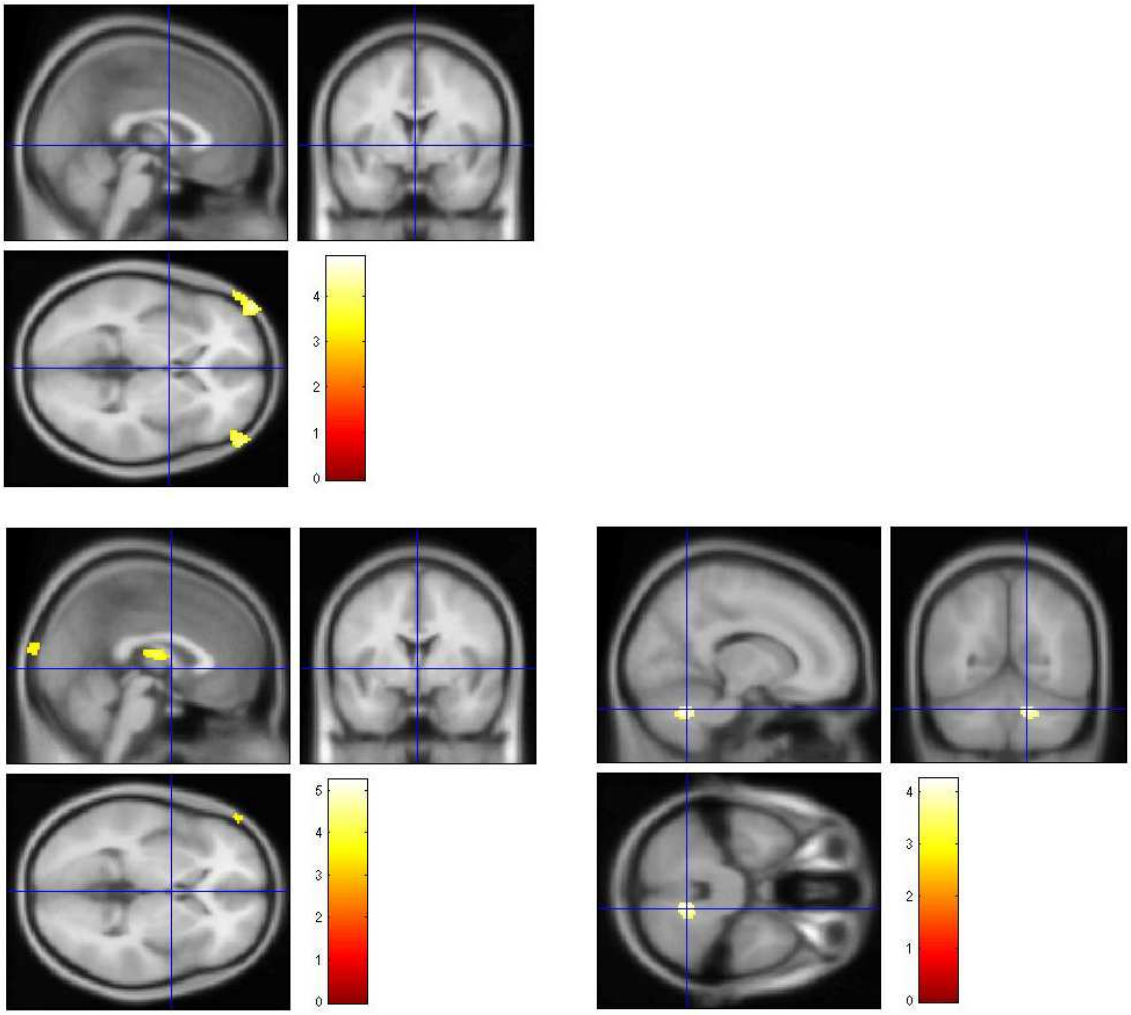

Figure 19: Grey matter correlating negatively with the change in depression scores during the follow-up (top) and grey matter correlating negatively (down, left) and positively (down, right) with the change in confusion scores.

Table 9: The regions correlating with changes in neuropsychological test scores.

Verbal Memory (pos. correlation) Brain Region	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, Caudate Tail	-22, -38, 22	127	0.8450	0.0002	3.89
L, Insula (BA 13)	-26, -26, 28			0.0008	3.34

Focused Attention (pos. correlation) Brain Region	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, MeFG (BA 32)	18, 22, 40	180	0.1999	< 0.0001	5.54
L, STG (BA 39)	-38, -52, 30	625	0.0516	< 0.0001	5.42
L, Caudate Tail	-26, -36, 20			0.0002	3.91
L, AC (BA 32)	-26, 38, 0	192	0.1999	< 0.0001	4.66

Focused Attention (neg. correlation) Brain Region	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, MFG (BA 47)	-42, 40, -12	143	0.5891	< 0.0001	4.48

Depression (neg. correlation) Brain Region	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, IFG (BA 10)	-58, 52, -12	414	0.9410	< 0.0001	4.86
L, MFG (BA 10)	-48, 64, -2			< 0.0001	4.36
R, IFG (BA 10)	56, 58, -8	500	0.2769	< 0.0001	4.55
R, IFG (BA 47)	54, 34, -24			0.0003	3.66
L, CT	-56, -54, -50	181	0.9410	0.0003	3.68

Confusion (pos. correlation) Brain Region	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
R, Nodule	14, -58, -32	140	0.9427	0.0001	4.25

Confusion (neg. correlation) Brain Region	**MNI Coordinates**	**cluster size**	**cluster p (FDR cor.)**	**peak p (unc.)**	**peak T**
L, SPL (BA 7)	-24, -60, 70	783	0.3208	< 0.0001	5.24
L, IPL (BA 40)	-42, -44, 66			0.0004	3.58
L, PCG (BA 7)	-24, -48, 78			0.0006	3.44
L, IFG (BA 10)	-58, 52, -10	243	0.9427	0.0000	4.57
L, MFG (BA 11)	-44, 50, -26			0.0004	3.58
L, MFG (BA 46)	-48, 62, -2			0.0009	3.32
L, SOG (BA 19)	-38, -76, 36	184	0.9427	< 0.0001	4.36
L, Precuneus (BA 39)	-42, -68, 40			0.0001	4.14
L, IPL (BA 7)	-38, -60, 52			0.0004	3.58
L, Thalamus	0, -12, 12	118	0.9427	0.0001	4.16
L, CT	-54, -52, -50	522	0.7493	0.0001	4.06
L, CT	-52, -54, -38			0.0002	3.91
L, Cuneus (BA 18)	-4, -102, 22	105	0.9427	0.0003	3.72

L = left, R = right, AC = Anterior Cingulate, CT = Cerebellar Tonsil, IFG = Inferior Frontal Gyrus, IPL = Inferior Parietal Lobule, MeFG = Medial Frontal Gyrus, MFG = Middle Frontal Gyrus, PCG = Postcentral Gyrus, SOG = Superior Occipital Gyrus, SPL = Superior Parietal Lobule, STG = Superior Temporal Gyrus

5 Discussion

In this thesis, structural grey matter changes induced by the sound environment after stroke were studied using voxel-based morphometry. Statistical design was created to identify regions with decreased and increased grey matter volumes from all of the subjects and separately for the music group, the audio book group, and the control group. In addition, a multiple regression model was created to study the correlation between grey matter volume and neuropsychological test scores, mood scores, and MMNm amplitudes.

The following discussion is divided into two subsections, first of which focuses on summarizing the main results of the study and suggesting future improvements in both experimental and clinical research, while the second one discusses critically the limitations and possible bias introduced into this study.

5.1 Summary

Our results indicate that after stroke there are major grey matter decreases occuring mostly in the right frontal and sub-lobar areas. A major decrease was in fact detected in the right Brodmann area 44, a region with functions linked to speech production, although usually it is thought that language functions are located mostly in the left hemisphere (left BA 44, the Broca's area).

In addition, decreased grey matter was detected in the Brodmann area 6, the premotor cortex. This was the case regardless of the group under study: all three groups experienced grey matter decrease in that particular area. However, only the music group had increased grey matter volume in Brodmann area 6. Thus, our results might suggest that listening to music when recovering from stroke prevents grey matter loss in the premotor area. Previously, Brodmann area 6 has been linked to auditory-motor interactions [55].

On the other hand, increased grey matter volumes were mainly detected bilaterally in the frontal areas as well as in the cerebellum and in the limbic lobe. The major increases were detected in the left hemisphere. The frontal areas are thought to be connected to language functions such as in selecting semantic information from among competing alternatives [56], whereas the limbic system plays a role in the formation of memories.

The three groups seemed, however, to differ from each other during the follow-up. Although there were no significant differences in the changes occuring during the follow-up between the study groups, when examining only RHD subjects, significant effects could be seen. These results suggest that the music group either had more increase or less decrease in the grey matter volume in the right insula, precentral gyrus and inferior frontal gyrus (BAs 13, 6, and 44). This effect was more evident when compared to the control group but it was detected when compared to the audio book group too. Since music is thought to evoke stronger responses in the right hemisphere (see for example [54]), it is natural that the RHD subjects benefitted from the music listening. Interestingly enough, the same region also emerged when comparing the changes in the three groups to each other without the LHD-RHD

subdivision. However, this effect was not statistically significant and there were notably less than 100 voxels in the cluster.

Although the role of the insula is not yet fully understood, recent studies have linked its activity to several key auditory processes, such as allocating auditory attention and tuning into novel auditory stimuli, temporal processing, phonological processing, and visual-auditory integration [57]. Thus, the improved recovery in the domains of verbal memory and focused attention in the music group could be related to structural changes in the insula. These structural changes, in this case, can mean two things: either the music group experienced more grey matter increase or less grey matter decrease compared to the other groups in this particular area.

The difference between the groups was also seen when examining the regions with decreased and increased grey matter volumes separately for the three groups. The music group suffered grey matter decrease mostly in the sub-lobar and temporal areas. The audio book group, in contrast, had regions with decreased grey matter volume mostly in the sub-lobar and frontal areas. The control group had decreased grey matter only in the frontal areas. However, it is possible, that the control group too had decreased grey matter volumes in other regions of the brain, but the changes in the frontal areas just were the most significant ones.

When it comes to grey matter increase, all three groups had increased grey matter volumes in the cerebellum and in the frontal areas. However, the music group was the only one with notable increase in the limbic area, whereas the control group had quite a large increase in grey matter volume in the parietal lobe. These results suggest that music listening can enhance grey matter increase in the limbic and frontal areas and possibly also prevent grey matter loss in the frontal area after stroke.

The multiple regressions used to study the relationship between the grey matter volume and neuropsychological test scores provided evidence supporting the results obtained previously: the subjects with more grey matter in the inferior frontal gyrus and in the insula had higher test scores in tests measuring verbal memory and focused attention. Previously, it was found that the music group achieved significantly higher scores in these tests than the audio book group and the control group [37].

In addition, changes in mood scores (depression and confusion) were correlated with grey matter volumes in certain areas: patients whose depression reduced strongly during the follow-up had larger grey matter volumes bilaterally in the inferior frontal gyruses. Similarly, patients with reduced confusion had larger grey matter volumes in the left inferior and middle frontal gyruses among other regions such as parietal and occipital areas.

5.1.1 Grey matter changes in the limbic lobes

While the processing of the acoustic features of music happens mostly in the temporal lobes as described in the beginning of this thesis, they also have effects on several other brain structures. In this study, it seems that the limbic lobe, that is, the emotional network including the amygdala, orbitofrontal cortex, and portions

of the basal ganglia [20], is greatly responsible for the increase of the grey matter in the music group. In fact, the limbic lobe alone was responsible of 18% of the total increase in the music group.

The grey matter increase in the limbic area is congruent with earlier studies regarding music and emotions. For example, Baumgartner et al. [58] found that fearful and sad pictures presented with congruent emotional musical excerpts increased activation in limbic structures such as the amygdala, the hippocampus, the parahippocampus, and the insula. Also Blood and Zatorre [59] detected activation caused by music in brain regions associated with motivation, emotion, and arousal, such as the ventral striatum, the midbrain, the amygdala, the orbitofrontal cortex, and ventral medial prefrontal cortex.

Thus, the findings of this study suggest that the improvement in the cognitive outcome as measured by neuropsychological tests might be due to the activation and neural plasticity in the limbic lobe triggered by listening to music. Since the audio book group did not show such a major increase in grey matter in the limbic lobe, it can be stated that the stimulation offered by music is more capable of promoting neural plasticity than simple auditory stimulation offered by narrated stories.

It has been suggested that that there is an association between changes in autonomic activity and the activity changes in the anterior cingulate cortex and the insular cortex [60]. Music too has been shown to be linked with these structures [60], although the activity changes in these brain structures are not necessarily related to emotional processing. However, the anterior cingulate cortex is involved in cognition, autonomic nervous system activity, motor activity, motivation, and monitoring, and can thus be indispensable for subjective emotional experiences [60].

Since it has been reported that the music group experienced less depressed and confused mood than the control group [37] and listening to music also seemed to promote relaxing, improve mood, and provide physical and mental activation [38], it can be suggested that the changes in the limbic lobe may be at least partly responsible for these effects.

5.1.2 Grey matter changes in the cortical areas

Considering the results obtained when studying the decreasing of the grey matter, two brain regions can be distinguished: the frontal and the sub-lobar areas. These two brain regions together were responsible for major part of the decreasing in all of the three groups. In the music group, the frontal lobe and the sub-lobar areas constituted 78% of the total decrease. In the audio book group and in the control group the percentages were 91% and 100% respectively.

In the frontal areas, the decrease in grey matter volumes occured mainly in the right hemisphere: in the audio book group 82% of the decrease in the frontal areas was right hemisphere lateralized, and in the control group, the corresponding proportion was 96%. However, in the music group, there was only a minor decrease in the left middle frontal gyrus while no decrease at all was detected in the right hemisphere.

All the three groups had increased grey matter volumes both in the left (50%

for the music group, 63% for the audio book group, and 26% for the control group) and in the right frontal lobe (50%, 37%, and 74%, respectively). Thus, it can be concluded that the music group actually increased grey matter equally in both hemispheres. The audio book group seemed to increase grey matter mostly in the left hemisphere, which is congruent with previous studies suggesting the left-lateralized nature of language functions.

In fact, neuroimaging studies have shown that listening to music involves a widespread, mostly bilateral network in the brain [60], while listening to narrated stories activates a more left-lateralized and cortically located network [61]. This view was supported by this thesis: the music group experienced grey matter increase bilaterally, whereas the audio book group had more increase in grey matter in the left hemisphere.

Since the human frontal cortex occupies almost one-third of the entire cerebral cortical surface [62], it is not surprising that most of the changes were located in the frontal lobes in all of the three groups. Still, the frontal lobes are associated with many processes related to stroke recovery, such as personality changes, verbal and motor skills, lower-extremity weakness, sensory loss, cognitive and social skills, and emotional lability [62]. Thus the changes in the grey matter volume in the frontal lobes could explain at least partly the music group's better cognitive outcome during the follow-up.

One of the most curious results of this study was that neither music nor audio book listening actually increased grey matter volume in the auditory cortices, that is, in the temporal lobes. In the future, VBM studies investigating neural plasticity induced by sound environment after stroke could be restricted in specific regions of interest, for example in the frontal, the temporal, the limbic, and the sub-lobar areas.

5.1.3 Grey matter volumes correlating with neuropsychological tests

Previously, it has been reported that the recovery in the domains of focused attention and verbal memory improved significantly more in the music group than in the audio book and control groups [37]. In this thesis, the focused attention scores six months after stroke were found to positively correlate with grey matter volume in the left frontal areas. Not surprisingly, the frontal areas also showed relatively more grey matter increase in the music group than in the audio book and the control groups. Thus, it seems that the better test scores could be due to larger increase or smaller decrease in grey matter volume in the frontal areas.

Also verbal memory scores correlated positively with grey matter volume in the left frontal areas. It can thus be stated, that the music group had increased grey matter volumes and improved test scores, and most presumably, these positive effects result from the intervention. However, it is not clear, how this increasing actually happens and if there are other factors facilitating it than music.

5.1.4 Future research and clinical significance

In the future, it would be interesting to investigate grey matter changes more specifically in a homogeneous group of subjects. It would be preferable that the subjects had their lesion in the same hemisphere, and even better would be if the lesion was restricted to the temporal or frontal areas. Still, the most important thing would be to collect as much data as possible: although this study provided some important knowledge about the structural grey matter changes, the results would be more reliable with more subjects participating in the study.

In addition to neuropsychological tests, tests measuring motor activity and skills could shed more light on the changes occuring in the brain and their effects on the everyday life of the stroke patients. Since there were grey matter changes in the cerebellum detected in all of the three groups and cerebellar dysfunctions often result in motor-related problems, it would be interesting to find out if these changes were associated with improvment or deterioration of motor skills. In addition, music listening has been observed to increase motor activity in stroke patients [38], and therefore it could be hypothesised that listening to music might also improve motor skills after stroke.

To investigate in detail the effects of listening to music on the mood of the stroke patients, the levels of different neural transmitters and neuroendocrine markers (e.g., cortisol) could be measured and correlated with the grey matter changes in different groups. Since there are connections between autonomic nervous system and certain brain areas activated by music, a more detailed view about the causality and origin of plasticity could be constructed. In fact, it has already been suggested that, in the long run, daily listening to music could promote cognitive recovery by preventing depression [63].

Another interesting topic worth examining could be the grey matter changes induced by active music therapy compared to those induced by passive music listening. This approach could shed some more light on the field of music therapy and its neural effects. In addition, a community-based intervention with rhythmic music and specialized rehabilitation movement, as already designed by Jeong et al. [64] combined with structural imaging and VBM analysis could be of great interest.

Although there are no waterproof evidence of the beneficial, structural changes in the brain caused by music listening, it can certainly be said to have no negative effects. Thus, listening to music should be encouraged especially during the first weeks after the stroke while the brain is going through major plastic changes. Music listening is easily arranged since it does not require the attention of the nursing staff and creates no disruption to other patients possibly accomodated in the same room if headphones are used. In addition, music listening is an affordable means of offering pleasurable experiences to patients who might have difficulties in enjoying their lives after the dramatic turn of events, which stroke most certainly brings about for most patients.

5.2 Limitations

The most important limitation of this study is definitely the quite small sample size. Because of the drop-outs, there were only 51 subjects who completed the study, and as these subjects were divided into three groups, the final group size was only 16 for the music and the control groups and 19 for the audio book group. While important results were obtained using these subjects, statistically more significant results would have required more subjects. Still, it is important to keep in mind, that in order to have a large sample ($n > 100$), one would have to use considerably more time and effort.

The MR images used in this study were generally speaking of good quality, but there were a couple of images clearly disturbed by motion artefact. This has to do with another restriction of the study arrangement: while it is important to get subjects with both small and large lesions to participate in the study, it is crucial that the subject can understand the instructions and the aims of the study and is able to, for example, lay still during the imaging sessions. On the other hand, very small lesions do not offer interesting data to the study.

Regarding the VBM analysis, some things have to be taken into consideration. Firstly, it is important to check that the groups are comparable: if there is, for example, significant difference in the size of the ventricles between the two groups, this structural, non-volumetric difference can be misinterpreted as volumetric [50, 65]. In this study, a so-called optimised VBM, an iterative process between segmentation and normalization was used to avoid misinterpretation, and modulation was used to preserve the actual grey matter volume during the normalization.

After unified normalization (model for tissue classification, bias correction, and image registration within the same generative model [66]) being introduced into SPM, it has been argued whether or not cost function masking should be used in normalization of lesioned brains. In 2007, Crinion et al. [67] suggested that the normalization produced by unified segmentation resulted in significantly better results compared to standard normalization with cost function masking. However, their data were MR images from ten neurologically normal participants with simulated lesions, so the results may not be generalized to stroke patients with large, extensive lesions.

In this thesis, cost function masking was used to assure better segmentation results, but in the future, it would be of great importance to find out if it really is necessary. The time required to draw lesion masks was quite notable, and therefore skipping the masking stage would make the analysis more efficient. In addition, the drawing of the lesion masks was not always unambiguous: the borders of the lesioned area could still be poorly distinguishable after six months.

Despite of its restrictions, this study provides us important information of the neural plasticity occuring in the brain after stroke. As we do not know for sure what is happening in the brain on cellular level, at least we know that no harm can be done by providing the brain with pleasurable stimuli after stroke. As Hercule Poirot, a famous yet imaginary Belgian detective frequently points out, "The little grey cells, they need exercise".

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