Music in the recovering brain

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Academic dissertation to be publicly discussed,
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at the University of Helsinki in the Auditorium of the Helsinki University Museum
Arppeanum, Snellmaninkatu 3,
on the 18th of March, 2011, at 12 o'clock

University of Helsinki
Institute of Behavioural Sciences
Studies in Psychology 76: 2011

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ISSN-L 1798-842X
ISSN 1798-842X
ISBN 978-952-10-6831-7 (pbk.)
ISBN 978-952-10-6832-4 (PDF)
http://www.ethesis.helsinki.fi
Unigrafia
Helsinki 2011

Contents

Abstract

Listening to music involves a widely distributed bilateral network of brain regions that controls many auditory perceptual, cognitive, emotional, and motor functions. Exposure to music can also temporarily improve mood, reduce stress, and enhance cognitive performance as well as promote neural plasticity. However, very little is currently known about the relationship between music perception and auditory and cognitive processes or about the potential therapeutic effects of listening to music after neural damage. This thesis explores the interplay of auditory, cognitive, and emotional factors related to music processing after a middle cerebral artery (MCA) stroke. In the acute recovery phase, 60 MCA stroke patients were randomly assigned to a music listening group, an audio book listening group, or a control group. All patients underwent neuropsychological assessments, magnetoencephalography (MEG) measurements, and magnetic resonance imaging (MRI) scans repeatedly during a six-month post-stroke period. The results revealed that amusia, a deficit of music perception, is a common and persistent deficit after a stroke, especially if the stroke affects the frontal and temporal brain areas in the right hemisphere. Amusia is clearly associated with deficits in both auditory encoding, as indicated by the magnetic mismatch negativity (MMNm) response, and domain-general cognitive processes, such as attention, working memory, and executive functions. Furthermore, both music and audio book listening increased the MMNm, whereas only music listening improved the recovery of verbal memory and focused attention as well as prevented a depressed and confused mood during the first post-stroke months. These findings indicate a close link between musical, auditory, and cognitive processes in the brain. Importantly, they also encourage the use of listening to music as a rehabilitative leisure activity after a stroke and suggest that the auditory environment can induce long-term plastic changes in the recovering brain.

Tiivistelmä

Musiikin kuuntelu aktivoi aivoissa laajaa, molemmille aivopuoliskoille ulottuvaa hermoverkkoa, joka säätelee useita auditiivisia, kognitiivisia, emotionaalisia sekä motorisia toimintoja. Musiikki voi hetkellisesti kohentaa mielialaa, vähentää stressiä ja tehostaa kognitiivista suoriutumista sekä myös saada aivoissa aikaan neuroplastisia muutoksia. Vielä ei kuitenkaan tiedetä, miten musiikin havaitseminen liittyy muihin auditiivisiin ja kognitiivisiin toimintoihin ja voiko musiikin kuuntelulla olla positiivisia vaikutuksia kuntoutumiseen aivovaurion jälkeen. Tässä väitöskirjassa tutkittiin auditiivisten, kognitiivisten ja emotionaalisten tekijöiden yhteyttä musiikin käsittelyyn keskimmäisen aivovaltimon (MCA) akuutin aivoinfarktin jälkeen. Tutkimukseen osallistui 60 aivoinfarktiin sairastunutta potilasta, jotka jaettiin satunnaistetusti musiikin kuunteluryhmään, äänikirjojen kuunteluryhmään ja verrokkiryhmään. Kaikille potilaille tehtiin neuropsykologiset tutkimukset sekä aivojen magnetoenkefalografiamittaukset (MEG) ja magneettikuvaukset (MRI) toistetusti kuuden kuukauden seuranta-ajan kuluessa. Tulokset osoittivat, että amusia, musiikin havaitsemisen vaikeus, on yleinen ja usein pysyvä häiriö aivoinfarktin jälkeen, erityisesti jos vaurio on oikean aivopuoliskon ohimo- tai otsalohkolla. Amusia on myös selvästi yhteydessä häiriöihin varhaisessa kuuloinformaation käsittelyssä, jota mitattiin ns. poikkeavuusvasteella (MMNm), sekä yleisissä kognitiivisissa toiminnoissa, kuten tarkkaavaisuuden säätelyssä, työmuistissa ja toiminnanohjauksessa. Sekä musiikin että äänikirjojen päivittäinen kuuntelu voimisti MMNm-vastetta, kun taas ainoastaan musiikin kuuntelu paransi kielellisen muistin ja tarkkaavaisuuden suuntaamisen toipumista sekä ehkäisi masentuneisuutta ja sekavuutta ensimmäisten aivoinfarktin jälkeisten kuukausien aikana. Tulokset viittaavat siihen, että musiikilliset, auditiiviset ja kognitiiviset toiminnot ovat aivoissa läheisesti kytköksissä toisiinsa. Mikä tärkeintä, tulokset myös kannustavat musiikin kuuntelun käyttöön kuntouttavana vapaa-ajantoimintona aivoinfarktin jälkeen sekä osoittavat, että ääniympäristön virikkeet voivat saada aikaan pitkäkestoisia plastisia muutoksia toipuvissa aivoissa.

Acknowledgements

This study is the fruit of a joined collaborative effort between the Cognitive Brain Research Unit (CBRU) at the Institute of Behavioural Sciences (IBS), University of Helsinki; the Departments of Neurology and Radiology and the BioMag laboratory at the Helsinki University Central Hospital (HUCH); and the Department of Music at the University of Jyväskylä. Over the years, I have been lucky and privileged to work with and be guided by several talented, competent, and wonderful people.

I am deeply grateful to my supervisors Professor Mari Tervaniemi and Docent Marja Hietanen for their guidance, advice, and support for my work. My heartfelt thanks to Mari for providing me the opportunity to take part in an exciting and challenging research project, for being the solid bedrock who encouraged and motivated me to complete it, for sparking my interest in the neuroscience of music, and for her continuous warm support, trust, and friendship over the years. I warmly thank Marja for sharing her expertise in clinical neuropsychology, which helped immensely in designing the study, as well as for her cheery encouragement, understanding, and mentoring throughout this PhD. I extend my appreciation to Professors Teija Kujala, Risto Näätänen, and Petri Toiviainen and Docent Minna Huotilainen for their encouragement and advice as well as for creating such a supporting research environment at the CBRU and at the Finnish Centre of Excellence in Interdisciplinary Music Research (FCoEIMR).

This study would not have been possible without the expertise, dedication, and hard work of the members of the MUKU team. My warmest appreciation goes to Sari Laitinen and Anita Forsblom for making the idea a reality by implementing the music and audio book intervention with warmth, care, and lot of personal effort; Mikko Mikkonen for his supportive friendship, insight, and enormous help in recruiting the patients and performing a part of the neuropsychological assessments and MEG measurements; Professor Seppo Soinila for his enthusiasm, neurological expertise, and precious help in recruiting the patients; Docent Elina Pihko for training me to use MEG and helping immensely in analyzing and reporting the MEG data; Docent Taina Autti and Heli Silvennoinen for their invaluable work with the MRI data; and Professors Jaakko Erkkilä, Matti Laine, and Isabelle Peretz for their important contributions in designing and reporting the study.

I am grateful to the staffs of the BioMag laboratory, especially Docent Jyrki Mäkelä, Suvi Heikkilä, and Jussi Nurminen, and the HUCH Department of Radiology, especially Pentti Pölönen, for their help and technical assistance. I am most indebted also to the staffs of the HUCH Department of Neurology and other rehabilitation hospitals in the Helsinki metropolitan area for their help and collaboration as well as to the stroke patients and their families for having the will and energy to take part in the study during a very hard and straining time in their lives. The financial support from the Academy of Finland, the Jenny and Antti Wihuri Foundation, the Finnish Graduate School of Psychology, and the Finnish Brain Foundation is gratefully acknowledged.

I was very fortunate to receive reviews of my thesis from two esteemed experts in the field of music and neuroscience, Professors Eckart Altenmüller and Gottfried Schlaug, and I am grateful for their positive and encouraging evaluations. I thank also Dr. Glenda Dawn Goss for her fine work on the language revision of the thesis.

I count myself lucky to have been supported, spurred, and entertained by many wonderful friends throughout the preparation of the thesis. My warmest thanks especially to Perttu Immonen, Viljami Salmela, Ville Villberg, Kia Aarnio, Hanna Jokinen-Salmela, Toni Saarela, Maria Olkkonen, and Tuukka Mehtälä for their friendship, for all the insightful discussions about life and science as well as for all the fun, memorable times over the years. I am also grateful for the companionship, encouragement, and aid of my colleagues at the CBRU and FCoEIMR, especially Esa Ala-Ruona, Docent Elvira Brattico, Professor Tuomas Eerola, Jörg Fachner, Eva Istok, Kaisu Krohn, Vera Leo, Riikka Lindström, Riikka Lovio, Clemens Maidhof, Riia Milovanov, Satu Pakarinen, Eino Partanen, Marko Punkanen, Vesa Putkinen, Suvi Saarikallio, Miia Seppänen, Veerle Simoens, Marc Thompson, Ritva Torppa, Henna Vepsäläinen, and Sari Ylinen. I thank also Professor Jussi Saarinen and my colleagues at the IBS for creating a motivating and pleasant working environment and especially Marja Junnonaho, Piiu Lehmus, Riitta Salminen, Miika Leminen, and Tommi Makkonen for their important administrative and technical assistance.

A special thanks to Docents Laura Hokkanen and Hely Kalska and Professor Kimmo Alho at IBS from whom I have learned a great deal about neuropsychology and science and who have always inspired and spurred me on my academic path.

I express my special gratitude to my father Jyrki and his wife Barbro, my sister Terhi and her family, my in-laws Hannele and Lasse as well as my sister-in-law Miia and brother-in-law Antti and their families for their continuous encouragement, understanding, and help. With longing and loving memory, I dedicate this thesis to my mother Oili (1948-1999) whose warmth, support, and example have guided me throughout life. Finally, I owe my deepest gratitude to my family: my wife Essi-Reetta for all her love, care, and understanding, which has given me strength, and to our wonderful sons Eero and Kaapo for bringing me endless joy and happiness and for showing me what is truly important in life.

Helsinki, February 2011

Teppo Särkämö

List of original publications

This thesis is based on the following original publications, referred to in the text by Roman numerals (I-V).

I Särkämö, T., Tervaniemi, M., Soinila, S., Autti, T., Silvennoinen, H. M., Laine, M., & Hietanen, M. (2009). Amusia and cognitive deficits after stroke: Is there a relationship? *Annals of the New York Academy of Sciences, 1169*, 441-445.

II Särkämö, T., Tervaniemi, M., Soinila, S., Autti, T., Silvennoinen, H. M., Laine, M., & Hietanen, M. (2009). Cognitive deficits associated with acquired amusia after stroke: A neuropsychological follow-up study. *Neuropsychologia, 47*, 2642-2651.

III Särkämö, T., Tervaniemi, M., Soinila, S., Autti, T., Silvennoinen, H. M., Laine, M., Hietanen, M., & Pihko, E. (2010). Auditory and cognitive deficits associated with acquired amusia after stroke: A magnetoencephalography and neuropsychological follow-up study. *PLoS ONE, 5*, e15157.

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

V Särkämö, T., Pihko, E., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., Autti, T., Silvennoinen, H. M., Erkkilä, J., Laine, M., Peretz, I., Hietanen, M., & Tervaniemi, M. (2010). Music and speech listening enhance the recovery of early sensory processing after stroke. *Journal of Cognitive Neuroscience, 22*, 2716-2727.

Abbreviations

AC	auditory cortex
ANOVA	analysis of variance
BDAE	Boston Diagnostic Aphasia Examination
BVRT	Benton Visual Retention Test
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CS	CogniSpeed© reaction time software
DA	dopamine
EE	enriched environment
EEG	electroencephalography
EOG	electro-oculogram
ERP	event-related potential
FAB	Frontal Assessment Battery
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
HUCH	Helsinki University Central Hospital
HSD	Tukey's Honestly Significant Difference test
IFG	inferior frontal gyrus
LHD	left hemisphere damage
LSD	Fisher's Least Significant Difference test
MBEA	Montreal Battery of Evaluation of Amusia
MCA	middle cerebral artery
MCE	Minimum Current Estimation
MEG	magnetoencephalography
MIT	Melodic Intonation Therapy
MMN	mismatch negativity
MMNm	magnetic mismatch negativity
MRI	magnetic resonance imaging
NAc	nucleus accumbens
NMDA	N-methyl-D-aspartate
POMS	Profile of Mood States
RCT	randomised controlled trial
ROI	region of interest
PET	positron emission tomography
QOL	quality of life
RBMT	Rivermead Behavioural Memory Test
RHD	right hemisphere damage
RAS	Rhythmic Auditory Stimulation
RT	reaction time
SAQOL	Stroke and Aphasia Quality of Life
SD	standard deviation
SEM	standard error of the mean
VTA	ventral tegmental area
WMS-R	Wechsler Memory Scale – Revised

1 Introduction

1.1 Stroke

A stroke is caused by a disruption of the blood supply to the brain, resulting from either blockage (an ischemic stroke) or rupture (a haemorrhagic stroke) of a blood vessel, which cuts off the supply of oxygen and nutrients to the brain tissue and causes permanent damage. Approximately 70–80 per cent of all stroke cases are caused by an ischemic brain infarction (Feigin et al., 2009), most often in the areas supplied by the middle cerebral artery (MCA) (Ng et al. 2007). According to a recent systematic review of 56 population-based studies (Feigin et al., 2009), approximately 80 out of 100,000 persons worldwide suffer an ischemic stroke each year. In Finland, there were 17,000 cases of ischemic stroke in the adult population in 2007 (Kansanterveyslaitos, 2007). Globally, it has been estimated that roughly one-third of stroke patients die and one-third are left permanently disabled due to the physical, emotional, cognitive, and social impairment caused by the stroke (Mackay & Mensah, 2004). Many stroke patients who regain their functional independence still continue to experience physical, emotional, and social deficits months after the stroke (Lai et al., 2002), leading to clearly reduced quality of life (QOL) (Carod-Artal & Edigo, 2009).

Although improvements in prevention have led to a decline in stroke incidence in many developed countries (Feigin et al., 2009), the incidence of stroke in Europe is expected to increase by as much as 30 per cent between 2000 and 2025 owing to the ageing of the population and other demographic changes (Truelsen et al., 2006). Also the World Health Organization (WHO) predicts that the disability-adjusted life years lost to stroke will rise from 38 million in 1990 to 61 million in 2020 (Mackay & Mensah, 2004), almost doubling the burden on the society caused by the disease. Overall, stroke is an enormous physical and emotional affliction on the patient as well as an increasing social and economic burden for society, making it a major global public health issue now and in years to come.

1.1.1 Cognitive and emotional consequences of strokes

In addition to motor deficits, which affect approximately 80 per cent of stroke patients (Rathore et al., 2002), cognitive dysfunction is a common consequence (Hochstenbach et al., 1998; Nys et al., 2007; Rasquin et al., 2002; Tatemichi et al., 1994). Evidence from large neuropsychological group studies, which have compared stroke patients to matched control subjects, indicates that during the first post-stroke month approximately 50 per cent of patients with an ischemic stroke show signs of impairment in one or more cognitive domains, most often in attention and executive functioning (39–50%), visuospatial cognition (31–38%), language (26%), reasoning (26%), and memory (22–26%) (Nys et al., 2005, 2007; Rasquin et al., 2002). The number of impaired cognitive domains has been shown to decrease during the first ten months of recovery (Nys et al., 2005). Yet, three to ten months after a stroke, a considerable percentage of patients still suffer from deficits in attention and executive functioning (13–39%), visuospatial cognition (9–35%), language (15–36%), reasoning (18%), and memory (8–20%) (Hochstenbach et al., 1998; Nys et al., 2005; Rasquin et al., 2002; Tatemichi et al., 1994).

Suffering an acute stroke is a dramatic experience, which is often characterized by feelings of extreme shock, fear, uncertainty, and loss of control (Hafsteinsdottir & Grypdonck, 1997). During the first days after a stroke, patients typically exhibit strong and varying emotional reactions, including sadness, disinhibition, lack of adaptation, environmental withdrawal, crying, being unaware of the impairment caused by the stroke (anosognosia), passivity, and aggressiveness (Bogousslavsky, 2003). Emotional and behavioural disturbances are also frequent after the acute stage in stroke survivors (Ferro et al., 2009). According to a recent meta-analysis of 51 studies, post-stroke depression affects approximately 33 per cent of stroke patients (Hackett et al., 2005). In a Finnish longitudinal study of 100 stroke patients (Berg et al., 2003), 29 per cent of the patients suffered from at least minor depression during the first two post-stroke months, and 46 per cent also continued to be depressed 18 months post-stroke, suggesting that symptoms of depression are frequent and often have a chronic course. Another typical emotional complaint after a stroke is fatigue, which is experienced by 29–68 per cent of stroke patients (Annoni et al., 2008). Other, slightly less common neuropsychiatric

symptoms, which can often accompany depression, include anxiety, posttraumatic stress, personality changes (e.g., apathy), and disorders of emotional expression control (Ferro et al., 2009).

1.1.2 Stroke recovery and the environment

In most stroke patients, some degree of spontaneous behavioural recovery is usually seen in the first weeks and months after the stroke. Converging evidence from animal and human studies indicates that most spontaneous recovery tends to occur within the first three months after stroke onset, although cognitive deficits can show spontaneous gains beyond the three-month post-stroke stage (Cramer, 2008). Experimental animal studies have demonstrated that a brain infarct is associated with a number of plastic growth-related events, including structural changes in axons, dendrites, and synapses; increased activation and migration of neural stem cells; and changes in the extracellular matrix, glia cells, and blood vessels (Carmichael, 2006; Cramer, 2008; Komitova et al., 2006). In the human brain, functional recovery after stroke correlates with a remapping of the cognitive operations in areas surrounding the infarct as well as in the contralesional hemisphere and other remote regions connected to the lesion site. Within these regions, axons sprout new connections and establish novel projection patterns, and newly-born immature neurons migrate into areas of damage (Carmichael, 2006), leading to increased neural activity. During recovery, the brain becomes more excitable, for example, showing increased N-methyl-D-aspartate (NMDA) receptor binding (Que et al., 1999), γ-aminobutyric acid (GABA) receptor downregulation (Redecker et al., 2002), and increased growth factor levels (Finklestein et al., 1990). Crucially, the brain also becomes more susceptible to environmental influence.

The environment in which recovery takes place has a major influence on the outcome after a stroke (Johansson, 2004; Nithianantharajah & Hannan, 2006). Animal studies have shown that housing animals after an ischemic stroke in an enriched environment (EE), which provides motor and cognitive stimulation, improves the functional recovery of motor and cognitive skills, decreases infarct volume, and increases dendritic spine density, neurotrophic factor levels, stem cell proliferation, and neurogenesis (Biernaskie

& Corbett, 2001; Dahlqvist et al., 1999, 2004; Gobbo & O'Mara, 2004; Hicks et al., 2002; Johansson, 1996; Johansson & Belichenko, 2002; Komitova et al., 2002, 2005; Risedal et al., 2002). Interestingly, adding multimodal stimulation (e.g., auditory, visual, and olfactory stimuli) to the standard EE has been shown to reduce lesion volume as well as enhance motor and cognitive recovery more than the standard EE alone (Maegele et al., 2005a, 2005b). Thus, environmental stimuli play an important role in shaping the brain after neural damage.

In human stroke patients, most of the evidence supporting the therapeutic role of the environment on stroke recovery comes from studies that have assessed the effectiveness of specialized stroke units (Stroke Unit Trialists' Collaboration, 2007) or specific stroke rehabilitation methods targeted for motor (Langhorne et al., 2009), speech (Bhogal et al., 2003), and cognitive functions (Cicerone et al., 2005). However, owing to their low supply and high cost, these rehabilitation services are usually not available for most stroke patients or they are provided too late or in insufficient quantity to meet the true rehabilitation needs of the stroke population. Furthermore, studies examining the daily time use of stroke patients have found that even in stroke units and rehabilitation centres the patients typically end up spending the best part of their days in their beds, alone, inactive, and without interaction (Bernhardt et al., 2004; De Wit et al., 2005; Huijben-Schoenmakers et al., 2009). In their survey of 434 stroke victims, Mayo et al. (2002) also found that 72 per cent of the patients lacked an important and meaningful activity to fill the day. Together with the evidence from animal studies supporting the role of the EE in enhancing stroke recovery, these findings suggest that stroke patients would benefit from a more stimulating recovery environment that could promote well-being and aid recovery. However, this topic has not been systematically studied.

1.2 Music in the human brain

One of the most powerful sources of sensory stimulation for the human brain comes from music (Sacks, 2006; Trainor, 2008; Zatorre, 2005). Although the adaptive function of music in human evolution is still unclear (Patel, 2008), music, like language, can be considered as a human universal that reaches deep into our species' past (Nettl, 2000).

Recent archaeological findings suggest that playing music has been part of human culture for over 30,000 years (Conard et al., 2009). The ability to sing may be even older, possibly even pre-dating the development of speech about 200,000 years ago (Mithen, 2005). Developmental and cross-cultural studies also suggest that the enjoyment and capacity for music develops early in life (Trehub, 2003) and spans all known human cultures (Merriam, 1964). But what is the biological and neural basis for our ability to perceive, feel, and understand music?

1.2.1 Processing music in the healthy brain

During the past twenty years, the neural basis of music processing in the normal brain has been extensively studied using brain imaging methods, such as electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Regarding the perception of basic acoustical features in music, evidence from fMRI and PET studies suggests that that the auditory cortex (AC) and other temporal lobe areas, especially in the right hemisphere, are active during passive listening to melodies (Brown & Martinez, 2007; Patterson et al., 2002; Zatorre et al., 1994) and respond to small pitch changes (Hyde et al., 2008; Jamison et al., 2006; Schönwiesner et al., 2005; Zatorre & Belin, 2001). Similarly, perception of the timbre of sounds and voices activates superior temporal lobe areas, primarily in the right hemisphere (Belin et al., 2000; Warren et al., 2005). By contrast, sound duration seems to be processed in the AC in a more left-lateralized or bilateral fashion (Jamison et al., 2006; Schönwiesner et al., 2005; Zatorre & Belin, 2001). Corroborating evidence for the involvement of the AC in encoding basic acoustical features (e.g., pitch and duration) in music also comes from EEG and MEG studies using the mismatch negativity (MMN) response (e.g., Tervaniemi, 2003).

In addition to the perception of basic acoustical cues, listening to music triggers a series of cognitive, emotional, and motor responses involving neural activity that extends well beyond the AC and adjacent temporal lobe areas. First of all, the processing of more complex musical attributes (e.g., chords, harmony, and tonality), which requires a rule-based analysis of simultaneous and sequential pitch structures,

engages the inferior frontal cortex, the medial prefrontal cortex, the premotor cortex, and the anterior superior temporal gyrus (Janata et al., 2002a; Koelsch et al., 2002, 2005; Levitin & Menon, 2003; Maess et al., 2001; Tillmann et al., 2003; for a review, see Koelsch & Siebel, 2005). Second, a similar frontoparietal network, including inferior frontal, dorsolateral prefrontal, precentral, anterior cingulate, and intraparietal areas, is also activated when we follow a melody and keep it in mind for a short period of time, activities requiring attention and working memory (Brown & Martinez, 2007; Gaab et al., 2003; Griffiths et al., 1999; Janata et al., 2002b; Zatorre et al., 1994). Third, recognising or imagining familiar tunes involves the participation of many prefrontal regions, especially the inferior frontal gyrus (IFG) and the supplementary motor area, as well as the left angular and middle temporal gyri (Halpern & Zatorre, 1999; Peretz et al., 2009; Platel et al., 2003). Fourth, music that evokes emotions engages virtually the entire limbic/paralimbic system, including the amygdala, the hippocampus, the parahippocampal gyrus, the nucleus accumbens (NAc), the ventral tegmental area (VTA), the anterior cingulate, and the orbitofrontal cortex (Baumgartner et al., 2006; Blood et al., 1999; Blood & Zatorre, 2001; Brown et al., 2004; Eldar et al., 2007; Koelsch et al., 2006; Menon & Levitin, 2005; Mitterschiffthaler et al., 2007; for a recent review, see Koelsch, 2010). Finally, the perception of rhythm involves areas in the cerebellum, the basal ganglia, and the motor cortex (Grahn & Brett, 2007; Popescu et al., 2004; Rao et al., 2001; Sakai et al., 1999; Xu et al., 2005).

1.2.2 Acquired and developmental deficits of music perception

Our ability to perceive music, especially the fine-grained pitch changes in melodies, can be selectively impaired in a condition known as amusia or tone (tune) deafness (e.g., Ayotte et al., 2002). It has been estimated that congenital amusia caused by abnormal brain development occurs in about four per cent of the population (Kalmus & Fry, 1980), while acquired amusia due to cerebral damage is relatively more common (Ayotte et al., 2000; Liégeois-Chauvel et al., 1998; Peretz, 1990; Schuppert et al., 2000). Since the 1960s, there have been approximately 65 published case or group studies of patients with acquired amusia caused by brain infarction, haemorrhage,

tumour, atrophy, sclerosis, meningitis, trauma, or neural surgery (for recent reviews, see Peretz & Zatorre, 2005; Stewart et al., 2006). Evidence from the case studies suggests that impaired perception of the spectral acoustical features in music (pitch intervals, pitch patterns, or timbre) is most often caused by damage to the primary AC, the planum temporale, the anterior superior temporal gyrus, the temporoparietal junction, the insula, or the frontal lobe in the right hemisphere (Stewart et al., 2006). Group studies also indicate that damage to the right AC and other right temporal lobe areas leads to impaired discrimination of pitch, melody, and timbre (Johnsrude et al., 2000, Liégeois-Chauvel et al., 1998; Milner, 1962; Peretz, 1990; Samson & Zatorre, 1988, 1994; Zatorre, 1988). Similarly, recent morphometric studies suggest that cortical anomalies in the IFG, the superior temporal gyrus, and the superior temporal sulcus of the right hemisphere could also underlie the musical pitch perception deficit in congenital amusia (Hyde et al., 2006, 2007). By contrast, a deficit in perceiving the temporal acoustical features in music (e.g., duration, rhythm, and tempo) is associated with damage beyond the AC in many temporal, frontal, and temporal-parietal areas in both the left and the right hemispheres (Milner, 1962; Robin et al., 1990; Schuppert et al., 2000; Shapiro et al., 1981; Stewart et al., 2006).

In addition to the impaired perception of the acoustical features in music, cerebral damage can also lead to an impaired memory for music or to a loss of emotional reactivity to music. Case and group studies indicate that deficits in recognising familiar tunes or novel melodies usually occur after damage to the anterior superior temporal gyrus, the insula, the middle or inferior temporal cortex, or the frontal lobe in either hemisphere (Ayotte et al., 2000; Samson & Zatorre, 1992; Stewart et al., 2006). Right anterior temporal lobe resections have also been associated with impaired working memory for pitch (Zatorre & Samson, 1991). Loss of emotional reactivity to music is most consistently associated with damage involving the posterior temporal lobe as well as medial temporal lobe structures, such as the insula, the amygdala, or the parahippocampal cortex (Gosselin et al., 2005, 2006; Griffiths et al., 2004; Stewart et al., 2006).

In summary, converging evidence from studies of both healthy subjects and amusic patients suggests that listening to music involves distributed cortical systems extending well beyond the AC and includes a vast network of temporal, frontal, parietal,

subcortical, and cerebellar areas. This raises the question of the relationship between the cortical systems processing music and other cognitive functions, such as speech, attention, and memory. Although approximately half the patients with acquired amusia have at least minor aphasia (Stewart et al., 2006), there have also been documented cases of amusia without impaired perception of speech or of other familiar sounds as well as cases of auditory agnosia (verbal or non-verbal) without amusia (Griffiths et al., 1997; Mendez, 2001; Peretz et al., 1994; Takahashi et al., 1992; for a review, see Peretz & Coltheart, 2003). Based on these observed double dissociations, it has been proposed that there are mental modules in the brain specific to the processing of music (Peretz & Coltheart, 2003).

However, recent behavioural evidence from congenital amusia suggests that amusic people can also have deficits in basic auditory discrimination (Jones et al., 2009a), pitch memory (Gosselin et al., 2009; Tillmann et al., 2009; Williamson et al., 2010), phonological and phonemic awareness (Jones et al., 2009b), speech intonation processing (Jiang et al., 2010; Liu et al., 2010; Patel et al., 2005, 2008), emotional prosody perception (Thompson, 2007), and spatial processing (Douglas & Bilkey, 2007; however, see Tillmann et al., 2010 for conflicting results). These findings suggest that the impairment in amusia may not be entirely specific to music perception. Current EEG evidence also indicates that congenital amusics have relatively normal early responses (N2, MMN), but abnormal later attention-modulated responses (P3, P600) to small pitch changes within tone sequences or melodies (Moreau et al., 2009; Peretz et al., 2005, 2009; however, see Braun et al., 2008, for conflicting results). Also in a recent fMRI study (Hyde et al., 2011), congenital amusics showed reduced activity in the right IFG to small pitch changes, whereas the activity in their left and right AC was comparable to that of the control subjects. Collectively, these results suggest that domain-general auditory and cognitive processes, mediated by neural structures beyond the AC, are linked to the music perception deficit in congenital amusia. However, little is currently known about the contribution of auditory and cognitive factors to acquired amusia. In the present thesis, this topic is addressed in Studies I–III.

1.3 Music in rehabilitation

Throughout human history, music has been associated with well-being and used in healing rituals and ceremonies. Today, most people interact with music on a daily basis, either by listening, singing, dancing, or playing, and music is valued by many, especially for its capacity to evoke and regulate emotions, provide enjoyment and comfort, and relieve stress (e.g., Juslin & Laukka, 2004; Saarikallio, in press; Sloboda & O'Neill, 2001). But what effects do musical activities have on our mood, cognition, and brain?

1.3.1 Effects of music listening, training, and therapy

Music is tightly coupled with emotions and mood, and many listeners report using music especially for mood regulation (Chamorro-Premuzic & Furnham 2007; Saarikallio, in press). Listening to music has been shown to evoke strong, subjectively-felt emotions, such as happiness, joy, peacefulness, and nostalgia (Juslin & Laukka, 2004; Zentner et al., 2008). These emotions are often accompanied by physiological reactions, such as changes in heart rate, respiration, skin temperature and conductance, and hormone (e.g., cortisol and testosterone) secretion (Fukui & Yamashita, 2003; Khalfa et al., 2003; Krumhansl, 1997; Lundqvist et al., 2009; Suda et al., 2008). By inducing positive affect and heightened arousal (Thompson et al., 2001), listening to pleasant and enjoyable music can also temporarily enhance performance in many cognitive domains, including psychomotor or information processing speed (Clark & Teasdale, 1985; Pignatiello et al., 1986; Schellenberg et al., 2007; Wood et al., 1990), reasoning (Chabris, 1999; Rauscher et al., 1993; Rowe et al., 2007; Thompson et al., 2001), attention and memory (Beh & Hirst, 1999; Greene et al., 2010; Hallam et al., 2002; Mammarella et al., 2007; Thompson et al., 2005), and creativity (Schellenberg et al., 2007). Listening to music has also been shown temporarily to improve arithmetic performance in children with attention-deficit hyperactivity disorder (Abikoff et al., 1996), autobiographical recall in Alzheimer's disease patients (Foster & Valentine, 2001; Irish et al., 2006), and visual awareness of the left side of the environment in

stroke patients suffering from unilateral spatial neglect (Hommel et al., 1990; Soto et al., 2009). These findings suggest that the transient stimulating effect of music is not limited to the healthy brain. Evidence from learning studies also indicates that words presented in a musical context (such as song lyrics) are learned and recalled better than spoken words, both in healthy subjects (Schön et al., 2008; Wallace, 1994; however, see Racette & Peretz, 2007, for conflicting results) and in patients with multiple sclerosis (Thaut et al., 2005) or Alzheimer's disease (Simmons-Stern et al., 2010).

In addition to the short-term enhancement of mood and cognition, music can also induce long-term plasticity changes in the brain. Experimental animal research has shown that exposure to an auditory EE, which contains complex sounds or music, enhances evoked potentials, gating, discrimination, and glutamate expression in the AC (Engineer et al., 2004; Nichols et al., 2007; Percaccio et al., 2005; Xu et al., 2007, 2009) and increases the dendritic length and spine density of AC neurons (Bose et al., 2010). Notably, exposure to music can also improve non-auditory learning and memory (Angelucci et al., 2007a; Chikahisa et al., 2006; Kim et al., 2006), increase dopamine (DA) levels in the striatum (Sutoo & Akiyama, 2004), and enhance neurogenesis and neurotrophin production in the hippocampus, the hypothalamus, and the neocortex (Angelucci et al., 2007a, 2007b; Chaudhury & Wadhwa, 2009; Chikahisa et al., 2006; Kim et al., 2006).

Corroborating evidence for the neural plasticity induced by music comes from studies of musical training in children and adult musicians. Active musical training has been shown to enhance auditory skills (Fujioka et al., 2004, 2006; Koelsch et al., 1999, 2003; Pantev et al., 1998; Schneider et al., 2002; Tervaniemi et al., 2001), motor skills (Elbert et al., 1995; Jäncke et al., 1997, 2000; Meister et al., 2005), and cognitive skills, such as reasoning, memory, and language (Anvari et al., 2002; Chan et al., 1998; Gardiner et al., 1996; Moreno et al., 2008; Schellenberg, 2004; for a recent review, see Hannon & Trainor, 2007). Furthermore, such training can also lead to increased grey and white matter volume in many cortical and subcortical areas controlling these skills (Amunts et al., 1997; Bengtsson et al., 2005; Gaser & Schlaug, 2003; Hyde et al., 2009; Schlaug et al., 1995; Sluming et al., 2002).

During the past fifty years, music therapy has been actively used and studied in the treatment and rehabilitation of many somatic, psychiatric, and developmental disorders.

Based on recent meta-analyses of music intervention studies, there is now evidence that music listening or therapy can relieve anxiety and pain in many chronic illnesses and surgical procedures (Bradt & Dileo, 2009; Cepeda et al., 2006; Galaal et al., 2007); it can have a positive effect on depression, anxiety, and global functioning in patients with severe mental disorders (e.g., depression, schizophrenia, and bipolar disorder) (Gold et al., 2005, 2009; Maratos et al., 2008); improve communication skills in autistic children (Gold et al., 2006); and also temporarily decrease agitation in dementia patients (Livingston et al., 2005).

1.3.2 Use of music in neurological rehabilitation

Given that music widely engages brain regions involved in emotion, cognition, and motor functions and that music therapy is used in many other clinical fields, it is surprising that the potential rehabilitative effects of musical activities in patients with neural damage have received relatively little scientific attention. Rhythmic Auditory Stimulation (RAS) and other interventions, which utilise the rhythm embedded in music to entrain motor behaviour, have been shown to improve the recovery of gait and arm movements in hemiparetic stroke patients (Jeong & Kim, 2007; Schauer & Mauritz, 2003; Thaut et al., 1997, 2002, 2007). Similarly, training with musical instruments can improve the speed, precision, and smoothness of arm movements after a stroke (Altenmüller et al., 2009; Schneider et al., 2007, 2010). Another application of music in rehabilitation is Melodic Intonation Therapy (MIT) (Albert et al., 1973; Norton et al., 2009), which uses the musical elements of speech (melody and rhythm) to train speech production in non-fluent aphasic patients. Although there are currently no clinical trials about the effectiveness of MIT, case studies suggest that MIT may improve spontaneous speech output, articulation, and naming in aphasic patients (Schlaug et al., 2008, 2009; Sparks et al., 1974; Wilson et al., 2006). Different forms of active music therapy can also improve mood and emotional adjustment, reduce depression and anxiety, and increase social interaction and participation in rehabilitation after a stroke or traumatic brain injury (Baker et al., 2005; Guétin et al., 2009; Magee & Davidson, 2002; Nayak et al., 2000; Thaut et al., 2009).

In summary, converging evidence suggests that specific elements of music, such as rhythm and melody, as well as its emotional power can be used to promote the recovery of motor skills, speech, and mood after neural damage. However, very little is currently known about the potential rehabilitative effects of music listening as an everyday leisure activity. This topic is addressed in Studies IV and V.

2 Aims of the study

The present thesis explores the interplay of auditory, cognitive, and emotional factors related to music processing in the recovering brain after an acute MCA stroke. The specific purpose was to examine the relationship between music perception and non-musical cognitive functions in acquired amusia one week after the stroke (Study I) and during a six-month follow-up (Study II), explore the relative contribution of auditory encoding deficits and non-musical cognitive deficits in acquired amusia (Study III), and to determine the effects of daily listening to music and speech on the recovery of cognitive functions and mood (Study IV) and auditory encoding (Study V).

3 Methods

3.1 Subjects and procedure

The study was carried out at the Departments of Neurology and Radiology and the BioMag laboratory of the Helsinki University Central Hospital (HUCH). The study was approved by the HUCH Ethics Committee, and all subjects signed an informed consent. The subjects (n = 60) were stroke patients recruited between March 2004 and May 2006 from the HUCH Department of Neurology. All patients had been admitted to the hospital for treatment of an acute ischemic stroke in the left or right MCA territory. The following additional inclusion criteria were used: (1) no prior neurological or psychiatric disease, (2) no drug or alcohol abuse, (3) no hearing deficit, (4) right-handed, (5) ≤ 75 years old, (6) Finnish-speaking, and (7) able to cooperate. As soon as possible after their hospitalization, the recruited patients were randomly assigned to one of three groups: a music group, an audio book group, or a control group (n = 20 in each). All patients received standard treatment for stroke in terms of medical care and rehabilitation. All patients underwent neuropsychological assessments and magnetoencephalography (MEG) measurements one week (a mean of 6.2 days, a range of 1–15 days), three months (a mean of 96.5 days, a range of 64–150 days), and six months (a mean of 186.9 days, a range of 160–229 days) post-stroke. In addition, magnetic resonance imaging (MRI) scans were taken within two weeks of stroke onset and at the six-month follow-up. All measures were performed and analysed blind to the group allocation of the patients.

Of the 60 patients originally recruited for the study, five dropped out before the three-month follow-up (due to a false diagnosis, a new stroke, dementia, or refusal) and one died before the six-month follow-up. In addition, two aphasic patients were unable to perform the Montreal Battery of Evaluation of Amusia (MBEA) used to diagnose amusia at the one-week post-stroke stage. As a result, data from 53 patients (52 at the six-month stage) were used in the analyses of Studies I–III, and data from 55 patients (54 at the six-month stage) were used in the analyses of Studies IV and V.

3.2 Interventions

As soon as possible after their hospitalization (a mean of 8.6 days, a range of 3–21 days), 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. In the music group, the therapist provided the patients with portable CD players and CDs of their own favourite 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 (http://www.celia.fi). The control group was not given any listening material. Patients in the music and audio book groups were trained in using the players and were instructed to listen to the material by themselves daily (for a minimum of one hour per day) for the following two months while still in the hospital or at home. During this time, the music therapist kept close weekly contact with the patients to encourage listening and to provide more material and practical aid. The nursing staff of the hospital wards and relatives of the patients were also informed of the study and were asked to help the patients in using the equipment if needed. After the two-month period, the patients were encouraged to continue listening to the material on their own. Patient participation was verified from listening diaries, which the music and audio book groups kept during the intervention period, and from questionnaires on leisure activities, including music and audio book listening, which all patients filled in after the intervention period and at the six-month follow-up. Analysis of the listening diaries kept by the music group patients showed that 62 per cent of all music selections were popular music (pop, rock, or rhythm and blues), 10 per cent was jazz, 8 per cent was folk music, and 20 per cent was classical or spiritual music. All in all, 63 per cent of the music material contained lyrics.

3.3 Neuropsychological assessment

Neuropsychological assessments were performed at the HUCH Department of Neurology, using an extensive neuropsychological testing battery (duration three hours)

that included tests of short-term and working memory, verbal memory, orientation, language skills, visuospatial cognition, music perception, executive functions, and attention (Table 1). Parallel versions of the memory tests were used in different testing occasions to minimise practice effects. Reaction time (RT) tests were always performed using the non-paretic hand. The assessments were carried out in one to three testing sessions in a quiet room. In analysing the data, individual test scores were used in Studies I–III and V, and summary scores of the tests measuring each cognitive domain in Study IV. In addition to the cognitive functions, mood and QOL after the stroke were also evaluated, using the Finnish version (Hänninen, 1989) of the Profile of Mood States (POMS; McNair et al., 1981) and the Stroke and Aphasia Quality Of Life Scale-39 (SAQOL-39; Hilari et al., 2003).

Table 1. Neuropsychological tests performed 1 week, 3 months, and 6 months post-stroke

Test	Task of the subject	Reference
Short-term and working memory		
Digit span (WMS-R)	Recall number sequences	Wechsler, 1987
Memory interference	Recall sets of 3 words after interfering tasks	Lezak et al., 2004
Verbal memory		
Word-list learning	Recall 10 words (3 trials + delayed recall)	Lezak et al., 2004
Story recall (RBMT)	Recall a narrated story (immediate + delayed)	Wilson et al., 1985
Orientation		
Orientation (RBMT)[a]	Answer questions about time and place	Wilson et al., 1985
Language		
Repetition (BDAE)	Repeat words and sentences	Goodglass & Kaplan, 1983
Reading (BDAE)	Read words and sentences	Goodglass & Kaplan, 1983
Semantic fluency (CERAD)	List animals within 60 seconds	Morris et al., 1989
Naming (CERAD)	Name objects from line drawings	Morris et al., 1989
Short Token test	Follow verbal instructions	De Renzi & Faglioni, 1978
Visuospatial cognition		
Clock task	Recognise time and draw clock hands	Lezak et al., 2004
Copying designs	Draw copies of 4 geometric designs	Lezak et al., 2004
Shortened BVRT	Draw 5 geometric designs from memory	Benton, 1974
Balloons test	Cancel targets in a visuospatial array	Edgeworth et al., 1998
Music perception		
Shortened MBEA[b]	Detect changes in melodies	Peretz et al., 2003
Executive functions		
FAB	Perform a set of short mental and motor tasks	Dubois et al., 2000
Focused attention		
Subtraction task (CS)	Press key after mental subtraction	Revonsuo & Portin, 1995
Stroop task (CS)	Press key in a colour response conflict situation	Revonsuo & Portin, 1995
Sustained attention		
Simple reaction time (CS)	Press key when visual target appears	Revonsuo & Portin, 1995
Vigilance task (CS)	Press key when target letter appears (15 min.)	Revonsuo & Portin, 1995

BDAE: Boston Diagnostic Aphasia Examination, BVRT: Benton Visual Retention Test, CERAD: The Consortium to Establish a Registry for Alzheimer's Disease, CS: CogniSpeed© reaction time software, FAB: Frontal Assessment Battery, MBEA: Montreal Battery of Evaluation of Amusia, RBMT: Rivermead Behavioural Memory Test, WMS-R: Wechsler Memory Scale – Revised.
[a] performed at the 1-week post-stroke stage (included in Study II)
[b] performed at the 1-week and 3-month post-stroke stages

3.3.1 Assessment of music perception

Music perception was evaluated one week and three months post-stroke using a shortened version of the MBEA (Peretz et al., 2003). The original MBEA includes six subtests (each with 30 items), which measure different components of music cognition (scale, contour, interval, rhythm, and metre perception as well as recognition memory). For the purpose of the present study, a shortened version of the MBEA was created using the same stimuli and structure as in the original test. The shortened MBEA included only 14 items per subtest and thereby reduced the length of the test from 1.5 hours to 45 minutes, making it possible to include it as a part of the larger neuropsychological testing battery (using the full-length test would not have been possible owing to time constraints, patient fatigue, and the severity of cognitive deficits at the acute post-stroke stage). As it turned out, 53 patients were able to perform the Scale and Rhythm subtests, but only 44 were able to complete all six subtests one week after the stroke. Since the Scale and Rhythm subtests were highly correlated with most other subtests ($r \geq .50$, $p < 0.001$) as well as with each other ($r = .68$, $p < 0.001$), their average (referred to hereafter as the MBEA average score) was used in determining the presence of acquired amusia. Based on the distribution of the MBEA average score (Figure 1) and the previously established cut-off values of the original MBEA (Peretz et al., 2003), the patients scoring less than 75 per cent correct were considered amusic.

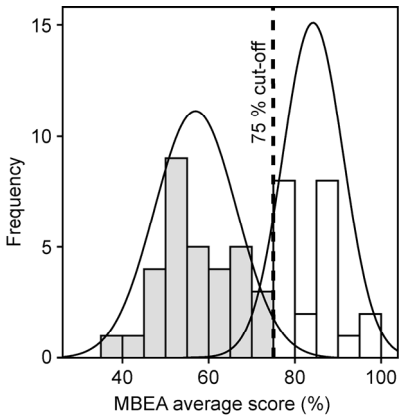

Figure 1. Distribution of MBEA scale and rhythm average scores across all patients (n = 53) at the one-week post-stroke stage. Patients scoring less than 75 per cent correct were classified as amusic (grey bars).

3.4 Magnetic resonance imaging (MRI)

MRIs were performed at the HUCH Department of Radiology using a 1.5 T Siemens Vision scanner to verify the stroke diagnosis and to evaluate the size and location of the lesion. Size was evaluated from fluid-attenuated inversion recovery (FLAIR) images by measuring the maximum diameter of the lesion, or in the case of multiple lesions, the sum of the diameters, in the sagittal, coronal, or horizontal plane. The following subcategories were used in classifying the location(s) of the lesion(s) within the damaged hemisphere: frontal lobe, temporal lobe, parietal lobe, insula, and subcortical. In addition, lesions of the AC were recorded.

3.5 Magnetoencephalography (MEG)

MEG experiments were performed at the BioMag laboratory (HUCH). In the experiments, an auditory oddball paradigm was used to elicit an event-related potential (ERP) component called the mismatch negativity (MMN). The MMN (or its magnetic counterpart MMNm) is a cortical response to a violation of an auditory regularity, such as an acoustical change in a repetitive sound stream, typically peaking about 100–200 ms from the onset of the violation (Kujala et al., 2007; Näätänen et al., 2007). Since the MMN is elicited even when the subject is not attending to the stimuli (Alho et al., 1989; Näätänen, 1991), corresponds well with behavioural sound discrimination accuracy (Amenedo & Escera, 2000; Jaramillo et al., 2000; Novitski et al., 2004; Tiitinen et al., 1994), and has good test–retest reliability (Tervaniemi et al., 1999, 2005), the MMN has often been used to study auditory encoding in clinical patient groups such as stroke patients (e.g., Csépe et al., 2001; Deouell et al., 2000; Ilvonen et al., 2001, 2003). In the present study, an MMN paradigm, which measures changes in two types of basic acoustical features (frequency and duration), was used. Previously, the same paradigm has been used in many non-clinical and clinical studies (e.g., Ilvonen et al., 2001, 2003; Tervaniemi et al., 1999, 2005).

3.5.1 MEG stimuli

The stimuli were harmonically rich tones delivered binaurally through plastic tubes and earplugs at the intensity of an 80 dB sound pressure level (SPL) with a fixed 300 ms stimulus onset asynchrony (BrainStim software). The stimulus sequence consisted of standard tones (p = 0.8; 500, 1000, and 1500 Hz frequency components; 75 ms duration with 5 ms rise-and-fall times) and deviant tones. The deviant tones had either higher frequency (p = 0.1; 575, 1150, and 1725 Hz frequency components) or shorter duration (p = 0.1; 25 ms duration) than the standard tones. The tones were presented in random order, except that each deviant tone was preceded by at least two standard tones. In order to control for exogenous effects on the MMN, two control blocks (referred to hereafter as control-standards) were included (Kujala et al., 2007). In those, only the higher frequency and the shorter duration tones, which served as deviants in the oddball blocks, were presented at 100 per cent probability. The patients were instructed to ignore the sound stimuli and focus on watching a silent DVD without subtitles.

3.5.2 MEG acquisition

MEG was recorded in a magnetically shielded room (Euroshield Ltd., Finland) using a 306-channel whole-head magnetometer (Elekta Neuromag Oy, Helsinki, Finland). The position of the subject's head relative to the sensors was determined by measuring the magnetic field produced by four marker coils attached to the scalp (Ahlfors & Ilmoniemi, 1989). The locations of the coils in relation to cardinal points on the head were determined with a 3D digitizer (Polhemus^{TM}, USA). Online averaging of the MEG epochs (sampling rate 602 Hz, bandpass filtering 0.1–95 Hz) for the standard and deviant stimuli started 150 ms before and ended 350 ms after stimulus presentation. Epochs with MEG or electro-oculogram (EOG) deflections (recorded with electrodes placed above and below the left eye and lateral to the eyes) exceeding 3000 fT/cm or 150 μV, respectively, were discarded from averaging. Recording was continued until approximately 100 accepted artefact-free trials for each deviant type were collected, which took about 10 to 15 minutes.

3.5.3 MEG data analysis

For data visualisation, the averaged responses to the standard and deviant tones were first digitally filtered (bandpass 1–20 Hz) and baseline-corrected (time interval -50–0 ms before stimulus onset) and then, in order to adjust for head position variability between the measurement sessions, spatially corrected using the MaxFilter™ software (Elekta Neuromag, Finland). MMNm responses to changes in frequency and duration (referred to hereafter as frequency MMNm and duration MMNm, respectively) were determined by subtracting the averaged responses to the control-standard tones from the averaged responses to the deviant tones (Kujala et al., 2007). Source modelling of the MMNm responses was performed from the subtraction curves by using the Minimum Current Estimation (MCE) method (Elekta Neuromag, Finland), which is based on minimum L1-norm estimates and can represent several local or distributed sources (Uutela et al., 1999). The MCEs were calculated separately for each individual subject at each measurement session (1 week, 3 months, and 6 months post-stroke). The averaged responses were first pre-processed by filtering with a 20 Hz low-pass digital filter and applying a prestimulus baseline (50 ms before stimulus onset) and a detrend baseline (300–350 ms from the stimulus onset) in order to eliminate the effects of measurement noise. A spherical head model was used in calculating MCE solutions, which were then projected onto an averaged brain surface. The origin of this model was determined individually for each subject on the basis of a 3D set of T1-weighted anatomical MRIs by fitting a sphere to the curvature of the outer surface of the brain.

After calculating the MCE, the sources of the MMNm were identified in each hemisphere by selecting a region of interest (ROI), which produced the strongest response that was within the time window of 100–300 ms from tone onset and followed the vertical (“downward”) dipolar orientation typical of the MMNm (Alho, 1995). Using the graphical interface of the Neuromag MCE software, the ROI was selected individually for each patient at each measurement session so that it always produced the highest amplitude response within the hemisphere (for a case example illustrating the recovery-related change in the MMNm derived from the MCE analysis, see Figure 2). In line with the literature on the typical sources of the MMN in the normal brain (Alho, 1995; Giard et al., 1990; Levänen et al., 1996; Molholm et al., 2005; Opitz et al., 2002;

Rinne et al., 2000), the ROIs were primarily located in the temporal lobe, extending in some cases also frontally or parietally. MMNm latency was determined from the peak of the response. MMNm amplitude was determined as the mean amplitude within a 50-ms time window centred at the peak of the response.

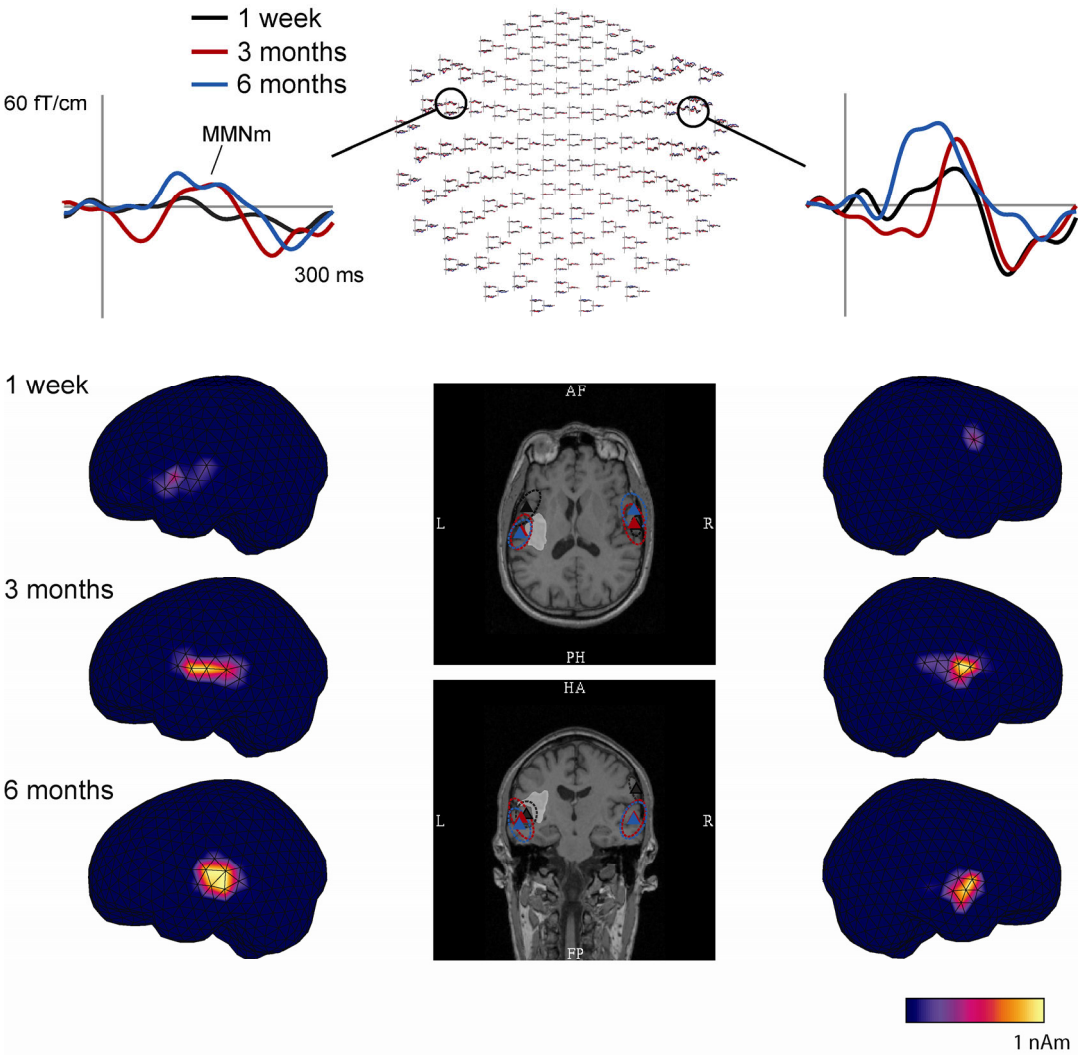

Figure 2. An example illustrating the typical recovery-related changes in the frequency MMNm response. Changes in the strength of the MMNm in the left and right hemispheres are shown with subtraction curves from individual MEG channels over the temporal lobes and with source modeling performed using the MCE method. MRI images show the location of the lesion (white area) as well as the centre (triangles) and the extent (ellipsoids) of the ROI used in the MCE analysis at the one-week (black), three-month (red), and six-month (blue) post-stroke stage.

3.6 Statistical analyses

Group differences in the demographic and clinical characteristics of the patients were analysed with chi-square tests, t-tests, Mann-Whitney U tests, Kruskal-Wallis tests, and univariate analyses of variance (ANOVA). Group differences in neuropsychological tests (Studies I–IV), mood and QOL questionnaires (Study IV), and MMNm parameters (Studies III and V) at different stages of stroke recovery were assessed with univariate and mixed-model ANOVAs. The Greenhouse-Geisser epsilon was used to correct for sphericity. Post hoc analyses were performed using Tukey's Honestly Significant Difference (HSD) and Fisher's Least Significant Difference (LSD) tests. In Study V, tests of the Time main effects with the Bonferroni correction for multiple comparisons were also used. Finally, the relationships between different neuropsychological test scores (Studies I, II, and IV) and neuropsychological test scores and MMNm parameters (Studies III and V) were analysed with Pearson and Spearman (for non-parametric variables) correlation coefficients. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS (version 14.0 or 15.0). Missing values in test scores were considered missing at random.

4 Results

4.1 Patient characteristics

The demographic and clinical characteristics of the patients are presented in Table 2 for Studies I–III and in Table 3 for Studies IV and V. In Studies I and II, 32 patients (60%) were classified as amusic and 21 as non-amusic, based on their MBEA average scores at the one-week post-stroke stage (Figure 1). As shown in Table 2, the patients in the amusic group included more females ($\chi^2 = 3.92$, $p = 0.048$) and had less education [$t(51) = 3.75$, $p < 0.001$] than those in the non-amusic group. Furthermore, the lesions were, on average, larger in the amusic group [$t(51) = -3.53$, $p < 0.001$] and extended more often to the frontal lobe ($\chi^2 = 4.84$, $p = 0.028$) as well as to the AC ($\chi^2 = 9.50$, $p = 0.002$) and other temporal lobe areas ($\chi^2 = 3.63$, $p = 0.057$). Thus, gender, education, and lesion size were included as covariates when comparing amusic and non-amusic patients in Studies I and II.

In Study III, the patient sample was divided into five groups based on the location of the lesion and the presence of amusia: left hemisphere-damaged (LHD) non-amusic patients (n = 12), LDH amusic patients (n = 12), right hemisphere-damaged (RHD) non-amusic patients (n = 9), RHD amusic patients whose lesion extended to the AC ("AC-amusic", n = 11), and RHD amusic patients whose lesion spared the AC ("non-AC-amusic", n = 9). Within the LHD subgroup, the amusic patients had less education [$t(22) = 3.78$, $p = 0.002$] and larger lesions [$t(22) = -2.85$, $p = 0.009$] and were also slightly older [$t(22) = -2.07$, $p = 0.051$] than the non-amusic patients. Within the RHD subgroup, there was a marginally significant group difference in lesion size [$F(2, 26) = 2.68$, $p = 0.087$] with larger lesions in the AC-amusic group than in the non-amusic group (LSD $p = 0.03$). Thus, education, age, and lesion size were included as covariates when comparing amusic and non-amusic LHD patients, and lesion size was included as a covariate when comparing AC-amusic, non-AC-amusic, and non-amusic RHD patients in Study III.

Table 2. Characteristics of the patients in Studies I-III

		Studies I and II			Study III						
		Amusic (n = 32)	Non-amusic (n = 21)	P value	LHD Amusic (n = 12)	LHD Non-amusic (n = 12)	P value	RHD AC-amusic (n = 11)	RHD non-AC-amusic (n = 9)	RHD Non-amusic (n = 9)	P value
Demographic	Age (years)	60.1 (7.6)	56.4 (10.2)	0.130 (t)	59.6 (8.6)	52.3 (8.5)	0.051 (t)	61.2 (7.5)	59.7 (7.1)	61.2 (10.2)	0.857 (F)
	Gender (male/female)	14/18	15/6	0.048 (χ^2)	8/4	9/3	0.653 (χ^2)	4/7	2/7	6/3	0.141 (χ^2)
	Education (years)	9.7 (3.2)	13.1 (3.3)	< 0.001 (t)	9.3 (2.0)	13.8 (3.7)	0.002 (t)	9.5 (3.1)	10.4 (4.6)	12.1 (2.5)	0.277 (F)
	Formal music training[a]	0 (0)	0.2 (0.7)	0.206 (U)	0 (0)	0.3 (0.9)	0.740 (U)	0 (0)	0 (0)	0 (0)	
	Instrument playing[a]	0.9 (1.3)	1.9 (2.0)	0.110 (U)	0.7 (1.2)	1.9 (2.2)	0.198 (U)	1.4 (1.5)	0.8 (1.3)	1.8 (1.9)	0.476 (K)
	Music listening prior to stroke[b]	3.3 (1.6)	3.9 (1.2)	0.303 (U)	3.2 (1.6)	4.1 (0.8)	0.198 (U)	2.9 (1.8)	4.1 (1.3)	3.7 (1.7)	0.403 (K)
Clinical	Aphasia[c] (no/yes)	22/10	13/8	0.607 (χ^2)	3/9	5/7	0.385 (χ^2)	11/0	8/1	8/1	0.368 (χ^2)
	Visual neglect[d] (no/yes)	18/14	21/0	< 0.001 (χ^2)	10/2	12/0	0.086 (χ^2)	2/9	6/3	9/0	< 0.001 (χ^2)
	Lesion laterality (left/right)	12/20	12/9	0.160 (χ^2)	12/0	12/0		0/11	0/9	0/9	
	Lesion size[e]	6.2 (2.1)	4.1 (2.3)	< 0.001 (t)	5.8 (2.2)	3.6 (1.6)	0.009 (t)	7.1 (1.4)	5.7 (2.6)	4.7 (3.0)	0.087 (F)
	Frontal lesion (no/yes)	5/27	9/12	0.028 (χ^2)	5/7	7/5	0.413 (χ^2)	0/11	0/9	2/7	0.081 (χ^2)
	Temporal lesion (no/yes)	6/26	9/12	0.057 (χ^2)	5/7	5/7		0/11	1/8	4/5	0.018 (χ^2)
	Auditory cortex lesion (no/yes)	14/18	20/1	0.002 (χ^2)	9/3	11/1	0.264 (χ^2)	0/11	9/0	9/0	< 0.001 (χ^2)
	Parietal lesion (no/yes)	11/21	11/10	0.193 (χ^2)	4/8	5/7	0.673 (χ^2)	1/10	6/3	6/3	0.006 (χ^2)
	Insular lesion (no/yes)	10/22	9/12	0.389 (χ^2)	7/5	5/7	0.413 (χ^2)	0/11	3/6	4/5	0.016 (χ^2)
	Subcortical lesion (no/yes)	16/16	10/11	0.865 (χ^2)	9/3	6/6	0.203 (χ^2)	2/9	5/4	4/5	0.189 (χ^2)

Data are mean (SD) unless otherwise stated. χ^2 = chi-square test; F = one-way ANOVA; K = Kruskal-Wallis test t = T test; U = Mann-Whitney U test; AC = auditory cortex

[a] Numbers denote values on a Likert scale where 0 = no, 1 = less than 1 year, 2 = 1–3 years, 3 = 4–6 years, 4 = 7–10 years, and 5 = more than 10 years of training / playing

[b] Numbers denote values on a Likert scale with a range of 0 (never does) – 5 (does daily)

[c] Classification based on BDAE Aphasia Severity Rating Scale: scores 0–4 = aphasia, score 5 = no aphasia

[d] Classification based on the Lateralized Inattention Index of the Balloons Test

[e] Maximum lesion diameter in cm (see Methods for details)

In Studies IV and V, there were no statistically significant differences between the music, audio book, and control groups on any baseline demographic or clinical variable (Table 3). Furthermore, the groups were comparable in baseline cognitive performance, mood, and MMNm amplitudes as well as in antidepressant medication and stroke rehabilitation received during the follow-up (Table 3). In contrast, the music group listened to music more than the audio book and control groups, whereas the audio book group listened to audio books more than the music and control groups during the two-month intervention period (Kruskal-Wallis $\chi^2 = 28.24$, $p < 0.001$ and $\chi^2 = 39.57$, $p < 0.001$; HSD $p < 0.001$ in all comparisons), thereby indicating that the study protocol worked well. Notably, these group differences in listening activity were still significant at the six-month post-stroke stage (Kruskal-Wallis $\chi^2 = 17.85$, $p < 0.001$ and $\chi^2 = 30.46$, $p < 0.001$; HSD $p < 0.005$), suggesting that most of the music and audio group patients continued the listening on their own as a leisure activity even after the two-month intervention period.

Table 3. Characteristics of the patients in Studies IV and V

		Music group (n = 19)	Audio book group (n = 19)	Control group (n = 17)	P value
Demographic (baseline)	Age (years)	56.1 (9.6)	59.3 (8.3)	61.5 (8.0)	0.178 (F)
	Gender (male/female)	12/7	9/10	8/9	0.531 (χ^2)
	Education (years)	11.2 (4.3)	11.8 (3.0)	9.7 (3.3)	0.198 (F)
	Music listening prior to stroke[a]	4.0 (1.5)	3.2 (1.4)	3.4 (1.6)	0.115 (K)
	Radio listening prior to stroke[a]	4.5 (1.1)	4.1 (1.2)	4.3 (1.2)	0.560 (K)
	Reading prior to stroke[a]	4.0 (0.9)	4.0 (0.7)	4.2 (0.9)	0.558 (K)
Clinical (baseline)	Motor deficit severity[b]	1.4 (1.0)	1.2 (1.0)	1.4 (1.2)	0.849 (K)
	Aphasia[c] (no/yes)	12/7	13/6	11/6	0.941 (χ^2)
	Amusia[d] (no/yes)	10/8	7/11	4/13	0.153 (χ^2)
	Visual neglect[e] (no/yes)	14/5	12/7	13/4	0.644 (χ^2)
	Antidepressant medication (no/yes)	13/6	14/5	15/2	0.356 (χ^2)
	Lesion laterality (left/right)	10/9	8/11	8/9	0.809 (χ^2)
	Lesion size[f]	5.4 (2.7)	5.0 (2.1)	5.8 (2.4)	0.543 (F)
	Frontal lesion (no/yes)	3/16	7/12	4/13	0.322 (χ^2)
	Temporal lesion (no/yes)	8/11	4/15	3/14	0.195 (χ^2)
	Parietal lesion (no/yes)	9/10	7/12	7/10	0.804 (χ^2)
	Insular lesion (no/yes)	8/11	6/13	5/12	0.686 (χ^2)
	Subcortical lesion (no/yes)	10/9	8/11	9/8	0.753 (χ^2)
Cognitive domain (baseline)[g]	Verbal memory (max.124)	45.1 (21.2)	60.7 (21.7)	50.0 (25.6)	0.105 (F)
	Short-term & working memory (max. 42)	19.7 (9.4)	23.3 (7.2)	17.7 (9.5)	0.164 (F)
	Language (max. 162)	109.2 (36.8)	122.1 (28.3)	110.7 (31.7)	0.405 (K)
	Music cognition (max. 28)	19.9 (4.5)	19.2 (5.2)	17.1 (3.5)	0.183 (K)
	Visuospatial cognition (max. 105)	82.8 (23.4)	89.2 (13.3)	77.3 (23.7)	0.174 (K)
	Executive functions (max. 18)	12.6 (3.7)	13.9 (3.5)	12.6 (3.6)	0.344 (K)
	Focused attention (hits, max. 90)	74.8 (19.5)	84.3 (8.5)	87.3 (3.2)	0.105 (K)

		Music group (n = 19)	Audio book group (n = 19)	Control group (n = 17)	P value
	Focused attention (RT, seconds)	3.0 (1.1)	3.4 (1.5)	3.7 (2.0)	0.797 (K)
	Sustained attention (hits, max. 100)	87.0 (23.0)	91.1 (12.1)	95.9 (7.4)	0.542 (K)
	Sustained attention (RT, seconds)	1.0 (0.3)	1.2 (0.5)	1.0 (0.2)	0.656 (K)
POMS subscale (baseline)	Tension (max. 16)	3.9 (3.4)	4.4 (3.6)	3.9 (2.7)	0.870 (F)
	Depression (max. 28)	7.0 (7.3)	6.1 (6.7)	8.5 (7.4)	0.615 (F)
	Irritability (max. 28)	4.4 (6.2)	4.7 (6.4)	4.7 (4.2)	0.987 (F)
	Vigour (max. 24)	10.7 (5.6)	9.1 (5.3)	10.1 (6.3)	0.698 (F)
	Fatigue (max. 12)	5.4 (2.9)	4.6 (2.7)	4.2 (4.1)	0.514 (F)
	Inertia (max. 12)	2.7 (2.4)	2.8 (2.8)	3.6 (3.2)	0.578 (F)
	Confusion (max. 20)	7.1 (4.0)	7.4 (4.5)	8.8 (4.8)	0.481 (F)
	Forgetfulness (max. 12)	4.3 (2.6)	4.5 (2.6)	4.8 (3.1)	0.862 (F)
MMNm (baseline)	Frequency MMNm (left hemisphere)[h]	3.1 (1.8)	2.5 (2.0)	2.6 (1.8)	0.610 (F)
	Frequency MMNm (right hemisphere)[h]	2.2 (1.1)	3.1 (2.5)	2.9 (1.8)	0.291 (F)
	Duration MMNm (left hemisphere)[h]	6.1 (4.1)	5.2 (3.6)	5.4 (3.1)	0.688 (F)
	Duration MMNm (right hemisphere)[h]	7.0 (4.5)	6.3 (5.2)	6.2 (3.1)	0.841 (F)
Listening activity	Music listening[a] (3 m)	5.0 (0)	1.6 (1.9)	1.7 (2.2)	< 0.001 (K)
	Music listening[a] (6 m)	4.5 (0.6)	2.8 (1.7)	2.0 (1.8)	< 0.001 (K)
	Audio book listening[a] (3 m)	0.1 (0.2)	4.5 (1.2)	0.4 (1.2)	< 0.001 (K)
	Audio book listening[a] (6 m)	0.3 (1.0)	3.3 (1.8)	0.4 (1.0)	< 0.001 (K)
Rehabilitation	Physical therapy[i] (6 m)	21.1 (34.9)	21.2 (34.4)	11.6 (19.5)	0.922 (K)
	Occupational therapy[i] (6 m)	10.4 (16.7)	5.7 (11.8)	7.1 (14.3)	0.753 (K)
	Speech therapy[i] (6 m)	8.3 (14.0)	2.9 (6.7)	5.4 (9.3)	0.476 (K)
	Neuropsychological rehabilitation[i] (6 m)	4.3 (7.8)	5.2 (7.6)	2.4 (4.2)	0.849 (K)

Data are mean (SD) unless otherwise stated. 3 m = 3 month post-stroke stage, 6 m = 6 month post-stroke stage; χ^2 = chi-square test; F = one-way ANOVA; K = Kruskal-Wallis test; MMNm = magnetic mismatch negativity; POMS = Profile of Mood States; RT = reaction time.

[a] Numbers denote values on a Likert scale with a range of 0 (never does) – 5 (does daily)

[b] Numbers denote values on a Likert scale with a range of 0 (no deficit) – 3 (hemiplegia)

[c] Classification based on BDAE Aphasia Severity Rating Scale: scores 0–4 = aphasia, score 5 = no aphasia

[d] Classification based on MBEA Scale and Rhythm average score (see Methods for details)

[e] Classification based on the Lateralized Inattention Index of the Balloons Test

[f] Maximum lesion diameter in cm (see Methods for details)

[g] Summary scores of the neuropsychological tests measuring each cognitive domain

[h] MMNm source amplitude (nAm)

[i] Number of therapy sessions

4.2 Cognitive deficits associated with acquired amusia (Studies I and II)

The aim of Studies I and II was to determine whether acquired amusia was associated with deficits in other higher cognitive functions both in early and later post-stroke stages. Based on their performance on the shortened version of the MBEA at the one-week post-stroke stage, 32 patients (60%) were classified as amusic and 21 as non-amusic. Compared to the non-amusic group, the MBEA average score was significantly

lower in the amusic group both one week [$t(51) = 11.30$, $p < 0.001$] and three months post-stroke [$t(51) = 6.08$, $p < 0.001$] (Figure 3). Using the same classification criterion, 22 of the 53 patients (42%) remained amusic also at the three-month post-stroke stage.

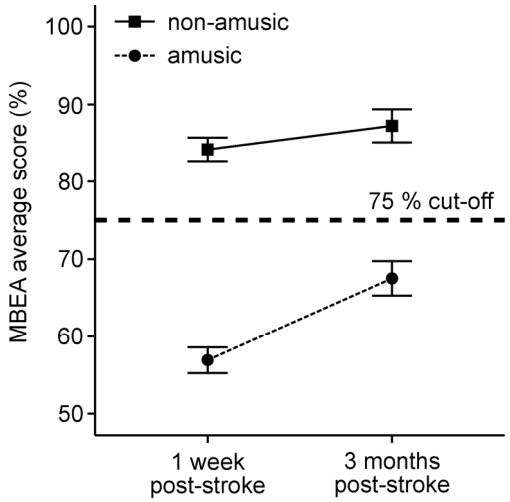

Figure 3. MBEA scale and rhythm average scores (mean ± SEM) of the amusic (n = 32) and non-amusic (n = 21) patient groups one week and three months post-stroke. Cut-off level (75%) shown in grey.

Differences between the amusic and non-amusic patients in neuropsychological test performance at different stages of stroke recovery were evaluated using two-way ANOVAs with Group (amusic/non-amusic) and Lesion laterality (left/right) as factors. As shown in Figure 4 and Table 4, the amusic patients performed worse than the non-amusic patients on tests of working memory and learning (digit span, memory interference, and word-list learning), visuospatial cognition (copying designs and BVRT), verbal expression (semantic fluency), and executive functioning (FAB and Stroop time). In addition, separate analyses within the LHD and RHD subgroups indicated that the amusic LHD patients had more severe deficits in verbal comprehension (Token test) and recall (story recall) than the non-amusic LHD patients. Conversely, the amusic RHD patients had more severe deficits in mental flexibility (phonemic fluency) and spatial attention (Balloons test part B score) than the non-amusic RHD patients.

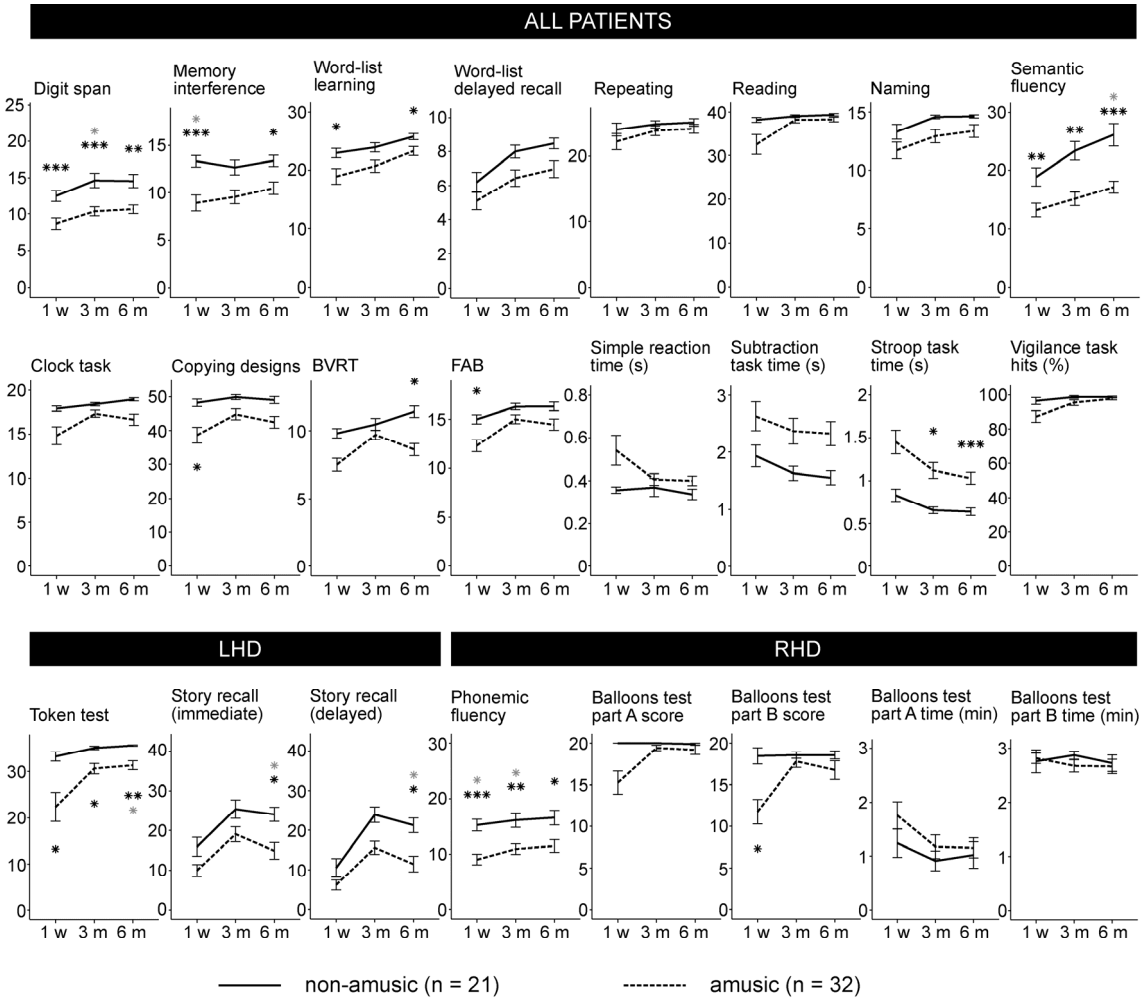

Figure 4. Cognitive performance of amusic (n = 32, dotted lines) and non-amusic (n = 21, solid lines) patients at different stages of stroke recovery. Neuropsychological test scores are shown separately for patients with left hemisphere damage (LHD) and right hemisphere damage (RHD) when there was a significant Group x Lesion laterality interaction in the two-way ANOVA. See Table 1 for test descriptions. Data are shown as mean ± SEM with the Y axis scaled to the maximum score (except in fluency and reaction time tests). *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$ in the ANOVA (black: gender and education as covariates; grey: gender, education, and lesion size as covariates). 1 w = one week post-stroke, 3 m = three months post-stroke, 6 m = six months post-stroke.

Table 4. Group differences in cognitive performance at different stages of stroke recovery (controlled for gender and education)

Statistics[a]	1-week F value	df	P value	3-month F value	df	P value	6-month F value	df	P value
Group main effect									
Digit span	10.97	46	0.002	10.24	46	0.002	7.67	46	0.008
Memory interference	11.77	46	0.001	2.21	46	0.144	6.85	46	0.012
Word-list learning	4.62	47	0.037	3.391	47	0.072	5.25	46	0.027
Copying designs	5.22	46	0.027	2.35	45	0.132	3.31	46	0.076
BVRT	3.28	47	0.077	0.12	45	0.731	10.41	46	0.002
Semantic fluency	7.34	47	0.009	7.25	47	0.010	11.18	46	0.002
FAB	6.05	47	0.018	1.27	46	0.266	2.33	46	0.133
Stroop time	3.90	43	0.055	6.58	45	0.014	10.02	44	0.003
Group x Lesion laterality interaction									
Token test	9.08	46	0.004	8.60	46	0.005	11.18	45	0.002
Story recall (immediate)	2.83	47	0.099	1.90	47	0.174	5.20	46	0.027
Story recall (delayed)	0.70	47	0.406	3.15	47	0.082	4.40	46	0.041
Phonemic fluency	2.76	47	0.104	3.35	47	0.074	2.13	46	0.135
Balloons test (part B score)	7.55	47	0.009	1.26	46	0.268	0.90	46	0.349
Group main effect (LHD patients)									
Token test	5.82	20	0.025	7.66	20	0.012	9.86	19	0.005
Story recall (immediate)	2.01	20	0.172	0.68	20	0.419	5.29	19	0.033
Story recall (delayed)	0.50	20	0.487	2.92	20	0.103	4.54	19	0.046
Group main effect (RHD patients)									
Phonemic fluency	13.32	25	0.001	9.38	25	0.005	5.79	25	0.024
Balloons test (part B score)	4.94	25	0.036	1.28	24	0.270	1.10	25	0.305

Note: only tests with significant ($p < 0.05$) or marginally significant ($p < 0.1$) effects are shown. See Table 1 for test descriptions. LHD = left hemisphere damage, RHD = right hemisphere damage

[a] two-way ANOVA with Group (amusic/non-amusic) and Lesion laterality (left/right) as factors and female gender and years of education as covariates

After taking into account the potentially confounding effect of larger lesion size in the amusic group as a covariate, the amusic group still showed significantly worse performance on the digit span, memory interference, and semantic fluency tests as well as a slightly slower performance on the Stroop test (Table 5 and Figure 4). Similarly, the hemisphere-specific group differences on the Token test, story recall, and phonemic fluency remained significant. Furthermore, no differences were observed between the amusic and non-amusic groups on the RBMT orientation subtest at the one-week stage [mean 13.94 (SD 2.05) vs. mean 15.61 (SD 0.80); $F(1, 46) = 1.53$, $p = 0.22$], further suggesting that the cognitive differences between the groups were not due to more general cognitive dysfunction or disorientation caused by extensive cerebral damage.

Table 5. Group differences in cognitive performance at different stages of stroke recovery (controlled for gender, education, and lesion size)

Statistics[a]	1-week F value	df	P value	3-month F value	df	P value	6-month F value	df	P value
Group main effect									
Digit span	2.35	45	0.132	4.21	45	0.046	2.56	45	0.116
Memory interference	4.68	45	0.036	0.40	45	0.532	3.49	45	0.068
Word-list learning	1.01	46	0.320	1.15	46	0.290	3.07	45	0.087
Semantic fluency	1.34	46	0.252	1.97	46	0.168	6.61	45	0.013
Stroop time	1.01	42	0.320	0.54	44	0.467	3.90	43	0.055
Group x Lesion laterality interaction									
Token test	6.25	45	0.016	9.35	45	0.004	11.24	44	0.002
Story recall (immediate)	2.57	46	0.116	1.67	46	0.203	5.09	45	0.029
Story recall (delayed)	0.53	46	0.470	2.92	46	0.094	4.30	45	0.044
Phonemic fluency	3.29	46	0.076	3.81	46	0.057	2.33	45	0.134
Group main effect (LHD patients)									
Token test	0.79	19	0.384	1.83	19	0.192	4.75	18	0.043
Story recall (immediate)	0.14	19	0.713	0.20	19	0.658	6.33	18	0.022
Story recall (delayed)	0.003	19	0.961	0.54	19	0.470	5.09	18	0.037
Group main effect (RHD patients)									
Phonemic fluency	7.31	24	0.012	4.56	24	0.043	2.13	24	0.157

Note: only tests with significant ($p < 0.05$) or marginally significant ($p < 0.1$) effects are shown. See Table 1 for test descriptions. LHD = left hemisphere damage, RHD = right hemisphere damage

[a] two-way ANOVA with Group (amusic/non-amusic) and Lesion laterality (left/right) as factors and female gender, years of education, and lesion size as covariates

The potential contribution of cognitive factors to the severity of amusia at the one-week stage was evaluated by using correlation analyses (Figure 5). Within the amusic group (n = 32), lower MBEA average scores correlated significantly with slower reaction times on the simple reaction time (Spearman r = -.63, p < 0.001), vigilance (Pearson r = -.63, p < 0.001), Stroop (Spearman r = -.47, p = 0.011), and mental subtraction tasks (Spearman r = -.46, p = 0.025) as well as with worse performance on the vigilance task (Spearman r = .57, p = 0.001) and the Balloons test part B (Spearman r = .55, p = 0.001).

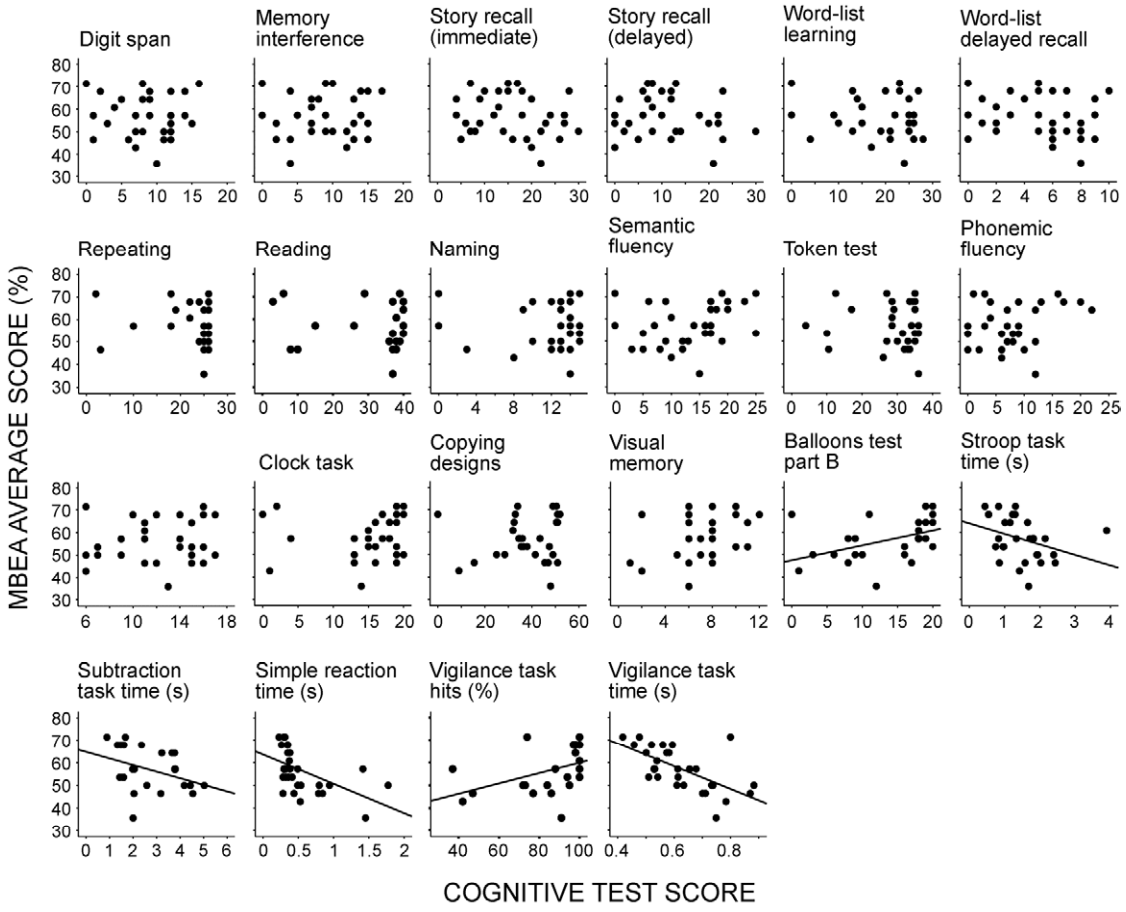

Figure 5. Relationship between music perception (MBEA scale and rhythm average score) and other cognitive functions at the one-week post-stroke stage in amusic (n = 32) patients. See Table 1 for test descriptions. Regression lines are shown only for significant correlations.

Correlation analyses were also performed on the change scores (3-month minus 1-week) of the MBEA average score and other cognitive test scores (Figure 6). In all patients (n = 53), improvement on the MBEA correlated significantly with improvement on word-list learning (Pearson r = .41, p = 0.002) and delayed recall (Spearman r = .34, p = 0.014) as well as copying designs (Spearman r = .29, p = 0.042). Additionally, it correlated with Balloons test part A time (Spearman r = -.39, p = 0.005) and part B score (Spearman r = .36, p = 0.009) and time (Spearman r = -.35, p = 0.013). Within the amusic group (n = 32), similar correlations were observed for word-list learning (Pearson r = .46, p = 0.008) and delayed recall (Spearman r = .44, p = 0.012) as well as Balloons test part A time (Spearman r = -.34, p = 0.066). Interestingly, in the amusic

patients the improvement on the MBEA also correlated significantly with faster performance on the mental subtraction task (Spearman r = -.42, p = 0.044).

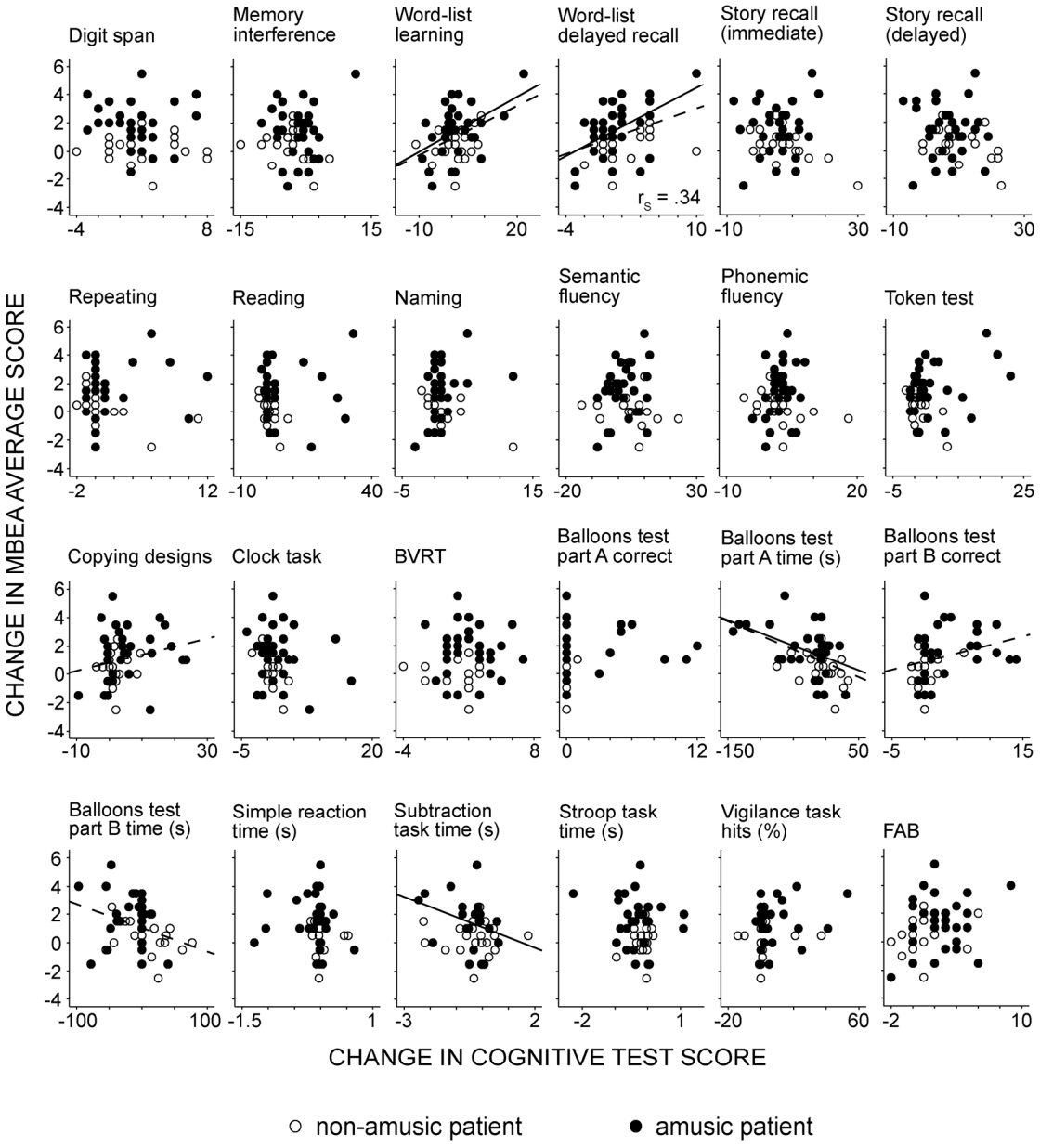

Figure 6. Relationship between the recovery of music perception (MBEA scale and rhythm average score) and other cognitive functions during the three-month post-stroke period. Scatterplots of the change scores (3-month post-stroke score minus 1-week post-stroke score) are shown for amusic (n = 32, closed circles) and non-amusic (n = 21, open circles) patients. See Table 1 for test descriptions. Regression lines are shown only for significant correlations across patients (dotted lines) and within the amusic group (solid lines).

In summary, the results from Studies I and II indicate that acquired amusia is a common and persistent deficit following an ischemic MCA stroke, especially if the stroke affects the frontal and temporal brain areas. Compared to non-amusic patients, the amusic patients showed more severe deficits in a wide range of cognitive functions, including working memory, attention, and executive functions. Attention deficits were also widely associated with the severity of amusia, and improvement in attention and memory contributed to the recovery of amusia.

4.3 Auditory and cognitive deficits associated with acquired amusia (Study III)

The aim of Study III was to determine the relative contribution of basic auditory encoding and higher cognitive functions in acquired amusia as well as its dependence on the location of the cerebral damage. For this purpose, the patient sample was first divided according to the laterality of the lesion, yielding 12 amusic and 12 non-amusic patients with LHD and 20 amusic and 9 non-amusic patients with RHD. Comparison of the MBEA average scores of the amusic LHD and RHD patients using univariate and mixed-model ANOVAs showed that the amusic RHD patients had significantly lower MBEA average scores both at the one-week stage [$F(1, 29) = 8.29$, $p = 0.007$] and throughout the three-month period [$F(1, 29) = 5.58$, $p = 0.025$] (Figure 7).

A correlation analysis also indicated that smaller MBEA average scores were associated with smaller frequency MMNm amplitudes only in the amusic RHD patients (Pearson $r = .63$, $p = 0.003$), whereas no positive correlations between the MBEA and the MMNm were observed in the amusic LHD patients (Figure 8).

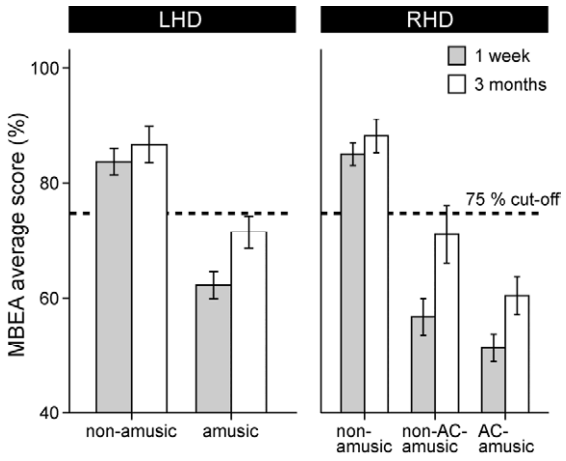

Figure 7. MBEA average scores of the patients one week and three months post-stroke. Data (mean ± SEM) are shown for non-amusic (n = 12) and amusic (n = 12) patients with left hemisphere damage (LHD) and for non-amusic (n = 9), non-AC-amusic (n = 9), and AC-amusic (n = 11) patients with right hemisphere damage (RHD). The dotted line indicates the amusia cut-off level (75%).

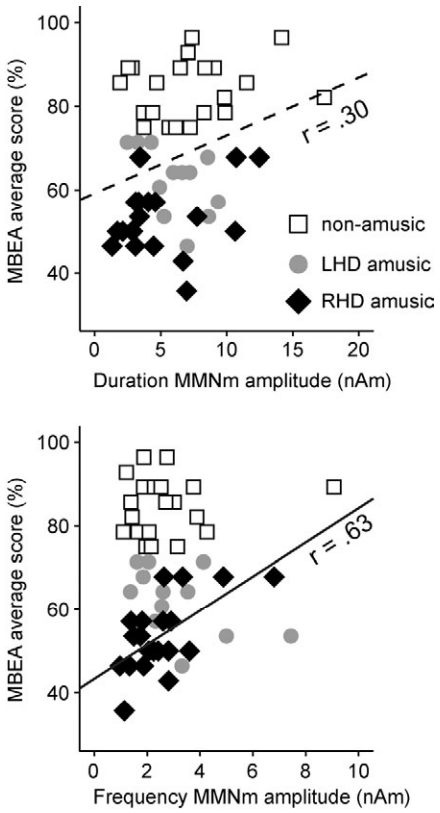

Figure 8. Correlation between the MBEA average score and the duration and frequency MMNm overall amplitudes (average of left and right hemisphere responses) one week after a stroke. Scatterplots are shown for non-amusic patients (n = 21), amusic patients with left hemisphere damage (LHD amusic, n = 12), and amusic patients with right hemisphere damage (RHD amusic, n = 20). Regression lines are shown only for statistically significant correlations (dotted line: all patients; solid line: amusic RHD patients).

Regarding the MMNm response (Figure 9), there were significant group differences in the right hemisphere duration MMNm latency [$F(2, 25) = 4.47$, $p = 0.022$] and amplitude [$F(2, 25) = 3.56$, $p = 0.043$] in the RHD subgroup one week post-stroke. Post

hoc tests (LSD) indicated a longer latency and a smaller amplitude in the AC-amusic group than in the non-amusic ($p = 0.029$ and 0.017) or non-AC-amusic ($p = 0.002$ and 0.017) groups. These Group effects remained significant also during the 6-month period [$F(2, 25) = 3.5$, $p = 0.046$ and $F(2, 25) = 3.47$, $p = 0.047$]. Additionally, significant Group effects were also observed in the amplitude of the duration MMNm [$F(2, 25) = 4.55$, $p = 0.021$] and the frequency MMNm [$F(2, 25) = 3.84$, $p = 0.035$] in the left hemisphere during the six-month period. Post hoc tests showed that the left hemisphere duration MMNm amplitude was smaller in the AC-amusic group than in the non-amusic group ($p = 0.006$), and the left hemisphere frequency MMNm amplitude was smaller in the AC-amusic group than in both non-amusic ($p = 0.014$) and non-AC-amusic ($p = 0.056$) groups. There were no significant differences between the non-AC-amusic and

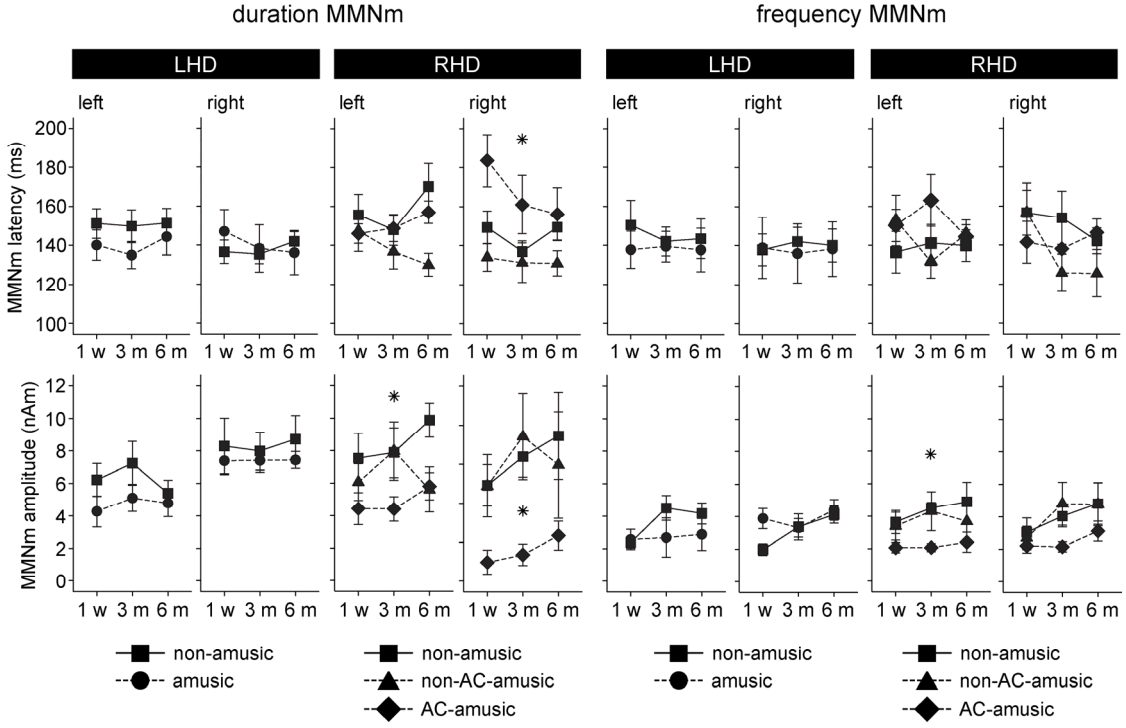

Figure 9. Group results of the latency and amplitude of the duration MMNm and the frequency MMNm in the left and right hemispheres one week (1 w), three months (3 m), and six months (6 m) post-stroke. Data (mean ± SEM) are shown for non-amusic (n = 12) and amusic (n = 12) patients with left hemisphere damage (LHD) and for non-amusic (n = 9), non-AC-amusic (n = 9), and AC-amusic (n = 11) patients with right hemisphere damage (RHD). *$p < 0.05$ in mixed-model ANOVA (Group effect).

non-amusic groups during the six-month follow-up ($p = 0.132 – 0.937$). Also the amusic and the non-amusic LHD patients did not differ on any MMNm parameter during the six-month period.

Regarding the cognitive performance of the RHD patients (Figure 10), there were significant group differences in the phonemic [$F(2, 25) = 6.13$, $p = 0.007$] and semantic [$F(2, 25) = 4.97$, $p = 0.015$] fluency tasks as well as in the reaction times on the Stroop task [$F(2, 22) = 5.21$, $p = 0.014$] one week post-stroke. These group effects also remained significant throughout the six-month post-stroke period [$F(2, 25) = 3.54$, $p = 0.044$; $F(2, 25) = 6.3$, $p = 0.006$; and $F(2, 22) = 4.05$, $p = 0.032$, respectively]. Additionally, a significant effect was observed for the digit span test [$F(2, 23) = 4.21$, $p = 0.028$]. Post hoc testing indicated that both the AC-amusic patients and the non-AC-amusic patients performed significantly worse than the non-amusic patients on the digit span ($p = 0.012$ and 0.033), phonemic fluency ($p = 0.023$ and 0.035), and semantic fluency ($p = 0.008$ and 0.003) tests throughout the six-month period. Compared with the non-amusic patients, the reaction times on the Stroop task were slower in the AC-amusic patients ($p = 0.011$) and, to a lesser degree, also in the non-AC-amusic patients ($p = 0.066$). A significant group difference was also observed for performance on the Balloons test part B at the one-week post-stroke stage [$F(2, 25) = 3.59$, $p = 0.042$], but this effect did not remain significant at later stages. Importantly, there were no significant differences between the AC-amusic patients and the non-AC-amusic patients in any test ($p = 0.313 – 0.792$).

In summary, the results of Study III suggest that amusia caused by RHD is more severe than amusia caused by LHD and may be related to deficient pitch encoding in the brain. Damage to the right AC and other temporal and frontal structures especially leads to a severe and persistent form of amusia that is characterized by deficits in both low-level auditory processing (MMNm) and higher cognitive functions such as working memory, cognitive flexibility, and attention. In contrast, damage to temporal and frontal areas that spares the AC results in a more transient form of amusia, which is related primarily to cognitive deficits.

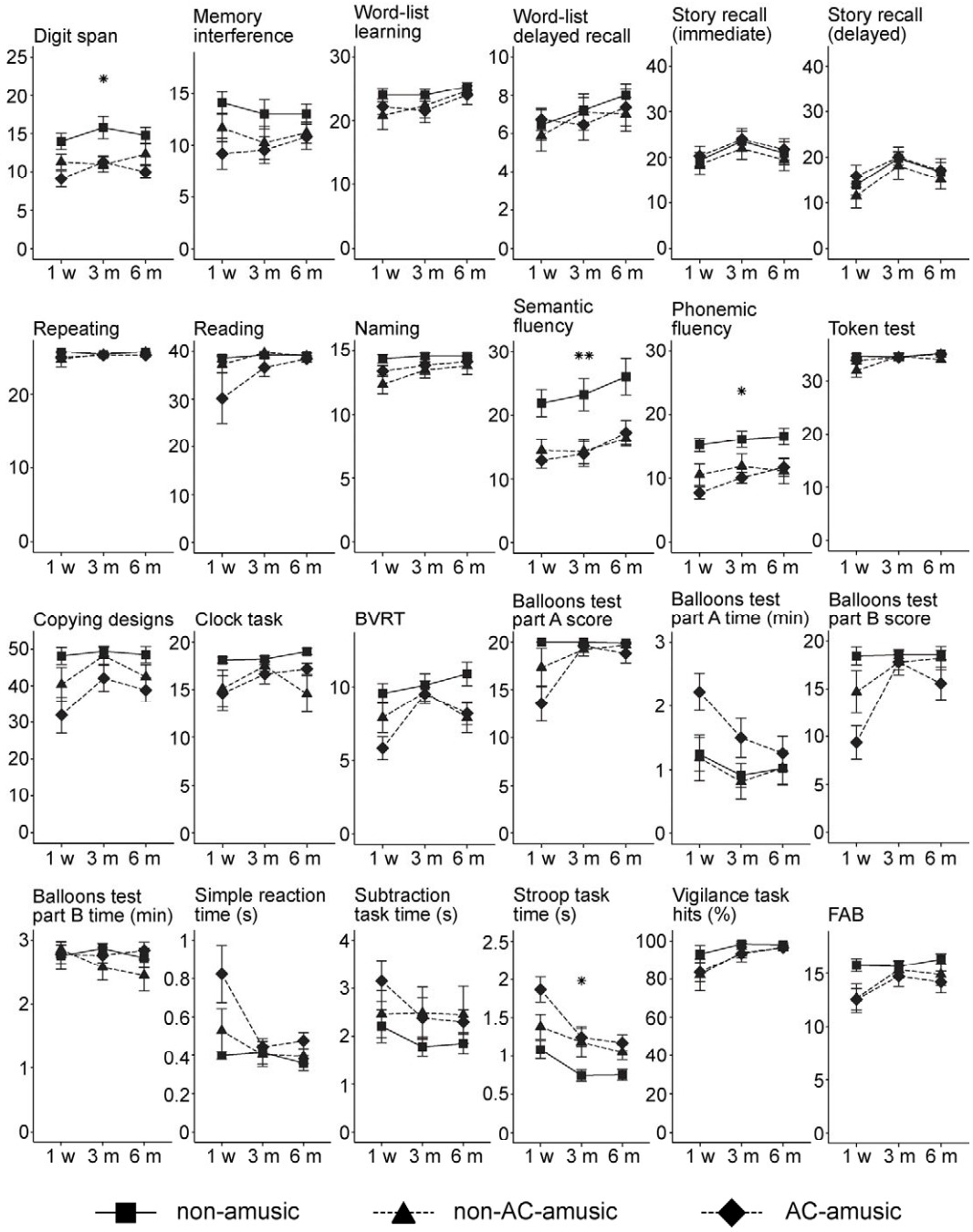

Figure 10. Cognitive performance of right hemisphere-damaged patients with no amusia (n = 9), amusia without auditory cortex damage (non-AC-amusic, n = 9), and amusia with auditory cortex damage (AC-amusic, n = 11) one week (1 w), three months (3 m), and six months (6 m) post-stroke. Data are shown as mean ± SEM with the y axis scaled to the maximum score (except in fluency and reaction time tests). See Table 1 for test descriptions. *$p < 0.05$ and **$p < 0.01$ in mixed-model ANOVA (Group effect).

4.4 Effects of music and speech listening on cognitive recovery and mood (Study IV)

The aim of Study IV was to determine whether daily music or audio book listening could facilitate the recovery of cognitive functions and mood after an acute MCA stroke. Figure 11 illustrates the changes in patients in the music (n = 19), audio book (n = 19), and control (n = 17) groups on the ten different cognitive domains (see Methods for details) during the six-month follow-up. Group differences were analysed using mixed-model ANOVAs with Time (1 week/3 months/6 months), Group (music/audio book/control) and Lesion laterality (left/right) as factors. There were significant Time x Group interactions in the domains of verbal memory [$F(4, 96) = 4.7$, $p = 0.002$] and focused attention (hits) [$F(3.2, 59.3) = 3.9$, $p = 0.012$]. Post hoc testing (HSD) was performed on the change scores (3-month minus 1-week and 6-month minus 1-week). Both verbal memory and focused attention scores improved more in the music group than in the audio book ($p = 0.006$ and 0.058) and control ($p = 0.049$ and 0.049) groups during the three-month follow-up period. At the six-month post-stroke stage, verbal memory recovery was still better in the music group than in the audio book group ($p = 0.006$), and focused attention recovery remained better in the music group than in the control ($p = 0.008$) and audio book ($p = 0.016$) groups. A further correlation analysis (Pearson) across all patients indicated that the focused attention (hits) and verbal memory scores were significantly correlated at the one-week ($r = 0.32$, $p = 0.037$), three-month ($r = 0.54$, $p < 0.001$), and six-month ($r = 0.49$, $p < 0.001$) stages.

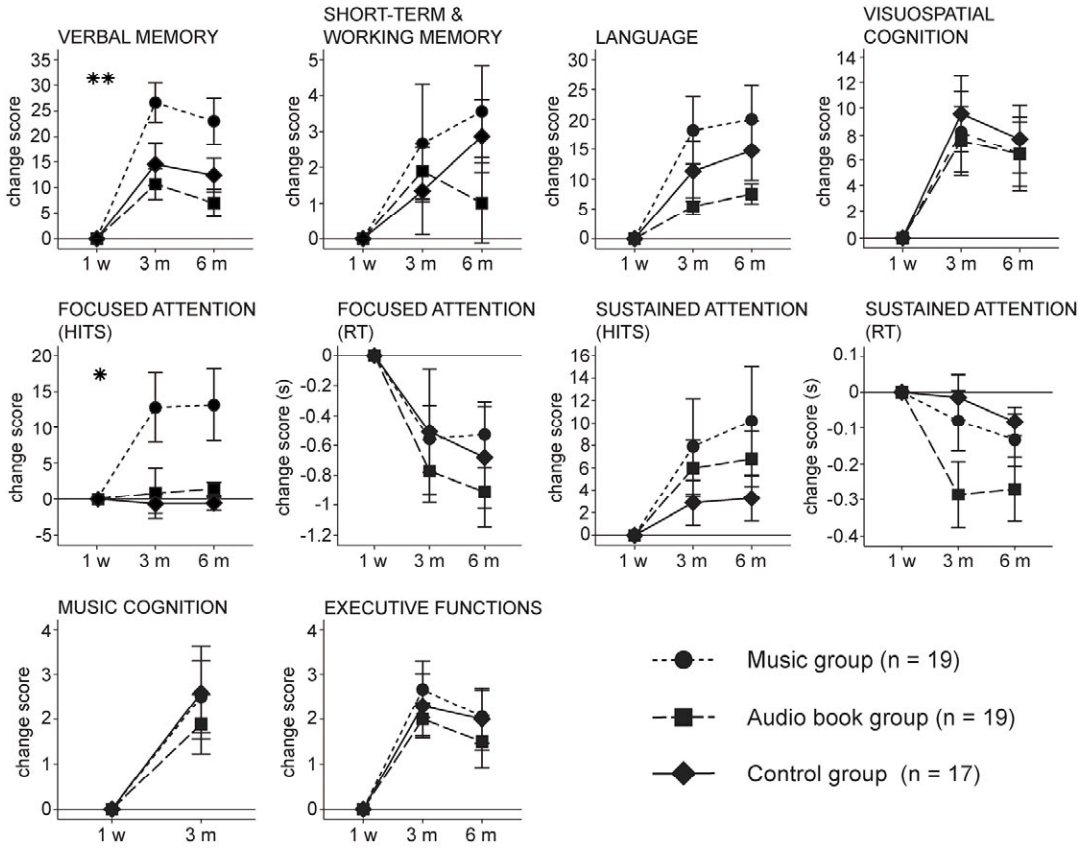

Figure 11. Changes in the 10 cognitive domains (mean ± SEM) from the one-week (1 w) to the three-month (3 m) and six-month (6 m) post-stroke stages (1-week score subtracted from the values) in the music, audio book, and control groups. **p < 0.01, *p < 0.05 Time x Group interaction in a mixed-model ANOVA.

The Profile of Mood States (POMS) scores of the three patient groups at the three-month and six-month post-stroke stages are shown in Figure 12. Significant group differences were observed in the depression [one-way ANOVA $F(2, 51) = 3.7$, $p = 0.031$] and confusion [$F(2, 51) = 3.3$, $p = 0.045$] scores at the three-month stage with post hoc tests (HSD) indicating lower scores in the music group than in the control group ($p = 0.024$ and 0.061). At the six-month stage, these group differences were still marginally significant [$F(2, 50) = 2.6$, $p = 0.086$ and $F(2, 50) = 2.9$, $p = 0.064$]. There were no significant group differences in the self- or proxy-rated SAQOL-39 questionnaire at either the three-month or the six-month stage.

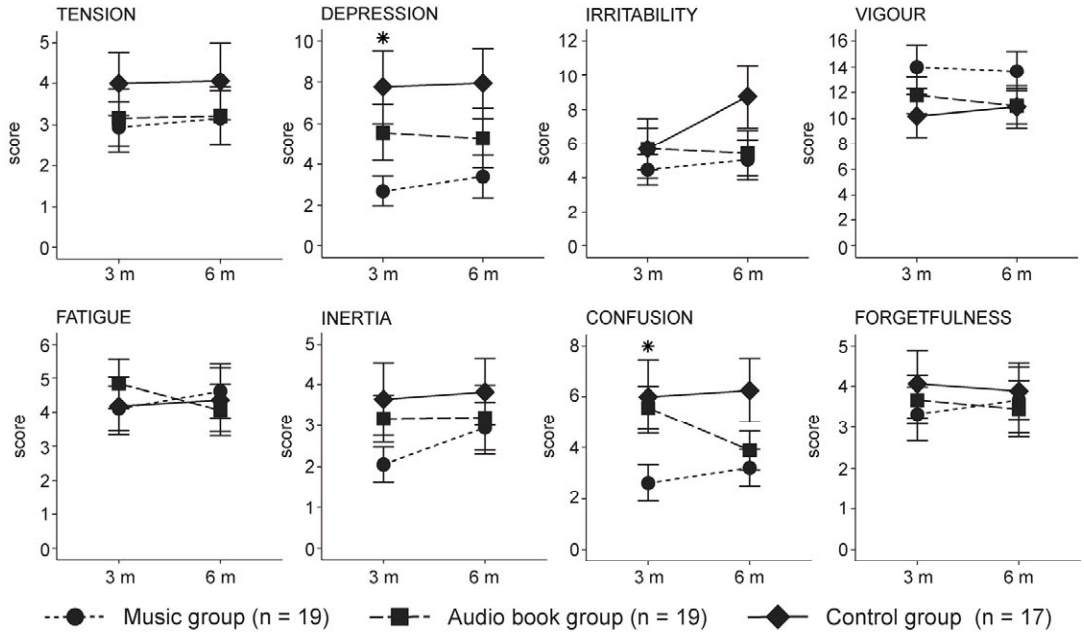

Figure 12. Profile of Mood States (POMS) scale scores (mean ± SEM) in the music, audio book, and control groups at the three-month (3 m) andsix-month (6 m) post-stroke stages *p < 0.05 Group effect in a one-way ANOVA.

The potential relationship between the enhanced cognitive recovery and the improved mood induced by listening to music was also studied by using correlation analyses. The improvement in verbal memory correlated significantly with reduced depression (Pearson r = -.61, p = 0.005) and confusion (Pearson r = -.68, p = 0.001) during the three-month period within the music group, but not within the audio book or control groups. No significant correlations were observed between the changes in mood and focused attention. However, when the three-month POMS depression and confusion scores were included as covariates in the aforementioned mixed-model ANOVAs, the Time x Group interactions still remained significant for both verbal memory [F(4, 96) = 3.4, p = 0.012] and focused attention (hits) [F(3.3, 56.2) = 4.3, p = 0.007]. These results indicate that, although the positive effects of music on mood and cognition were clearly interrelated, the enhancing effect of music on cognitive recovery was not entirely mediated by the improved mood.

In summary, the results of Study IV suggest that listening to music daily during the first months after an MCA stroke can enhance the recovery of memory and attention as well as prevent a depressed and confused mood.

4.5 Effects of music and speech listening on the recovery of auditory encoding (Study V)

The aim of Study V was to explore whether daily music or audio book listening after an acute MCA stroke could have long-term effects on auditory encoding in the brain as indicated by the MMNm response. Group differences in the frequency and duration MMNm responses were analysed using mixed-model ANOVAs with Time (1 week/3 months/6 months), Group (music/audio book/control) and Lesion laterality (left/right) as factors. As illustrated in Figure 13, there was a significant Time x Group interaction in the amplitude of the right hemisphere frequency MMNm [$F(4, 96) = 2.72$, $p = 0.034$]. Separate within-group analyses showed that the frequency MMNm amplitude increased significantly in the music [$F(2, 34) = 5.81$, $p = 0.007$] and audio book [$F(1.4, 25.2) = 8.74$, $p = 0.003$] groups, but not in the control group [$F(2, 32) = 0.25$, $p = 0.78$] during the six-month post-stroke period. Also post hoc tests (LSD) verified that the frequency MMNm amplitude increased more in the music ($p = 0.047$) and audio book ($p = 0.049$) groups than in the control group from the one-week to the six-month stage. However, the music and audio book groups did not differ from each other ($p = 0.96$).

For the duration MMNm amplitude (Figure 13), a significant Time x Group x Lesion laterality interaction was observed in the right hemisphere [$F(4, 96) = 5.79$, $p < 0.001$]. Further mixed-model ANOVAs performed separately for the LHD and RHD patients showed that the Time x Group interaction was significant only in RHD patients [$F(4, 52) = 4.16$, $p = 0.005$]. Within the RHD patients, the duration MMNm increased significantly in the audio book group [$F(2, 20) = 6.71$, $p = 0.006$], but not in the music [$F(2, 16) = 2.60$, $p = 0.11$] or control [$F(2, 16) = 1.18$, $p = 0.33$] groups during the six-month period. Post hoc tests also confirmed that the duration MMNm increased more in the audio book group than in the control ($p = 0.006$) or music ($p = 0.054$) groups from the one-week to the six-month stage.

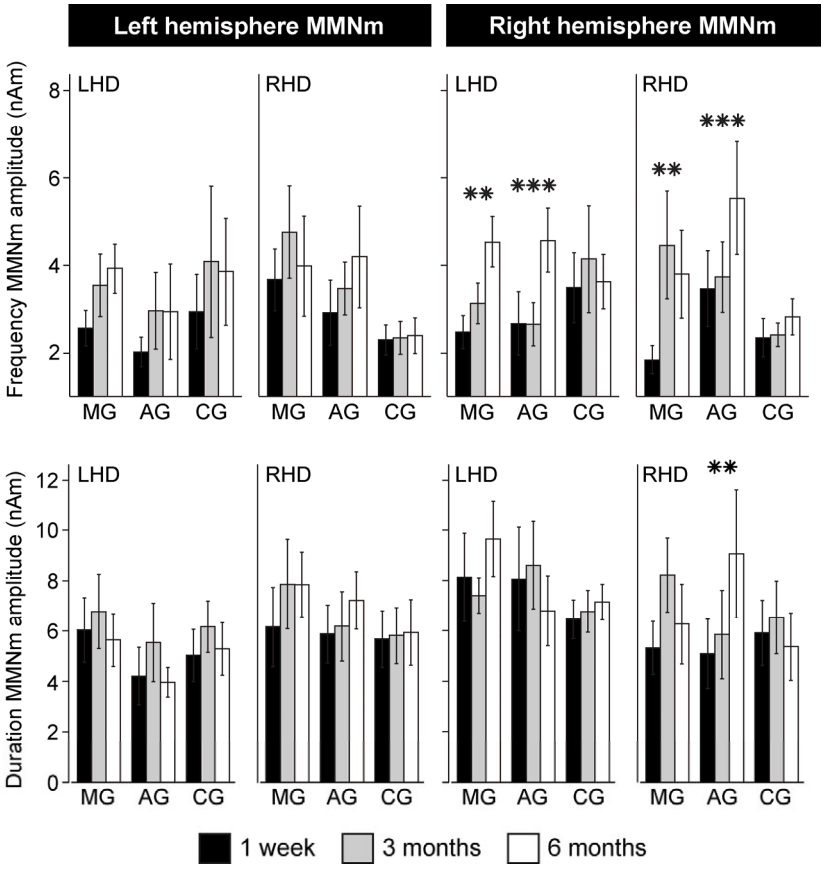

Figure 13. Group results of the frequency and duration MMNm amplitudes at different stages of stroke recovery. Data (mean ± SEM) are shown separately for patients with left hemisphere damage (LHD) and right hemisphere damage (RHD). *p < 0.05, **p < 0.01, ***p < 0.005 Time main effect in a mixed-model ANOVA. MG = Music group; AG = Audio book group; CG = Control group.

In order to determine whether the enhancement of the frequency MMNm was related to the improvement of verbal memory and focused attention induced by listening to music, further correlation analyses were performed. As shown in Figure 14, the increased MMNm responses correlated with the recovery of immediate story recall in the audio book group (Pearson r = .41, p = 0.043) and with the recovery of delayed story recall and mental subtraction both in the music group (Pearson r = .46, p = 0.027 and Spearman r = .61, p = 0.011, respectively) and in the audio book group (Pearson r = .50, p = 0.015 and Spearman r = .49, p = 0.021, respectively. In contrast, no significant positive correlations were observed between these tests and the MMNm in the control group.

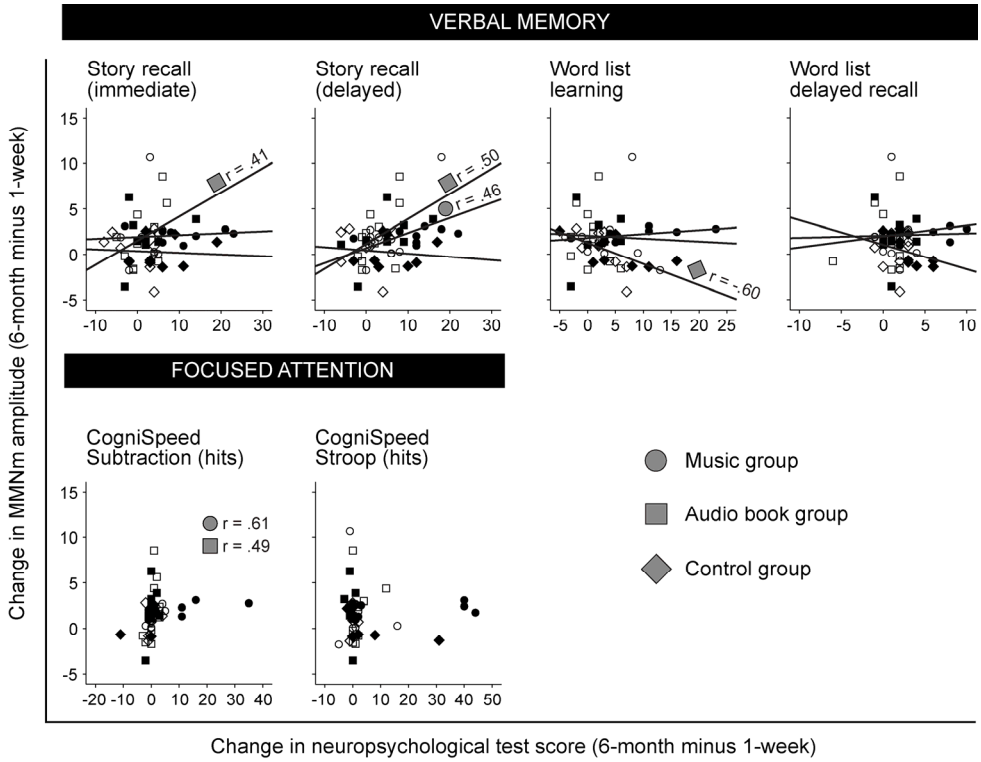

Figure 14. Correlations between the recovery of frequency MMNm, verbal memory, and focused attention during the six-month post-stroke period. Scatterplots of the change scores (6-month score minus 1-week score) are shown for the music group (n = 18, circles), the audio book group (n = 19, squares), and the control group (n = 17, diamonds), and for the LHD (filled) and RHD (unfilled) patients. Regression lines are shown only for Pearson correlation coefficients.

In summary, the results of Study V indicate that daily music or audio book listening during the first six months after an MCA stroke can improve early auditory encoding as indicated by the strengthening of the MMNm response. Specifically, both music and audio book listening increased the amplitude of the frequency MMNm, whereas audio book listening alone increased the amplitude of the duration MMNm. Moreover, the enhancement of the frequency MMNm was associated with the behavioural improvement of verbal memory and focused attention induced by listening to music.

5 Discussion

The five studies discussed here investigated the interplay of auditory, cognitive, and emotional factors related to music processing in the recovering brain. Specifically, neuropsychological tests, mood questionnaires, and MEG measurements were repeatedly performed on 60 MCA stroke patients over a six-month post-stroke period to explore the cognitive and auditory factors associated with acquired amusia (Studies I–III) as well as to determine the therapeutic impact of listening to music on the recovery of cognition and mood (Study IV) and auditory functions (Study V) utilising a randomised controlled trial (RCT) setting. The main findings were that amusia is a relatively common and persistent deficit after an ischemic MCA stroke, especially if the stroke affects the frontal and temporal brain areas in the right hemisphere, and that amusia is clearly associated with both low-level auditory processing and domain-general cognitive deficits. Furthermore, both active music and audio book listening during the first post-stroke months can improve early auditory encoding in the brain, whereas only music listening was found to enhance the recovery of memory and attention as well as to prevent a negative mood after a stroke. In the following sections, four topics relevant to the studies will be discussed in more detail: (1) the clinical characteristics of amusia, (2) the neural basis of amusia, (3) the potential mechanisms underlying the positive effects of music on stroke recovery, and (4) the clinical relevance of listening to music in stroke rehabilitation.

5.1 Clinical characteristics of amusia

Although the first reported clinical observations of acquired amusia date back to the nineteenth century (Johnson & Graziano, 2003), the scientific study of amusia has mostly been limited to case reports and small ($n \leq 20$) group studies. To date, Studies I–III are the first longitudinal group studies of acquired amusia with a relatively large patient sample ($n = 53$), and thus they can provide novel information about the clinical characteristics of the disorder. In Studies I and II, the incidence of amusia was 60 per cent at the one-week post-stroke stage and 42 per cent at the three-month post-stroke

stage. Almost two-thirds (66%) of the amusic patients remained amusic at the three-month stage. This is fully in line with the results of previous smaller studies, which have reported amusia in 69 per cent of patients five to ten days post-lesion (Schuppert et al., 2000) and in 35 per cent of patients six months to seven years post-lesion (Ayotte et al., 2000) after MCA damage. Together, these findings suggest that amusia is a common disorder in the acute post-stroke stage, and in many cases it can persist for longer periods of time. Clinically, this information is important because the evaluation of music perception is usually not part of the neuropsychological assessment (unless the patient happens to be a professional musician), and consequently, the presence of amusia may often be overlooked, with the result that the condition is underdiagnosed in the stroke population.

Regarding the lateralization of the deficit, amusia was slightly more common after RHD (69%) than after LHD (50%), but this difference was not statistically significant. Previous studies have reported relatively similar incidences of amusia after LHD and RHD, although the exact musical functions, which are deficient, can differ (Ayotte et al., 2000; Liégeois-Chauvel et al., 1998; Peretz, 1990; Schuppert et al., 2000). By contrast, evidence from case studies suggests a preponderance of RHD among amusic patients (Stewart et al., 2006). However, this is likely to reflect a sampling bias caused by the fact that musical testing is often difficult in patients with more severe aphasia. The results of Study III showed that the amusic deficit caused by RHD was more severe than the deficit caused by LHD. Correlation analyses indicated that smaller frequency MMNm amplitudes correlated with lower MBEA scores in amusic patients with RHD, but not with LHD, suggesting that the deficit in music perception caused by RHD may be more closely related to deficient pitch processing in the brain. Also previous clinical and neuroimaging evidence suggests the importance of the right hemisphere: a deficit in perceiving pitch within melodies is more typically caused by RHD than by LHD (Ayotte et al., 2000; Liégeois-Chauvel et al., 1998; Peretz, 1990; Schuppert et al., 2000). Similarly, comparing the pitch of two notes within a melody activates a network of right frontal and temporal areas in healthy subjects (e.g., Zatorre et al., 1994).

Studies I–III also indicated that the severity and persistence of amusia depended on the location and extent of the cerebral damage. Across all patients, the incidence of frontal lobe damage as well as temporal lobe damage, especially to the auditory cortex

(AC), was clearly higher in the amusic group than in the non-amusic group. Within the RHD subgroup, the AC-amusic patients who had extensive damage covering the AC and other temporal and frontal lobe areas were found to perform worse on the MBEA throughout the three-month post-stroke period than the non-AC-amusic patients whose damage was to the temporal and frontal lobes, but spared the AC. Overall, fewer than half (44%) of the non-AC-amusic patients could still be classified as amusic at the three-month stage, whereas a vast majority (91%) of the AC-amusic patients remained amusic at the three-month stage. Thus, severe and persistent amusia seems to be caused especially by damage to the AC as well as to other temporal and frontal areas in the right hemisphere.

5.2 Neural basis of amusia

The neural basis of music processing, especially the extent to which it differs or overlaps with the mechanisms used in other cognitive domains, has been an area of active research and debate for the past twenty years (e.g., Peretz, 2006; Patel, 2008). According to Peretz (Peretz & Coltheart, 2003; Peretz, 2006), the observed double dissociations between the deficits in perceiving music (amusia), speech (aphasia), and environmental sounds as well as in perceiving different musical features suggest that "music is an autonomous function, innately constrained and made up of multiple modules that overlap minimally with other functions (such as language)" (Peretz, 2006, p. 25). This view of music as a domain-specific cognitive function that is largely independent of language has, however, been challenged by more recent neuroimaging studies of healthy subjects showing that the neural processing of linguistic and musical structures involves similar ERP components, such as the P600 (Patel et al., 1998) and early right anterior negativity (ERAN) (Maess et al., 2001), and activates overlapping brain regions, including Broca's area (Brown et al., 2006; Koelsch et al., 2002; Tillmann et al., 2003). Similarly, clinical studies also indicate that patients with Broca's aphasia are impaired and show abnormal ERAN responses in processing musical structures (Patel, 2005; Patel et al., 2008b; Sammler et al., in press), and conversely, that people with congenital amusia have deficits in phonological and phonemic

awareness (Jones et al., 2009b) and in speech intonation processing (Jiang et al., 2010; Liu et al., 2010; Patel et al., 2005, 2008). These findings suggest that the processing of pitch and syntax in language and music may share common neural mechanisms. Regarding syntax processing, it has been suggested that language and music have distinct and domain-specific representations, but that activating these representations as part of online processing draws on a common pool of limited neural resources (*Shared syntactic integration resource hypothesis;* Patel, 2003; 2008).

The results of Studies I–III extend this ongoing discussion about the specificity vs. non-specificity of music to include the potential role of more domain-general cognitive processes, such as attention, memory, and executive functions, in music perception. Previously, this topic has been briefly addressed only in one small group study (Münte et al., 1998), which reported decreased P3a responses to environmental sounds and deficient performance on a behavioural auditory alertness test in amusic stroke patients. Compared to the non-amusic patients, the amusic patients in the present studies were found to perform worse on tests of working memory and learning (digit span, memory interference, word-list learning, and story recall), executive functioning (FAB, Stroop, and phonemic fluency), verbal expression and comprehension (semantic fluency and Token test), and visuospatial perception and attention (copying designs, BVRT, and Balloons test part B). Crucially, the group differences in working memory and learning, executive functioning, and verbal expression and comprehension remained significant after lesion size was statistically controlled for, suggesting that these cognitive deficits were not simply a by-product of the amusic patients having more extensive cerebral damage. Correlation analyses within the amusic group also revealed that deficits in attention were associated with the severity of amusia and that the improvement of attention and memory contributed to the recovery of amusia.

Given the pivotal role of the prefrontal cortex in regulating attention, working memory, executive functions, and verbal skills (e.g., Duncan & Owen, 2000; Stuss & Levine, 2002), these results also concur with the MRI finding that frontal lobe lesions were more common in the amusic than in the non-amusic patients. Evidence from previous studies of acquired (Stewart et at., 2006) and congenital (Hyde et al., 2006, 2007, 2011; Loui et al., 2009) amusia suggests that, together with the AC and other temporal areas, areas in the frontal lobe, especially the inferior frontal gyrus (IFG),

which is generally involved in processing response conflict, perceptual difficulty, novelty, and working memory (Duncan & Owen, 2000), form a critical node in the neural network underlying amusia. Collectively, these findings suggest that amusia can result from the dysfunction of brain regions that are not exclusively related to auditory encoding, but also serve other domain-general cognitive functions.

Evidence from previous clinical and neuroimaging studies strongly indicates that the right AC plays an important role in musical pitch processing. Damage to the right AC has been shown to produce a severe deficit in discriminating between melodies (Milner, 1962; Peretz, 1990) and perceiving pitch (Johnsrude et al., 2000; Liégeois-Chauvel et al., 1998; Zatorre, 1988). Likewise, neuroimaging studies of healthy subjects suggest that the AC and other auditory areas in the right hemisphere are active during passive listening to melodies (Brown & Martinez, 2007; Patterson et al., 2002; Zatorre et al., 1994) and respond especially to small pitch changes (Hyde et al., 2008; Jamison et al., 2006; Schönwiesner et al., 2005; Zatorre & Belin, 2001). However, when the subject has to perform an active task (e.g., same-different discrimination between two melodies or between two pitches within a single melody), a network of areas in the frontal lobe, including precentral, inferior frontal, and dorsolateral prefrontal cortical areas as well as the anterior cingulate cortex, becomes activated in addition to the temporal areas (Brown & Martinez, 2007; Gaab et al., 2003; Griffiths et al., 1999; Zatorre et al., 1994). Thus, the music perception deficit in the amusic brain, as indicated by poor performance on the MBEA, could in principle result either from a deficit in auditory encoding caused by damage to the AC or other temporal areas or from a deficit in the more cognitive, conscious processing of the auditory information caused by frontal lobe damage.

Study III showed that the amusic patients who had extensive RHD involving the AC and other temporal and frontal areas had smaller and slower MMNm responses than the non-amusic RHD patients or the amusic RHD patients whose lesions included frontal and temporal areas, but spared the AC. In contrast, both the AC-amusic patients and the non-AC-amusic patients performed worse than the non-amusic patients on the digit span, verbal fluency, and Stroop tasks. These findings suggest that cognitive deficits in attention, working memory, and executive functions are the primary mechanism underlying amusia without AC damage, whereas amusia with AC damage is associated with both auditory and cognitive deficits.

5.3 Potential mechanisms underlying the positive effect of music on stroke recovery

The main findings of Studies IV and V were that listening to music daily during the early post-stroke stage improved the recovery of verbal memory and focused attention as well as prevented depressed and confused mood, whereas both music and audio book listening enhanced auditory sensory memory during a six-month follow-up. A parallel qualitative study, in which the music and audio group patients were interviewed about their subjective experiences after the two-month intervention period, yielded similar results: music listening was specifically associated with better relaxation, increased physical activity, and improved mood, while both music and audio book listening provided refreshing stimulation and evoked thoughts and memories of the past (Forsblom et al., 2009, 2010). These findings are discussed next in the context of the following three mechanisms potentially underlying the effects: (1) improved mood and arousal, (2) reduced stress, and (3) enhanced neural plasticity.

Improved mood and arousal. Accumulating evidence from studies of both healthy subjects and various clinical patient groups indicates that listening to music has a positive influence on mood and cognitive performance (e.g., Abikoff et al., 1996; Beh & Hirst, 1999; Chabris, 1999; Foster & Valentine, 2001, Hallam et al., 2002; Juslin & Laukka, 2004; Mammarella et al., 2007; Schellenberg et al., 2007; Soto et al., 2009; Thompson et al., 2001). The reported beneficial effects of music on cognition are transient and span many different cognitive domains, including speed of information processing, reasoning, attention, and memory, suggesting that the short-term effect of music on cognition is more general than specific to any one domain. According to the *Arousal and mood hypothesis* (Thompson et al., 2001), this effect can be attributed to the positive affect and the heightened arousal induced by music, which in turn can lead to improved cognitive performance.

Recent animal studies and functional neuroimaging studies have shed some light on the neural mechanisms that mediate these effects. Listening to pleasant music activates an interconnected network of subcortical and cortical brain regions, which includes the amygdala, the hippocampus, the parahippocampal gyrus, the nucleus accumbens (NAc),

the ventral tegmental area (VTA), the anterior cingulate, and the orbitofrontal cortex (e.g., Baumgartner et al., 2006; Blood et al., 1999; Blood & Zatorre, 2001; Brown et al., 2004; Eldar et al., 2007; Koelsch, 2010; Koelsch et al., 2006; Menon & Levitin, 2005; Mitterschiffthaler et al., 2007). VTA produces dopamine (DA) and has direct projections to the locus ceruleus, the NAc, the amygdala, the hippocampus, the anterior cingulate, and the prefrontal cortex (Ashby et al., 1999). Together, this dopaminergic mesocorticolimbic system is crucial to mediating arousal, emotion, reward, motivation, memory, attention, and executive functioning (Ashby et al., 1999).

In rats, listening to music has been shown to increase dopaminergic neurotransmission and neostriatal DA concentrations (Sutoo & Akiama, 2004) as well as to enhance the effect of MDMA (ecstasy) on DA levels in the NAc (Feduccia & Duvauchelle, 2008). In humans, DA has been found to mediate many cognitive functions, including working memory, attention, and executive functioning (Nieoullon, 2002). Pharmacological studies have shown that DA agonists as well as stimulants that increase DA levels in the brain can improve working memory and executive functions in healthy subjects (Mehta & Riedel, 2006) and in patients with brain damage (Bales et al., 2009). Thus, it is possible that the repeated activation of the dopaminergic mesocorticolimbic system induced by listening to one's favourite music on a daily basis may have contributed to the enhanced cognitive recovery of the music group in the present study. Furthermore, the DA system has also been shown to regulate motor activity, motivation, and reward behaviour (Knab & Lightfoot, 2010), results that may be related to the self-reported increased physical activity (e.g., doing housework and dancing) in the music group (Forsblom et al., 2009, 2010).

Correlation analyses indicated that the positive changes in mood and cognition were clearly interrelated in the music listeners. This result is in line with previous clinical studies showing that early cognitive impairment can predict depression and quality of life (QOL) six to ten months after a stroke (Nys et al., 2006) and, conversely, that patients with psychiatric symptoms show more cognitive decline six months post-stroke (Rasquin et al., 2005). Thus, it is possible that, in the long run, daily listening to music could promote cognitive recovery by preventing depression. Previous research on the effectiveness of active music therapy has suggested that it can improve mood and emotional adjustment, reduce depression and anxiety as well as increase social

interaction and participation in rehabilitation after a stroke or traumatic brain injury (Baker et al., 2005; Guétin et al., 2009; Magee & Davidson, 2002; Nayak et al., 2000; Thaut et al., 2009). Although both cognitive deficits and mood disorders are known to be important factors limiting QOL after a stroke (Carod-Artal & Edigo, 2009), there were no significant effects of music on self- or proxy-reported QOL in the present study, suggesting that the effect of music listening on everyday functions (e.g., physical and psychosocial activities) is clearly limited.

Reduced stress. Another possible set of mechanisms underlying the positive effect of music on cognition involves the neuroendocrine system (Patel, 2010). As noted earlier, music has a strong influence on the limbic system (Koelsch, 2010), including the hypothalamus, which regulates the release of a broad range of hormones (e.g., oxytocin and cortisol). Cortisol, a glucocorticoid hormone secreted by the adrenal glands in response to stress, is particularly relevant with respect to music, since previous studies have shown that listening to music can transiently reduce cortisol levels, both after experimentally-induced stress (Khalfa et al., 2003; Kreutz et al., 2004; Suda et al., 2008, Pelletier, 2004) and after stress induced by a medical procedure (Leardi et al., 2007; Nilsson, 2009; Nilsson et al., 2005; Schneider et al., 2001). A stroke is a major life-changing event that can cause considerable anxiety and stress (Ferro et al., 2009). In the months following a stroke, patients typically have chronically elevated cortisol levels (hypercortisolism), which is associated with poor cognitive function and depression (Åström et al., 1993; Franceschini et al., 2001; Lee et al., 2007). Prolonged stress can also have maladaptive effects on neural plasticity, causing, for example, dendritic atrophy, excitatory synapse loss, and decreased neurogenesis in the hippocampus (Radley & Morrison, 2005). The qualitative results of the parallel interview study (Forsblom et al., 2009, 2010) indicated that the patients felt that listening to music helped them to relax better, especially in the early post-stroke stage, suggesting that listening to music could alleviate the anxiety and psychological stress experienced by the patients. Thus, reduced stress and cortisol levels may be one factor underlying the enhancing effect of music on cognitive recovery.

Enhanced neural plasticity. Evidence from neuroimaging studies indicates that music listening triggers an array of auditory perceptual, cognitive, emotional, and motor processes involving the activity of a widespread, mostly bilateral network of temporal, prefrontal, motor, parietal, cerebellar, and subcortical areas (e.g., Belin et al., 2000; Blood & Zatorre, 2001; Brown & Martinez, 2007; Grahn & Brett, 2007; Hyde et al., 2008; Janata et al., 2002b; Koelsch, 2010; Koelsch & Siebel, 2005; Platel et al., 2003; Popescu et al., 2004; Zatorre, 2005; Zatorre et al., 1994; 2002). A similar, but more left-lateralized and cortically located network of temporal, prefrontal, premotor, and parietal areas is also activated when a person listens to narrated stories (Lindenberg & Scheef, 2007; Mazoyer et al., 1993; Papathanassiou et al., 2000; Schmithorst et al., 2006; Tzourio-Mazoyer et al., 2004). Hemodynamic studies, which have used transcranial Doppler sonography (TCD), have demonstrated that listening to music or speech can temporarily increase cerebral blood flow, especially in the MCA in healthy subjects (Carod-Artal et al., 2004; Matteis et al., 1997; Vollmer-Haase et al., 1998) and possibly also in stroke patients (Antić et al., 2008). Taken together, this evidence suggests that listening to music or narrated stories after an MCA territory stroke increases the neural activity of the areas surrounding the ischemic lesion or in the contralesional hemisphere, potentially enhancing the adaptive plastic changes, which typically occur in these areas in the subacute post-stroke phase (Kreisel et al., 2006). Thus, the neural stimulation provided by the listening may have contributed to the recovery of cognitive functions and MMNm observed in the present studies.

Evidence supporting the notion that auditory stimuli may enhance neural plasticity in the recovering brain comes from animal studies using the environmental enrichment (EE) paradigm. After an ischemic stroke, EE can improve motor and cognitive recovery and induce many neuroplastic changes, such as decreased infarct volume and increased neurotrophic factor levels and neurogenesis (Biernaskie & Corbett, 2001; Dahlqvist et al., 1999, 2004; Gobbo & O'Mara, 2004; Hicks et al., 2002; Johansson, 1996; Johansson & Belichenko, 2002; Komitova et al., 2002, 2005; Risedal et al., 2002). These changes are even more pronounced if the EE also contains multimodal sensory stimuli, including sound stimuli (Maegele et al., 2005a, 2005b). The effect of a purely auditory EE on stroke recovery has not been studied previously, but developmental studies suggest that it can enhance the structure and function of the AC (Bose et al.,

2010; Engineer et al., 2004; Nichols et al., 2007; Percaccio et al., 2005; Xu et al., 2007, 2009) and improve learning and memory (Angelucci et al., 2007a; Chikahisa et al., 2006; Kim et al., 2006). Crucially, in the developing brain an auditory EE has also been observed to enhance neurogenesis and neurotrophin production (Angelucci et al., 2007a, 2007b; Chaudhury & Wadhwa, 2009; Chikahisa et al., 2006; Kim et al., 2006), both of which are important plasticity mechanisms after a stroke as well (Jin et al., 2006; Schäbitz et al., 2007).

One neural plasticity mechanism that may also account for the effects of listening on both cognition and MMNm is enhanced glutamatergic neurotransmission. Glutamate is the primary excitatory amino transmitter in the cortex and plays a critical role in learning and memory through its action at NMDA receptors (Cotman et al., 1988). Pharmacological studies have demonstrated that NMDA function is important for MMN generation in animals (Ehrlichman et al., 2008; Javitt et al., 1996; Tikhonravov et al., 2008) and humans (Korostenskaja et al., 2007; Kreitschmann-Andremahr et al., 2001; Umbricht et al., 2002). Suggesting a potential link to glutamate functioning, the MMN has also been shown to correlate with working memory, learning, executive functioning, and verbal skills in both children and adults (Ahveninen et al., 1999; Baldeweg et al., 2004; Ilvonen et al. 2003; Jansson-Verkasalo et al., 2004; Kawabuko et al., 2006; Kiang et al., 2007; Kujala et al., 2001; Mikkola et al., 2007; Pettigrew et al., 2005; Toyomaki et al., 2008). Animal studies have demonstrated that an auditory EE can enhance the expression and receptor function of glutamate in the AC and the anterior cingulate (Nichols et al., 2007; Xu et al., 2007), whereas auditory deprivation can decrease NMDA receptor expression levels in the AC (Bi et al., 2006). Since changes in glutamate transmission also parallel the recovery from brain infarction (Centonze et al., 2007; Keyvani & Schallert, 2002), glutamate may therefore be one crucial mechanism underlying the positive effect of music and speech on the recovery of memory and auditory encoding.

These suggested mechanisms are by no means mutually exclusive and most likely work in concert to bring about the environment-induced enhancement of recovery observed in the present studies. Moreover, it seems that no single mechanism can account for the effects. For example, including mood as a covariate did not eliminate the group

differences in cognitive recovery, suggesting that improvement in mood alone cannot account for the positive effect of music listening on cognitive recovery. Owing to the relative novelty of the research field, however, there is currently no direct experimental evidence to support these hypothesised mechanisms. Thus, more studies utilising physiological measures (e.g., heart rate, blood pressure), neuroendocrinological markers (e.g., cortisol), and structural and functional neuroimaging methods (e.g., fMRI, PET) in a joint manner are clearly needed in order to verify the effect of music listening on stroke recovery and to understand better its neural basis.

5.4 Clinical relevance of music listening in stroke rehabilitation

During the first weeks after a stroke, the brain undergoes dramatic plastic changes, which, according to animal EE studies, can be enhanced by stimulation provided by the recovery environment (Johansson, 2004; Nithianantharajah & Hannan, 2006). In the human stroke rehabilitation setting, previous research has primarily been directed to determining the impact of specific care units (Stroke Unit Trialists' Collaboration, 2007), pharmacotherapy interventions (Wardlaw et al., 2009), and rehabilitation methods (Bhogal et al., 2003; Cicerone et al., 2005; Langhorne et al., 2009). Thus, very little is currently known about the potential effects of everyday leisure activities or the recovery environment in general.

Owing to sensory, motor, and cognitive deficits, the ability of stroke patients to engage in their prior hobbies or activities is often greatly reduced. Decreased participation in hobbies and leisure activities has been documented in as many as 50–83 per cent of stroke patients (Daniel et al., 2009). Especially within the first post-stroke weeks, patients spend over 50 per cent of their day lying alone and inactive in their beds (Bernhardt et al., 2004; De Wit et al., 2005), even though from a plasticity standpoint this time-window would be ideal for rehabilitative training (Witte, 1998; Kreisel et al., 2006). Owing to limited mobilization and physical complications of the patients or lack of staff resources, active rehabilitation (e.g., physical or occupational therapy, speech therapy, or cognitive rehabilitation) is usually not possible in the early post-stroke stage. Since many common pastimes, such as reading and watching TV, are also often

hampered by the verbal or visual deficits caused by the stroke, the patients are usually left with very little to do during the first weeks in the hospital.

The results of the present thesis suggest that after an acute stroke, listening to music is a beneficial leisure activity that can provide an individually targeted, easy-to-conduct, and inexpensive way to help the patients cope with the adverse emotional and psychological impacts of stroke as well as to support their cognitive recovery. As with other rehabilitation interventions, early timing (Diserens & Rothacher, 2005) and high intensity (Kwakkel et al., 1997) are likely to be of the essence for music listening. Thus, starting a listening regime within the first week of stroke onset and continuing daily (for at least one hour per day) are likely to yield the best gains for recovery. As for the type of music, the patients' favourite music would seem to be the best choice, given its familiarity and its capacity to evoke emotions and episodic memories. Musical lyrics may also be an important factor, especially for aphasic patients, since listening to songs activates bilateral temporal and frontal areas more than listening to speech (Callan et al., 2006; Schön et al., 2010). More studies are needed to determine the specific impacts of different types of music as well as the optimal timing and intensity for using music to aid recovery after a stroke.

5.5 Conclusions

During the past twenty years, there has been increasing scientific interest in the neural basis and potential therapeutic effects of music (e.g., Koelsch 2010; Koelsch & Siebel, 2005; Patel, 2008; Peretz & Zatorre, 2005; Stewart et al., 2006). At the neural level, the relationships between music and other cognitive processes, such as language, memory and attention, are still under debate. This thesis suggests that after a stroke, the inability to perceive music, as indicated by poor performance on the MBEA, depends on the functioning of a frontotemporal neural network and, consequently, is associated with deficits in attention, working memory, executive functioning, and verbal skills (Studies I and II). Additionally, deficits in low-level auditory encoding, as indicated by diminished MMNm responses, contribute to amusia if the damaged area includes the

AC (Study III). Thus, musical, auditory, and cognitive functions seem to be closely related in the recovering brain.

Contrary to earlier beliefs, the results here suggest, that clinically amusia is a common and persistent deficit after an ischemic MCA stroke and thus should be seriously taken into account when assessing the cognitive profile of stroke patients (Studies I and II). Finally, the results indicate that daily listening to music during the early post-stroke stage can improve the recovery of verbal memory and focused attention as well as prevent a depressed and confused mood (Study IV), while both music and audio book listening can enhance auditory sensory memory (Study V). These findings encourage the use of listening to music as a rehabilitative leisure activity after a stroke and suggest that the auditory environment can induce long-term plastic changes in the recovering brain.

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